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

Farquhar CM, Marjoribanks J, Lethaby A, Lamberts Q, Suckling JA and the Cochrane HT Study Group

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TABLE OF CONTENTS

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ABSTRACT

Background
Hormone therapy (HT) is widely used for controlling menopausal symptoms. It has also been used for the management and prevention of cardiovascular disease, osteoporosis and dementia in older women but the evidence supporting its use for these indications is largely observational.

Objectives
To assess the effect of long-term HT on mortality, heart disease, venous thromboembolism, stroke, transient ischaemic attacks, breast cancer, colorectal cancer, ovarian cancer, endometrial cancer, gallbladder disease, cognitive function, dementia, fractures and quality of life.

Search strategy
We searched the following databases up to November 2004: the Cochrane Menstrual Disorders and Subfertility Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Biological Abstracts. Relevant non-indexed journals and conference abstracts were also searched.

Selection criteria
Randomised double-blind trials of HT (oestrogens with or without progestogens) versus placebo, taken for at least one year by perimenopausal or postmenopausal women.

Data collection and analysis
Fifteen RCTs were included. Trials were assessed for quality and two review authors extracted data independently. They calculated risk ratios for dichotomous outcomes and weighted mean differences for continuous outcomes. Clinical heterogeneity precluded meta-analysis for most outcomes.

Main results
All the statistically significant results were derived from the two biggest trials. In relatively healthy women, combined continuous HT significantly increased the risk of venous thromboembolism or coronary event (after one year's use), stroke (after 3 years), breast cancer (after 5 years) and gallbladder disease. Long-term oestrogen-only HT also significantly increased the risk of stroke and gallbladder disease. Overall, the only statistically significant benefits of HT were a decreased incidence of fractures and colon cancer with long-term use. Among relatively healthy women over 65 years taking continuous combined HT, there was a statistically significant increase in the incidence of dementia. Among women with cardiovascular disease, long-term use of combined continuous HT significantly increased the risk of venous thromboembolism.

No trials focussed specifically on younger women. However, one trial analysed subgroups of 2839 relatively healthy 50 to 59 year-old women taking combined continuous HT and 1637 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 very low.

Authors' conclusions
HT is not indicated for the routine management of chronic disease. We need more evidence on the safety of HT for menopausal symptom control, though short-term use appears to be relatively safe for healthy younger women.

PLAIN LANGUAGE SUMMARY

Long-term use of hormone therapy in women around the time of and after menopause.

Hormone therapy (HT) is widely used for controlling menopausal symptoms. It has also been used for the management and prevention of chronic diseases such as cardiovascular disease, osteoporosis and dementia in older women. The present review set out to assess the long-term clinical effects of using HT. Fifteen randomised double-blind trials (involving 35,089 women aged 41 to 91 years) compared HT (all oestrogens, with or without progestogens, administered by oral, transdermal, subcutaneous or intranasal routes) with placebo when taken for at least one year. In healthy women (8 studies), combined continuous HT significantly increased the risk of obstruction of a vein by a blood clot (venous thromboembolism), fatal or non-fatal heart attack (after a year's use), stroke (after 3 years), breast cancer (after 5 years), gallbladder disease and (in women over 65 years) dementia. Long-term oestrogen alone also significantly increased the risk of stroke and gallbladder disease. Among women with cardiovascular disease (6 studies) long-term use of combined HT significantly increased the risk of venous thromboembolism and gallbladder disease. HT offered the benefit of a significant reduction in the risk of fracture (no greater in women at high risk of fractures) or colorectal cancer but only after four or five years treatment with HT. The highest risk of cardiovascular events with combined HT occurred in the first year of use.

BACKGROUND

Most women experience the menopause (the last menstrual period) in their early fifties, after a phase of changing ovarian function (the perimenopause) which may last several years and which is characterised by irregular menstrual cycles (Greendale 1999). Women are said to be post-menopausal when menstruation has ceased for 12 months. Many peri- and postmenopausal women (though not all) report a variety of symptoms including hot flushes and vaginal dryness, which probably relate to the natural decline of 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 focussed on white women, but the experience of menopause differs between different races and ethnicities, as well as by menopausal stage (Avis 2001). Although the duration of regular hot flushes is very variable, most women report that they last for between 6 months and 2 years (Kronenberg 1994).

Hormone therapy (HT) includes either oestrogen alone (oestrogen-only HT) or oestrogen combined with a progestogen (combined HT) It is used in a variety of formulations and doses which can be taken orally, vaginally, transnasally or as an implant, skin patch or cream. 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 (Lethaby 2004), but the issue is problematic because progestogens have adverse effects on blood lipids as well as the potential to cause symptoms such as headaches, 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 either continuously (every day) or sequentially (for part of each month or less frequently). It appears that continuous therapy may be more protective than sequential therapy in the long term prevention of endometrial hyperplasia (Lethaby 2004).

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

During the past twenty-five 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 potentially causal or preventative of 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 evi-

dence that HT reduced the risk of coronary heart disease (CHD) by 30% or more. A meta-analysis of 25 cohort, case-control and angiographic studies published up to 1997 reported a risk ratio of 0.70 (95% CI 0.65-0.75) for CHD among oestrogen users compared to never-users. Moreover the cardioprotective benefits of oestrogen were biologically plausible, given that oestrogen has a favourable effect on many biomarkers, in particular HDL and LDL cholesterols. Other benefits reported in observational studies of HT were strong evidence of a reduction in osteoporotic fractures, a possible preventative or delaying effect on cognitive decline and/or dementia and even a reduction in overall mortality for current users (Barrett-Connor 1998).

Observational studies also indicated a range of *adverse* effects of HT including a doubling or tripling of the risk of thromboembolic events, a large increase in endometrial cancer risk in women taking oestrogen without progestogen, an increased incidence of gallbladder disease and a possible link between HT and breast cancer. The suggestion that HT increased 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 were inconsistent and controversial (Barrett-Connor 1998). The results of a very large observational study 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 for users of combined HT, with no large variations between the effects of specific oestrogens or specific progestogens. However, these findings have been challenged: in particular, the duration of HT use prior to the occurrence of breast cancer was based on data recorded at study entry without allowing for subsequent use up to the time of diagnosis (Lancet 2003).

Because CHD is the most common cause of death and morbidity in older women, it was held that a significant reduction in CHD risk from HT would outweigh any potential adverse effects. However there was strong potential for selection and/or compliance bias in these uncontrolled studies, with oestrogen-takers more likely to be healthy, well-educated and compliant women with a lower baseline risk of cardiovascular disease. The need for randomised controlled trials was therefore recognised (Barrett-Connor 2001Hemminki 2000a). It has been suggested that the wide prescribing of HT in the 1990s, despite the lack of randomised evidence of its efficacy and safety, might reflect a conflict between commercial/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. A systematic review of the available randomised evidence was conducted in 1997 and was updated with unpublished evidence in 2000 (Hemminki 1997, Hemminki 2000). The 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 fifteen secondary events in women allocated HT and seven in the control groups and provided insufficient evidence to exclude a potential benefit from HT.

Beral et al. (Beral 2002) pooled the results of four RCTs of HT published between 1998 and 2002 (EVTET 2000; HERS 1998; WEST 2001; WHI 1998). No significant excess or reduction in the relative risk of CHD was reported and the findings negated the large beneficial effect of HT reported for cardiovascular outcomes in the earlier observational studies. Moreover, excess risks of stroke, pulmonary embolus and breast cancer were reported. The risk of colorectal cancer or fractured neck of femur were found to be significantly reduced for the HT group, while the findings for endometrial cancer risk were inconclusive. In this review the authors pooled the results of studies which used different types of HT over differing time frames.

Salpeter et al (Salpeter 2004) meta-analysed 17 RCTs of HT that reported at least one death. They concluded that there was a significantly-reduced risk of death in women with a mean age of under 60 years taking HT compared to a placebo group, though no difference was found when older women were compared. This meta-analysis pooled studies which differed widely with respect to the type of HT used and the clinical status of the participants and in several studies death was not a prespecified outcome. Moreover, women with poor prognosis ovarian cancer accounted for 60% of the events in the meta-analysis of studies of younger women.

Hopkins et al (Hopkins 2004) conducted a systematic review of outcomes among ovarian cancer patients taking HT. The authors found only one relevant RCT and two observational studies. They concluded that until more evidence became available, HT appeared to be acceptable for supportive and symptomatic therapy among ovarian cancer patients.

Another recent 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 very wide range of trials 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 the findings apply to peri- and postmenopausal women.

Previous Cochrane systematic reviews have considered HT and others are in preparation, as follows:

Bone mineral density (Tugwell 2003; Wells 2002)
Cardiovascular disease in postmenopausal women (Sanchez 2005)
Dementia and cognitive function (Hogervorst 2002a; Hogervorst 2002b)
Endometrial hyperplasia and carcinoma (Lethaby 2004).

Hot flushes and other menopausal symptoms (Lester 2001) (MacLennan 2004)
Weight and body fat distribution (Norman 1999)
Vaginal atrophy (Suckling 2003)

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

OBJECTIVES

Our objectives were to compare the effect of long-term hormone therapy (given over at least one year) versus placebo in peri- or postmenopausal women on mortality, heart disease, venous thromboembolism, stroke, transient ischaemic attacks, breast cancer, colorectal cancer, ovarian cancer, endometrial cancer, gall bladder disease, cognitive function, dementia, incidence of fractures and quality of life.

HT was defined as oestrogen therapy alone or oestrogen therapy with combined, continuous or sequential progestogen therapy; delivered by oral, transdermal, subcutaneous or intranasal routes.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only randomised, double-blind trials that included at least one HT therapy group and one placebo group and that reported at least one of the above outcomes were considered for inclusion in this review. Double-blinding required blinding of the participants and all researchers/outcome assessors.

Types of participants

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

Perimenopausal women were defined as women with spontaneous menopause who had menstruated irregularly within the last 12 months.

Postmenopausal women were defined as women with surgical menopause (removal of both ovaries) or women with spontaneous menopause and amenorrhoea for more than 12 months. Women with or without prior history of disease (e.g. cardiovascular disease, fracture, osteoporosis etc.) were included.

Types of intervention

All oestrogens, with and without progestogens, administered by oral, transdermal, subcutaneous or intranasal routes and given as peri-or postmenopausal therapy for any reason for twelve months or more, compared with placebo.

We excluded studies with co-interventions that might affect the outcomes being measured or which used topical vaginal HT creams, topical HT tablets or HT rings. Studies evaluating these interventions are covered in another Cochrane review (Suckling 2003).

Types of outcome measures

Total mortality
Cause specific mortality
Coronary events (myocardial infarction or coronary death)
Venous thromboembolism (pulmonary embolism or deep vein thrombosis)
Stroke (ischaemic or haemorrhagic)
Transient ischaemic attack (TIA)
Breast cancer
Colorectal cancer
Ovarian cancer
Endometrial cancer
Gallbladder disease
Cognitive function, as measured in the included trials
Dementia (including Alzheimer's disease), as measured in the included trials
Incidence of hip fractures, clinically diagnosed vertebral fractures and total clinically diagnosed fractures
Quality of life

We restricted our focus to long-term clinical outcomes and did not include menopausal symptom control (e.g. hot flushes) or early onset side-effects of HT as outcomes. These are the subject of other reviews (Lester 2001; MacLennan 2004).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We obtained publications describing randomised placebo-controlled double-blind trials of long-term HT therapy, by adapting the strategy developed by the Menstrual Disorders and Subfertility Group (see Review Group details for more information). We performed electronic searches of the Cochrane Menstrual Disorders and Subfertility Group Trials Register (November 2004), the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library Issue 3, 2004,

MEDLINE (1966 to November 2004), EMBASE (1980 to November 2004), and Biological Abstracts (1969 to November 2004). The search was not restricted by language. The specific search string used for MEDLINE was as follows:

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. Randomized controlled trials/
4. random allocation/
5. double-blind method/
6. single-blind method/
7. or/1-6
8. clinical trial.pt.
9. exp clinical trials/
10. (clin$ adj25 trial$).ti,ab,sh.
11. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh.
12. placebos/
13. placebo$.ti,ab,sh.
14. random$.ti,ab,sh.
15. Research design/
16. or/8-15
17. animal/ not (human/ and animal/)
18. 7 or 16
19. 18 not 17
20. hormone therapy.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
21. HT.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
22. (estrogen or oestrogen or estradiol or oestradiol).mp. [mp= title, abstract, cas registry/ec number word, mesh subject heading]
23. (Alora or Climara or Estraderm or Estrofem or Femtran or Cliane or Estrapak or Kliogest or Kliovance or Trisequens or Progynova or Nuvelle or Ovestin or Premarin or Prempro or Progynova or Menoprem or Premia).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
24. (menopaus$ or postmenopaus$ or perimenopaus$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
25. (22 or 23) and 24
26. 20 or 21 or 25
27. 19 and 26

We checked the reference lists of relevant publications identified by the above searches. We also searched the National Research Register (NRR), a register of ongoing and recently completed research projects funded by, or of interest to, the United Kingdom's National Health Service, as well as entries from the metaRegister of Controlled Trials and the details on reviews in progress collected by the NHS Centre for Reviews and Dissemination (January 2004).

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 in their files: Schering AG, Novartis, NovoNordisk, Paines and Byrnes/NZMS, 3M Pharmaceuticals, Organon, Wyeth. Reprints of published trials were received from one company (NovoNordisk), one company had no unpublished trials with completed study reports available (Wyeth) and our request was acknowledged by a further two companies (3M Pharmaceuticals, Organon).

METHODS OF THE REVIEW

Selection of trials

One review author screened the titles and/or abstracts of all publications obtained by the search strategy for eligible trials. Where the screened abstract suggested the trial was potentially eligible for inclusion, we obtained the full article. One of the reviewers checked each study against the inclusion criteria. This assessment was performed unblinded. Where there was uncertainty regarding eligibility, a second reviewer also assessed the study and a decision was reached through discussion. Where necessary additional information was sought from the corresponding author of the study.

Quality assessment and data extraction

Two review authors independently used a proforma to assess the quality of the trials, record methodological details, and extract outcome data. This was checked for agreement and any disagreements were resolved by discussion. The following were assessed:

- 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 and/or administration route)
5. Number of participants screened for eligibility, randomised, analysed, excluded, lost to follow-up or dropped out (i.e. withdrew from the trial 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 crossover, single centre or multi-centre)
11. Source of funding

- Characteristics of the Study Participants

1. Inclusion/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

- Interventions Used

1. Type, dosage and administration route of HT/placebo
2. Duration of therapy (minimum of one year)

- Outcomes

1. Which outcomes relevant to review were measured
2. How relevant outcomes were measured and defined

For cross-over trials, it was 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, no cross-over trials were included.

Analysis

Statistical analysis was undertaken following the guidelines of the Cochrane Review Authors' Handbook. Analysis of treatment effects compared outcomes for each therapy group measured at follow up and/or at the end of therapy.

For dichotomous data, two-by-two tables were generated for each trial and expressed as a risk ratio (RR) with 95% confidence intervals (CI). This data was combined for meta-analysis with RevMan software, using the Peto-modified Mantel-Haenszel method. Since there is no consensus about whether fixed-effect or random-effects models should be used for meta-analysis, both types of analyses were performed. This might be viewed as a sensitivity analysis to assess the impact of the choice of model on the results of the analysis as unless the results were robust to both models, they would need to be treated with caution. Published graphs display the results of the fixed-effect model approach.

Continuous data were expressed as weighted mean differences (WMD) and 95% confidence intervals. We planned to combine continuous data for meta-analysis, had any such data been available for pooling. We considered quality of life scores, although measured as ordinal variables, to be drawn from an underlying continuous distribution and they were analysed as continuous outcomes. Meta-analytic methods for continuous data assume that the underlying distribution of the measurements is normal. The ratio of the mean to its standard deviation gave a crude method of assessing skew so that if this ratio was less than 1.65 for any group in a trial, unless the original data were available for log transformation, the results were not included in analyses tables but were reported in Other data tables. We also planned to report results in the Other data section where data were clearly skewed and results were reported in the publication as median and range with non-parametric tests of significance; however, no such data were reported.

Where trials 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 while others had been followed up for longer) the simplifying assumption was made that the risk was constant across the follow-up period and the data were reported as dichotomous data at a fixed time point. Where a risk varied significantly across the follow-up period, this variation was noted in the text in the Results section.

For outcomes where studies reported no events in either the HT group or the placebo group, results were not entered in the Tables of comparison.

Heterogeneity

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

We planned to assess statistical heterogeneity (variation) between the results of different studies included in meta-analyses by inspecting the scatter in the data points on the graphs and the overlap in their confidence intervals, and by checking the I^2 quantity (Higgins 2003). This quantity describes the percentage of total variation across studies that is due to heterogeneity rather than chance. Interpretation of a given degree of heterogeneity will differ according to whether the estimates show the same direction of effect, but we planned to tentatively assign adjectives of low, moderate and high heterogeneity to I2 values of 25%, 26-74% and 75% respectively.

We planned to conduct sensitivity analyses to examine the effect of methodological differences between the trials, provided there were sufficient trials (greater than five). These can help to explain any moderate or high statistical heterogeneity that might be detected. Specific differences we planned to explore were as follows.
1. Trials with adequate methodology versus those of poor methodology. Adequate methodology is defined for this purpose as adequate allocation concealment, analysis by intention to treat and losses to follow up of less than 10%.
2. Trials which might differ from the others with respect to their participants, interventions or clinical criteria for defining outcomes. It was planned not to combine trials which were obviously dissimilar in these respects.

It was planned to conduct further subgroup or sensitivity analyses if other possible sources of heterogeneity became evident during the preparation of the review; however, the results of any such post-hoc analyses would need to be interpreted with great caution.

CHANGES TO PROTOCOL

- Background section: minor revisions have been made
- Outcome measures: these have been clarified and revised to make the review more inclusive. Dementia and cognitive

function have been included; endometrial cancer, transient ischaemic attack and quality of life have been added. Cardiovascular and thromboembolic events have been more specifically defined. Adherence to treatment has not been included as an outcome measure as it was not considered to be a clinical outcome; it has been reported for individual studies in an additional table (Additional table 1) (Additional Table 1)

- Search strategy: the Medline search strategy has been detailed
- Methods section: A statement has been added explaining the rationale for using both fixed and random effects models, some repetition has been deleted, a description has been added of the method to be used to explore statistical heterogeneity and the conditions in which sensitivity analyses will be performed have been described in more detail

DESCRIPTION OF STUDIES

Forty-three studies were retrieved by the search and considered for inclusion, of which 28 were excluded. The primary reasons for exclusion are listed below:

- 21 studies reported no outcomes of interest to this review
- 3 studies used an intervention of less than one year's duration
- 1 study did not include a placebo group
- 3 studies were not double blinded

Fifteen studies met our inclusion criteria, including one very large study (WHI 1998). WHI 1998 incorporated randomised comparisons of two different HT regimes versus placebo and published the results separately. One (WHI 2002) compared combined oestrogen and progesterone versus placebo and is referred to in this review as WHI 1998(*combined HT arm*)and the other compared oestrogen-only HT with 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 (Shumaker 2003; Shumaker 2004; Espeland 2004; Rapp 2003). This subgroup study measured cognitive outcomes among women aged 65 to 79 years at trial entry from both arms of WHI 1998, and is referred to in this review as WHI 1998*(WHIMS)*.

The fifteen included trials randomised 35,089 women: 18,337 to receive some form of HT and 16,736 to receive placebo (treatment allocation was unknown for 16 women on one trial (Ferenczy 2002)). Results for over 99% of these women were analysed by intention to treat. Although some of the trials had biological measures as their primary outcome (e.g. lumen of carotid artery) they were included because they also reported clinical endpoints relevant to this review as pre-specified secondary outcomes. One of the included studies (HERS 1998) conducted prolonged outcome surveillance after trial completion. This was in the form of an open (unblinded) continuation of the study, in which 93% of the original participants agreed to participate. Results from this unblinded part of the study are described below but are not included in any meta-analyses.

The trials varied dramatically in size. The largest by far was WHI 1998 which randomised 27,347 participants, while the other studies varied in sample size from 151 to 2763 participants (Obel 1993 and HERS 1998 respectively). There were over 8000 women in each group in WHI 1998*(combined HT arm)* and over 5000 in each group in WHI 1998*(oestrogen-only HT arm).* Over 1400 women were in each group on the oestrogen-only HT arm of WHI 1998*(WHIMS)* and over 2200 in each group on the combined arm of WHI 1998*(WHIMS)*. Otherwise none of the trials included more than 200 women in each comparison group. Four of the smaller trials were carried out in a single centre (EPAT 2001; Haines 2003; Nachtigall 1979; Obel 1993) and it is unclear whether one trial (EVTET 2000) had more than one trial centre. The other ten trials involved between seven and 40 trial centres.

Nine of the trials were held in the USA, one in the USA and Canada, one in Canada and the Netherlands, and one in each of the UK, Norway, Denmark and Hong Kong.

PARTICIPANTS

The women included in these studies were all peri- or postmenopausal, either spontaneously or surgically induced. The age of participants ranged from 41 to 91 years, with the mean age in each study ranging from 48 to 72 years (no age was stated in Obel 1993). Inclusion criteria varied according to the primary objectives of individual trials. Some were designed to investigate the use of HT for treatment of menopausal symptoms or for disease prevention and thus enrolled women in reasonably good health. Others were designed to assess whether HT had a beneficial effect on women with established diseases, including heart disease, thromboembolic disease, stroke, Alzheimer's disease and long-term medical conditions requiring hospitalisation; these trials restricted entry to women diagnosed with the condition of interest.

- Studies of women without established medical conditions

Seven of the studies enrolled relatively healthy women (EPAT 2001; Ferenczy 2002; Haines 2003; Notelovitz 2002; Obel 1993; PEPI 1995; WHI 1998). Women on some of these seven trials had risk factors (such as raised cholesterol) and a small minority within individual trials had a history of cardiovascular disease, but predominantly participants were fit women without overt disease. Five of the seven trials were interested in the use of HT for disease prevention.

Two of these studies were very large American trials investigating the use of HT to prevent cardiovascular disease but also reporting a wide range of other endpoints; they had very detailed lists of inclusion and exclusion criteria (PEPI 1995; WHI 1998). 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 proportion recorded in the US census for the 50 to 79 years age group.

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 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 were in general 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 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 were generally in better health than the wider US population, they were not so markedly different as to limit the generalisability of study results. The other two "prevention" trials were much smaller and had more narrowly defined outcomes, namely the possible beneficial effect of HT on arterial wall density and bone density respectively (EPAT 2001; Notelovitz 2002). Four much smaller studies also enrolled women without stated health problems, who were either in early menopause (Obel 1993) or postmenopausal (Ferenczy 2002; Haines 2003) they gave relatively little information about inclusion and exclusion criteria (see Table of Included Studies for details).

- Studies of women with established medical conditions

Six of the studies included women with established cardiovascular disease (ESPRIT 2002; ERA 2000; EVTET 2000; HERS 1998; WAVE 2002; WEST 2001). ERA 2000 and WAVE 2002 included women who had coronary artery stenosis seen on an 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 were studies of women who had suffered a thromboembolic event (PE or DVT) or a cerebrovascular event (stroke or TIA). The largest of these six studies (HERS 1998) compared their 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 had significantly fewer smokers, women with hypertension and diabetic women than the comparison group but 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, while an older study (Nachtigall 1979) included women with a range of medical conditions including diabetes, a need for custodial care, arteriosclerosis and chronic neurological disorders. All participants in this study were hospitalised for the duration of the ten year study.

INTERVENTIONS

A wide variety of oestrogen alone or oestrogen and progestogen combinations were used as interventions in the included trials. Some had more than one intervention arm each with a different dose, formulation or route of HT. Most of the comparisons used a moderate dose of oestrogen (e.g. oestradiol 1 mg, CEE 0.625 mg daily or transdermal oestradiol 0.05 mg twice weekly). Nachtigall 1979 used a much higher dose than other included trials, reflecting the fact that it was conducted many years earlier than the others.

The range of interventions used was as follows:

Oestrogen-only HTs

- Oestradiol (17-B oestradiol) an oestrogen derived from derived from equine (horse) urine. Doses used were 1mg (EPAT 2001; Haines 2003; WEST 2001) and 2 mg (Haines 2003)
- 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)
- Transdermal 17-B oestradiol skin patches. The doses used were 0.025 mg, 0.05 mg or 0.075 mg twice weekly (Notelovitz 2002).
- Conjugated equine oestrogen (CEE), a blend of 17-B oestradiol with nine other equine oestrogens. The doses used were 0.625 mg daily (ERA 2000; Mulnard 2000; PEPI 1995; WAVE 2002; WHI 1998*(oestrogen-only HT arm)* and 1.25 mg daily (Mulnard 2000)

Several trials using oestrogen-only HT did not randomise women to this comparison unless they had had a hysterectomy (Haines 2003; 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:

- Medroxyprogesterone acetate (MPA): a synthetic progestogen structurally related to progesterone
- Dydrogesterone: a synthetic progestogen structurally related to progesterone
- Norethisterone (norethindrone): a synthetic progestogen structurally related to testosterone
- Micronised progesterone**:** a natural progestogen synthesised from plant sources and finely ground to improve its absorption

Continuous combined regimens included the following:

- CEE 0.625 mg with MPA 2.5 mg daily (ERA 2000; HERS 1998; PEPI 1995; WAVE 2002; WHI 1998*(combined arm*)
- CEE 2.5 mg with MPA 10 mg daily (Nachtigall 1979)
- Oestradiol 2 mg with 1 mg norethisterone daily (EVTET 2000)

Combined sequential regimens included the following:

- Oestradiol 1 mg daily with MPA 5 mg for 12 days once a year (WEST 2001)
- Oestradiol 2 mg days 1-22, 1 mg days 22-28, with norethisterone 1 mg days 13-22 (Obel 1993)
- Oestradiol 1 mg daily with dydrogesterone 5 mg or 10 mg days 14-28 (Ferenczy 2002)
- Oestradiol 2 mg daily with 10-20 mg dydrogesterone days 14-28 (Ferenczy 2002)
- CEE 0.625 with MPA 10 mg days 1-12 (PEPI 1995)
- CEE 0.625 mg with micronised progesterone 200 mg days 1-12 (PEPI 1995)

The control arm on each study received placebo tablets or patches or both, as appropriate.

The duration of HT use varied, with the longest trial lasting ten years (Nachtigall 1979). Three trials measured outcomes after HT use for one year or just over (EVTET 2000; Haines 2003; Mulnard 2000); five measured outcomes after two years (EPAT 2001; ESPRIT 2002; Ferenczy 2002; Notelovitz 2002; Obel 1993) and four at around three years (ERA 2000; PEPI 1995; WAVE 2002; WEST 2001). HERS 1998 measured outcomes after 4.1 years and continued the study unblinded for a further 2.7 years.

The interventions in the WHI trial were planned to continue for 8.5 years but both components of the trial were terminated early. WHI 1998*(combined HT arm)* was stopped early due to net harm. Outcomes were reported at 5.2 years and subsequently for a further four 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 the effects of the intervention was unlikely to outweigh potential harms, although no predefined safety boundaries had been crossed. Results have been reported for an average follow-up of 6.8 years, with further findings to be published when available.

See Table of Included Studies for more details of interventions in individual trials.

OUTCOMES

The outcomes measured by individual trials varied according to the trial objectives. Major clinical events were not primary outcomes for several of these studies but were measured as adverse effects. Thus although their *primary* outcomes were not relevant to this review they also measured pre-specified *secondary* outcomes which included clinical endpoints of interest, for example cardiovascular events and/or the incidence of cancer and fractures in the trial population. Five trials had biological measures as their primary outcome (EPAT 2001; ERA 2000; PEPI 1995; WAVE 2002; Notelovitz 2002).

The largest trial in the review (WHI 1998) was concerned mainly with the cardio-protective role of HT in relatively healthy women, and reported cardiovascular clinical endpoints as the primary outcome. Invasive breast cancer was designated a primary *adverse* outcome and secondary outcomes were the incidence of other cancers, fractures, gallbladder disease and death. WHI 1998*(WHIMS)* comprised a large subset of older women from this trial who were evaluated for probable dementia (the planned primary outcome) and for mild cognitive impairment (a planned secondary outcome). Global cognitive function was also reported, though was not a formally pre-planned endpoint. WHI 1998*(WHIMS)* reported separate results for the two trial arms and also pooled the results; however the pooled results were not included in this review (see Methods).

WHI 1998*(combined HT arm)* measured quality of life in the whole cohort at one year and for a smaller subset at three years. As noted above, this study excluded women with menopausal symptoms severe enough to preclude randomisation. Two very much smaller trials also reported quality of life in healthy women (in one case Chinese women) (Haines 2003; Obel 1993). The latter trial (Obel 1993) reported endometrial cancer as an outcome as well.

One small trial reported only one outcome of interest to this review, namely endometrial cancer (Ferenczy 2002).

Five other trials were concerned with the effect of HT on established clinical disease. Four reported cardiovascular outcomes: their 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 outcomes such as the incidence of cancers, fractures and gallbladder disease (ESPRIT 2002; HERS 1998). One trial reported the effect of HT on the progression of symptoms in women with Alzheimer's disease (Mulnard 2000) and another measured a wide range of clinical outcomes over a period of ten years' treatment with HT, in women who were in long term hospital care for a range of medical conditions (Nachtigall 1979).

METHODOLOGICAL QUALITY

RANDOMISATION AND ALLOCATION CONCEALMENT

Of the fifteen included studies, twelve described a satisfactory method of randomisation, which in all cases was computer-generated. Ten of these trials scored A for allocation concealment: in

these trials allocation to treatment was either generated by computer once information about an eligible participant had been entered, or was accomplished by remote contact between the recruiting centre and the study co-coordinating centre or pharmacy. Two studies described using computer-generated randomisation but did not give details of the procedure for allocation to treatment (EVTET 2000; Mulnard 2000). Three studies gave no detailed information about either randomisation or allocation concealment (Ferenczy 2002; Nachtigall 1979; Notelovitz 2002).

STRATIFICATION

Nine studies described using stratification. Eight studies stratified according to study centre. Some also stratified according to cardiovascular risk factors, hysterectomy status, previous use of HT and age. In the case of the WHI 1998 study, stratification was designed to meet target numbers of women within preset age bands in order to increase the power of the study with respect to cardiovascular disease (its primary outcome), which is commoner in older women, while still providing useful information on intermediate outcomes for younger women (see Table of Included Studies for more details). Five studies did not mention stratification (Ferenczy 2002; Mulnard 2000; Nachtigall 1979; Notelovitz 2002; Obel 1993). One study stated that it did not use stratification (Haines 2003).

BLINDING

All the included trials described themselves as (at least) double-blinded. Eight trials explicitly stated that all participants, clinical staff and outcome assessors were blinded to treatment allocation, though in the WHI trial, 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)* following a change in protocol. Nachtigall 1979 stated that the trial was double-blinded and specified that this applied to the research physicians .The other five trials were not explicit about who was blinded (EVTET 2000; Ferenczy 2002; Haines 2003; Mulnard 2000; Notelovitz 2002).

The larger trials described an unblinding mechanism to be used when required for the management of adverse effects. PEPI 1995 unblinded 39 women (4%) during the course of the trial, 32 of whom were taking oestrogen-only HT. WHI 1998*(combined HT arm)*reported that during 5.2 years of follow-up 3,444 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. The other trials 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 2.7 years' duration *unblinded* .

INTENTION TO TREAT ANALYSIS, DROP-OUTS, ADHERENCE TO TREATMENT and LOSSES to FOLLOW UP

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

Ten of the included studies analysed all participants by intention to treat, at least for all the outcomes of interest to this review (EPAT 2001; ERA 2000; ESPRIT 2002, Haines 2003, HERS 1998; Mulnard 2000; Nachtigall 1979; Notelovitz 2002; WEST 2001; WHI 1998) and a further two studies analysed over 97% of participants by intention to treat (PEPI 1995; WAVE 2002). Three studies did not include all participants in an intention to treat analysis for the outcomes of interest (EVTET 2000; Ferenczy 2002; Obel 1993). See Characteristics of Included studies Table for details

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 five 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 Characteristics of Included Studies Table and Additional Table 2 for details of drop outs and non-adherence in all studies.

Losses to follow up were low in most of the 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%-5.2% lost in four other studies, which were all large and of long duration (3-6.8 years) (HERS 1998; PEPI 1995; WAVE 2002; WHI 1998). However in three smaller studies of 1-2 year duration a higher proportion of women (8.5%-14.5%) were lost to follow up (Haines 2003; Notelovitz 2002; Obel 1993) and in Ferenczy 2002 results were unavailable for 34% of participants for the outcome of interest to this review. See Characteristics of Included Studies Table for more details

POWER CALCULATIONS.

Eleven studies gave details of their power calculations. One of these (ESPRIT 2002) did not achieve the sample size required to achieve its target power, as accrual was lower than expected, and neither arm of WHI 1998 achieved the length of follow up required by the

power calculations because both arms were terminated early. Four studies did not give any information about power calculations.

We attempted to contact investigators involved in the following trials for more information: EPAT 2001; EVTET 2000; Ferenczy 2002; Haines 2003; HERS 1998; Mulnard 2000; Notelovitz 2002; Obel 1993; PEPI 1995; WAVE 2002; WEST 2001; WHI 1998. In response they kindly supplied additional unpublished data relating to the following trials: ERA 2000; Haines 2003; HERS 1998; Obel 1993; PEPI 1995 and WAVE 2002. See Characteristics of Included Studies Table for methodological details about all included studies and Additional Table 1 for an overview of study quality.

RESULTS

Presentation of results

Results are described below. In most cases effect measures were reported in the text only where results were statistically significant: for relative risks and confidence intervals for *all* comparisons please see the Tables of Comparison.

Results are grouped as follows:
a) By outcome:

- Outcomes such as death, cardiovascular events, cognitive measures and quality of life were grouped 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, fractures and gallbladder disease group all participants were grouped together as "all women".

B) By intervention

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

Within these categories, interventions have been grouped according to the oestrogen dose used, the equivalence between doses being based on expert sources (Ansbacher 2001; MacLennan 1998; Pharmac 2003).

Meta-analysis

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

Because there were very few results suitable for pooling, 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 trials with few events and we attributed the heterogeneity to chance (see Table of comparisons 2:25).

Time points for reporting results

WHI 1998*(oestrogen-only HT arm)* reported results after a *mean* follow-up of 6.8 years and WHI 1998*(combined HT arm)* reported results after a *mean* follow up of 5.2 or 5.6 years. As mentioned above (see Methods), we analysed these results as if all women had an equal length of follow up. In addition, WHI 1998*(combined HT arm)* reported selected clinical outcomes for each year of follow up. Since all women in this arm had been enrolled for at least 3.5 years at the time of the trial publication, we used these data to calculate outcomes on an intention to treat basis after one, two and three years' use of HT, using all randomised participants as the denominator.

HERS 1998 reported results from the blinded part of the trial after a mean follow up of 4.1 years, which as mentioned above (see Methods), we have reported as dichotomous data. In addition, selected clinical outcomes were reported for each year of follow up. Since all women had been enrolled for at least three years at the time of the report, in this review these data have been used to calculate outcomes on an intention to treat basis after one, two and three years' use of HT, using all randomised participants as the denominator.

RESULTS FOR OUTCOMES OF INTEREST

All of the statistically significant findings of this review derived from the two biggest trials, HERS 1998 and WHI 1998, both of which scored A for allocation concealment, analysed all participants by intention to treat and had low losses to follow up (1% to 5.2%).

- **Death from any cause**

Relevant comparisons:

This outcome was measured in healthy women in three trials (EPAT 2001; PEPI 1995; WHI 1998) 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 one year to nearly seven years.

This outcome was also measured in five trials of women with cardiovascular disease (EPAT 2001; ESPRIT 2002; Haines 2003; 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 ver-

sus placebo for varying durations from two to four years, with unblinded follow up to 6.8 years (HERS 1998).

Results:
None of the trials found any statistically significant difference between HT and placebo for this outcome.

- **Death from coronary heart disease**

Relevant comparisons:
This outcome was measured in relatively healthy women in three trials (EPAT 2001; PEPI 1995; WHI 1998) 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 one year to nearly seven years.

This outcome was also measured in five trials 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 two to four years, with unblinded follow up to 6.8 years (HERS 1998)

Results:
None of the trials found any statistically significant difference between HT and placebo for this outcome.

- **Death from stroke**

Relevant comparisons:
This outcome was measured in two comparisons of relatively healthy women taking combined continuous HT for 5.2 years (WHI 1998*(combined HT arm)*) or taking oestrogen alone for 6.8 years (WHI 1998*(oestrogen-only HT arm))*, and also in one trial of women with a history of stroke taking oestrogen-only HT with annual progesterone for women who had a uterus for 2.8 years (WEST 2001). These trials randomised 16,608 and 664 women respectively.

Results:
No statistically significant difference was found between HT and placebo for this outcome.

- **Death from breast cancer**

This outcome was reported in one trial of relatively healthy women taking combined continuous HT for 5.2 years (WHI 1998). No statistically significant difference was found between HT and placebo for this outcome.

- **Death from any cancer**

This outcome was reported in one trial of relatively healthy women taking continuous HT for 5.2 years (WHI 1998*(combined HT arm)*) and one of women with cardiovascular disease taking combined continuous HT for 4.1 years, with unblinded follow up to 6.8 years (HERS 1998).

Neither of the trials found any statistically significant difference between HT and placebo for this outcome.

- **Coronary events (myocardial infarction or cardiac death)**

Relevant comparisons:
This outcome was measured in relatively healthy women in three trials (EPAT 2001; PEPI 1995; WHI 1998) 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 one year to nearly seven years.

This outcome was also measured in women with cardiovascular disease in six trials (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 two to four years, with unblinded follow up to 6.8 years (HERS 1998).

Results:
In WHI 1998*(oestrogen-only HT arm)* there was no statistically significant difference between the two groups for this outcome and there was a significant time trend whereby a non-significant risk in the HT group in the first two years diminished over time. However, in WHI 1998*(combined HT arm)*, relatively healthy women taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) were at a significantly higher risk of a coronary event after taking HT for one, two, three and four years (at one year: RR 1.74 (95% CI 1.05 to 2.89), at two years: RR 1.49 (95% CI 1.05 to 2.12), at three years: RR 1.43 (95% CI 1.05 to 1.95), at four years: RR 1.37 (95% CI 1.05 to 1.79)). At a mean follow up of 5.6 years there was no statistically significant difference between the groups (RR 1.22 (95% CI 0.98 to 1.51)).

None of the other trials found any statistically significant difference between HT and placebo for this outcome, though HERS 1998 reported results of borderline statistical significance at one year, suggesting increased risk for women with cardiovascular disease taking combined continuous therapy (RR 1.5, 95% CI 1.00 to 2.25). Although initial analysis of time trends in HERS 1998 suggested a trend towards increased risk in the HT group diminishing over time, subsequent analysis based on the entire 6.8 years of follow-up (blinded and unblinded) showed no statistically significant variation in risk over time.

- **Stroke**

Relevant comparisons:
This outcome was measured in relatively healthy women in three trials (EPAT 2001; PEPI 1995; WHI 1998) 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 one year to nearly seven years.

This outcome was also measured in women with cardiovascular disease in six trials (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 one year to four years, with unblinded follow up to 6.8 years (HERS 1998).

Results:
In WHI 1998*(oestrogen-only HT arm)* there was a statistically significant increase in the incidence of strokes at 6.8 years' follow up (RR 1.37 (95% CI 1.08 to 1.73)). In WHI 1998*(combined HT arm*), although there was no statistically significant difference between the groups in the incidence of stroke during the first two years of the trial, women taking combined continuous HT were at a significantly higher risk of stroke after taking it for three or more years (at three years: RR 1.47 (95% CI 1.02 to 2.11), at a mean of 5.2 years: RR 1.42 (95% CI 1.08 to 1.87).

None of the other trials found any statistically significant difference between HT and placebo for this outcome; as noted above, most of the relevant trials were small.

- **Transient ischaemic attack**

Relevant comparisons:
This outcome was measured in relatively healthy women in two trials (EPAT 2001; PEPI 1995) with a total of four different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo for two or three years.

This outcome was also measured in three trials (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 two to four years, with unblinded follow up to 6.8 years (HERS 1998).

Results:
None of the trials found any statistically significant difference between HT and placebo for this outcome.

- **Stroke or transient ischaemic attack**

One small trial (ERA 2000) of women with known coronary disease reported stroke or TIA as a combined outcome. oestrogen-only HT and combined continuous therapy were compared with placebo. No statistically significant difference was found between HT and placebo
for this outcome.

- **Venous thromboembolism (pulmonary embolus or deep vein thrombosis)**

Relevant comparisons:
This outcome was measured in relatively healthy women in three trials (EPAT 2001; PEPI 1995; WHI 1998) 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 one year to nearly seven years.

This outcome was also measured in five trials 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 one to four years, with unblinded follow up to 6.8 years (HERS 1998).

Results:
In WHI 1998(*combined HT arm)*, relatively healthy women taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) were at a significantly higher risk of a thromboembolic event than women taking placebo; this applied at one to over five years' follow up (at one year: RR 3.59 (95% CI 1.95 to 6.61), at two years: RR 2.98 (95% CI 1.88 to 4.71), at three years: RR 2.54 (95% CI 1.73 to 3.72), at four years: RR 2.34 (95% CI 1.69 to 3.25)), at a mean follow up of 5.6 years: RR 2.09 (95% CI 1.60 to 2.74)). Analysis of time trends in this comparison found a statistically significant time trend for a diminishing risk of venous thromboembolism over time.

Similarly, in HERS 1998, women with cardiovascular disease taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) for one to four years were significantly more likely to experience a venous thromboembolism than women on placebo (at one year: RR 3.26 (95% CI 1.06 to 9.96), at two years: RR 3.51 (95% CI 1.42 to 8.66), at three years: RR 3.01 (95% CI 1.50 to 6.04), at mean of 4.1 years: RR 2.62 (95% CI 1.39 to 4.94)).

None of the other trials found any statistically significant difference between HT and placebo for this outcome, though WHI 1998*(oestrogen-only HT arm)* reported a non-statistically-significant increased risk in the HT group at 6.8 years follow up (RR 1.32 (95% CI 0.99 to 1.77)).

- **Breast cancer**

Relevant comparisons:
This outcome was measured in relatively healthy women in four trials (EPAT 2001; Notelovitz 2002; PEPI 1995; WHI 1998) 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 one year to nearly seven years.

This outcome was also measured in women with cardiovascular disease in four trials (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 two to four years, with unblinded follow up to 6.8 years (HERS 1998).

Results:
In WHI 1998*(oestrogen-only HT arm*), among relatively healthy women taking oestrogen-only HT (CEE 0.625 mg) there was a non-statistically-significant decrease in the risk of breast cancer at 6.8 years' follow up, compared with women taking placebo (RR 0.78 (95% CI 0.59 to 1.01)). WHI 1998*(combined HT arm)* reported this outcome at yearly intervals and found no statistically significant difference between the groups in the incidence of breast cancer during the first four years of follow-up but the HT group were at a significantly higher risk of breast cancer after taking HT for five or more years (at mean of 5.6 years: RR 1.26 (95% CI 1.02 to 1.56). Analysis of time trends in this arm of WHI 1998 found a statistically significant trend for increasing breast cancer risk over time in the group taking HT.

No statistically significant difference was shown between any other type of HT and placebo for this outcome, though (as noted above) the relevant trials were small.

- **Colorectal cancer**

Relevant comparisons:
This outcome was measured in four trials (EPAT 2001; HERS 1998; PEPI 1995; WHI 1998) 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 one year to almost seven years.

Results:
WHI 1998(*combined HT arm*) reported that among relatively healthy women taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg), there was no statistically significant difference in the incidence of colorectal cancer, compared with women taking placebo, at one to four years' follow-up. However, women taking combined continuous HT had a significantly lower incidence of colon cancer after five or more years (at mean of 5.6 years: RR 0.62 (95% CI 0.43 to 0.89)).

No statistically significant difference was shown between any other type of HT and placebo for this outcome; however the relevant trials were small.

- **Endometrial cancer**

Relevant comparisons:
This outcome was measured in seven trials (EPAT 2001; ESPRIT 2002; Ferenczy 2002; HERS 1998; Obel 1993; PEPI 1995; WHI 1998) with a total of eleven different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo for varying durations from one year to over five years.

Results:
None of the trials showed any statistically significant difference in the incidence of endometrial cancer between women taking any type of HT and women taking placebo. This result included comparisons of oestrogen-only HT versus placebo (EPAT 2001; ESPRIT 2002; PEPI 1995); however all women with a uterus in these trials had close monitoring for endometrial hyperplasia and two trials specified that study medications were withdrawn if atypical hyperplasia was detected (ESPRIT 2002; PEPI 1995).

- **Ovarian cancer**

Ovarian cancer incidence was reported only in WHI 1998*(combined HT arm)*, which used combined continuous CEE 0.625 mg + MPA 2.5 mg and has 5.6 years' follow up for this outcome. No statistically significant difference was shown between the groups.

- **Gallbladder disease requiring surgery**

Relevant comparisons:
This outcome was reported in four trials (ERA 2000; HERS 1998; PEPI 1995; WHI 1998) which compared oestrogen-only HT, combined continuous HT and sequential combined HT with placebo for three to seven years. For this outcome, the two largest studies stated that they excluded from analysis women who had had their gallbladder removed (HERS 1998) and/or had a history of gallbladder disease (WHI 1998).

Results:
Meta-analysis of the three trials comparing oestrogen-only HT with placebo for this outcome (ERA 2000; PEPI 1995; WHI 1998) showed a statistically significant increase in risk in the HT group (RR 1.72, 95% CI 1.40-2.19). Meta-analysis of the four trials comparing combined continuous HT with placebo (ERA 2000; HERS 1998; PEPI 1995; WHI 1998) also showed significantly increased risk in the HT group (RR 1.55, 95%CI 1.29 to 1.86). Although these trials had differing lengths of follow-up no statistical heterogeneity was observed. Similarly, the unblinded follow-up of HERS 1998 reported an increase in events in the HT group which reached the borders of statistical significance (RR 1.63, 95% CI 1.00 to 2.70).

WHI 1998 investigators reported that the hazard estimates for risk in the active and placebo groups started to diverge in the first year of follow-up, with the oestrogen group separating earlier than the combined continuous HT group.

- **Hip fractures**

Relevant comparisons:
The incidence of hip fractures was reported in three trials (HERS 1998; WEST 2001; WHI 1998; WHI 2004). These compared combined continuous HT (HERS 1998; WHI 1998)and oestrogen-only HT (WEST 2001; WHI 1998) with placebo for between 2.8 and 6.8 years.

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 6.8 years' mean follow up (RR 0.61 (95% CI 0.41 to 0.91). WHI 1998*(combined HT arm)* reported this outcome at yearly intervals and found no statistically significant difference in the incidence of hip fractures during the first four years of follow-up, but at 5.6 years' mean follow up there was a statistically significant reduction in the risk of hip fracture for women taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) (RR 0.68 (95% CI 0.48 to 0.97)).

However, HERS 1998 found no statistically significant difference between combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) and placebo for this outcome, and the unblinded extension of this trial showed an statistically significant *increased* risk to the group taking HT from years 4.1 to 6.8 (post randomisation) (RR 2.10 (95% CI 1.06 to 4.16)).

- **Clinical vertebral fractures**

The incidence of vertebral fractures was reported only in WHI 1998. In WHI 1998*(oestrogen-only HT arm)*, at a mean of 6.8 years' follow-up there were significantly fewer fractures in the group taking oestrogen-only HT (CEE 0.625 mg) than in the group taking placebo (RR 0.62 (95% CI 0.42 to 0.93)). Similarly, in WHI 1998*(combined HT arm)*, at a mean of 5.6 years' follow-up there were significantly fewer fractures in the group taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) than in the group taking placebo (RR 0.68 (95% CI 0.48 to 0.97).

- **Any fracture**

Relevant comparisons:
The incidence of any fracture was reported in four trials (ERA 2000; ESPRIT 2002; HERS 1998; WHI 1998) comprising comparisons of oestrogen-only HT and combined continuous HT versus placebo for three to nearly seven years.

Results:
Both arms of WHI 1998 found a statistically significant reduction in the risk of any fracture for women taking HT. This was reported at 5.6 years' mean follow-up in women taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) (RR 0.78 (95% CI 0.71 to 0.85)) and at 6.8 years' mean follow -up in women taking oestrogen-only HT (CEE 0.625 mg) (RR 0.71 (95% CI 0.64 to 0.79). None of the other trials found any statistically significant difference between HT and placebo for this outcome.

- **Global cognitive function**

Relevant comparisons:
This outcome was reported by WHI 1998*(WHIMS)*, which included only women over 65 years of age and compared oestrogen-only HT versus placebo for a mean of 5.2 years and combined continuous CEE 0.625 mg + MPA 2.5 mg versus placebo for a mean of 4.2 years. Global cognitive function was measured using a cognitive screening test known as the Modified Mini-Mental State Examination (3MSE), in which a higher score reflects better cognitive functioning.

Results:
In both treatment groups and in both placebo groups, mean 3MSE scores increased from baseline and continued to increase for 3-5 years before starting to decline. There was a pattern of higher increases from baseline in 3MSE scores in the placebo groups which emerged after 1-2 years and was maintained throughout the study. The mean difference between the groups in MSE 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*: WMD -0.25 (95% CI -0.52 to 0.00); *combined HT arm*: WMD -0.18 (95% CI -0.35 to 0.00)).

In the WHI 1998*(WHIMS)* combined HT arm, a decline of 10 points or more in 3MSE scores (which represents >2 standard deviations from the 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)). The same trend was observed in the oestrogen-only HT group, but was not of statistical significance.

- **Mild cognitive impairment**

This outcome was reported by WHI 1998*(WHIMS 2003)*, which included only women over 65 years of age and compared oestrogen-only HT versus placebo for a mean of 5.2 years, and combined continuous CEE 0.625 mg + MPA 2.5 mg versus placebo for a mean of 4.2 years. No statistically significant difference was found between the groups in either arm.

- **Probable dementia**

Relevant comparisons:
This outcome was reported by 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 5.2 years, and combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) versus placebo for a mean of 4.2 years.

Results:
In the oestrogen-only HT arm, no statistically significant difference was found between the 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)).

- **Mild cognitive impairment or dementia**

Relevant comparisons:
This composite endpoint was reported by 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 5.2 years, and combined continuous HT (CEE 0.625 mg + MPA 2.5 mg)versus placebo for a mean of 4.2 years.

Results:
In the oestrogen-only HT arm, the incidence of mild cognitive impairment or dementia was significantly higher in the group taking oestrogen-only HT than in the placebo group (RR 1.36 (95% CI 1.01 to 1.84). In the combined HT arm, there was no statistically significant difference between the two groups.

- **Quality of life**

Relevant comparisons:
This outcome was reported by three studies (Haines 2003; Obel 1993; WHI 1998*(combined HT arm*)), which compared oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo for varying durations from one year to three years. The two smaller studies had only 30-50 women in each active treatment group. The largest of these studies (WHI 1998*(combined HT arm)*) did not include women with menopausal symptoms sufficiently severe to preclude randomisation, for whom this outcome may be considered most relevant.

Results:
At one year, women taking combined continuous HT (CEE 0.625 mg + MPA 2.5 mg) reported a significant difference in quality of life change scores for two out of eight categories in the RAND 36 survey. These two categories were *physical functioning* (WMD 0.80 (95% CI 0.36 to 1.24)) and *role limitations due to physical problems* (RR 1.40 (95% CI 0.30 to 2.50)). However after taking HT for three years there was no statistically significant difference between the groups in any categories (WHI 1998*(combined HT arm*)).

Haines 2003 found no statistically significant difference in overall quality of life change scores between women taking oestrogen-only HT (at moderate or moderate/high doses) and women taking placebo. The measure used was a modified version of the World Health Organisation Quality of Life rating scale (WHOQOL)

Obel 1993 reported overall quality of life scores but did not report change scores nor their standard deviations. Results for this outcome are reported in the Other Data section. There was no statistically significant difference between the active and placebo groups for this outcome.

HT FOR WOMEN HOSPITALISED WITH CHRONIC ILLNESS

One small study (Nachtigall 1979) included women hospitalised either for chronic disease or because they required for custodial care. It comprised a comparison of combined sequential HT for ten years versus placebo. The following outcomes were measured: all cause death, myocardial infarction, venous thromboembolism, breast cancer, colorectal cancer and endometrial cancer. No statistically significant difference was found between the groups for any of these outcomes.

HT FOR WOMEN WITH DEMENTIA

One small study (Mulnard 2000) included women with mild to moderate Alzheimer's disease. It comprised a comparison of unopposed oestrogen for one year versus placebo and the primary outcome was change in overall status with relation to Alzheimer's disease, as measured by the Clinical Global Impression of Change scale. No statistically significant difference was found between the groups.

DISCUSSION

All of the statistically significant findings of this review derived from the two biggest trials, HERS 1998 and WHI 1998. These trials evaluated oral CEE 0.625 mg, with or without continuous methoxyprogesterone (MPA 2.5 mg). Smaller trials using other types of HT reported very few or no major clinical events. We were generally unable to combine results from individual trials, either because they used different types of HT which may not be equivalent in effect and/or because they differed with respect to the trial population.

Other Cochrane reviews have found strong evidence that HT is effective in treating menopausal symptoms. One review reported a 75% reduction in the frequency of hot flushes for perimenopausal and postmenopausal women taking HT relative to placebo and also a statistically significant reduction in symptom severity for the HT group (OR 0.13, 95% CI 0.07 to 0.23) (MacLennan 2004). Another review found that local oestrogens were more effective at relieving the symptoms of vaginal atrophy in postmenopausal women than placebo or non-hormonal gel (Suckling 2003). However, women contemplating the use of HT for menopausal symptoms need to be aware of less positive findings in other areas, as discussed below.

Cardiovascular disease
There is no evidence that HT has a role in either the treatment or the prevention of cardiovascular disease. On the contrary, HT significantly increased the incidence of stroke. Combined continuous HT also significantly increased the risk of coronary events and venous thromboembolism, with the increased risk becoming evident during the first year of use. Oestrogen-only HT failed to have any statistically significant effect (either positive or negative) on coronary disease or venous thromboembolism (WHI 1998*(oestrogen-only HT arm*)).

It has been suggested, on the basis of primate experiments, that HT may reduce atherosclerosis if it is given either to those with little or no coronary artery disease, or if started immediately after the menopause (Mikkola 2002). WHI 1998*(combined HT arm)* conducted many pre-specified 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 the menopause, presence or absence of vasomotor symptoms, prior hormone use, CHD risk factor status and presence or

absence of pre-existing cardiovascular disease. However none of these variables was found to significantly affect results.

The WHI 1998 investigators also conducted a nested case-control study investigating the relationship between cardiovascular biomarkers, treatment assignment and risk of CHD. This included 205 women who experienced coronary events during the first three years of the study versus 513 matched controls. Overall, only one subgroup of women was found to have a significantly different relative risk of coronary heart disease from that observed for all women: those in the HT arm with a higher baseline LDL cholesterol were found to be at significantly increased excess risk. The authors commented that in view of the number of subgroup analyses performed, this may have been a chance finding. They also noted that many of the subgroups were small with limited statistical power and that their findings should thus be interpreted with caution (Manson 2003).

With respect to venous thromboembolism, subgroup analysis in WHI 1998*(combined HT arm)* found that women in the HT arm who had factor V Leiden mutation, a blood coagulation disorder, were at higher risk than other women in the HT arm. Among women with a history of venous thromboembolism the HT group had a high event rate compared to the placebo group (7/79 versus 1/62), but there was insufficient statistical power to determine whether there was a significant excess risk in women with a history of venous thromboembolism taking HT, compared to other women in the HT arm. There was also a higher incidence of events among older and obese women taking HT, though this was related to their higher baseline risk of an event and their *relative* risk did not differ from other women in the HT arm.

Detailed subgroup analysis of the oestrogen-only arm of WHI 1998 is anticipated. In exploratory analyses the presence of additional risk factors (including MI or revascularisation, stroke and pulmonary embolus) did not significantly affect the relative risk of cardiovascular events in women taking HT compared to women taking placebo (WHI 2004).

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

Breast cancer

Evidence about the effect of HT on the incidence of breast cancer is difficult to interpret. Combined continuous HT appears to increase the risk. Thus in WHI 1998*(combined HT arm)* the breast cancer rates in the HT group were initially lower than in the placebo group, but by the fourth year of use there were more events in the HT group, with a statistically significant trend for increasing risk over time. The investigators commented that breast cancers in the HT group were diagnosed at a similar grade but a more advanced stage at the time of diagnosis. They suggested that combined HT may stimulate breast cancer growth but delay diagnosis, possibly by hindering mammographic detection (Chlebowski 2003). This may explain why there was a lower incidence of breast cancer among women in the HT group during the first two years of WHI 1998*(combined HT arm*).

In contrast, a *decrease* in the risk of breast cancer, narrowly missing statistical significance, was unexpectedly found in the unopposed oestrogen arm of WHI 1998. The reason for this finding may become clearer with further analyses of trial data and with the extended follow-up that is planned. Women in the oestrogen-only HT arm of WHI 1998 differed from those in the combined HT arm with respect to breast cancer risk at baseline: 40% in WHI 1998*(oestrogen-only HT arm)* had had bilateral oophorectomy and 28% had had their first child before the age of 20 (versus 16% in WHI 1998*(combined HT arm)* and these are both factors which tend to reduce the risk of breast cancer. Moreover women in the oestrogen-only HT arm were more likely to have used HT previously (48% versus 26%) and more of these prior users had taken it for more than five years (47% versus 21%). This differential prior use may have identified and excluded women with pre-existing tumours prior to study enrolment, thus favouring the treatment group. However in WHI 1998(*combined HT group)*, prior users in the treatment group appeared to have an *increased* risk of developing breast cancer during the trial, with the risk increasing over time. Thus among "never users" the hazard ratio for breast cancer was 1.06 (95% CI 0.81 to 1.38), representing 114 cases versus 102, while for women with 5-10 years' use the hazard ratio was 4.61 (95% C1.01 to 21.02), representing 9 cases versus 5.

Evidence from a very large observational study 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 for users of combined HT, with no large variations between the effects of specific oestrogens or specific progestogens. However the study was not randomised and its findings have been challenged. A particular concern was that the duration of HT use prior to the occurrence of breast cancer was based on data recorded at study entry, without allowing for subsequent use up to the time of diagnosis (Lancet 2003).

It has been suggested that the higher risk for breast cancer observed in the combined HT group of WHI 1998, which is supported by a similar trend in HERS 1998 and Beral 2003, indicates that MPA

and other progestogens increase the risk for breast cancer above any risk associated with oestrogen alone.

Gynaecological cancers

None of the trials showed an increase in the incidence of endometrial cancer in the group taking HT. In three studies women with a uterus were randomised to oestrogen-only treatment (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 interventional treatment with 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.

The association between HT and ovarian cancer remains unclear, though the risk may be related to the particular HT regimen used. There was a trend towards an increased risk of ovarian cancer in WHI 1998*(combined HT arm)* (RR 1.59, 95% CI 0.78 to 3.25) but this did not reach statistical significance (Anderson 2003). A Swedish case control study involving 655 cases and 3899 controls reported increased risk of ovarian cancer related to use of both oestrogen-only HT (OR 1.43, 95% CI 1.02 to 2.00) and combined continuous HT (OR 1.54, 95% CI 1.15 to 2.05), but no significantly increased risk for users of sequential combined HT (Riman 2002). A cohort study of 44,241 US women reported an association between ovarian cancer and the use of oestrogen-only HT (RR 1.6, 95% CI 1.2 to 2.0) but found no significant association with the short-term use of combined HT therapy: however the authors suggested that the risk associated with combined therapy warranted further investigation (Lacey 2002).

Cognitive outcomes

With regard to cognitive outcomes, WHI 1998*(WHIMS)* found that neither combined HT nor oestrogen-only HT conferred any benefit in global cognitive function for women aged over 65, nor did either active treatment confer any reduction in the risk of being diagnosed with mild cognitive impairment.

The rise in mean 3MSE scores (used to measure global cognitive function) that occurred in all participant groups over the first few years of WHIMS was attributed by the investigators to a learning effect known to result from repeated administration of cognitive tests (Espeland 2004). The difference in mean scores between the active therapy and placebo groups was of borderline statistical significance and consistently favoured the placebo groups, though this difference was too small to be clinically meaningful. However a *marked* decrease in 3MSE scores (defined as greater than 2 standard deviations from the baseline mean scores) occurred more frequently in the active treatment groups, and this trend reached statistical significance in the combined HT group. Moreover in both arms HT had a relatively greater adverse effect in women whose baseline 3MSE scores were lowest (Espeland 2004).

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

The WHI 1998*(WHIMS)* results were unexpected and in striking contrast to most earlier research. The investigators suggested that this might be due to the healthy user bias in observational studies, whereby HT users had a better prognosis at baseline than the control groups. They also conjectured that it might be due to differential effects of HT on specific domains of cognition not measured individually by 3MSE, or that there might be a critical period, such as menopause, during which HT must be initiated in order to protect cognitive function at a later age. The mean age of the WHIMS population was 71 and so the study could not address this theory, although previous users of HT in WHIMS did not have higher scores (Espeland 2004).

Gallbladder disease

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

Quality of life

With respect to quality of life, WHI 1998(*combined HT arm)* found that combined continuous HT gave no clinically meaningful benefit at either one or three years. In this trial, subgroup analyses were conducted at one year of women who had reported moderate to severe vasomotor symptoms at baseline. One subgroup included all 2046 women who reported such symptoms and the other was restricted to 574 women aged 50-54. Although HT significantly improved the severity of hot flushes and night sweats compared to placebo, results for general quality of life measures were similar to those observed among all women in the trial, with the exception of a statistically significant positive effect on sleep disturbance for the younger group ($p = 0.02$). As mentioned above, these findings are unlikely to be applicable to women tak-

ing HT specifically for vasomotor or other menopausal symptoms affecting their quality of life since severe menopausal symptoms precluded randomisation for WHI 1998.

Possible benefits

HT offers the benefit of a significant reduction in the risk of fracture or colorectal cancer, as discussed below. However these risk reductions only become statistically significant after four or five years' treatment with HT, while the highest risk of cardiovascular events with combined HT occurs in the first year of use.

- *Fractures*

Most women who would benefit from treatment for low bone mineral density require it lifelong and the benefits of HT will generally be outweighed by the ongoing and cumulative risk of cardiovascular disease or breast cancer. HT should, therefore, only be considered for the prevention of fractures if other treatments are contraindicated and if the cardiovascular risk is low. 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 given by HT was no greater in women at high risk of fracture (Cauley 2003). However, women with severe osteoporosis were excluded from WHI 1998 and bone mineral density was not routinely collected. Therefore the benefits of HT may outweigh the risks for some women with severe osteoporosis.

However the 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 for five years or more but HERS 1998 reported no benefit for women on continuous combined HT. Moreover the unblinded continuation of HERS 1998 found a significantly *increased* risk of hip fracture for such women. The 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). Overall, although HT is considered effective for the prevention of postmenopausal osteoporosis, other treatment options may be safer for some women and HT is generally recommended as an option only for women at significant risk for whom non-oestrogen therapies are unsuitable (Cranney 2002; NIH 2004).

- *Colorectal cancer*

With respect to colorectal cancer, the significantly reduced incidence in women taking combined continuous HT in WHI 1998(*combined HT arm)* was offset by the finding that colorectal cancers diagnosed in such women tended to be more advanced, with more likelihood of lymphatic or metastatic involvement. The investigators suggested that women taking combined HT might benefit from routine bowel screening, despite their reduction in overall risk of colorectal cancer (Chlebowski 2003).

HT for younger women

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 the major causes of morbidity and mortality in older women (Matthews 1997). It was *not* designed to evaluate the risks and benefits of hormone therapy for the treatment of menopausal symptoms, and specifically excluded any woman who reported menopausal symptoms severe enough to preclude her being assigned to placebo treatment (Anderson 2003). It should also be emphasised that WHI 1998 did not include women under 50 and its findings may not apply to young surgically menopausal women - for example a woman who has had both ovaries removed in her forties (Kaunitz 2002).

A woman considering the use of HT for vasomotor symptoms is likely to be in her early fifties. For most women in their fifties 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 aged 50-59 in WHI 1998*(combined HT arm)* found that for relatively healthy women taking combined continuous HT the only increase in risk which reached statistical significance was for venous thrombosis. The risk in the HT group increased from 8 venous thromboses per 10,000 women per year to 19 per 10,000 women per year. The increase in risk was highest in the first year of therapy, but continued over five years of treatment, and was particularly high in obese women (i.e. women with a body mass index of over 30), who had a five year risk of 1.4% compared to 0.5% in normal weight women. Preliminary subgroup analyses of women in their fifties in WHI 1998*(oestrogen-only HT arm)* found no statistically significant difference in risk for any outcome. There was even a suggestion of benefit from oestrogen-only HT for some outcomes such as coronary heart disease and breast cancer, though the authors recommended caution in interpreting this finding as they could not exclude the role of chance or limited study power (WHI 2004). However it is important to note that oestrogen-only HT is contraindicated for women with an intact uterus, as use from one to five 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).

A recent clinical decision model (Col 2004) evaluated the effect of two years' combined continuous HT on life expectancy and *quality-adjusted* life expectancy for a hypothetical 50 year old menopausal woman with an intact uterus. The authors used findings from WHI 1998 and from reported utility scores for menopausal symptoms - utility scores being an estimate of the duration of lifespan that symptomatic women would be prepared to trade off for an assurance of a shorter lifespan without menopausal symptoms. Taking into account the impact of HT on chronic disease outcomes as well as its utility value associated with menopausal symptoms, asymptomatic women taking HT for two years experienced a net loss in quality-adjusted life expectancy of one to three months, depending on their underlying risk of cardiovascular disease, while women with severe menopausal symptoms gained

seven to eight months. Among women at low risk of cardiovascular disease, two years' HT was associated with a three month gain in quality-adjusted life expectancy even when menopausal symptoms were mild. This model did not include cognitive outcomes, as WHI 1998 findings on this outcome pertain only to women over 65 and there are no equivalent data for younger women. In clinical practice a decision analysis needs to take into account individual baseline risks and the utility value that a woman ascribes to her own menopausal symptoms (Minelli 2004).There is currently a trend towards the use of low dose HT taken for the shortest possible time required to achieve treatment goals such as the relief of hot flushes, with doses individually tailored and reviewed at least annually (MHRA 2003; Grady 2003; Kaunitz 2002; NIH 2004).

Questions about the evidence

There is controversy over 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. There is also controversy as to the population to which the available evidence applies. For cardiovascular outcomes, the results of HERS 1998 largely support the results of WHI 1998*(combined HT arm)*, suggesting that their 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). However, there is little evidence on the long-term effects of HT on the healthy younger women who are most likely to use it for menopausal symptoms. Similarly, little 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).

It is questionable whether HT is safe for women with a history of breast cancer. Two unblinded trials have been conducted in Sweden which randomised breast cancer survivors with menopausal symptoms to HT or non-hormonal treatment. Both were terminated early due to a statistically significant increase in the incidence of recurrent breast cancer in the hormonal group in one of the trials (RR 3.5, 95% CI 1.5-8.1) (Holmberg 2004; Chlebowski 2004). A similar trial initiated in the UK terminated recruitment prematurely in January 2004 (ICR 2001).

The results for some of the outcomes measured in this review have been influenced by safety considerations. WHI 1998 was halted more than three years early when an excess incidence of breast cancer in the HT group crossed a relatively conservative prespecified safety boundary and a "global index" balancing overall harms and benefits was also indicative of overall harm. EVTET 2000 was also terminated early due to emerging evidence of possible thromboembolic risk with HT, as well as a non-significant clustering of events in one group (which on unblinding was the HT group).

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 took less than 80% was disproportionately high in the HT groups, presumably because of a higher incidence of adverse effects such as vaginal bleeding. The authors of WHI 1998 note 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 the harms and the benefits of HT among women who adhere to treatment (WHI 2002). In this trial there were also a disproportionate number of women unblinded in the HT group compared to 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 also been claimed that detection bias on a scale to explain the differences between the groups for coronary heart disease could not have occurred - and that any bias was more likely to have been in the opposite direction, mitigating *against* the detection of effects (Tucker 2003).

The findings of this review differ somewhat from those of previous systematic reviews of HT for peri- or postmenopausal women. The most notable difference from Beral 2002 is that the earlier review found no statistically significant increase in the risk of coronary heart disease among women taking HT. In contrast, the current review found a significant increase, particularly in the first year, among women taking combined continuous HT. Unlike the current review, Beral 2002 pooled results from studies of differing participant groups and types of HT, and this appears to be the reason why the overall findings differ. In contrast to the review by Salpeter et al (Salpeter 2004), no survival advantage was evident for women taking HT in the current review, though only one of the included trials (WHI 1998(*oestrogen-only HT*)) analysed younger women as a subgroup for this outcome. However, of the 17 trials which Salpeter et al included in their meta-analysis of younger women, only two met the inclusion criteria for the present review. The other 15 trials in the earlier review were not blinded, did not report mortality as a primary or secondary outcome and/or were of less than one year's duration.

It is likely that the divergence between the findings of the randomised controlled studies included in this review and previous observational studies is primarily due to the methodological limitations of observational studies, notably the "healthy woman effect" whereby women prescribed HT had more favourable prognostic factors at baseline than the comparison non-HT group.

AUTHORS' CONCLUSIONS

Implications for practice

Women who find menopausal symptoms intolerable and who are

at low risk of cardiovascular disease or breast cancer may wish to weigh the benefits of symptom relief against the small absolute risks of harm arising from short-term use. Although none of the trials included in this review focussed specifically on women in the age group most likely to require menopausal symptom relief, WHI 1998 analysed a subgroup of 2839 relatively healthy 50-59 year old women taking combined continuous HT and 1637 taking oestrogen-only HT. Their findings were relatively reassuring as the only significantly increased risk found in this subgroup analysis was an increased incidence of venous thromboembolism in those taking combined continuous HT. The absolute risk of venous thromboembolism in these women was low, at 0.5% overall for women taking HT for five years. However, the risk increased to 1.4% for obese women (Cushman 2004). Additional risk factors such as a history of venous thrombosis or factor V Leiden mutation must also be considered when deciding whether likely symptom relief from HT outweighs potential harm. Moreover the risk of endometrial cancer for women with a uterus taking oestrogen-only HT is well documented.

Hormone therapy may have a limited role in the treatment of osteoporosis for some women but there is no evidence that any form of HT is beneficial for other clinical indications (except menopausal symptom relief) and nor is it appropriate for the prevention of chronic disease. There is strong evidence 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 breast cancer and, in women over 65, the risk of dementia.

Implications for research

No studies have adequately assessed the safety of HT for symptom relief for younger women. Little 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 HRT, and different doses and routes of administration (e.g. unopposed oestrogen and intrauterine progestogen. There is also a pressing need for reliable evidence on the efficacy and safety of alternatives to HT for the control of menopausal symptoms for those women who may wish to avoid using HT or for whom it is unsuitable.

POTENTIAL CONFLICT OF INTEREST

None known.

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The following Cochrane Review Groups were invited to comment on this review: Breast Group, Colorectal Cancer Group, Dementia and Cognitive Improvement Group, Gynaecological Cancer Group, Heart Group, Menstrual Disorders and Subfertility Group, Musculoskeletal Group, Peripheral Vascular Diseases Group and Stroke Group. See "Contribution of Reviewers" for more details.

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	EPAT 2001
Methods	Stated purpose: To determine the effect of oestrogen-alone HT on the progression of subclinical atherosclerosis in healthy postmenopausal women without preesiting cardiovascular disease, as measured by changes in thickness of carotid artery wall Randomisation: Computer-generated random numbers in blocks of four Allocation: Computer displayed after participant details entered 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% 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 in evaluable women: 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 yr: 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: Feb 1993 - Sep 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 six years.
Participants	Included: Postmenopausal women aged>45 years, no pre-existing cardiovascular disease. LDL levels>3.37 mmol/litre Excluded: Women with previous breast or gynaecological cancer, frequent hot flushes, diastolic BP>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: U.S.A.
Interventions	HT arm: Unopposed micronised 17B-oestradiol 1 mg daily Control arm: Placebo Duration: 2 years
Outcomes	(Primary outcome: 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 a treatment effect size (the difference in carotid artery wall thickness)of 0.40 or greater with 80% power.
Allocation concealment	A – Adequate

Study	**ERA 2000**
Methods	Stated purpose: To evaluate the effects of HT on the progression of coronary atherosclerosis

Characteristics of included studies (*Continued*)

	Randomisation method: Computerised in random blocks Allocation method: Computer displayed treatment assignment after eligible participant details entered Stratification: According to lipid lowering therapy at baseline and hospital where angiogram was performed Blinding: Participants, clinic staff and all outcomes assessment blinded Unblinding: Treatment assignment available to designated member of data management staff. Questions relating 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) Dropouts: 5 women in the placebo group started taking HT. It is unclear if there were any other dropouts Adherence to treatment in the 248 evaluable participants was as follows: the unopposed oestrogen group took 74.5% of their prescribed medication, while the combined HT group took 84% and the placebo group took 85.8%. Analysis by intention to treat: Although only 248 participants were available for the primary trial end point (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: Jan 1996 - Dec 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	Included: Postmenopausal women aged 55 - 80 years (nonnatural menses for at least 5 years, or for one year and FSH > 40 mu/ml or oophorectomy) with at least one stenosis >30% in any single coronary artery confirmed by coronary angiography within 4 months of randomisation, baseline gynaecological examination normal Excluded: 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 CABG, revascularisation of only qualifying lesion (for study), inadequate baseline angiogram for study, other non-CHD diseases likely to be fatal or prevent adequate follow-up, participation in other intervention studies, plans to leave area within 3 years Mean age: 66 Age range: 41.8 -79.9 Means of recruitment: Media announcements, contact through hospital records and admissions, screening logs from other studies Baseline equality of treatment groups: Country: USA Follow up: 3 months, 6 months, then 6 monthly clinic visits annual smear and mammograms, annual endometrial aspiration
Interventions	HT arm: One of the following: 1. 0.625 mg CEE (Unopposed oestrogen) 2. 0.625 mg CEE plus 2.5 mg MPA (Combined continuous therapy) Control arm: Placebo Duration: 3.2 years mean
Outcomes	[Primary outcome angiographic] MI Stroke Death DVT PE

Characteristics of included studies (*Continued*)

Notes	Power calculation: 80% power for primary angiographic outcome
Allocation concealment	A – Adequate

Study	**ESPRIT 2002**
Methods	Stated purpose: To ascertain whether unopposed oestrogen reduces the risk of further cardiac events in postmenopausal women who survive a first myocardial infarction Randomisation method: List of random numbers generated by trial statistician in blocks of four Allocation method: Women assigned consecutively to numbers kept on list accessible to statistician only. Stratification: By clinical centre Blinding: Participants, clinicians, outcome assessors. Pharmaceutical company dispensed medication/placebo in identical numbered packages Unblinding: On request of family doctor or if participant withdrew from treatment (in later states of study, only if withdrawing participant had not had a hysterectomy). Outcome assessors remained blinded throughout No of women screened for eligibility: 3121 met inclusion criteria for MI (reasons for non-participation listed in study) No randomised: 1017 No analysed: 1017 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. Losses to follow up: None Known NON-adherence with allocated treatment was as follows: at one year 51% of participants on the HT arm and 31% on the placebo arm were not taking their allocated tablets regularly. At two years, 57% of participants on the HT arm and 37% on the placebo arm were not taking their allocated tablets regularly. Analysis by intention to treat: Yes No of centres: 35 Years of recruitment: July 1996-Feb 2000 Design: Parallel Funding: Schering AG provided medication
Participants	Included: Postmenopausal women admitted to coronary care units or general medical wards in participating centres, who met diagnostic criteria for myocardial infarction, were discharged alive within 31 days of admission Excluded: Women with a 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, approached potentially eligible women if their family doctor agreed to collaborate. Baseline equality of treatment groups: Yes Country: England and Wales
Interventions	HT arm: Unopposed oestradiol valerate 2mg daily Control arm: Placebo Duration: 2 years
Outcomes	Recurrent MI Cardiac death All cause death Endometrial cancer Breast cancer Stroke Thromboembolism

Characteristics of included studies (*Continued*)

Notes	Power calculation: Needed 1700 participants to give 80% power to detect 33.3% decrease in incidence of nonfatal reinfarction or cardiac death (2 sided p = 0.05). Accrual lower than anticipated: study closed with only 100 participants, giving 56% power to detect the above-mentioned outcomes, assuming full compliance
Allocation concealment	A – Adequate

Study	**EVTET 2000**
Methods	Stated purpose:To determine if HT alters the risk of venous thrombo-embolism in high risk women Randomisation method: computer generated 1:1 block randomisation with fixed block sizes of 10 Allocation method: computer displayed after participant details entered Stratification: By age < 60 years or> 60 years 37(23 HT and 14 placebo) women did not attend all visits due to premature termination of the study Blinding: Double blind No of women screened for eligibility: 328 No randomised: 140 (71 HT 69 placebo) No analysed: 140 Losses to follow-up: Nil, though 37(23 HT and 14 placebo) women did not attend all visits due to premature termination of the study Adherence to treatment: Not described Dropouts: 33: 10 in HT group (2 wanted be sure of being treated with oestrogen for postmenopausal symptoms, 8 had adverse effects), 23 in the placebo group (11 wanted be sure of being treated with oestrogen for postmenopausal symptoms, 10 had adverse effects, 2 no reason stated) Analysis by intention to treat: the main findings were not reported by intention to treat, since dropouts from the placebo group were not included in the denominator for the rate of recurrent thromboembolism. 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	Included: postmenopausal women with history of VTE, aged <70 years, previous VTE was verified by objective means, i.e. venography or ultrasound in cases of DVT, and lung scan, helical computed tomography, or angiography in cases of PE. Excluded: current use or use of anticoagulants within last 3 months, familial antithrombin deficiency, any type of malignant diseases 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; or women who had taken part in other clinical trials within 12 weeks before study entry. Mean age: 55.8 years Age range: 42 to 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 diseases(coronary heart disease hypertension, stroke,diabetes), smoking habits, and serum lipids. All women had previously suffered at least one VTE and the total number of previous VTE were 75 in the placebo group and 77 in the HT group. Country: Norway
Interventions	HT arm: 2mg estradiol plus 1 mg norethisterone acetate 1 mg Control arm: placebo Duration: Planned 2 years, stopped prematurely at median 1.3 years' follow up
Outcomes	Venous thrombosis Myocardial infarction, Transient ischaemic attacks Stroke.

Notes	Power calculation: At a significance level of 5% and a power of 90% the sample size was estimated to a maximum of 240 women . After publication of the results of the HERS study which showed as a secondary end-point an 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 end-points in one study group, but without knowing treatment allocation. The committee advised on premature termination of the study even though formal boundaries showing an 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 the participants had completed a final follow-up visit.
Allocation concealment	B – Unclear

Study	**Ferenczy 2002**
Methods	Stated purpose:To assess the endometrial safety and bleeding paterns of 17B-oestradiol sequentially combined with dydrogesterone Randomisation method: Not described Allocation method: Not described Stratification: Not mentioned Blinding: Double blind 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 to this review) Losses to follow up: Endometrial status was evaluated by a biopsy, which was available only to women who remained on active treatment for over a year or who received placebo and completed the two year study. This resulted in 153 losses to follow up for this outcome (87 from the 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 Design: parallel Funding: Solvay pharmaceutical
Participants	Included: Postmenopausal women with a uterus with amenorrhoea of at least 6 months or surgically post-menopausal (following bilateral oophorectomy without hysterectomy, more than 3 months prior to enrolment), FSH within normal postmenopausal range. Excluded: abnormal (uninvestigated bleeding), vaginal bleeding, the use of estrogens and or progestogens and or androgens in the preceding 6 months or more and any previous use of estradiol pellet/implant therapy Mean age: Age range: 45-65 years Means of recruitment: Baseline equality of treatment groups: Yes Country: Canada and Netherlands
Interventions	HT arm: 1) 1mg/d 17B estradiol/ 5mg dydrogesterone for the last 14 days of each 28 day cycle 2)1mg/d 17B estradiol/10 mg dydrogesterone for the last 14 days of each 28 day cycle 3) 2 mg/d 17B estradiol/10 mg dydrogesterone for the last 14 days of each 28 day cycle 4) 2mg/d 17B estradiol/20 mg dydrogesterone 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

Allocation concealment B – Unclear

Study	**HERS 1998**
Methods	Stated purpose: To determine if combined HRT alters the risk for CHD events in postmenopausal women with established coronary disease Randomisation: Computer-generated random numbers in blocks of four Allocation: Computer displayed after participant details entered 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% 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 in evaluable women: 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 yr: 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: Feb 1993 - Sep 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 six years.
Participants	Included: Postmenopausal women aged under 80, with a uterus, with coronary disease (myocardial infarction, coronary artery bypass surgery, percutaneous coronary revascularisation, or angiographic evidence of at least 50% narrowing of one 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 pre-existing 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 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 of additional 2.7 years as no more 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
Allocation concealment	A – Adequate

Study	**Haines 2003**
Methods	Stated purpose:To assess the effects of different doses of oestrogen on menopausal symptoms, mood and quality of life in postmenopausal Chinese women Randomisation method: computer generated numbers 1:1:1 ratio Allocation methods: Trial centre sent opaque sealed sequentially numbered containers for medications Stratification: No Blinding: Double blind Unblinding: Not described No of women screened for eligibility: 169 No randomised: 152 (52 1 mg oestradiol, 50 2 mg oestradiol, 50 placebo) No analysed: 152 (WHO-QOL analysis performed with missing data replaced by mean score of other responders) Losses to follow up: 13 (8.5%) (including one participant who was excluded for non-adherence to treatment) Dropouts: nil Adherence to treatment: >80% for all but one woman (by pill count) Analysis by intention to treat: Yes No of centres: One Years of recruitment: Feb 1998 - Feb 2000 Design: Parallel Funding: Novo Nordisk Asia Pacific
Participants	Included: Postmenopausal ethnically Chinese women (serum oestradiol concentration within menopausal range) not received any form of hormonal therapy during previous 3 months and had undergone a hysterectomy at least 6 months before entry into the study. Able to comply with trial protocol Excluded: Any known or suspected history of breast carcinoma, severe liver or renal disease, thromboembolic history, abnormal genital bleeding, history of DVT or thromboembolic disorder, cardiac failure, diabetes, asthma, migraine, epilepsy or treatment with liver enzyme inducing medications or those that could have affected bone metabolism. Steroids within 3 months, porphyria, severe obesity, suspected oestrogen dependent neoplasia

Characteristics of included studies (*Continued*)

	Mean age: 48 (34-65) Age range: Means of recruitment: Outpatient clinic for menopausal problems Baseline equality of treatment groups: Not stated Country: Hong Kong
Interventions	HT arm: Oestradiol 1mg or 2mg daily Control arm: Placebo Duration: 12 months
Outcomes	Primary outcomes biological. Outcome of interest for this review: Quality of Life, measured by WHOQOL (World Health Organisation Quality of Life)
Notes	Power calculation: Recruitment of 150 women was calulated to provide 80% power to show a 3% difference in bone mineral density at one year.
Allocation concealment	A – Adequate

Study	**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 Randomisation method: Computer generated in blocks of 6 Allocation method: Not described Blinding: Double blind 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 Dropouts: 23 (7 in placebo group, 7 in CEE 0.625 mg group, 9 in CEE 1.25mg/d). Adherence to treatment: This 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
Participants	Included: Women with a diagnosis of probable Alzheimer disease according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association Criteria in the mild or moderate stage(the study protocol specified a Mini-Mental State Examination[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);age older than 60 years; absence of major clinical depressive disorder(as measured by score of <17 on the Hamilton Depression Rating Scale [Ham D]; and normal gynaecological, breast, and mammography results Excluded: myocardial infarction within one year, history of thromboembolic disease or hypercoagulable state, hyperlipidaemia, or use of excluded medications (i.e. estrogens used 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 prior to baseline. Stable doses of neuroleptics, antidepressants, anxiolytics, sedatives, and hypnotics were allowed). At the initiation of the protocol, individuals treated with donepezil or tacrine were excluded, but a protocol amendment after 20 months of enrolment allowed the 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: Baseline equality of treatment groups: there were no significant differences between the three groups in terms of baseline and demographic characteristics. Country:USA
Interventions	HT arm: (1) CEE oral 0.625 mg/day (2) CEE 1.25 mg/day Control:placebo Duration: 1 year
Outcomes	Primary outcome: Progression of Alzheimer's disease (Alzheimer's Disease Cop-operative Study version of the Clinical Global Impression of Change scale)
Notes	Power Calculation: 81% to detect a 29% difference in the proportion of subjects who worsen in the two groups(60% worse in the placebo group vs 31% worse in the oestrogen group) using a 2-tailed[alpha] =.05 (based on data from a similar trial, with 40 subjects receiving placebo and 80 subjects receiving oestrogen. * Inclusion criteria state >60 years but age range at baseline is 56-91
Allocation concealment	B – Unclear

Study	**Nachtigall 1979**
Methods	Stated purpose: To evaluate the effects of HT Randomisation: 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: Method not stated. Stratification: Not mentioned Blinding: Patients and research physicians blinded 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, though any events occurring after unblinding were not recorded. No of centres: One Years of recruitment: Unclear - Study lasted 10 years and was complete by 1976 Design: Parallel Funding: Not stated
Participants	Included: Postmenopausal inpatients with chronic disease (last menstrual period >2 years previously, GFSH >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 Women matched on the basis of chronic disease diagnosis, as follows: diabetes mellitus (14 pairs), custodial care (20 pairs), arteriosclerosis (9 pairs) Other paris matched on the basis of chronic neurologic disorders. Excluded: Women with acute heart disease, hypertension (B/P >160/94), apparent malignancy, hysterectomy Mean age: 55 Age range: Means of recruitment: 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

Characteristics of included studies (*Continued*)

Interventions	HT arm: CEE 2.5 mg daily, plus MPA 10 mg for 7 days in each month Control arm: Placebo Duration: 10 years
Outcomes	Death, myocardial infarction, "serious embolism" (pulmonary embolus), breast cancer, colon cancer, endometrial cancer , gall stones
Notes	Power calculation: Not mentioned Re generalisability: 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 more prolonged bed rest than average woman.
Allocation concealment	B – Unclear

Study	**Notelovitz 2002**
Methods	Stated purpose: To determin e the lowest effective dose of an oestrdiol transdermal delivery system for preventing bone loss in postmenopausal women Randomisation and allocation methods: Not described Stratification: Not described Blinding: Double blind, double dummy Unblinding: Not described No of women screened for eligibility: Not stated No randomised: 355 (0.025 mg dose: 89, 0.05 mg dose: 90, 0.075 mg dose: 89, placebo: 87) No analysed: 355 (data imputed for losses to follow up) Losses to follow up: 34 (9.6%) Dropouts: 125 (35%) did not complete 2 years' treatment (88 in active treatment arms, 37 in placebo arm) Adherence to treatment: 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. Analysis by intention to treat: Yes No of centres: 22 Years of recruitment: Not stated Design: Parallel Funding: Proctor and Gamble Pharmaceuticals
Participants	Included: Postmenopausal, non-osteoporotic and ambulatory women under 70 years of age who had had a hysterectomy, with or with out bilateral oophorectomy, at least 12 months earlier. Postmenopausal status documented by serum E2< 23 pg/ml and FSH serum levels > 40 mlU/ml . Non-osteoporotic status defined by dual energy x-ray absorptiometry(DXA) minimum T-score of -2.5. Excluded: Participants who had received oral estrogens within 2 months of enrolment or who had contraindications to oestrogen therapy or a 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; or use of medications within 3 months of enrolment that could modify BMD, participants with radiographic abnormalities of the lumbar spine on anterior/posterior or lateral view, which would preclude precise DXA measurements Mean age: Not stated Age range: Not stated Means of recruitment: Not stated Baseline equality of treatment groups: Yes Country: USA
Interventions	HT arm: 2 patches, delivering total dose of oestradiol: 0.025 mg, 0.05 mg or 0.075 mgs Control arm: 2 placebo patches Duration: 2 years (26 cycles)

Characteristics of included studies (*Continued*)

Outcomes	Breast cancer (regular mammograms) Fractures
Notes	Power calculation: Not mentioned
Allocation concealment	B – Unclear

Study	**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. Randomisation and allocation methods: Not described Stratification: Not mentioned Blinding: Double blind 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: One Years of recruitment: Not stated Design: Parallel Funding: Pharmaceutical Division, Novo Nordisk
Participants	Included: 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, thrombo-embolic disease, liver or pancreatic disease, diabetes mellitus, severe obesity, diseases 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 invited to participate Baseline equality of treatment groups: Yes Country: Denmark
Interventions	HT arm: 1) Oral oestradiol 2 mg + norethisterone 1mg 2) 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
Allocation concealment	D – Not used

Study	**PEPI 1995**
Methods	Stated purpose: To investigate the 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. Randomisation: Computer-generated variable length blocks Allocation: 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)

Characteristics of included studies (*Continued*)

	Stratification: By clinical centre and hysterectomy status Blinding: Participants, clinical and laboratory personnel blinded, medication packages visually indistinguishable 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 No of women screened for eligibility: Approx. 1460 (states that 60% of women screened were randomised) No randomised: 875 No analysed: 847 (97%) Losses to follow up: 28 (CEE only group: 5/170, CEE + MPA sequential group 5/174, CEE + MPA continuous group 4/174, CEE + MP sequential group 5/178, Placebo group 9/174) Dropouts: Dropout rate disproportionately high in women with a uterus assigned unopposed oestrogen: 55% had to discontinue the assigned therapy, largely due to endometrial hyperplasia. Adherence to treatment: Of the 847 women who attended the 3 year follow-up, 75% of women with a uterus and 80% of women without had at least 80% adherence to treatment. [Note: 55% of women with a uterus assigned unopposed oestrogen were required to discontinue the assigned therapy due to endometrial hyperplasia]. Analysis by intention to treat: No - but 97% women analysed by ITT No of centres: 7 Years of recruitment: Dec 1989 - Feb 1990 Design: Parallel 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
Participants	Included: Healthy postmenopausal women aged 45-65, with or without a uterus. Ceased menstruation 12 months prior to entry or had hysterectomy at least 2 months prior to entry and FSH levels <40 mU/ml Excluded: 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 Mean age: 56 years (SD 4) Age range: 45-64 Means of recruitment: Through mass media and community efforts Baseline equality of treatment groups: Women assigned to placebo had higher mean levels of fibrinogen and LDL-C at baseline Country: USA
Interventions	HT arm: One of the following 4 regimens: 1. CEE 0.625 mg daily (Unopposed oestrogen) 2. CEE 0.625 mg daily plus MPA 10 mg daily for first 10 days (Combined sequential treatment) 3. CEE 0.625 mg plus MPA 2.5 mg daily (Combined continuous treatment) 4. CEE 0.625 mg plus MP 200 mg daily for first 12 days (Combined sequential treatment) Control arm: Placebo Duration: 3 years
Outcomes	Primary endpoints biological markers, not relevant to this review; however the following pre-specified outcomes were also measured: Breast cancer Endometrial cancer Cardiovascular disease Thromboembolism 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 pairwise comparison of treatment arms at 3 years

Characteristics of included studies (*Continued*)

Allocation concealment A – Adequate

Study	**WAVE 2002**
Methods	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 Randomisation: Computer randomised, permuted block design with random blocks of two and four Allocation methods: Remotely by phone call to study co-ordinating centre Stratification: Clinical centre, hysterectomy status Blinding: Participants, investigators and staff at clinical centres blinded except (when necessary) the study gynaecologist 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 No of women screened for eligibility: No randomised: 211 No analysed: 206 for clinical status at end of study Losses to follow up: 5 (3 in HT group, 2 in placebo group) 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 Analysis by intention to treat: No - but 98% of women analysed by ITT No of centres: 7 Years of recruitment: July 1997 - August 1999 Design: Parallel Funding: National Heart, Lung and Blood Institute contract, General Clinical Research Center grant, USA
Participants	Included: Postmenopausal women with one 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, under 55 years old with an FSH of 40 Mu/ml or higher, or older than 55 years Excluded: HT use within 3 months, concurrent use of over 60 mg day of vitamin C or 30 IBU 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. Mean age: 65 Age range: 56-74 Means of recruitment: Recruited at clinical sites in USA and Canada Baseline equality of treatment groups: Higher prevalence of diabetes and higher fasting blood glucose levels in the HT group Country: USA and Canada
Interventions	HT arm: One of the following regimens: 1) CEE 0.625 (oestrogen only therapy) - for women who had had a hysterectomy 2) CEE 0.625 and MPA 2.5 mg daily (continuous combined therapy) - for women who had not had a hysterectomy Control arm: Placebo Duration: 3 years In addition, this study included women on this study were prescribed a regimen of vitamins E and C or placebo vitamins. The only comparison considered in this review is HT/placebo vitamins versus placebo HT/placebo vitamins
Outcomes	Primary outcome biological: change in minimum lumen diameter of qualifying coronary lesions Outcomes of interest to review: All cause death Total mortality Cardiovascular events

	Venous thromboembolism Stroke Breast cancer Quality of life
Notes	Study publication pools results for women on 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)
Allocation concealment	A – Adequate

Study	**WEST 2001**
Methods	Stated purpose:To determine whether 17B oestradiol reduces the risk of recurrent stroke or death among postmenopausal women who have experienced a transient ischaemic attack or nondisabling ischaemic stroke Randomisation: Computer generated at pharmacy, in blocks of four Allocation methods: By remote contact with trial pharmacy Stratification: By trial centre and risk level (3 levels) Blinding: Participants, investigators and endpoint assessors blinded Unblinding: study internist unblinded in the case of overriding concern about a woman's clinical care No of women screened for eligibility: 5296 (2772 ineligible, 1843 declined to participate, 17 unable to be randomised within protocol time frame) No randomised: 664 (HT: 337, Placebo: 327) No analysed: 664 Losses to follow up: Nil Dropouts: 34% of the oestradiol group and 24% of placebo group. 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. Analysis by intention to treat: Yes 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 if it occurred while taking oestrogen. Women with a history of breast of endometrial cancer, who had had a venous thromboembolic event while on oestrogen replacement therapy, had a neurological or psychiatric disease that could complicate the evaluation of the endpoints, or had a co-existing condition that limited their 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 referrals from physicians Baseline equality of treatment groups: Yes Country: USA
Interventions	HT arm: 17-Beta estradiol 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 on unopposed and combined therapies Power calculation: 652 women required to give 80% power to detect a reduction in the rate of deaths or nonfatal strokes from 25% in the placebo group to 15% in the HT group (2 tailed p = 0.05)
Allocation concealment	A – Adequate

Study	**WHI 1998**
Methods	Stated purpose: To test the hypothesis that women taking HT will have lower rates of coronary heart disease and osteoporosis-related fractures. COMBINED HT ARM: Randomisation: Centrally randomised by permuted block algorithm Stratification: By clinical centre site and age group Allocation: By local access to study database Blinding: All participants, clinic staff, and outcome assessors blinded, with the exception of 331 participants who were unblinded from the unopposed oestrogen arm and reassigned to combined HT arm due to change in 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 switched to unopposed oestrogen or the corresponding placebo in the unopposed oestrogen study arm. Unblinding: When required for safety or symptom management, unblinding officer unblinded clinic 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) No randomised: 16,608 (8506 to experimental group, 8102 to placebo group) No analysed: 16,608 Losses to follow-up: 583 participants (3.5%) - i.e. no outcomes data for > 18 months: [307 in HT arm (3%), 276 in control group (3.5%). Vital status known for 96.5% Dropouts/Non adherence to allocated treatment: Women with adherence to treatment of under 80% (by pill count) were counted as dropouts. Dropout rates at 5.2 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. Analysis by intention to treat: Yes (analysed with and without unblinded group in experimental arm) No of centres: 40 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 (relative risk of 1.3 assumed for increased risk of breast cancer in intervention group) Years of recruitment: 1993-1998 Note: Planned 8.5 years follow up. Trial stopped after mean 5.2 years as test statistic for breast cancer exceeded predetermined stopping boundary and global risk index indicated risks exceeding benefits. WHI 1998 UNOPPOSED OESTROGEN ARM: Randomisation: as above Stratification: as above Allocation: as above Blinding: as above Unblinding: see above No randomised: 10739 (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) No analysed: 10739 Losses to follow-up: 563

Drop outs/ Non adherence to allocated treatment: Women with adherence to treatment of under 80% by pill count were counted as dropouts. The dropout rate was 53.8% by the end of the study (6.8 yrs), and did not vary significantly between study arms. In addition, 9.1% of women in the placebo arm and 5.7% of women 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 6.8 years (planned for 9), when it was determined that the prospect of obtaining more precise evidence about the effects of the intervention was unlikely to outweigh potential harms, although no predefined safety boundaries had been crossed.

WHIMS ANCILLARY STUDY:
Enrolled 7479 WHI 1998 participants who were free of probable dementia and aged 56-79. 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 the planned primary and secondary outcomes. For a third outcome (global cognitive function), which was not formally pre-planned, 178 participants (3.9%) were excluded from the combined arm (151 because relevant follow-up data was 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 underway) and 139 (4.7%) were excluded from the unopposed oestrogen arm (109 due to missing follow-up data and 30 due to 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 of detect an observed 40% relative reduction in the incidence rate of clinically diagnosed all-cause dementia
Duration: The mean time from randomisation into WHI 1998 to the last WHIMS cognitive screening examination was 4.05 years for women on the combined HT arm and 5.21 years for women on the unopposed oestrogen arm.

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: 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 of 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 nontraumatic or that had occurred in the previous six 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)

Characteristics of included studies (*Continued*)

	Age range: 50-79. Age ratio of 33%:45%:21% for the baseline age categories of 50-59, 60-69, 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 six-fold higher odds for selection than Caucasian women and resulted in sample with 84% racially/ethnically designated "white", 16% non-"white" Screening: Interested women 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 the baseline age categories of 50-59, 60-69, 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, aged at least 65 and free of probable dementia
Interventions	Combined HT arm: Experimental group: Combined oestrogen and progesterone as one daily tablet containing conjugated equine oestrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg Control group: Matching placebo Duration: 5.2 years 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 over one week, or other severe illness in which hormone use temporarily inappropriate Duration of intervention: 4.2 years N.B. The 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 two arms. However there were significant baseline prognostic differences between the two arms (see Quality Table) and the results have not been pooled 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 four phases of testing as follows 1. Participants underwent cognitive screening with the Modified Mini-Mental State Examination (3MSE) 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 from local physicians 4. CT and blood tests to rule out reversible pathology All cases judged locally as probable dementia were independently evaluated by two adjudicators blind 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) in a battery of neuropsychological tests, a report of mild functional impairment from designated informant, no evidence of a psychiatric or medical explanation for the cognitive decline, and an 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.
Allocation concealment	A – Adequate

CEE: Conjugated equine oestrogen
CHD: Coronary heart disease
DSM IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DVT: Deep vein thrombosis
FSH: Follocle stimulating hormone
MP: Micronised progesterone
MPA: Medroxyprogesterone acetate
MI: Myocardial infarction
PE: Pulmonary embolism
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 analysis.
Intention to treat: the analysis of all randomised participants in the groups to which they were randomised.
Losses to follow up: Participants for whom the outcomes of interest were unknown (and who may or may not have had outcomes imputed in statistical analysis).

Characteristics of excluded studies

Study	Reason for exclusion
Aitken 1971	No outcomes of interest
Aitken 1973	No outcomes of interest
Angerer 2000	Duration under one year

Characteristics of excluded studies (*Continued*)

Bloch Thomsen 2002	No outcomes of interest
Chen 2001	No placebo, no outcomes of interest
Christiansen 1981	No outcomes of interest
Corrado 2002	No placebo, no outcomes of interest
Corson 1999	No placebo, no outcomes of interest
EWA 2000	No placebo, no outcomes of interest
Eiken 1996	No outcomes of interest
Estratab 1977	No outcomes of interest
Genant 1990	No outcomes of interest
Graser 2001	Duration less than one year, no outcomes of interest
HABITS 2004	Not double-blinded
Hall 1998	Not double-blinded
Jensen 1985	No outcomes of interest
Kuopio 1998	Not blinded
Lufkin 1992	No outcomes of interest
Newhouse 2000	Duration less than one year
Ng 1992	No outcomes of interest
Ory 1998	No outcomes of interest
Os 2002	No placebo, no outcomes of interest
Papworth 2002	No placebo
Post 2001	No outcomes of interest
Saitta A 2001	Duration less than one year
Teede 2002	No outcomes of interest
Virtanen 1999	Duration less than one year, no outcomes of interest
de Roo 1999	No outcomes of interest

Characteristics of ongoing studies

Study	**Craft 2001**
Trial name or title	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Study	**Hemminki 2004**
Trial name or title	Advantages and disadvantages of postmenopausal hormone therapy: A preventive trial. The Estonian Postmenopausal Hormone Therapy trial.
Participants	1823 postmenopausal women
Interventions	0.0625 mg oestrogen + 2.5 mg medroxyprogesterone daily for 3 years or placebo
Outcomes	Preventative

Characteristics of ongoing studies (*Continued*)

Starting date	
Contact information	
Notes	

Study	**PREPARE 2002**
Trial name or title	Prevent Postmenopausal Alzheimer's with Replacement Estrogens
Participants	Women over 65 with a family history of Alzheimer's disease, not currently taking estrogen
Interventions	Oestrogen for women post hysterectomy or oestrogen plus progesterone for women with a uterus, versus placebo
Outcomes	Incidence of dementia
Starting date	1998
Contact information	Dr Mary Sano, Associate Professor of Clinical Neuropsychology, Gertrude Sergievsky Center, Columbia University
Notes	?Ended August 2003

ADDITIONAL TABLES

Table 01. Adherence to treatment

Study	**How defined**	**Assessment**	**HRT group**	**Placebo group**	**Note**
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 eveluated	
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 noncompliance in HRT group to prevalence of vaginal bleeding (reported by 56% in HRT group, 7% in controls)
Ferenczy 2002	Adherence not described				
HERS 1998	Taking at least 80% of study medication	Pill counts	79% adherent at 1 year 70% adherent at 3 yrs 3% initiated treatment outside study About 50% continued to use open-label HRT during unblinded follow up (4.2 - 6.8	91% adherent at 1 yr 81% non-adherent at 3 yrs Under 10% used HRT during unblinded follow-up (4.2 - 6.8 yrs)	Proportion of women who reported taking study medication at one year: HRT group: 82% Placebo group: 91%

Table 01. Adherence to treatment (*Continued*)

Study	How defined	Assessment	HRT group	Placebo group	Note
			yrs)		
Nachtigall 1979	Adherence not described				
Obel 1993	Adherence not described				
WAVE 2002	Percentage of study medication taken	Pill counts	At 2.8 yrs: Adherence 67% in the 78% of women analysed	At 2.8 yrs: Adherence 70% in the 81% of women analysed	
WHI 1998 (combined arm)	Taking at least 80% of study medication. Temporary discontinuation (e.g. during surgery) permitted	Weighing of returned medication bottles	42% non-adherent by 5.2 yrs Of these 6.2% initiated HRT outside study	10.7% crossed to active treatment by 5.2 yrs	Analyses censoring events 6 months after non-adherence increased effect sizes

Table 02. Quality of included studies

Study	Concealed allocation	Randomisation	Blinding	Follow-up	ITT	Power calculation	Prognostic balance
EPAT 2001	Yes: Allocated sequentially numbered packet of blinded study medication	Yes: Computer generated	Yes: Participants, clinicians, assessors	No losses to follow up	Yes	Yes	More on active arm had oophorectomy, otherwise balanced
ERA 2000	Yes: Computer displayed allocation after participant details entered	Yes: Computer generated	Yes: Participants, clinic staff and assessors	No losses to follow up (for clinical events)	Yes	Yes	More in unopposed oestrogen group using nitrates at baseline, otherwise balanced
ESPRIT 2002	Yes: Consecutive assignment by third party (statistician)	Yes: Random numbers generated by trial statistician	Yes: Participants, clinic staff and assessors	No losses to follow up	Yes	Yes	Balanced
EVTET 2000	Not described	Yes: Computer	Yes: Described as double-blinded, no further details	No losses to follow up	Published trial summary does not use ITT but it is calculable	Yes	Balanced

Table 02. Quality of included studies (*Continued*)

Study	Concealed allocation	Randomisation	Blinding	Follow-up	ITT	Power calculation	Prognostic balance
Ferenczy 2002	Allocation method not described	Yes but method not described	Yes: Described as double-blinded, no further details	153 losses to follow up (26%) for outcome of interest	No	Not described	Balanced
Haines 2003	Yes: Opaque sealed sequentially numbered envelopes	Yes: Computer generated	Yes: Described as double-blinded, no further details	13 losses to follow up (8.5%)	Yes	Yes	Balanced for mean menopausal symptom scores, other prognostic factors not reported
HERS 1998	Yes: Computer displayed allocation after participant details entered	Yes: Computer generated	Participants, clinic staff, assessors, data analysts, funders (On completion of trial there was 2.7 yrs unblinded follow up)	Vital status known for all, 59 did not complete follow-up (2%)	Yes	Yes	Balanced
Mulnard 2000	Allocation method not described	Yes: Computer generated	Yes: Described as double-blinded, no further details	No losses to follow up	Yes	Yes	Balanced
Nachtigall 1979	Allocation method not described	Yes: randomised in matched pairs but method not described	Yes: Described as double-blinded, no further details	No losses to follow up	Yes	Not described	Balanced
Notelovitz 2002	Allocation method not described	Yes but method not described	Yes: Described as double-blinded and double-dummy, no further details	34 losses to follow up (10%)	Yes	Not described	Balanced
Obel 1993	Allocation method not described	Yes but method not described	Yes: Described as double-blinded, no further details	22 losses to follow up (15%)	No	Not described	Baseline quality of life scores on several measures appear

Table 02. Quality of included studies (*Continued*)

Study	Concealed allocation	Randomisation	Blinding	Follow-up	ITT	Power calculation	Prognostic balance
							substantially lower for placebo group
PEPI 1995	Yes: Computer displayed allocation after participant details entered	Yes: Computer generated	Yes: Participants, clinical and laboratory staff	28 losses to follow up (3%)	Yes	Yes	Placebo group had higher levels of fibrinogen and LDL-C at baseline, otherwise balanced
WAVE 2002	Yes: By remote phone call to study co-ordinating centre	Yes: Computer generated	Yes: Participants, investigators and clinical staff	5 losses to follow up (2%)	Yes	Yes	Active group had higher prevalence of diabetes and higher fasting blood glucose levels, otherwise balanced
WEST 1998	Yes: By remote phone contact with trial pharmacy	Yes: Computer generated	Yes: Participants, investigaotrs and assessors	No losses to follow up	Yes	Yes	Balanced
WHI 1998 (Combined HRT arm)	Yes: By local access to remote study database	Yes: Computer generated	Yes: Participants, clinic staff and oucome assessors	583 losses to follow up (3.5%)	Yes	Yes	Balanced
WHI 1998 (Unopposed oestrogen arm)	Yes: By local access to remote study database	Yes: Computer generated	Yes: Participants, clinic staff and oucome assessors	563 losses to follow up (5%)	Yes	Yes	Balanced
WHI 1998(WHIMS)	As above	As above	As above	All included in primary analysis	Yes	Yes	In the unopposed oestrogen arm theonly statistically significant difference between the two groups at baseline was greater use

Table 02. Quality of included studies (*Continued*)

Study	Concealed allocation	Randomisation	Blinding	Follow-up	ITT	Power calculation	Prognostic balance
							of aspirin at bedtime in the placebo group. In the combined HRT arm there was a lower prevalence of stroke and a higher percentage of participants using statins in the active treatment group. When the two study arms were compared there were significant differences between them., in addition to all women in the unopposed oestrogen arm having had a hysterectomy. Women in the unopposed oestrogen group tended to be less educated and were more likely to come from an ethnic minority, to have a lower family income, weigh more,

Table 02. Quality of included studies (*Continued*)

Study	Concealed allocation	Randomisation	Blinding	Follow-up	ITT	Power calculation	Prognostic balance
							consume less alcohol and have cardiovascular disease, hypertension, diabetes, and vasomotor symptoms. They were also more likely to have used HRT in the past and for longer periods. Baseline mean 3MSE scores were significantly lower in the unopposed oestrogen group.

ANALYSES

Comparison 01. Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Death from any cause: Oestrogen-only HT (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
02 Death from any cause: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
03 Death from any cause: Combined sequential HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
04 Death from coronary heart disease: Oestrogen-only HT ((moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
05 Death from coronary heart disease: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
06 Death from stroke: Oestrogen-only HT (moderate dose)	1	10739	Relative Risk (Fixed) 95% CI	1.10 [0.53, 2.27]

07 Death from stroke: Combined continuous HT (moderate dose)	1	16608	Relative Risk (Fixed) 95% CI	1.04 [0.46, 2.35]
08 Death from breast cancer: Combined continuous HT (moderate dose oestrogen)	1	16608	Relative Risk (Fixed) 95% CI	0.95 [0.24, 3.81]
09 Death from cancer: Combined continuous HT (moderate dose oestrogen)	1	16608	Relative Risk (Fixed) 95% CI	1.16 [0.87, 1.53]
10 Coronary events (MI or cardiac death): Oestrogen-only HT (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
11 Coronary events (MI or cardiac death): Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
12 Coronary events (MI or cardiac death): Combined sequential HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
13 Stroke: Unopposed oestrogen (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
14 Stroke: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
15 Stroke: Combined sequential HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
16 Transient ischaemic attack: Oestrogen-only HT (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
17 Transient ischaemic attack: Combined sequential HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
18 Venous thrombo-embolism (DVT or PE): Oestrogen-only HT ((moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
19 Venous thrombo-embolism (DVT or PE): Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
20 Venous thrombo-embolism (DVT or PE): Combined sequential HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
21 Global cognitive function: mean difference in 3MSE score changes from baseline			Mean difference (Fixed) 95% CI	Subtotals only
22 Large decline (>2SD) in global cognitive function	2	7152	Relative Risk (Fixed) 95% CI	1.38 [1.08, 1.75]
23 Mild cognitive impairment: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only

24 Probable dementia: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
25 Mild cognitive impairment or probable dementia	2	7474	Relative Risk (Fixed) 95% CI	1.35 [1.08, 1.68]
26 Change in quality of life: General health (RAND 36): Combined continuous HT (moderate dose oestrogen)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
27 Change in quality of life: Physical functioning (RAND 36): Combined continuous HT (moderate dose oestrogen)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
28 Change in quality of life: Role limitations due to physical problems (RAND 36): Combined cont. HT (mod dose)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
29 Change in quality of life: Bodily pain (RAND 36): Combined continuous HT (moderate dose oestrogen)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
30 Change in quality of life:Energy and fatigue (RAND 36): Combined continuous HT (moderate dose oestrogen)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
31 Change in quality of life: Social functioning (RAND 36): Combined continuous HT (moderate dose oestrogen)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
32 Change in quality of life: Role limitations due to emotional problems (RAND 36): Combined cont. HT (mod dose)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
33 Change in quality of life: Mental health (RAND 36): Combined continuous HT (moderate dose oestrogen)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
34 Change in quality of life overall (HQOL): Oestrogen-only HT (moderate dose)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
35 Change in quality of life overall (HQOL): Oestrogen-only HT (mod/high dose)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
36 Change in quality of life score (GHQ-11 scale) (combined HT)			Other data	No numeric data

Comparison 02. Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Death from any cause: Oestrogen-only HT (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
02 Death from any cause: Oestrogen-only HT (mod/high dose)			Relative Risk (Fixed) 95% CI	Subtotals only
03 Death from any cause: Oestrogen-only HT (mod dose) for women without uterus, plus sequential MPA if uterus i			Relative Risk (Fixed) 95% CI	Subtotals only
04 Death from any cause: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
05 Death from coronary heart disease: Oestrogen-only HT (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
06 Death from coronary heart disease: Oestrogen-only HT (mod/high dose)			Relative Risk (Fixed) 95% CI	Subtotals only
07 Death from CHD: Oestrogen-only HT (mod dose) for women without uterus, plus sequential MPA if uterus intact			Relative Risk (Fixed) 95% CI	Subtotals only
08 Death from coronary heart disease: Combined continuous CEE + MPA			Relative Risk (Fixed) 95% CI	Subtotals only
09 Death from stroke: Oestrogen-only HT (mod dose) if no uterus, plus sequential MPA if uterus intact	1	664	Relative Risk (Fixed) 95% CI	2.91 [0.95, 8.93]
10 Death from cancer: Combined continuous HT (moderate dose oestrogen)	2	5084	Relative Risk (Fixed) 95% CI	1.16 [0.78, 1.74]
11 Coronary event (MI or cardiac death): Oestrogen-only HT (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
12 Coronary event (MI or cardiac death): Oestrogen-only HT (mod/high dose)			Relative Risk (Fixed) 95% CI	Subtotals only
13 Coronary event : Oestrogen-only HT (mod dose) for women without uterus, plus sequential MPA if uterus intac			Relative Risk (Fixed) 95% CI	Subtotals only
14 Coronary event (MI or cardiac death): Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only

15 Stroke (first or recurrent): Oestrogen-only HT (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
16 Stroke (first or recurrent): Oestrogen-only HT (mod/high dose)			Relative Risk (Fixed) 95% CI	Subtotals only
17 Stroke (first or recurrent): Oestrogen-only HT (mod dose) if no uterus, plus annual MPA if uterus intact			Relative Risk (Fixed) 95% CI	Subtotals only
18 Stroke (first or recurrent): Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
19 Stroke (first or recurrent): Combined continuous HT (mod/high dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
20 Transient ischaemic attack: Oestrogen-only HT (mod/high dose)			Relative Risk (Fixed) 95% CI	Subtotals only
21 Transient ischaemic attack: Oestrogen-only HT (mod dose) if no uterus, plus sequential MPA if uterus intact			Relative Risk (Fixed) 95% CI	Subtotals only
22 Transient ischaemic attack: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
23 Stroke or transient ischaemic attack: Combined continuous HT (moderate dose oestrogen)	1	209	Relative Risk (Fixed) 95% CI	1.01 [0.34, 3.03]
24 Stroke or transient ischaemic attack : Oestrogen-only HT (moderate dose)	1	205	Relative Risk (Fixed) 95% CI	0.88 [0.28, 2.78]
25 VTE (first or recurrent PE or DVT): Oestrogen-only HT (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
26 VTE (first or recurrent PE or DVT): Oestrogen-only HT (mod/high dose)			Relative Risk (Fixed) 95% CI	Subtotals only
27 VTE (first or recurrent PE or DVT): Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
28 VTE (first or recurrent PE or DVT): Combined continuous HT (mod/high dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 03. Women hospitalised with chronic illness (Selected outcomes: death, CVD, VTE)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 All cause death: Combined sequential HRT (high dose oestrogen)	1	168	Relative Risk (Fixed) 95% CI	0.43 [0.11, 1.60]
02 Myocardial infarction: Combined sequential HRT (high dose oestrogen)	1	168	Relative Risk (Fixed) 95% CI	0.33 [0.04, 3.14]
03 Venous thrombo-embolism (DVT or PE): Combined sequential HRT (high dose oestrogen)	1	168	Relative Risk (Fixed) 95% CI	0.33 [0.01, 8.07]

Comparison 04. Women with dementia

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Worsening of dementia on treatment (by ADCS-CGIC score): Oestrogen-only HRT (mod and high dose)			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 05. All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Breast cancer: Oestrogen-only HT (low dose)			Relative Risk (Fixed) 95% CI	Subtotals only
02 Breast cancer: Oestrogen-only HT (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
03 Breast cancer: Oestrogen-only HT (mod/high dose)			Relative Risk (Fixed) 95% CI	Subtotals only
04 Breast cancer: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
05 Breast cancer: Combined sequential HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
06 Breast cancer: Combined sequential HT (high dose oestrogen)	1	168	Relative Risk (Fixed) 95% CI	0.11 [0.01, 2.03]
07 Colorectal cancer: Oestrogen-only HT (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
08 Colorectal cancer: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
09 Colorectal cancer: Combined sequential HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only

10 Colorectal cancer: Combined sequential HT (high dose oestrogen)	1	168	Relative Risk (Fixed) 95% CI	1.00 [0.06, 15.73]
11 Endometrial cancer: Oestrogen-only HT (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
12 Endometrial cancer: Oestrogen only HT (mod/high dose)	1	245	Odds Ratio (Fixed) 95% CI	Not estimable
13 Endometrial cancer: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
14 Endometrial cancer: Combined sequential HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
15 Endometrial cancer: Combined sequential HT (high dose oestrogen)	1	168	Relative Risk (Fixed) 95% CI	0.33 [0.01, 8.07]
16 Endometrial cancer: Combined sequential HT (mod/high dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
17 Ovarian cancer: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
18 Hip fractures: Oestrogen-only HT (moderate dose)	1	10739	Relative Risk (Fixed) 95% CI	0.61 [0.41, 0.91]
19 Hip fractures: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
20 Vertebral fractures: Oestrogen-only HT (moderate dose)	1	10739	Relative Risk (Fixed) 95% CI	0.62 [0.42, 0.93]
21 Vertebral fractures: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
22 All clinical fractures: Oestrogen-only HT (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
23 All clinical fractures: Oestrogen-only HT (moderate dose)			Relative Risk (Fixed) 95% CI	Subtotals only
24 All clinical fractures: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
25 Gallbladder disease requiring surgery: Oestrogen-only HT (moderate dose)	3	8930	Relative Risk (Fixed) 95% CI	1.75 [1.40, 2.19]
26 Gallbladder disease requiring surgery: Combined continuous HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only
27 Gallbladder disease requiring surgery: Combined sequential HT (moderate dose oestrogen)			Relative Risk (Fixed) 95% CI	Subtotals only

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Aged; Female; Humans; Middle Aged

COVER SHEET

Title	Long term hormone therapy for perimenopausal and postmenopausal women
Authors	Farquhar CM, Marjoribanks J, Lethaby A, Lamberts Q, Suckling JA and the Cochrane HT Study Group
Contribution of author(s)	Protocol: Prof. Cindy Farquhar and Anne Lethaby developed the protocol and circulated it to members of the Cochrane HRT Study Group for comment. The following people added specifically to the protocol: Prof Shah Ebrahim, Dr Peter Tugwell, Teresa Moore and Maria Judd. Review: Jane Marjoribanks edited the protocol and with Jane Suckling searched for relevant studies and selected studies based on the inclusion criteria. Jane Marjoribanks extracted and entered data, wrote all sections of the review, circulated it to other members of the Cochrane HT Study Group for comment and edited the draft in accordance with comments from group members. Quirine Lamberts checked all the data extraction. The following members of the Cochrane HT Study Group commented on the draft: Sue Carrick , Sue Lockwood (Editor); Cochrane Breast Cancer Group Professor Leon Flicker (Editor), Professor Lon Schneider (Editor); Cochrane Dementia and Cognitive Improvement Group Lee Hooper (Editor), Theresa Moore (Review Group Coordinator) Cochrane Heart Group Cindy Farquhar (Co-ordinating Editor), Anne Lethaby (Editor), Quirine Lamberts (Research Associate), Michelle Proctor (Review Group Coordinator) Jane Suckling (Reviewer); Cochrane Menstrual Disorders and Subfertility Group Professor Ale Agra (Editor), Steff Lewis (Statistical Editor); Cochrane Stroke Group
Issue protocol first published	/
Review first published	/
Date of most recent amendment	25 May 2005
Date of most recent SUBSTANTIVE amendment	06 May 2005
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Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author

Date authors' conclusions section amended	Information not supplied by author
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Editorial group code	HM-MENSTR

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 01 Death from any cause: Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 01 Death from any cause: Oestrogen-only HT (moderate dose)

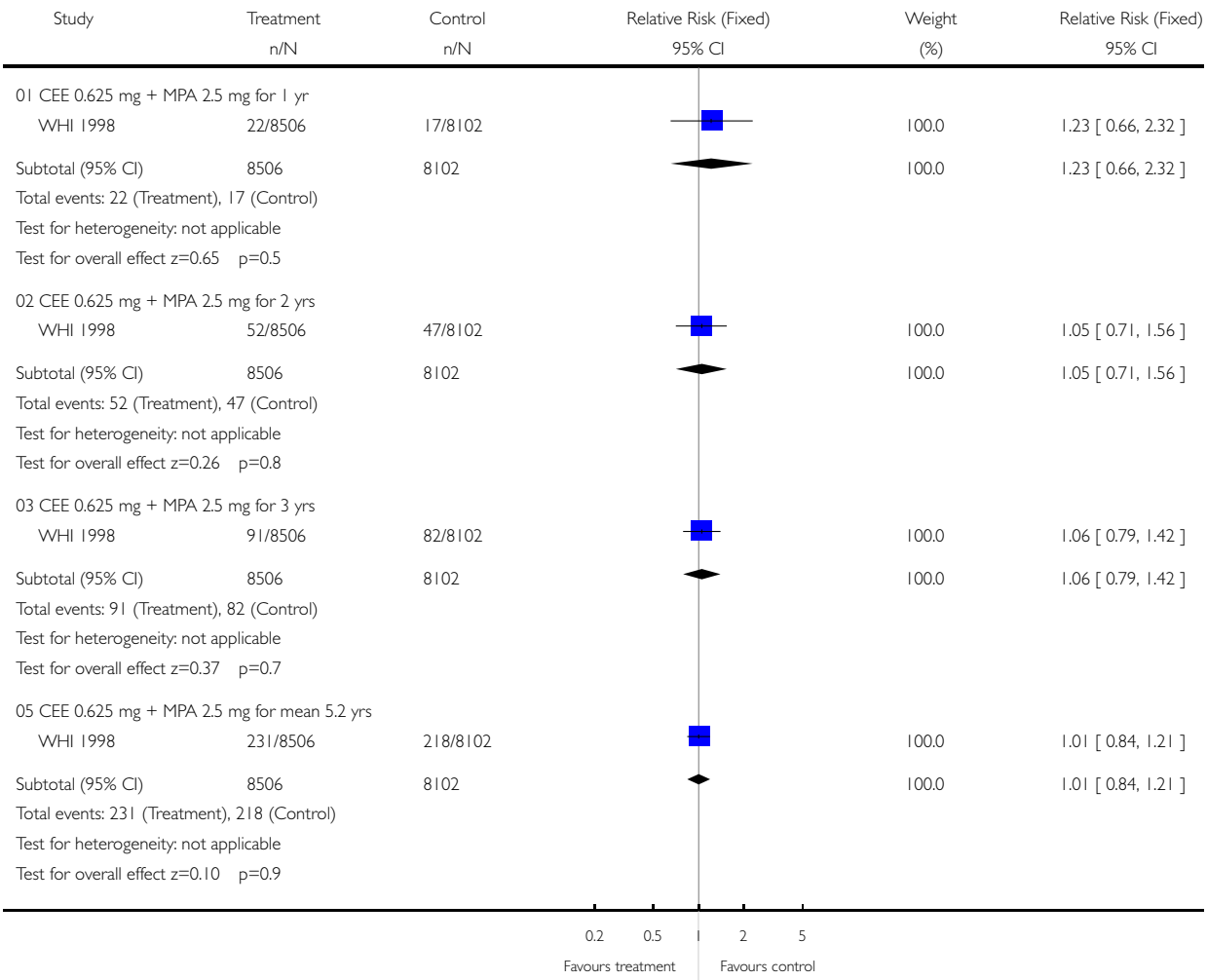
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Oestradiol 1mg for 2 yrs					
EPAT 2001	0/111	1/111		100.0	0.33 [0.01, 8.10]
Subtotal (95% CI)	111	111		100.0	0.33 [0.01, 8.10]
Total events: 0 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					
02 CEE 0.625 mg for 6.8 yrs					
WHI 1998	291/5310	289/5429		100.0	1.03 [0.88, 1.21]
Subtotal (95% CI)	5310	5429		100.0	1.03 [0.88, 1.21]
Total events: 291 (Treatment), 289 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.36 p=0.7					

Analysis 01.02. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 02 Death from any cause: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 02 Death from any cause: Combined continuous HT (moderate dose oestrogen)

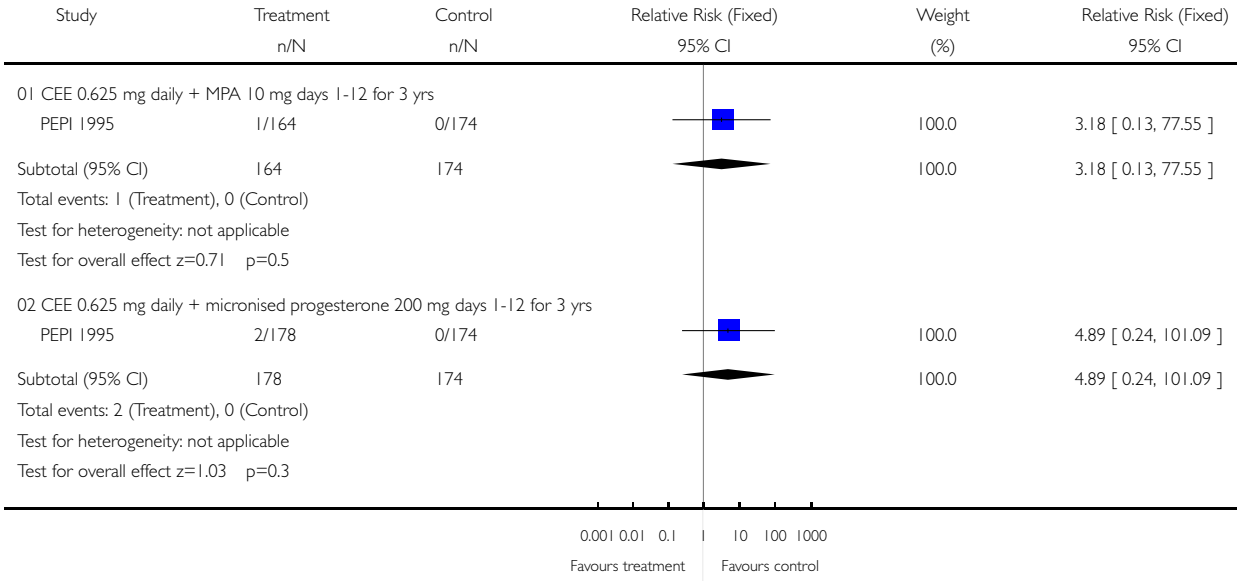


Analysis 01.03. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 03 Death from any cause: Combined sequential HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 03 Death from any cause: Combined sequential HT (moderate dose oestrogen)

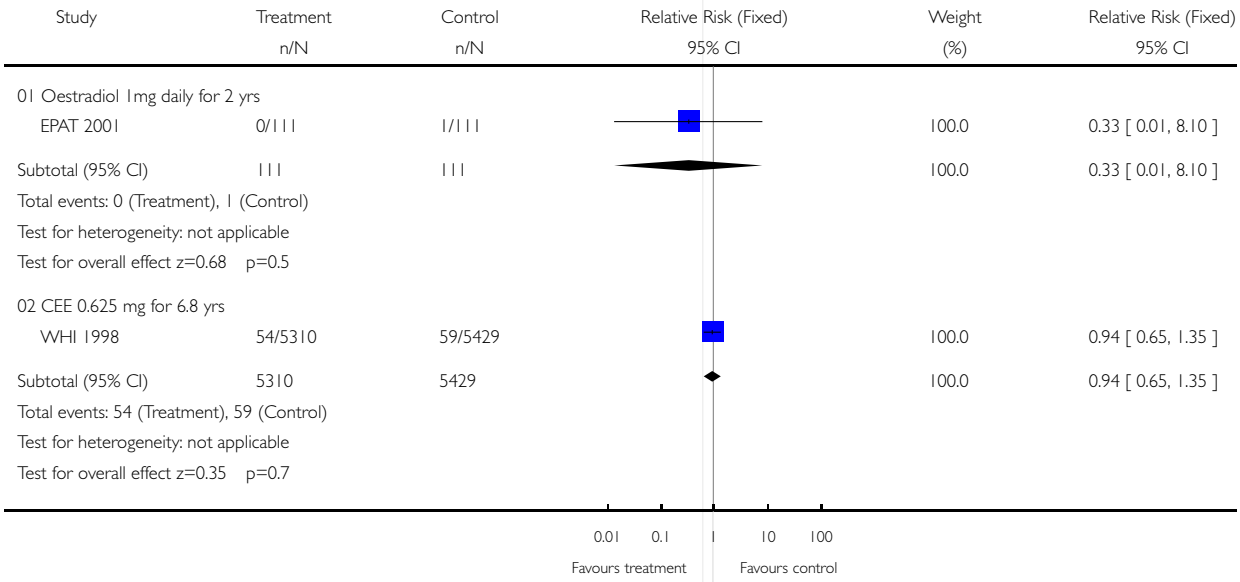


Analysis 01.04. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 04 Death from coronary heart disease: Oestrogen-only HT ((moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 04 Death from coronary heart disease: Oestrogen-only HT ((moderate dose)



Analysis 01.05. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 05 Death from coronary heart disease: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 05 Death from coronary heart disease: Combined continuous HT (moderate dose oestrogen)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg + MPA 2.5 mg for mean 5.6 yrs					
WHI 1998	39/8506	34/8102		100.0	1.09 [0.69, 1.73]
Subtotal (95% CI)	8506	8102		100.0	1.09 [0.69, 1.73]
Total events: 39 (Treatment), 34 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.38 p=0.7					

Analysis 01.06. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 06 Death from stroke: Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 06 Death from stroke: Oestrogen-only HT (moderate dose)

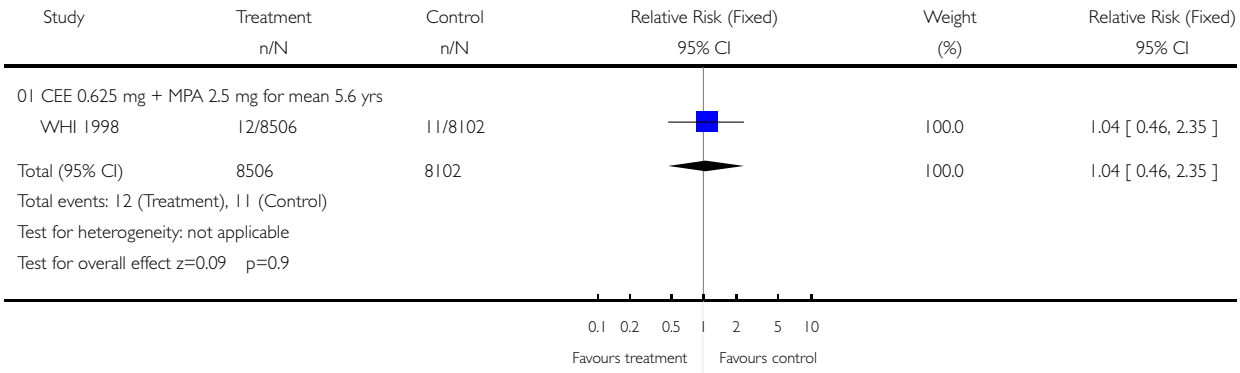
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg for 6.8 yrs					
WHI 1998	15/5310	14/5429		100.0	1.10 [0.53, 2.27]
Total (95% CI)	5310	5429		100.0	1.10 [0.53, 2.27]
Total events: 15 (Treatment), 14 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.25 p=0.8					

Analysis 01.07. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 07 Death from stroke: Combined continuous HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 07 Death from stroke: Combined continuous HT (moderate dose)

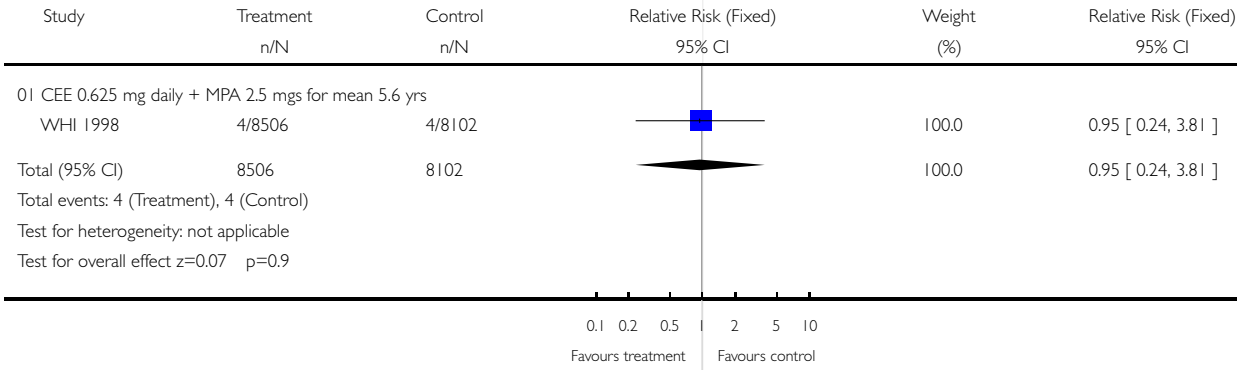


Analysis 01.08. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 08 Death from breast cancer: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 08 Death from breast cancer: Combined continuous HT (moderate dose oestrogen)

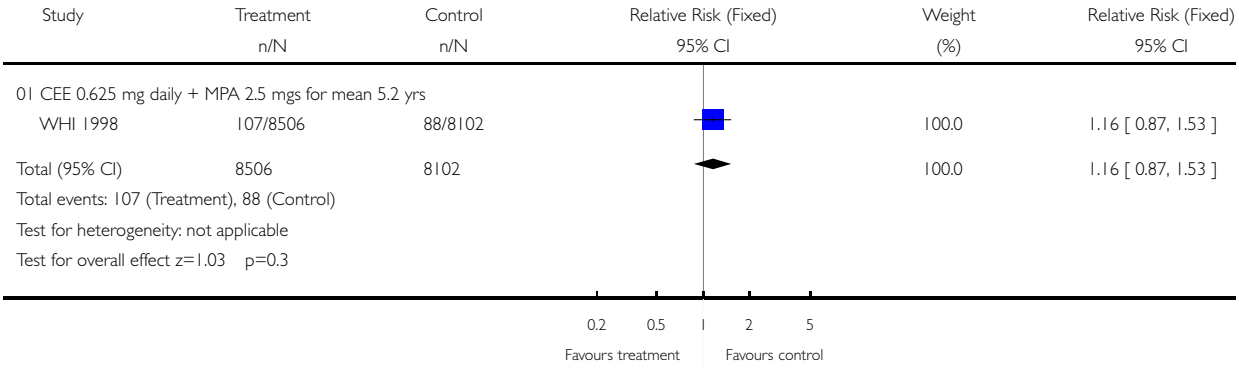


Analysis 01.09. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 09 Death from cancer: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 09 Death from cancer: Combined continuous HT (moderate dose oestrogen)

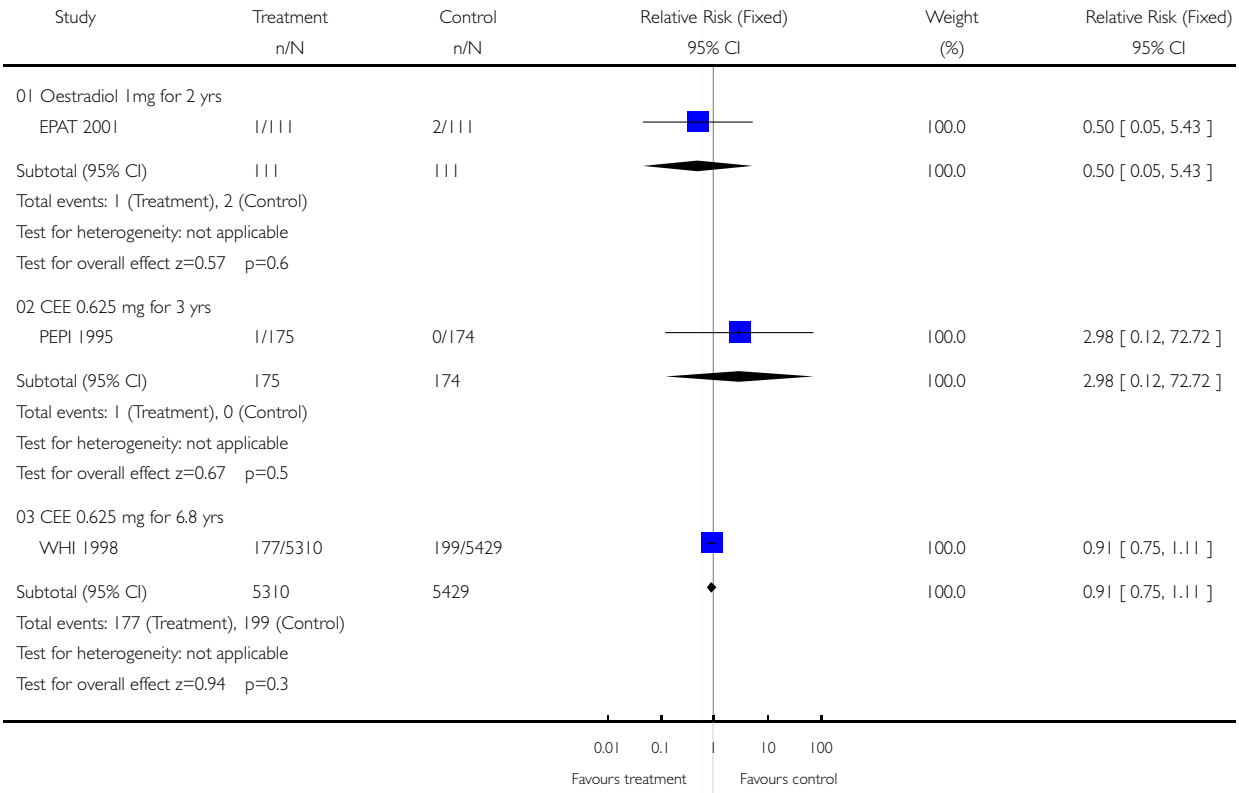


Analysis 01.10. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 10 Coronary events (MI or cardiac death): Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 10 Coronary events (MI or cardiac death): Oestrogen-only HT (moderate dose)

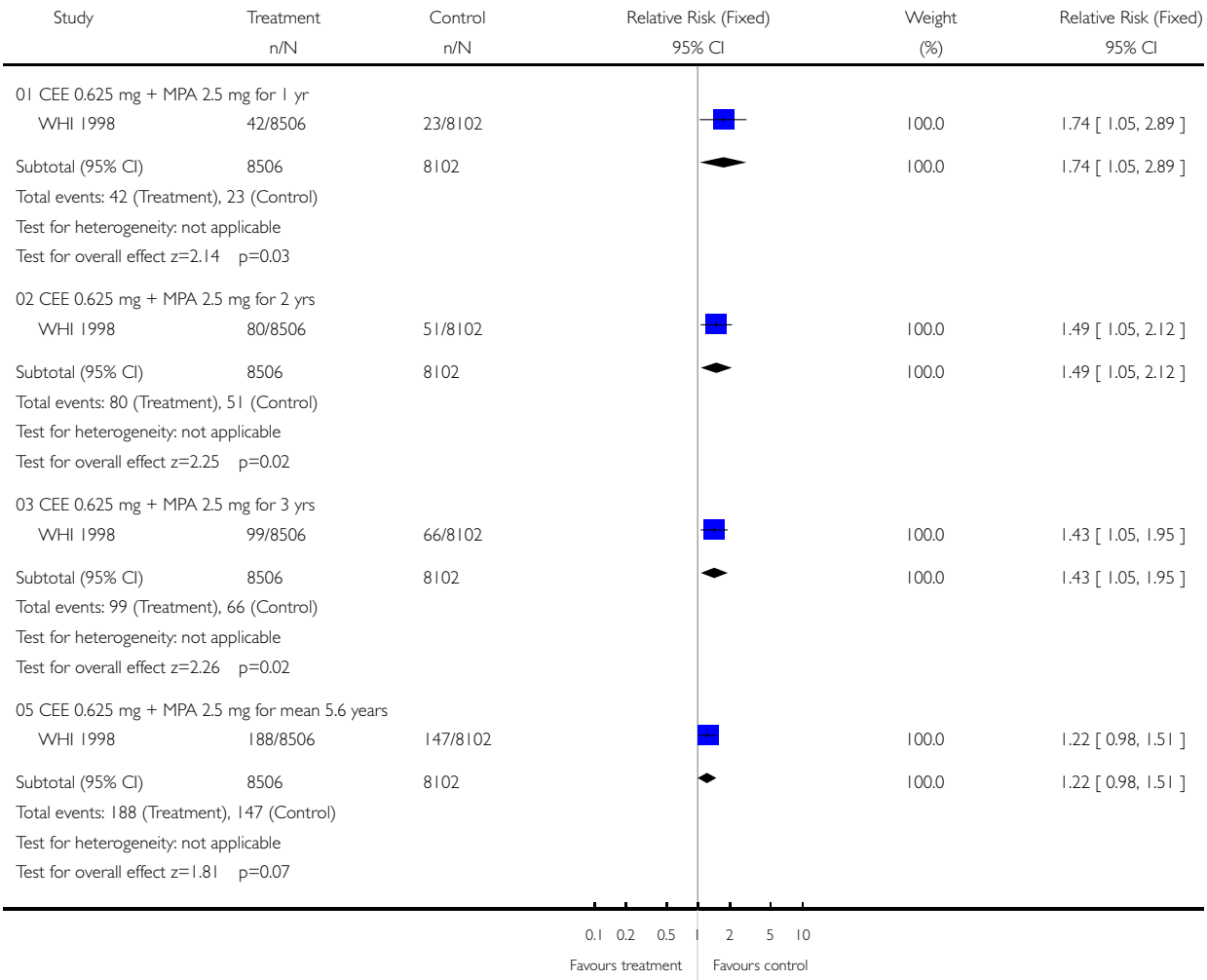


Analysis 01.11. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 11 Coronary events (MI or cardiac death): Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 11 Coronary events (MI or cardiac death): Combined continuous HT (moderate dose oestrogen)



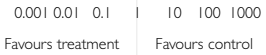
Analysis 01.12. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 12 Coronary events (MI or cardiac death): Combined sequential HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 12 Coronary events (MI or cardiac death): Combined sequential HT (moderate dose oestrogen)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg daily + micronised progesterone 200 mg days 1-12 for 3 yrs					
PEPI 1995	2/178	0/174		100.0	4.89 [0.24, 101.09]
Subtotal (95% CI)	178	174		100.0	4.89 [0.24, 101.09]
Total events: 2 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.03 p=0.3					



Analysis 01.13. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 13 Stroke: Unopposed oestrogen (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 13 Stroke: Unopposed oestrogen (moderate dose)

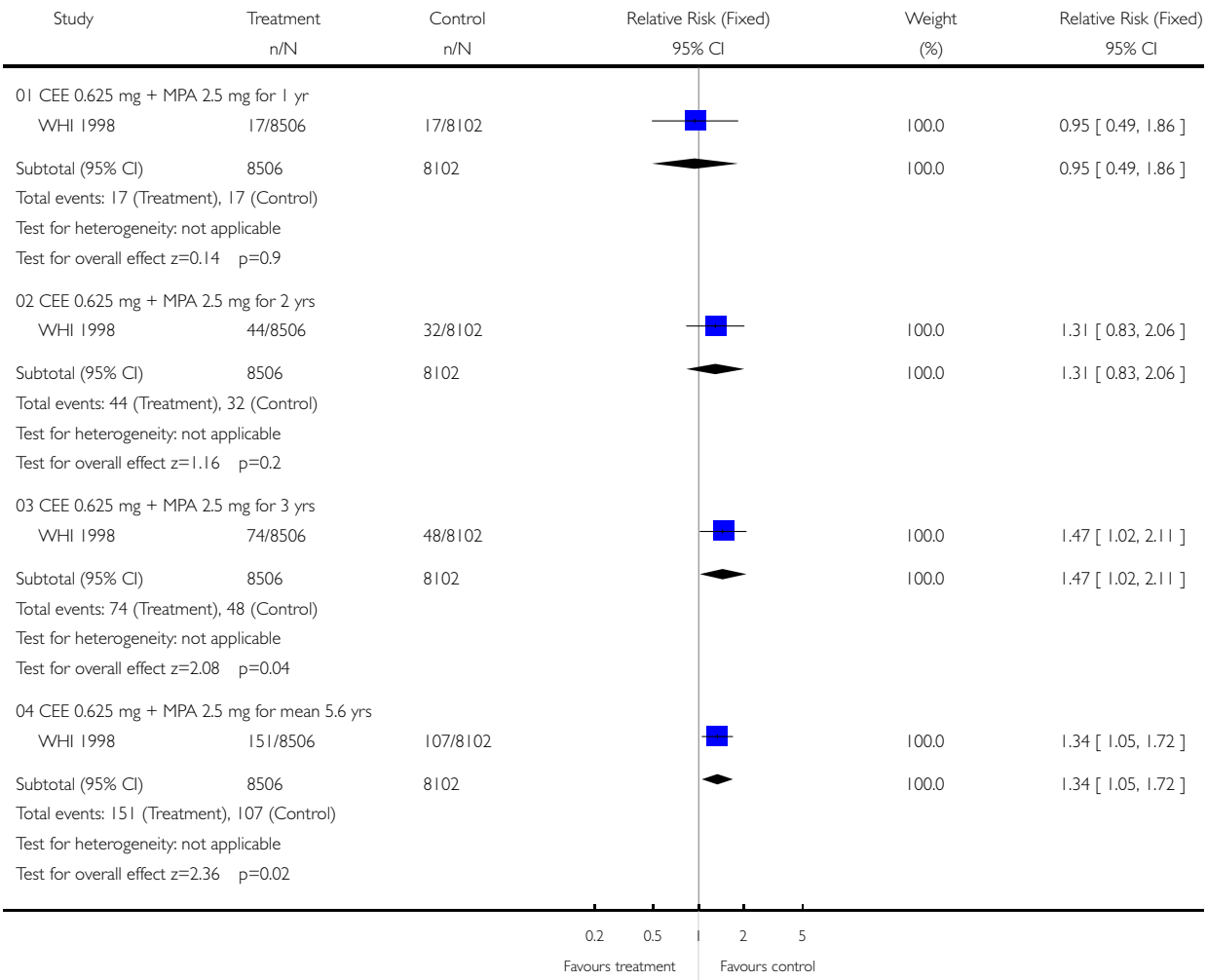
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Oestradiol 1mg for 2 yrs					
EPAT 2001	1/111	0/111		100.0	3.00 [0.12, 72.86]
Subtotal (95% CI)	111	111		100.0	3.00 [0.12, 72.86]
Total events: 1 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					
02 CEE 0.625 mg for 6.8 yrs					
WHI 1998	158/5310	118/5429		100.0	1.37 [1.08, 1.73]
Subtotal (95% CI)	5310	5429		100.0	1.37 [1.08, 1.73]
Total events: 158 (Treatment), 118 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.61 p=0.009					

Analysis 01.14. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 14 Stroke: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 14 Stroke: Combined continuous HT (moderate dose oestrogen)

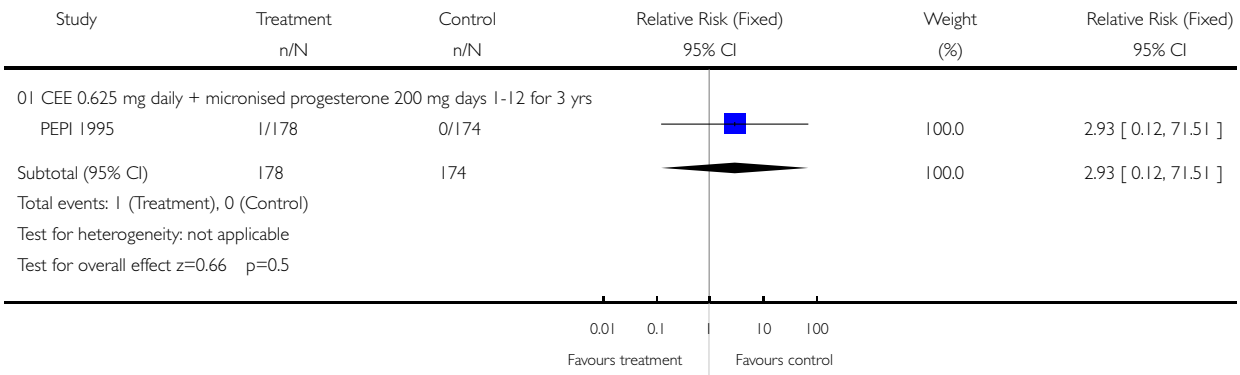


Analysis 01.15. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 15 Stroke: Combined sequential HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 15 Stroke: Combined sequential HT (moderate dose oestrogen)

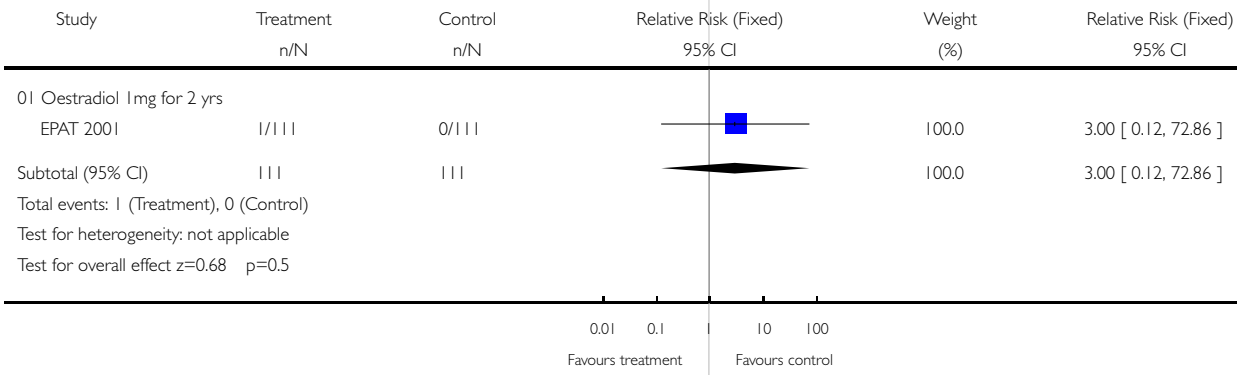


Analysis 01.16. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 16 Transient ischaemic attack: Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 16 Transient ischaemic attack: Oestrogen-only HT (moderate dose)



Analysis 01.17. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 17 Transient ischaemic attack: Combined sequential HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 17 Transient ischaemic attack: Combined sequential HT (moderate dose oestrogen)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg daily + MPA 10 mg days 1-12 for 3 yrs					
PEPI 1995	1/174	0/174		100.0	3.00 [0.12, 73.14]
Subtotal (95% CI)	174	174		100.0	3.00 [0.12, 73.14]
Total events: 1 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.67 p=0.5					

Analysis 01.18. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 18 Venous thrombo-embolism (DVT or PE): Oestrogen-only HT ((moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 18 Venous thrombo-embolism (DVT or PE): Oestrogen-only HT ((moderate dose)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg for 3 yrs					
PEPI 1995	3/175	0/174		100.0	6.96 [0.36, 133.75]
Subtotal (95% CI)	175	174		100.0	6.96 [0.36, 133.75]
Total events: 3 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.29 p=0.2					
02 CEE 0.625 mg for 6.8 yrs					
WHI 1998	101/5310	78/5429		100.0	1.32 [0.99, 1.77]
Subtotal (95% CI)	5310	5429		100.0	1.32 [0.99, 1.77]
Total events: 101 (Treatment), 78 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.88 p=0.06					

Analysis 01.19. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 19 Venous thrombo-embolism (DVT or PE): Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 19 Venous thrombo-embolism (DVT or PE): Combined continuous HT (moderate dose oestrogen)

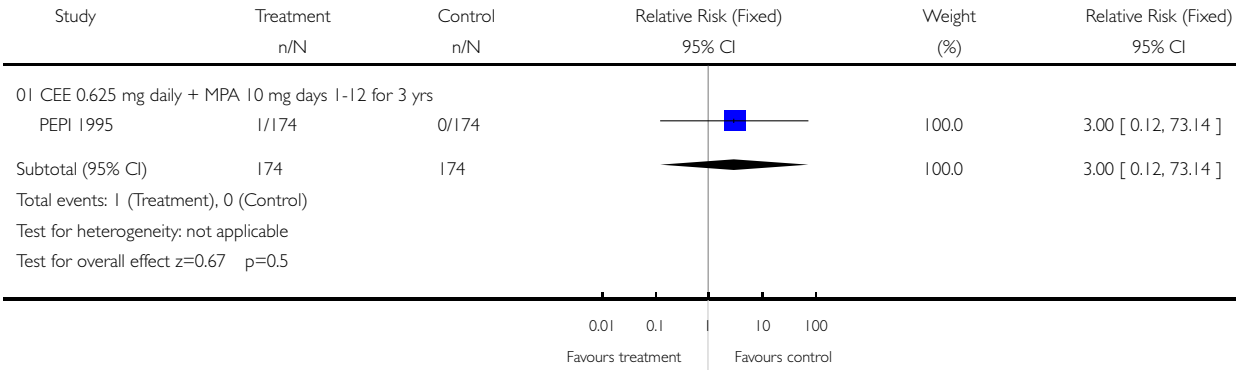
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg + MPA 2.5 mg for 1 yr					
WHI 1998	49/8506	13/8102		100.0	3.59 [1.95, 6.61]
Subtotal (95% CI)	8506	8102		100.0	3.59 [1.95, 6.61]
Total events: 49 (Treatment), 13 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.10 p=0.00004					
02 CEE 0.625 mg + MPA 2.5 mg for 2 yrs					
WHI 1998	75/8506	24/8102		100.0	2.98 [1.88, 4.71]
Subtotal (95% CI)	8506	8102		100.0	2.98 [1.88, 4.71]
Total events: 75 (Treatment), 24 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.66 p<0.00001					
03 CEE 0.625 mg + MPA 2.5 mg for 3 yrs					
WHI 1998	96/8506	36/8102		100.0	2.54 [1.73, 3.72]
Subtotal (95% CI)	8506	8102		100.0	2.54 [1.73, 3.72]
Total events: 96 (Treatment), 36 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.78 p<0.00001					
05 CEE 0.625 mg + MPA 2.5 mg for mean 5.6 yrs					
WHI 1998	167/8506	76/8102		100.0	2.09 [1.60, 2.74]
Subtotal (95% CI)	8506	8102		100.0	2.09 [1.60, 2.74]
Total events: 167 (Treatment), 76 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=5.37 p<0.00001					

Analysis 01.20. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 20 Venous thrombo-embolism (DVT or PE): Combined sequential HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 20 Venous thrombo-embolism (DVT or PE): Combined sequential HT (moderate dose oestrogen)

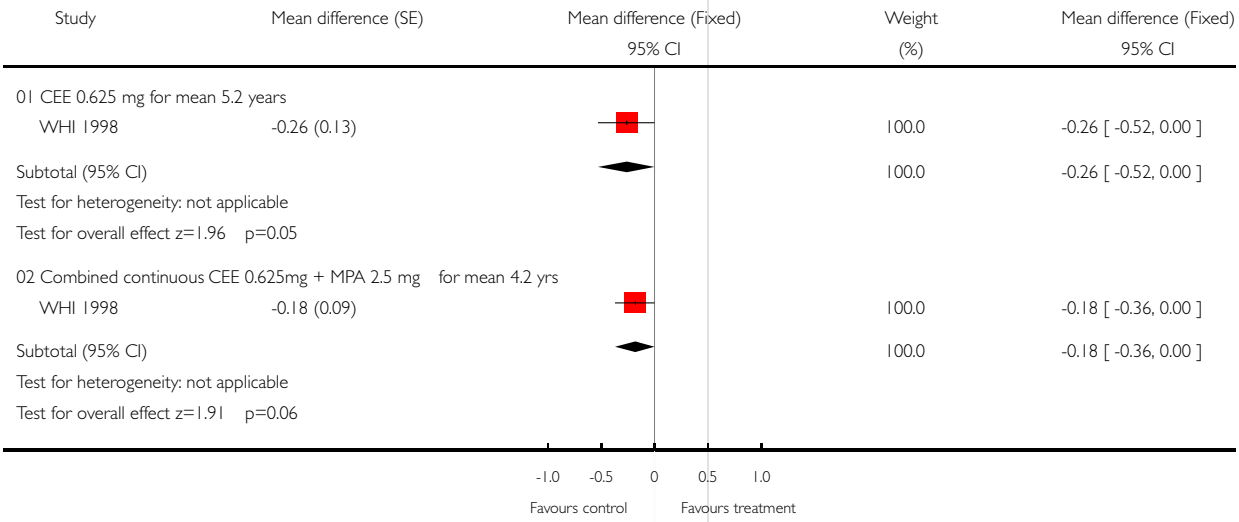


Analysis 01.21. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 21 Global cognitive function: mean difference in 3MSE score changes from baseline

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 21 Global cognitive function: mean difference in 3MSE score changes from baseline



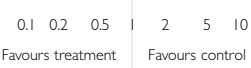
Analysis 01.22. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 22 Large decline (>2SD) in global cognitive function

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 22 Large decline (>2SD) in global cognitive function

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg for mean 5.2 years					
WHI 1998	77/1387	64/1421		56.8	1.23 [0.89, 1.70]
Subtotal (95% CI)	1387	1421		56.8	1.23 [0.89, 1.70]
Total events: 77 (Treatment), 64 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.27 p=0.2					
02 Combined continuous CEE 0.625mg + MPA 2.5 mg	for mean 4.2 yrs				
WHI 1998	74/2131	49/2213		43.2	1.57 [1.10, 2.24]
Subtotal (95% CI)	2131	2213		43.2	1.57 [1.10, 2.24]
Total events: 74 (Treatment), 49 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.48 p=0.01					
Total (95% CI)	3518	3634		100.0	1.38 [1.08, 1.75]
Total events: 151 (Treatment), 113 (Control)					
Test for heterogeneity chi-square=0.96 df=1 p=0.33 I^2 =0.0%					
Test for overall effect z=2.63 p=0.009					

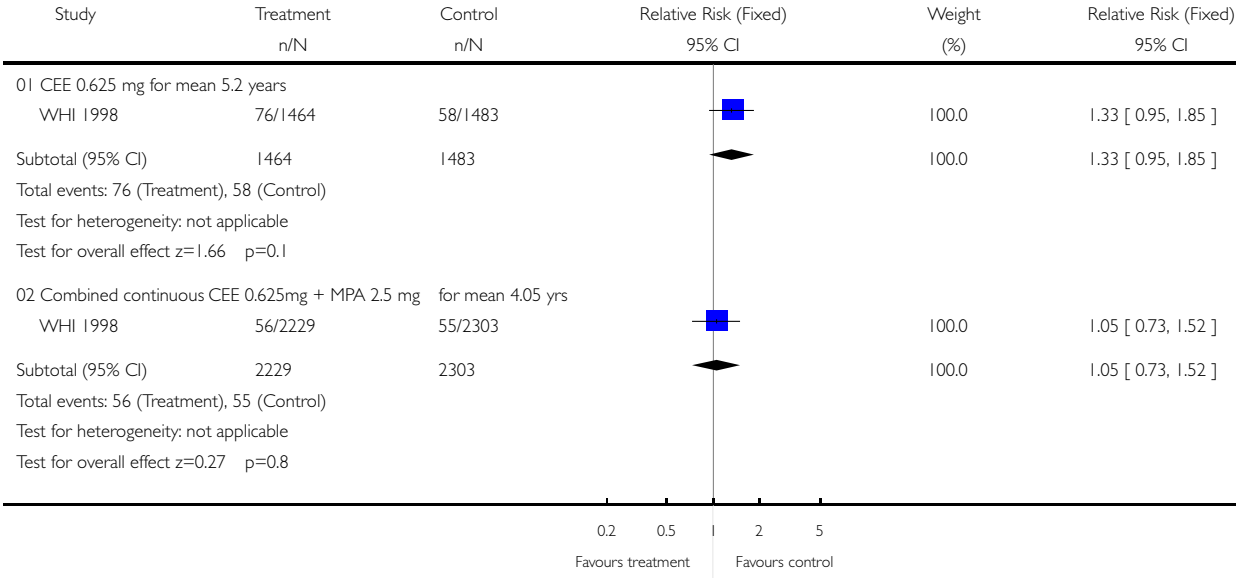


Analysis 01.23. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 23 Mild cognitive impairment: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 23 Mild cognitive impairment: Combined continuous HT (moderate dose oestrogen)

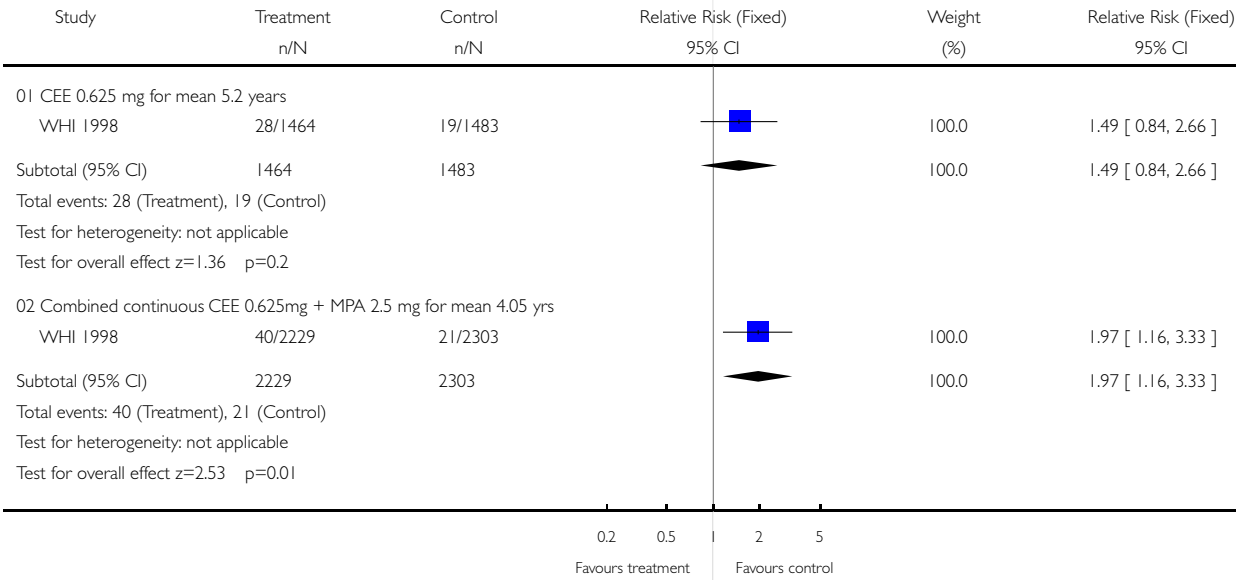


Analysis 01.24. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 24 Probable dementia: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 24 Probable dementia: Combined continuous HT (moderate dose oestrogen)



Analysis 01.25. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 25 Mild cognitive impairment or probable dementia

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 25 Mild cognitive impairment or probable dementia

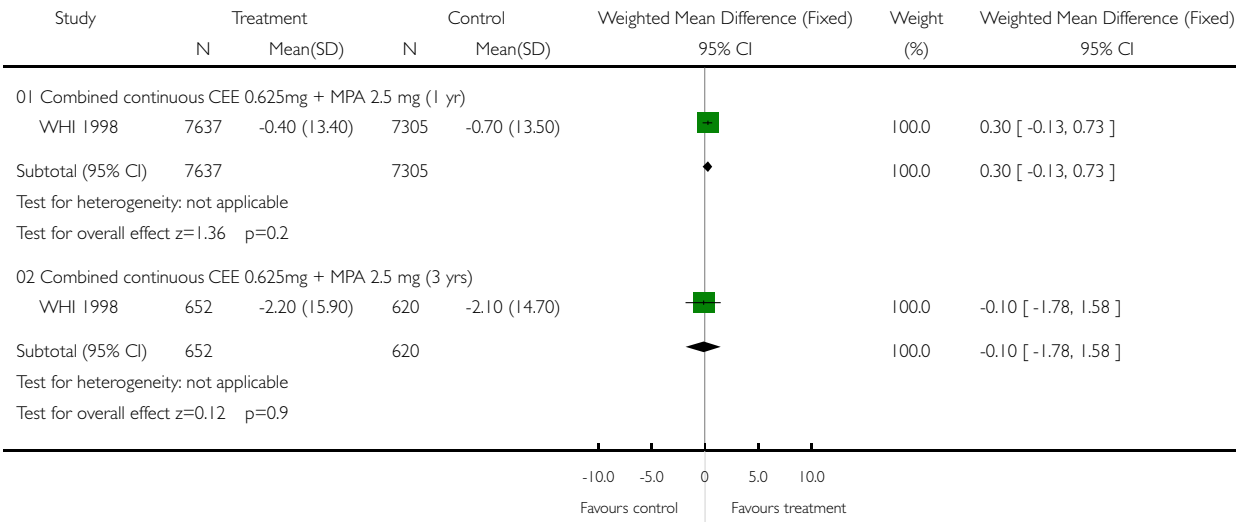
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg for mean 5.4 years					
WHI 1998	93/1463	69/1479		51.4	1.36 [1.01, 1.84]
Subtotal (95% CI)	1463	1479		51.4	1.36 [1.01, 1.84]
Total events: 93 (Treatment), 69 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.00 p=0.05					
02 Combined continuous CEE 0.625mg + MPA 2.5 mg for mean 4.05 yrs					
WHI 1998	85/2229	66/2303		48.6	1.33 [0.97, 1.83]
Subtotal (95% CI)	2229	2303		48.6	1.33 [0.97, 1.83]
Total events: 85 (Treatment), 66 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.77 p=0.08					
Total (95% CI)	3692	3782		100.0	1.35 [1.08, 1.68]
Total events: 178 (Treatment), 135 (Control)					
Test for heterogeneity chi-square=0.01 df=1 p=0.92 I^2 =0.0%					
Test for overall effect z=2.67 p=0.008					

Analysis 01.26. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 26 Change in quality of life: General health (RAND 36): Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 26 Change in quality of life: General health (RAND 36): Combined continuous HT (moderate dose oestrogen)

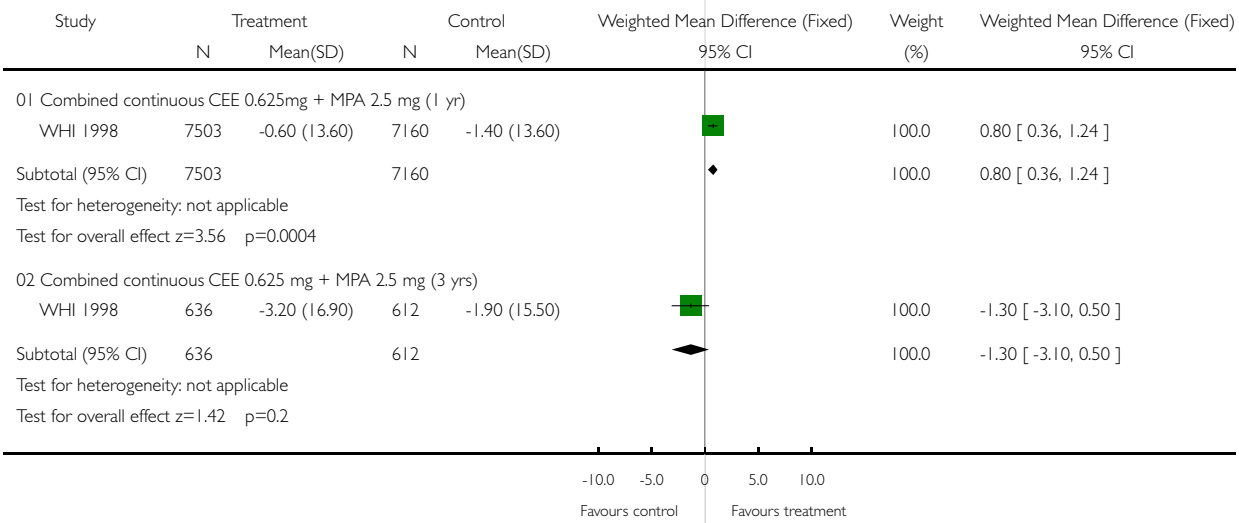


Analysis 01.27. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 27 Change in quality of life: Physical functioning (RAND 36): Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 27 Change in quality of life: Physical functioning (RAND 36): Combined continuous HT (moderate dose oestrogen)

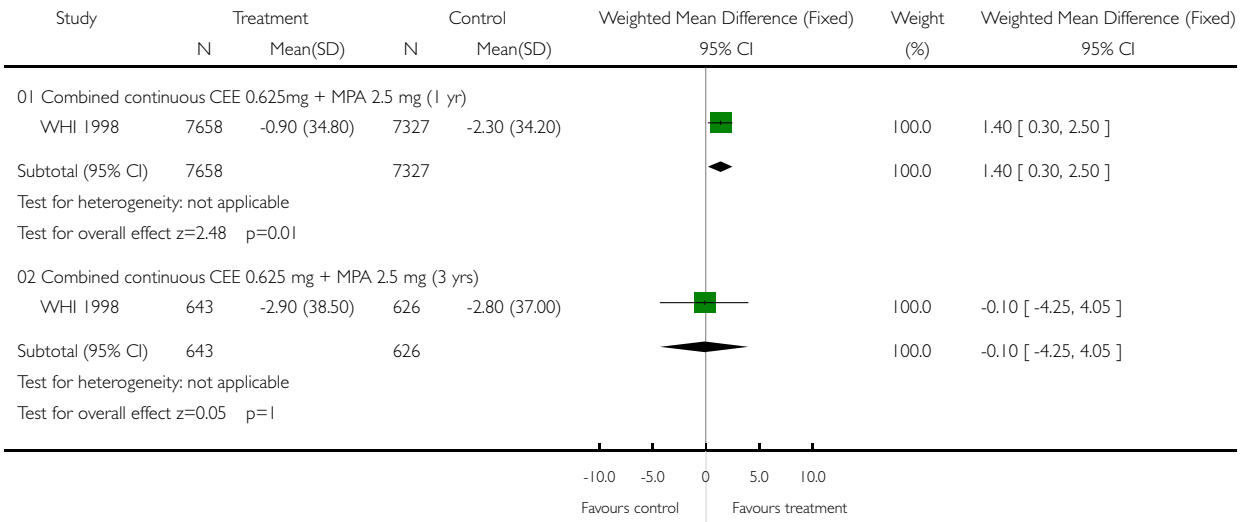


Analysis 01.28. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 28 Change in quality of life: Role limitations due to physical problems (RAND 36): Combined cont. HT (mod dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 28 Change in quality of life: Role limitations due to physical problems (RAND 36): Combined cont. HT (mod dose)

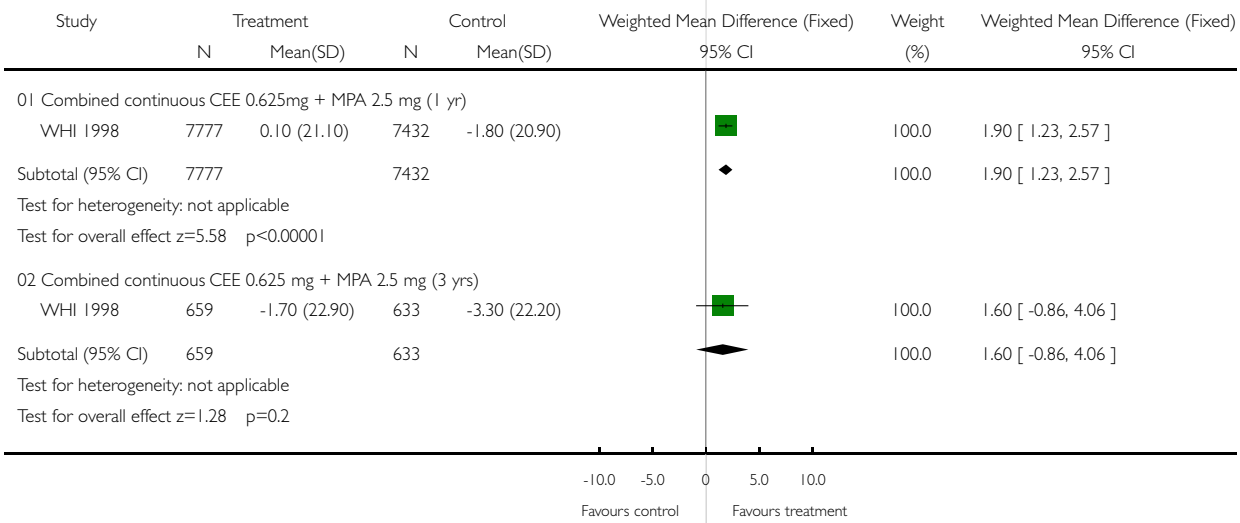


Analysis 01.29. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 29 Change in quality of life: Bodily pain (RAND 36): Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 29 Change in quality of life: Bodily pain (RAND 36): Combined continuous HT (moderate dose oestrogen)

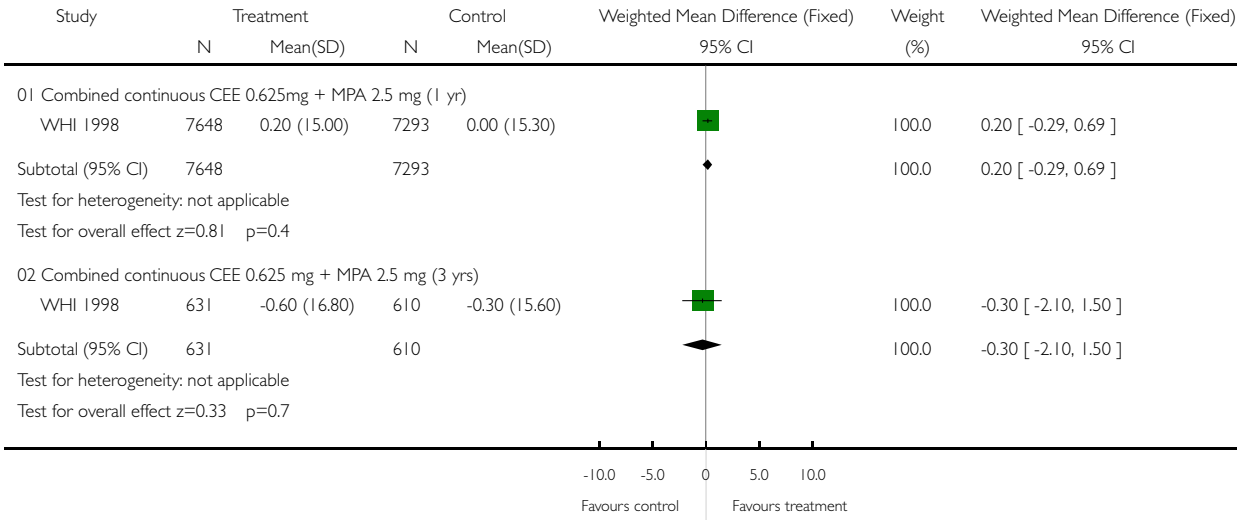


Analysis 01.30. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 30 Change in quality of life:Energy and fatigue (RAND 36): Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 30 Change in quality of life:Energy and fatigue (RAND 36): Combined continuous HT (moderate dose oestrogen)

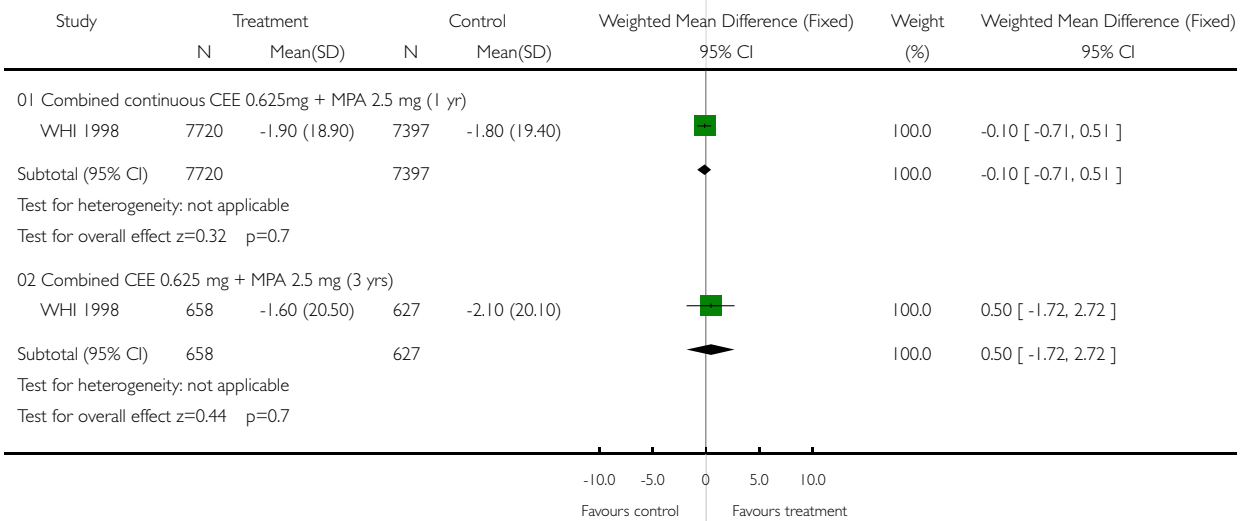


Analysis 01.31. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 31 Change in quality of life: Social functioning (RAND 36): Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 31 Change in quality of life: Social functioning (RAND 36): Combined continuous HT (moderate dose oestrogen)

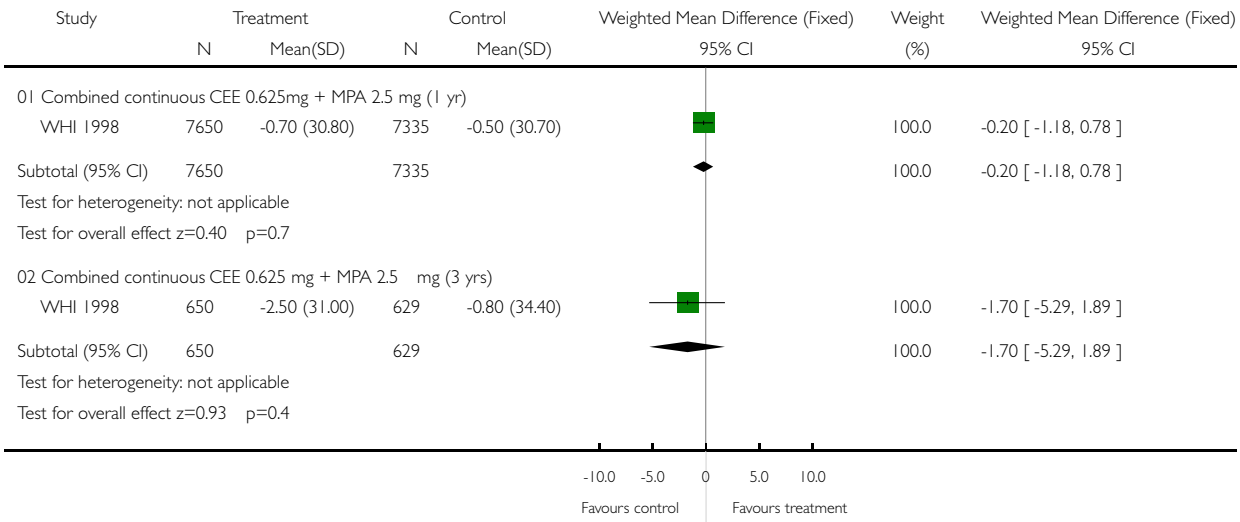


Analysis 01.32. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 32 Change in quality of life: Role limitations due to emotional problems (RAND 36): Combined cont. HT (mod dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 32 Change in quality of life: Role limitations due to emotional problems (RAND 36): Combined cont. HT (mod dose)

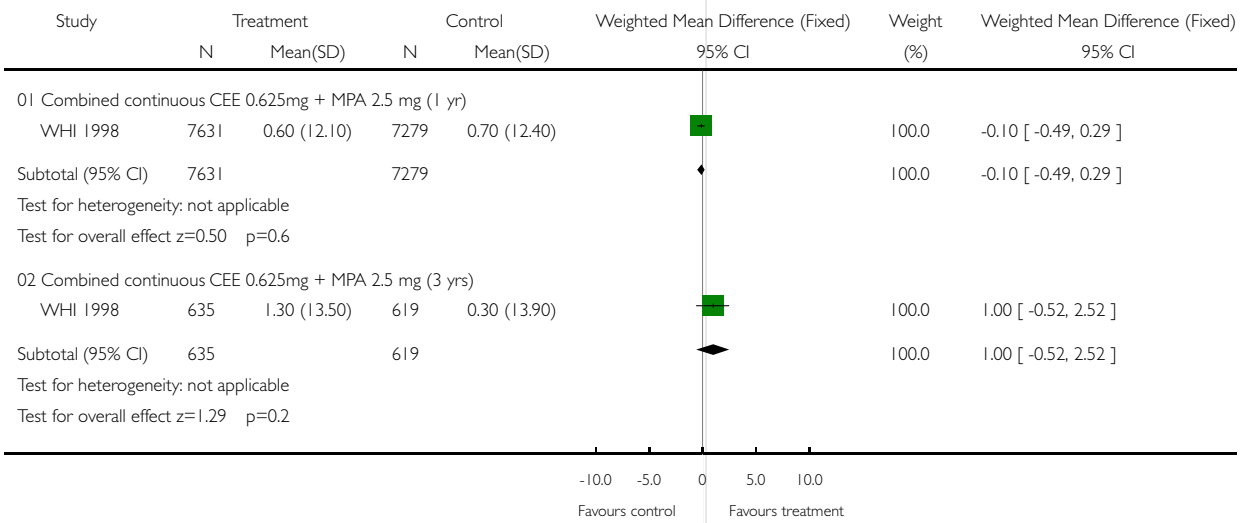


Analysis 01.33. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 33 Change in quality of life: Mental health (RAND 36): Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 33 Change in quality of life: Mental health (RAND 36): Combined continuous HT (moderate dose oestrogen)

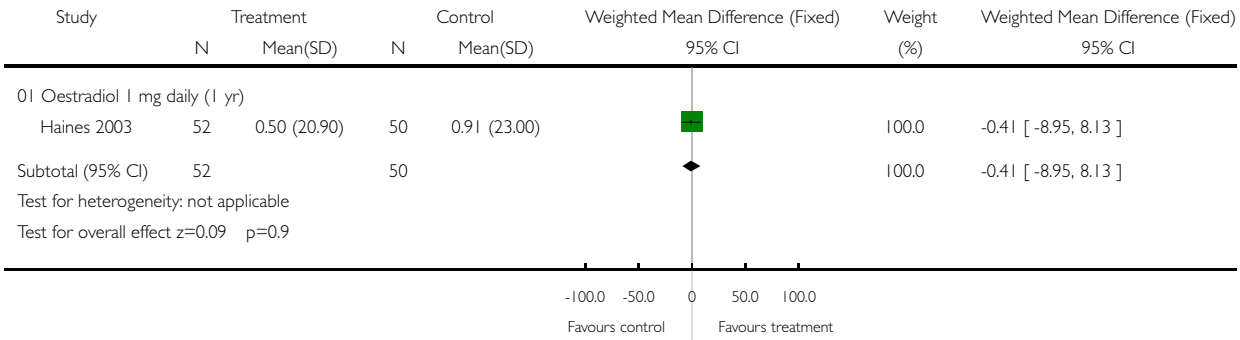


Analysis 01.34. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 34 Change in quality of life overall (HQOL): Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 34 Change in quality of life overall (HQOL): Oestrogen-only HT (moderate dose)

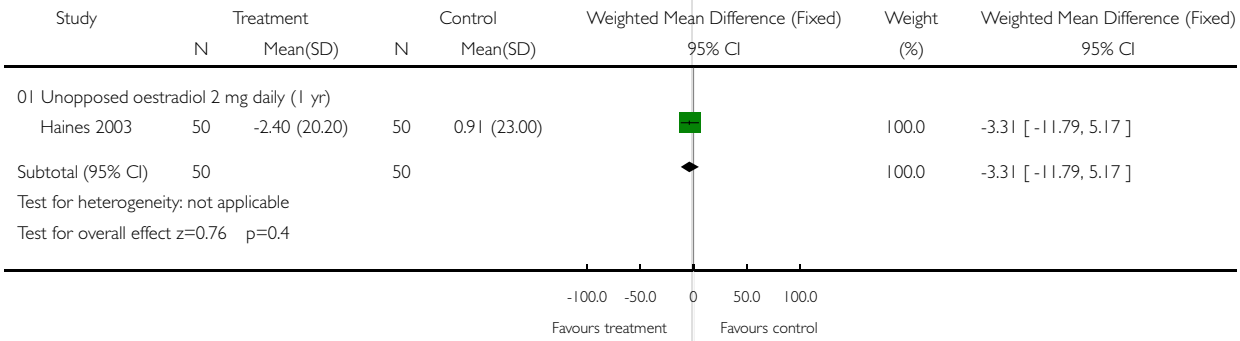


Analysis 01.35. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 35 Change in quality of life overall (HQOL): Oestrogen-only HT (mod/high dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 35 Change in quality of life overall (HQOL): Oestrogen-only HT (mod/high dose)



Analysis 01.36. Comparison 01 Women without major health problems (Selected outcomes: death, CVD, cognition, QOL), Outcome 36 Change in quality of life score (GHQ-11 scale) (combined HT)

Combined continuous: oestradiol 2mg + norethisterone 1 mg (2 yrs)

Study	HRT no.	Change score (SD)	Placebo no.	Change score (SD)	p value
Obel 1993	31 (of 50 randomised)	-0.26 (3.71)	37 (of 51 randomised)	1.11 (3.85)	p</= 0.10

Combined sequential: oestradiol (2 mg days 1-12, 1 mg days 13-22) + norethisterone 1 mg days 13-22) for 2 yrs

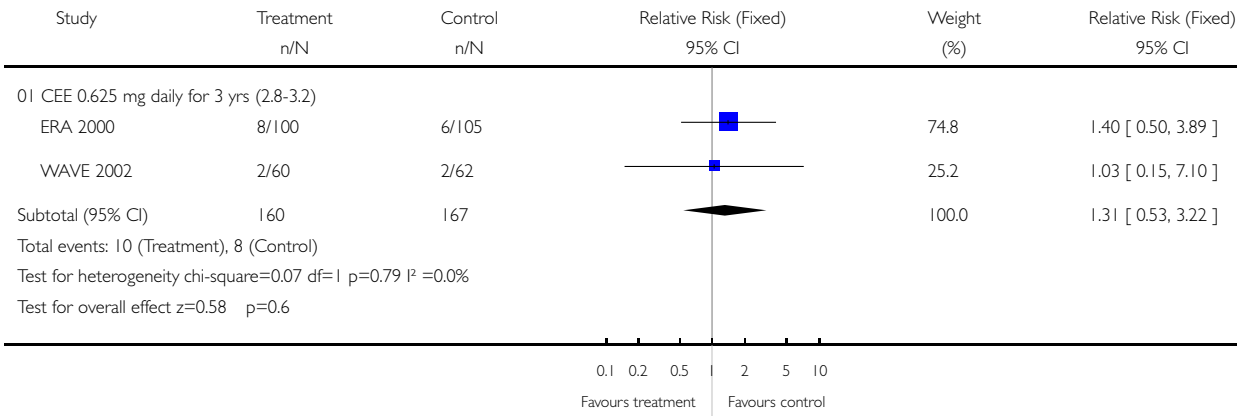
Study	HRT no.	Change score (SD)	Placebo no.	Change score (SD)	p value
Obel 1993	37 (of 50 randomised)	- 0.81 (3.08)	37 (of 51 randomised)	1.11 (3.85)	p = </= 0.10

Analysis 02.01. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 01 Death from any cause: Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 01 Death from any cause: Oestrogen-only HT (moderate dose)

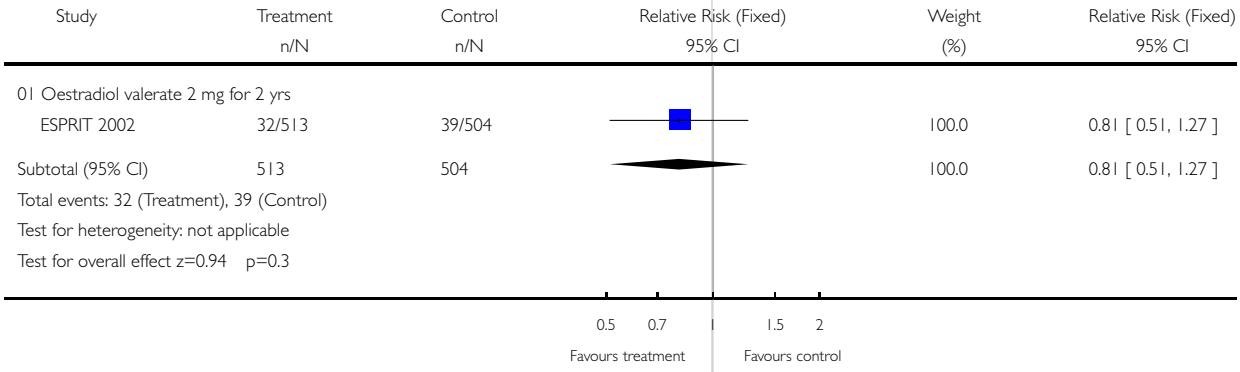


Analysis 02.02. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 02 Death from any cause: Oestrogen-only HT (mod/high dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 02 Death from any cause: Oestrogen-only HT (mod/high dose)



Analysis 02.03. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 03 Death from any cause: Oestrogen-only HT (mod dose) for women without uterus, plus sequential MPA if uterus i

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 03 Death from any cause: Oestrogen-only HT (mod dose) for women without uterus, plus sequential MPA if uterus i

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Oestradiol 1 mg daily (if no uterus) plus MPA 5mgs for 12 days a year (if uterus intact) for 2.8 yrs					
WEST 2001	48/337	41/327		100.0	1.14 [0.77, 1.67]
Subtotal (95% CI)	337	327		100.0	1.14 [0.77, 1.67]
Total events: 48 (Treatment), 41 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.64 p=0.5					

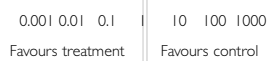
Analysis 02.04. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 04 Death from any cause: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 04 Death from any cause: Combined continuous HT (moderate dose oestrogen)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg + MPA 2.5 mg for 2.8 - 3.2 yrs					
ERA 2000	3/104	6/105		92.4	0.50 [0.13, 1.97]
WAVE 2002	2/43	0/45		7.6	5.23 [0.26, 105.85]
Subtotal (95% CI)	147	150		100.0	0.86 [0.28, 2.62]
Total events: 5 (Treatment), 6 (Control)					
Test for heterogeneity chi-square=1.97 df=1 p=0.16 I^2 =49.4%					
Test for overall effect z=0.26 p=0.8					
02 CEE 0.625 mg + MPA 2.5 mg for 4 yrs					
HERS 1998	130/1380	123/1383		100.0	1.06 [0.84, 1.34]
Subtotal (95% CI)	1380	1383		100.0	1.06 [0.84, 1.34]
Total events: 130 (Treatment), 123 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.48 p=0.6					
03 CEE 0.625 mg + MPA 2.5 mg for 4-7 yrs UNBLINDED					
HERS 1998	131/1156	116/1165		100.0	1.14 [0.90, 1.44]



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	1156	1165		100.0	1.14 [0.90, 1.44]
Total events: 131 (Treatment), 116 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.07 p=0.3					

Analysis 02.05. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 05 Death from coronary heart disease: Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 05 Death from coronary heart disease: Oestrogen-only HT (moderate dose)

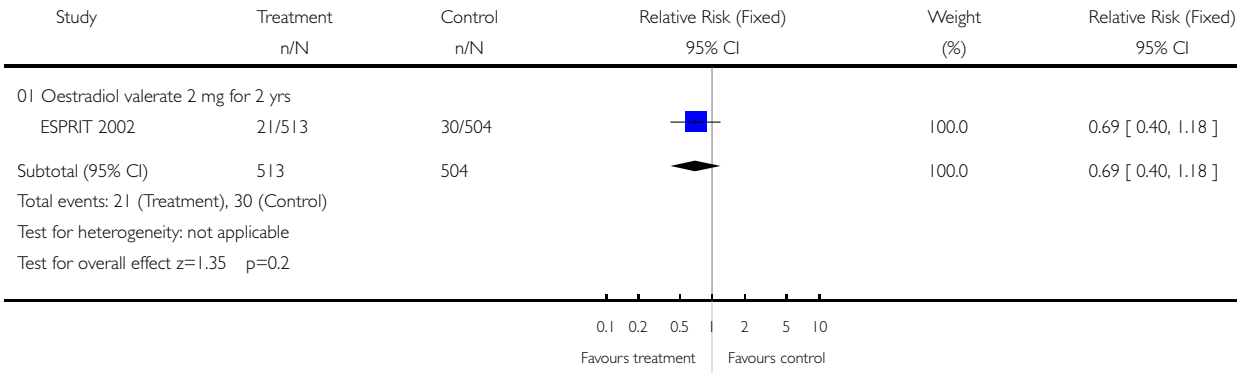
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 daily for 2.8 - 3.2 yrs					
ERA 2000	4/100	3/105		74.8	1.40 [0.32, 6.10]
WAVE 2002	1/60	1/62		25.2	1.03 [0.07, 16.15]
Subtotal (95% CI)	160	167		100.0	1.31 [0.36, 4.77]
Total events: 5 (Treatment), 4 (Control)					
Test for heterogeneity chi-square=0.04 df=1 p=0.85 I^2 =0.0%					
Test for overall effect z=0.41 p=0.7					

Analysis 02.06. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 06 Death from coronary heart disease: Oestrogen-only HT (mod/high dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 06 Death from coronary heart disease: Oestrogen-only HT (mod/high dose)

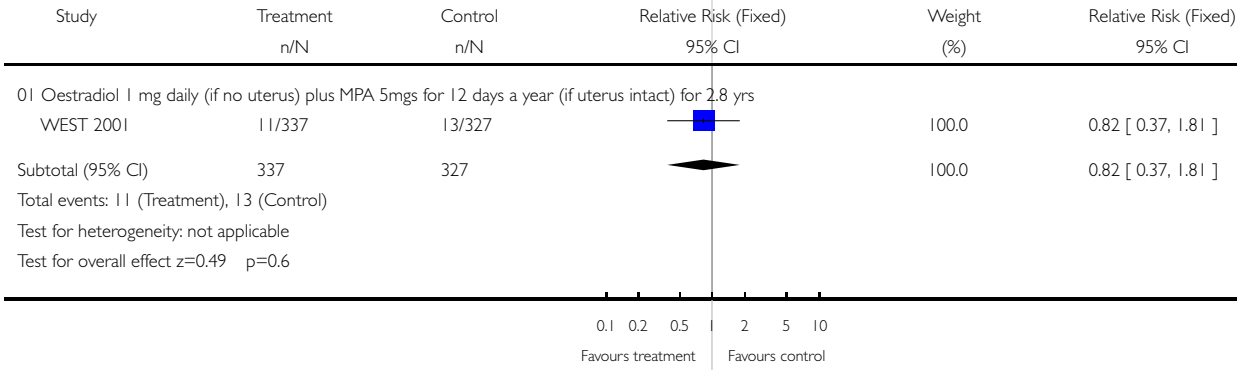


Analysis 02.07. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 07 Death from CHD: Oestrogen-only HT (mod dose) for women without uterus, plus sequential MPA if uterus intact

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 07 Death from CHD: Oestrogen-only HT (mod dose) for women without uterus, plus sequential MPA if uterus intact

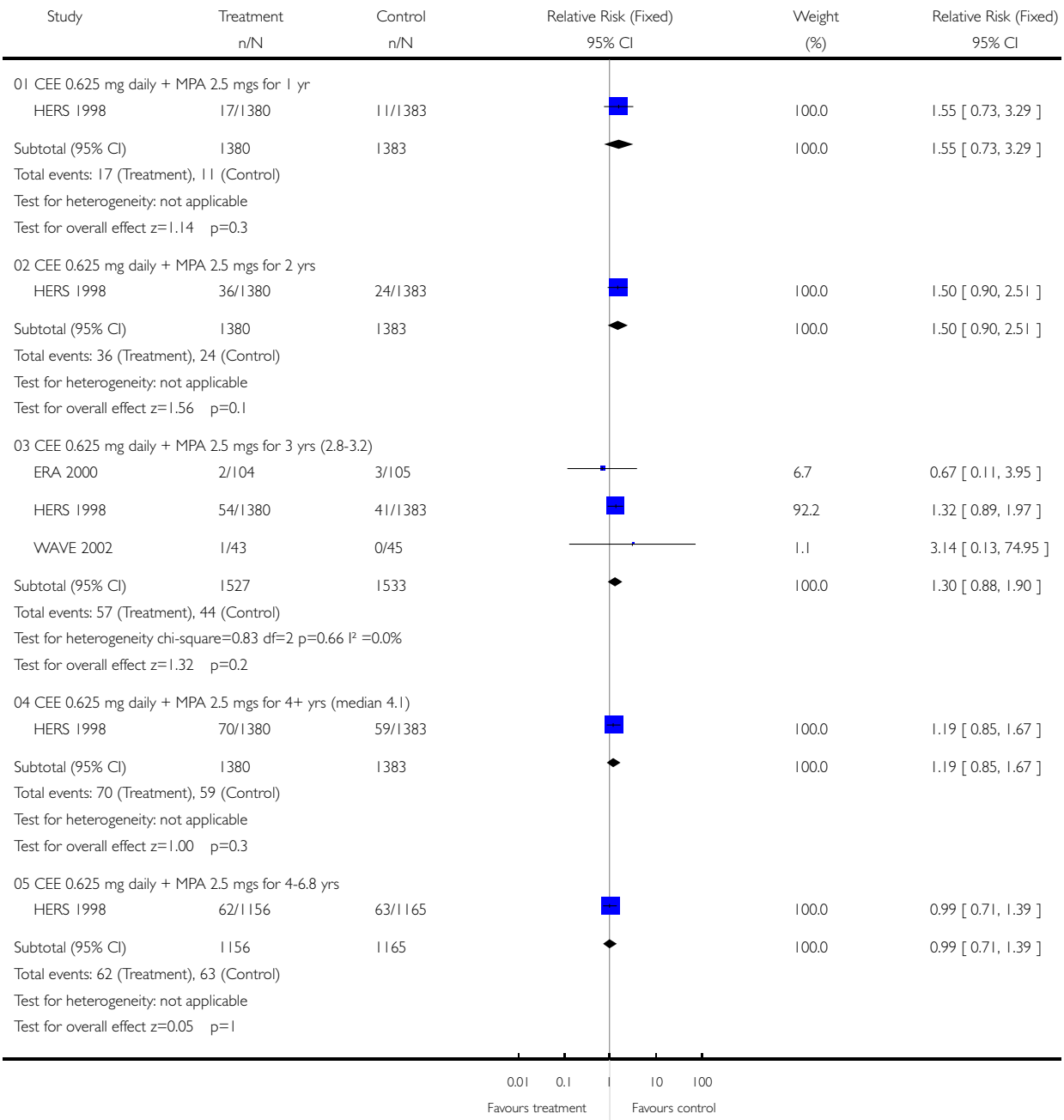


Analysis 02.08. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 08 Death from coronary heart disease: Combined continuous CEE + MPA

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 08 Death from coronary heart disease: Combined continuous CEE + MPA

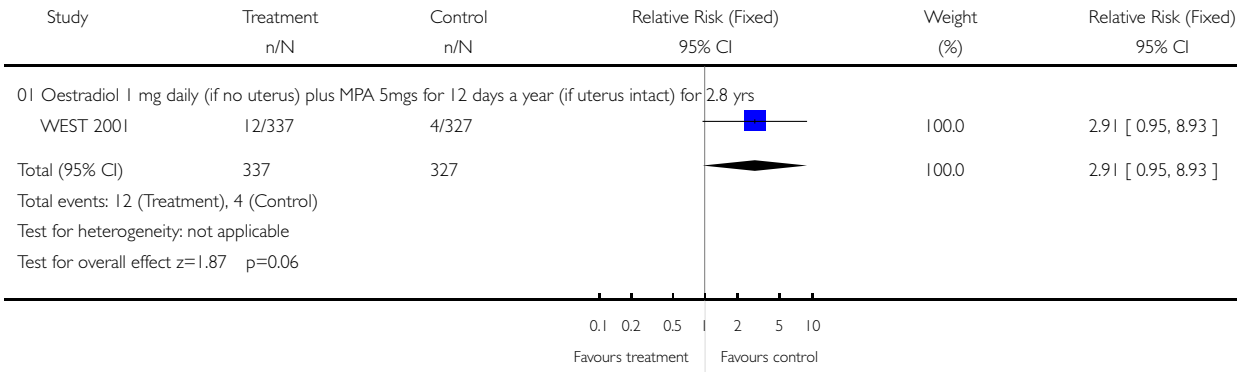


Analysis 02.09. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 09 Death from stroke: Oestrogen-only HT (mod dose) if no uterus, plus sequential MPA if uterus intact

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 09 Death from stroke: Oestrogen-only HT (mod dose) if no uterus, plus sequential MPA if uterus intact

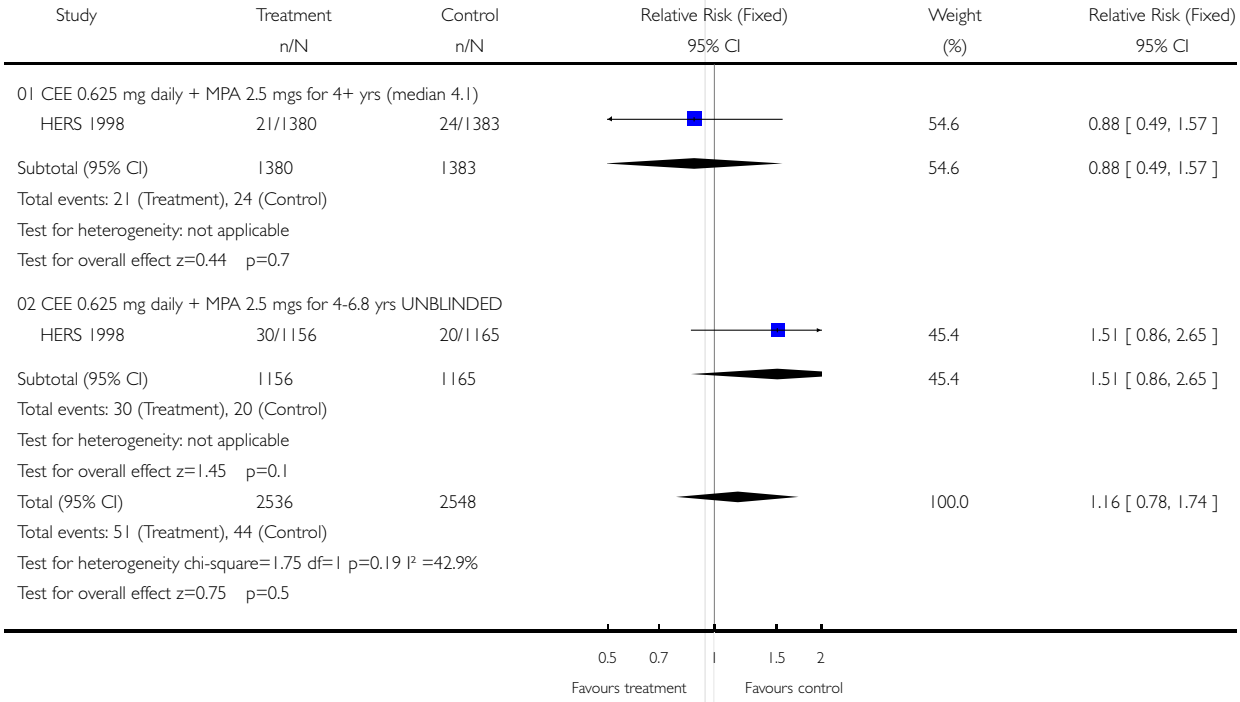


Analysis 02.10. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 10 Death from cancer: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 10 Death from cancer: Combined continuous HT (moderate dose oestrogen)

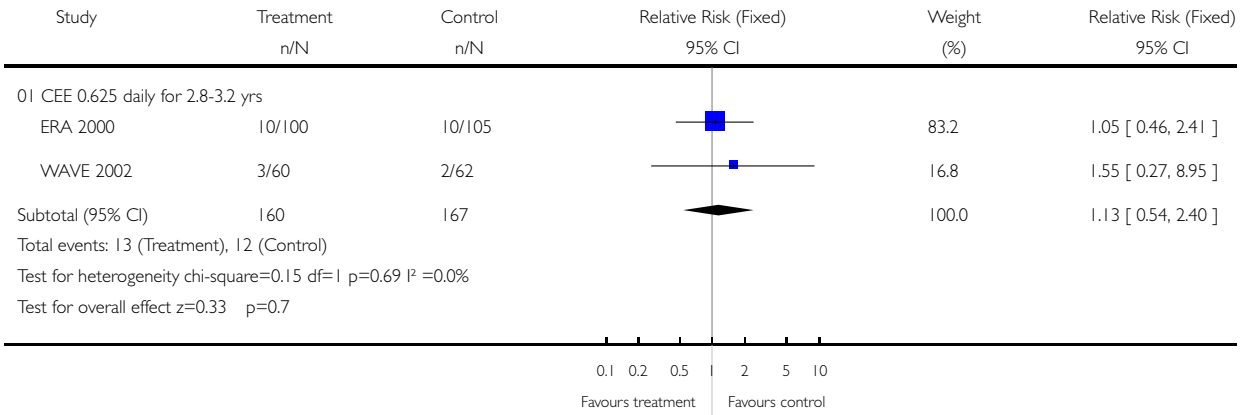


Analysis 02.11. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 11 Coronary event (MI or cardiac death): Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 11 Coronary event (MI or cardiac death): Oestrogen-only HT (moderate dose)

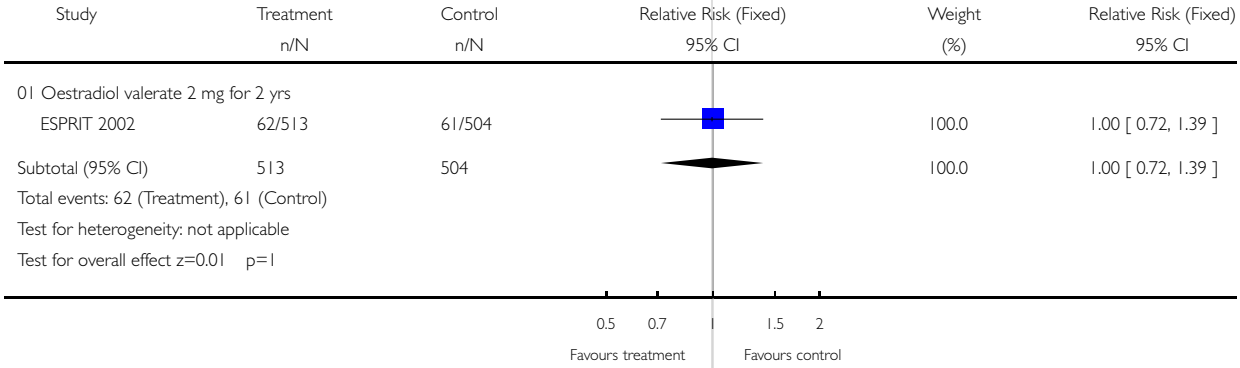


Analysis 02.12. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 12 Coronary event (MI or cardiac death): Oestrogen-only HT (mod/high dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 12 Coronary event (MI or cardiac death): Oestrogen-only HT (mod/high dose)



Analysis 02.13. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 13 Coronary event : Oestrogen-only HT (mod dose) for women without uterus, plus sequential MPA if uterus intac

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 13 Coronary event : Oestrogen-only HT (mod dose) for women without uterus, plus sequential MPA if uterus intac

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Oestradiol 1 mg daily (if no uterus) plus MPA 5mgs for 12 days a year (if uterus intact) for 2.8 yrs					
WEST 2001	25/337	25/327		100.0	0.97 [0.57, 1.65]
Subtotal (95% CI)	337	327		100.0	0.97 [0.57, 1.65]
Total events: 25 (Treatment), 25 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.11 p=0.9					

Analysis 02.14. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 14 Coronary event (MI or cardiac death): Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 14 Coronary event (MI or cardiac death): Combined continuous HT (moderate dose oestrogen)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg + MPA 2.5 mgs for 1 yr					
HERS 1998	57/1380	38/1383		100.0	1.50 [1.00, 2.25]
Subtotal (95% CI)	1380	1383		100.0	1.50 [1.00, 2.25]
Total events: 57 (Treatment), 38 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.98 p=0.05					
02 CEE 0.625 mg + MPA 2.5 mgs for 2 yrs					
HERS 1998	104/1380	87/1383		100.0	1.20 [0.91, 1.58]
Subtotal (95% CI)	1380	1383		100.0	1.20 [0.91, 1.58]
Total events: 104 (Treatment), 87 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.29 p=0.2					
03 CEE 0.625 mg + MPA 2.5 mg for 3 yrs (2.8 - 3.2)					
ERA 2000	8/104	10/105		7.1	0.81 [0.33, 1.97]

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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
HERS 1998	139/1380	129/1383		92.2	1.08 [0.86, 1.36]
WAVE 2002	2/43	1/45		0.7	2.09 [0.20, 22.25]
Subtotal (95% CI)	1527	1533		100.0	1.07 [0.86, 1.33]
Total events: 149 (Treatment), 140 (Control)					
Test for heterogeneity chi-square=0.70 df=2 p=0.70 I^2 =0.0%					
Test for overall effect z=0.58 p=0.6					
04 CEE 0.625 mg + MPA 2.5 mg for median 4.1 yrs					
HERS 1998	179/1380	182/1383		100.0	0.99 [0.81, 1.19]
Subtotal (95% CI)	1380	1383		100.0	0.99 [0.81, 1.19]
Total events: 179 (Treatment), 182 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.15 p=0.9					
05 CEE 0.625 mg + MPA 2.5 mg for 4-6.8 yrs UNBLINDED					
HERS 1998	111/1156	111/1165		100.0	1.01 [0.78, 1.29]
Subtotal (95% CI)	1156	1165		100.0	1.01 [0.78, 1.29]
Total events: 111 (Treatment), 111 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.06 p=1					

Analysis 02.15. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 15 Stroke (first or recurrent): Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 15 Stroke (first or recurrent): Oestrogen-only HT (moderate dose)

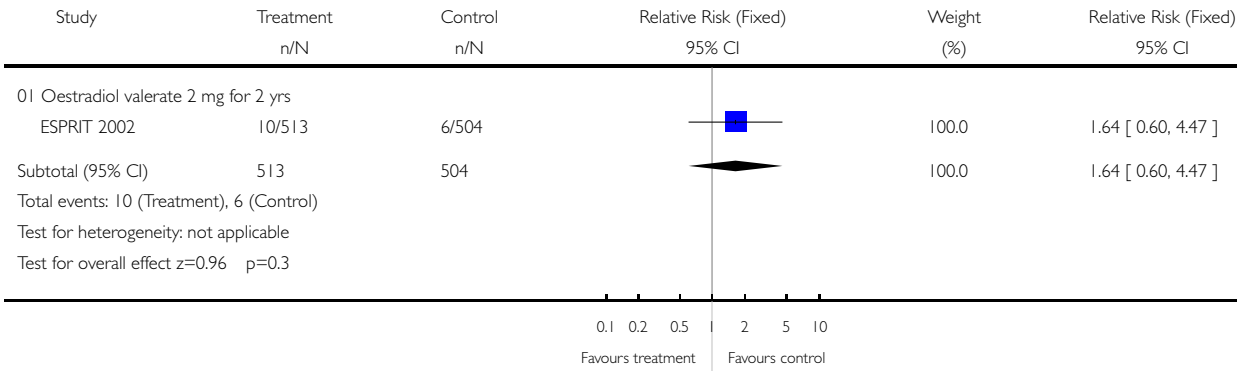
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 daily for 2.8 yrs					
WAVE 2002	2/60	3/62		100.0	0.69 [0.12, 3.98]
Subtotal (95% CI)	60	62		100.0	0.69 [0.12, 3.98]
Total events: 2 (Treatment), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.42 p=0.7					

Analysis 02.16. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 16 Stroke (first or recurrent): Oestrogen-only HT (mod/high dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 16 Stroke (first or recurrent): Oestrogen-only HT (mod/high dose)

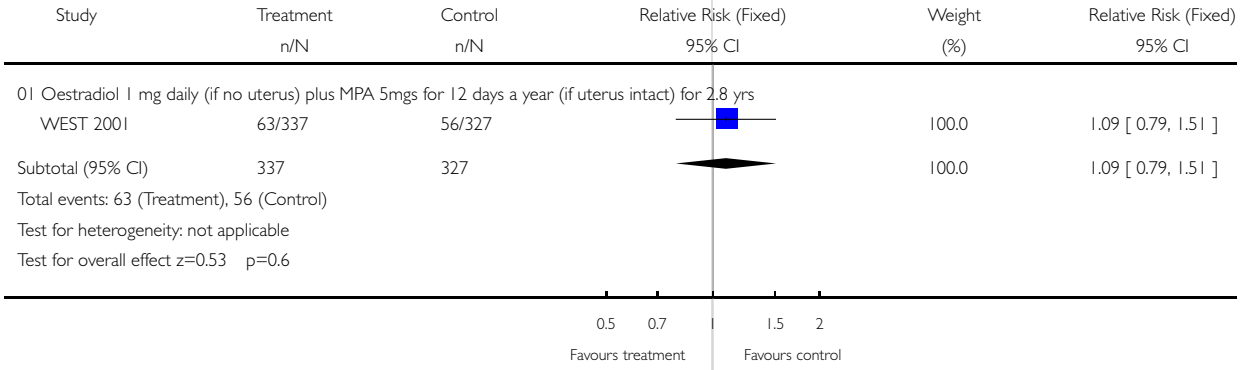


Analysis 02.17. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 17 Stroke (first or recurrent): Oestrogen-only HT (mod dose) if no uterus, plus annual MPA if uterus intact

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 17 Stroke (first or recurrent): Oestrogen-only HT (mod dose) if no uterus, plus annual MPA if uterus intact

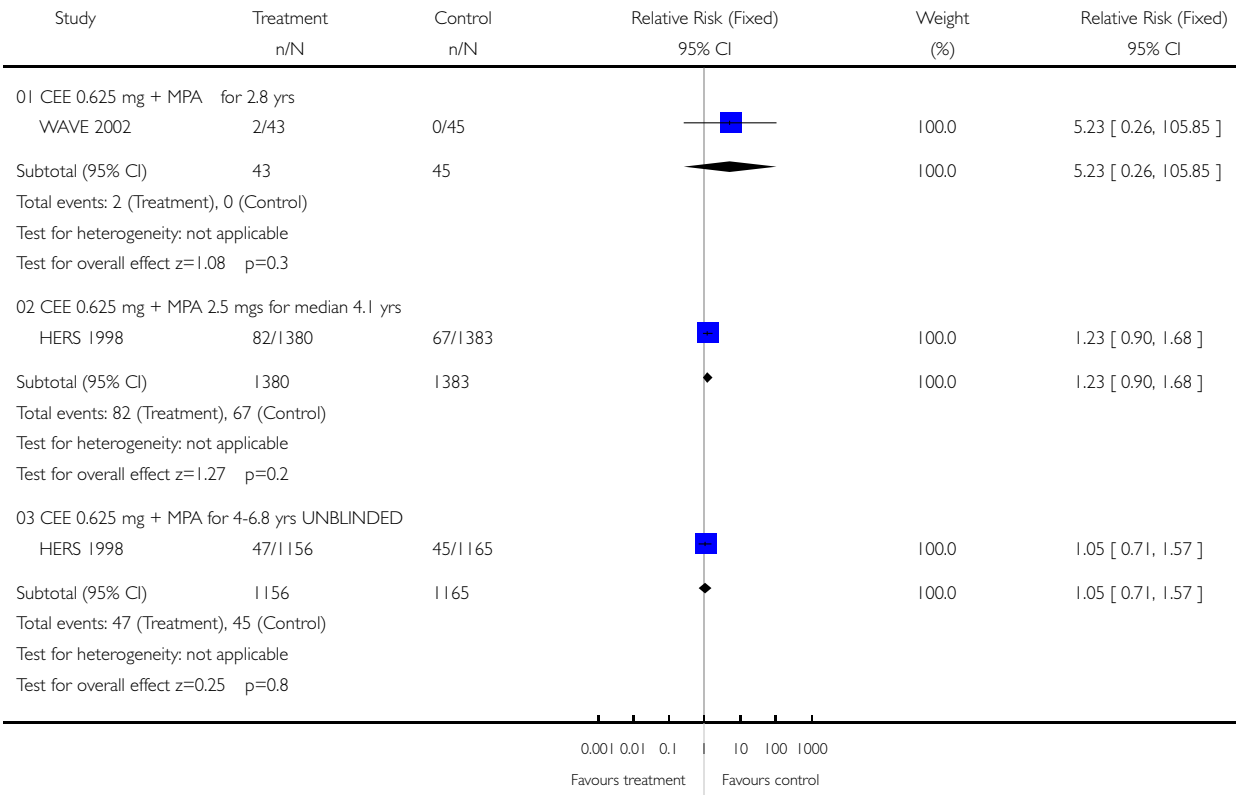


Analysis 02.18. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 18 Stroke (first or recurrent): Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 18 Stroke (first or recurrent): Combined continuous HT (moderate dose oestrogen)

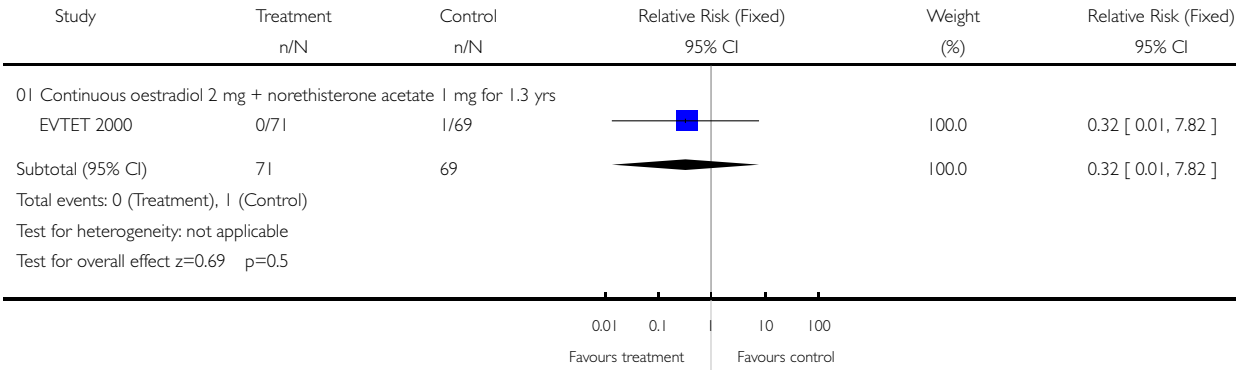


Analysis 02.19. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 19 Stroke (first or recurrent): Combined continuous HT (mod/high dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 19 Stroke (first or recurrent): Combined continuous HT (mod/high dose oestrogen)

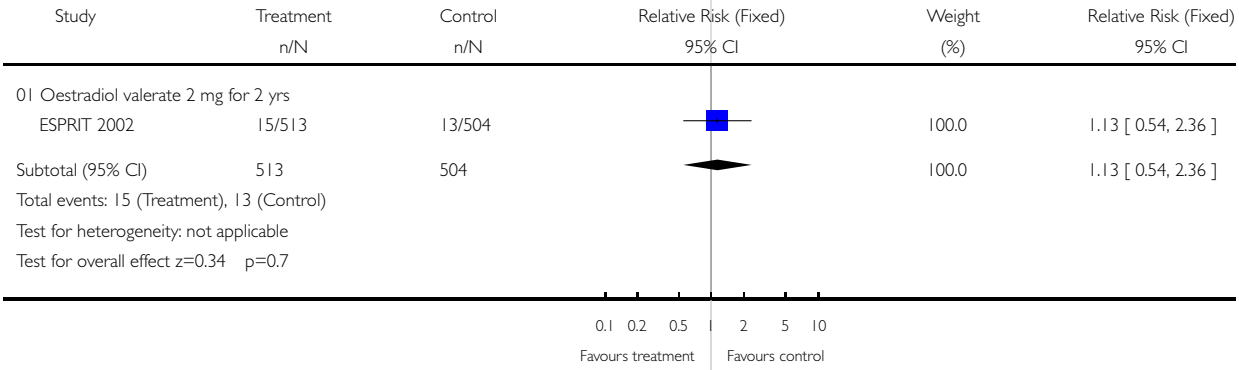


Analysis 02.20. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 20 Transient ischaemic attack: Oestrogen-only HT (mod/high dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 20 Transient ischaemic attack: Oestrogen-only HT (mod/high dose)



Analysis 02.21. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 21 Transient ischaemic attack: Oestrogen-only HT (mod dose) if no uterus, plus sequential MPA if uterus intact

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 21 Transient ischaemic attack: Oestrogen-only HT (mod dose) if no uterus, plus sequential MPA if uterus intact

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Oestradiol 1 mg daily (if no uterus) plus MPA 5mgs for 12 days a year (if uterus intact) for 2.8 yrs					
WEST 2001	30/337	25/327		100.0	1.16 [0.70, 1.94]
Subtotal (95% CI)	337	327		100.0	1.16 [0.70, 1.94]
Total events: 30 (Treatment), 25 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.59 p=0.6					

Analysis 02.22. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 22 Transient ischaemic attack: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 22 Transient ischaemic attack: Combined continuous HT (moderate dose oestrogen)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg + MPA 2.5 mg for 4 yrs					
HERS 1998	35/1380	44/1383		100.0	0.80 [0.51, 1.23]
Subtotal (95% CI)	1380	1383		100.0	0.80 [0.51, 1.23]
Total events: 35 (Treatment), 44 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.02 p=0.3					
02 CEE 0.625 mg + MPA 2.5 mg for 4-6.8 yrs UNBLINDED					
HERS 1998	17/1156	18/1165		100.0	0.95 [0.49, 1.84]
Subtotal (95% CI)	1156	1165		100.0	0.95 [0.49, 1.84]
Total events: 17 (Treatment), 18 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.15 p=0.9					

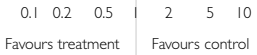
Analysis 02.23. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 23 Stroke or transient ischaemic attack: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 23 Stroke or transient ischaemic attack: Combined continuous HT (moderate dose oestrogen)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg + MPA 2.5 mg for 3.2 yrs					
ERA 2000	6/104	6/105		100.0	1.01 [0.34, 3.03]
Total (95% CI)	104	105		100.0	1.01 [0.34, 3.03]
Total events: 6 (Treatment), 6 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.02 p=1					



Analysis 02.24. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 24 Stroke or transient ischaemic attack : Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 24 Stroke or transient ischaemic attack : Oestrogen-only HT (moderate dose)

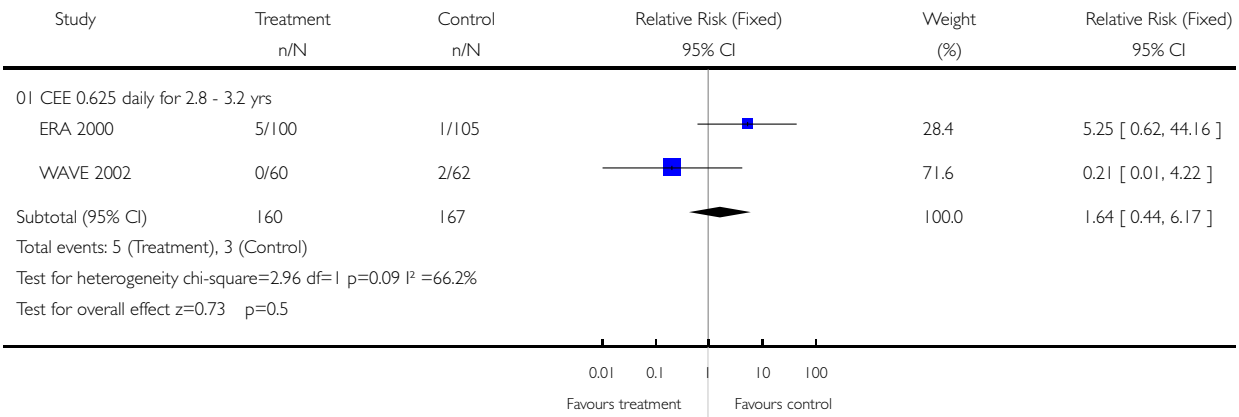
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 daily for 3.2 yrs					
ERA 2000	5/100	6/105		100.0	0.88 [0.28, 2.78]
Total (95% CI)	100	105		100.0	0.88 [0.28, 2.78]
Total events: 5 (Treatment), 6 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.23 p=0.8					

Analysis 02.25. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 25 VTE (first or recurrent PE or DVT): Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 25 VTE (first or recurrent PE or DVT): Oestrogen-only HT (moderate dose)

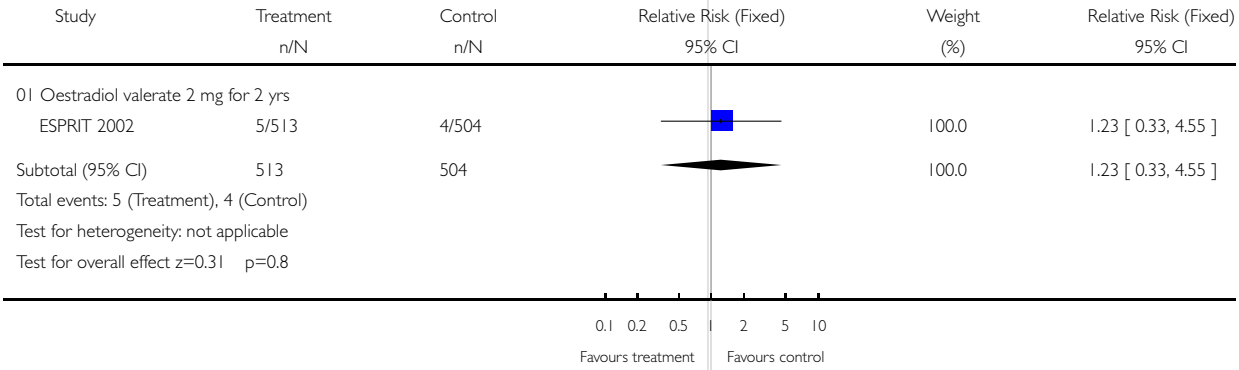


Analysis 02.26. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 26 VTE (first or recurrent PE or DVT): Oestrogen-only HT (mod/high dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 26 VTE (first or recurrent PE or DVT): Oestrogen-only HT (mod/high dose)

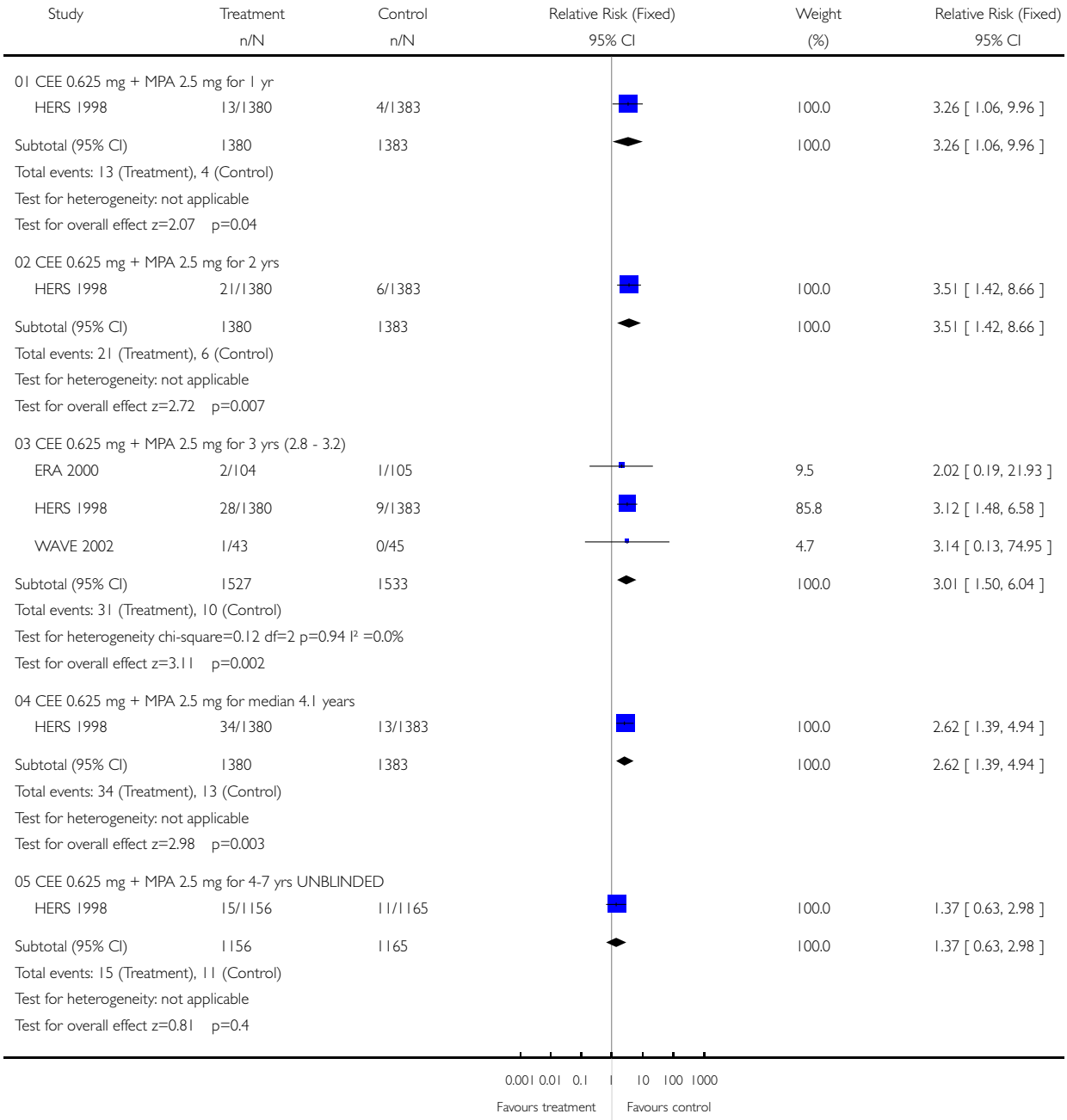


Analysis 02.27. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 27 VTE (first or recurrent PE or DVT): Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 27 VTE (first or recurrent PE or DVT): Combined continuous HT (moderate dose oestrogen)



Analysis 02.28. Comparison 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL), Outcome 28 VTE (first or recurrent PE or DVT): Combined continuous HT (mod/high dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 02 Women with cardiovascular disease (Selected outcomes: death, CVD, cognition, QOL)

Outcome: 28 VTE (first or recurrent PE or DVT): Combined continuous HT (mod/high dose oestrogen)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Continuous oestradiol 2 mg + norethisterone acetate 1 mg for 1.3 yrs					
EVTET 2000	7/71	1/69		100.0	6.80 [0.86, 53.85]
Subtotal (95% CI)	71	69		100.0	6.80 [0.86, 53.85]
Total events: 7 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.82 p=0.07					

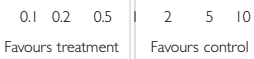
Analysis 03.01. Comparison 03 Women hospitalised with chronic illness (Selected outcomes: death, CVD, VTE), Outcome 01 All cause death: Combined sequential HRT (high dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 03 Women hospitalised with chronic illness (Selected outcomes: death, CVD, VTE)

Outcome: 01 All cause death: Combined sequential HRT (high dose oestrogen)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 2.5 mg daily + MPA 10 mg for 7 days each cycle					
Nachtigall 1979	3/84	7/84		100.0	0.43 [0.11, 1.60]
Total (95% CI)	84	84		100.0	0.43 [0.11, 1.60]
Total events: 3 (Treatment), 7 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.26 p=0.2					

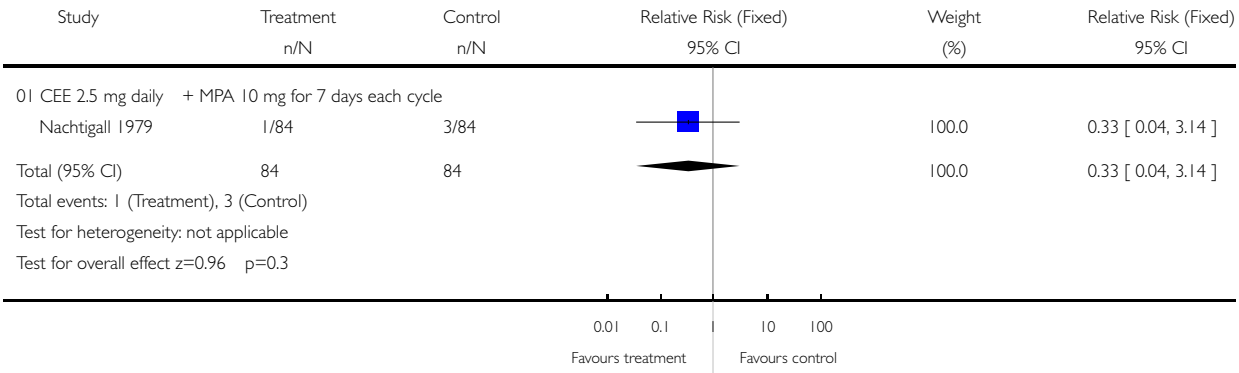


Analysis 03.02. Comparison 03 Women hospitalised with chronic illness (Selected outcomes: death, CVD, VTE), Outcome 02 Myocardial infarction: Combined sequential HRT (high dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 03 Women hospitalised with chronic illness (Selected outcomes: death, CVD, VTE)

Outcome: 02 Myocardial infarction: Combined sequential HRT (high dose oestrogen)

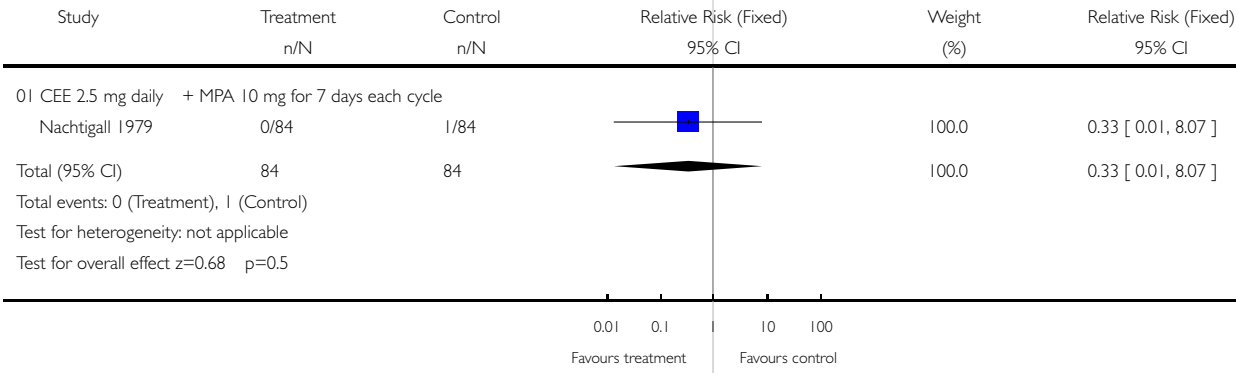


Analysis 03.03. Comparison 03 Women hospitalised with chronic illness (Selected outcomes: death, CVD, VTE), Outcome 03 Venous thrombo-embolism (DVT or PE): Combined sequential HRT (high dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 03 Women hospitalised with chronic illness (Selected outcomes: death, CVD, VTE)

Outcome: 03 Venous thrombo-embolism (DVT or PE): Combined sequential HRT (high dose oestrogen)

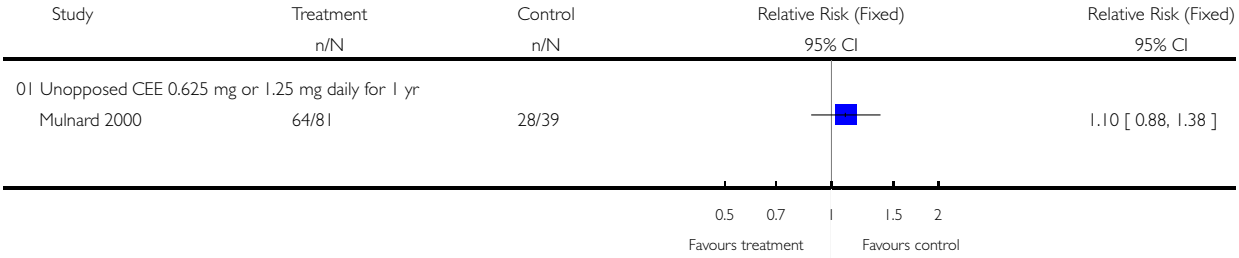


Analysis 04.01. Comparison 04 Women with dementia, Outcome 01 Worsening of dementia on treatment (by ADCS-CGIC score): Oestrogen-only HRT (mod and high dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 04 Women with dementia

Outcome: 01 Worsening of dementia on treatment (by ADCS-CGIC score): Oestrogen-only HRT (mod and high dose)

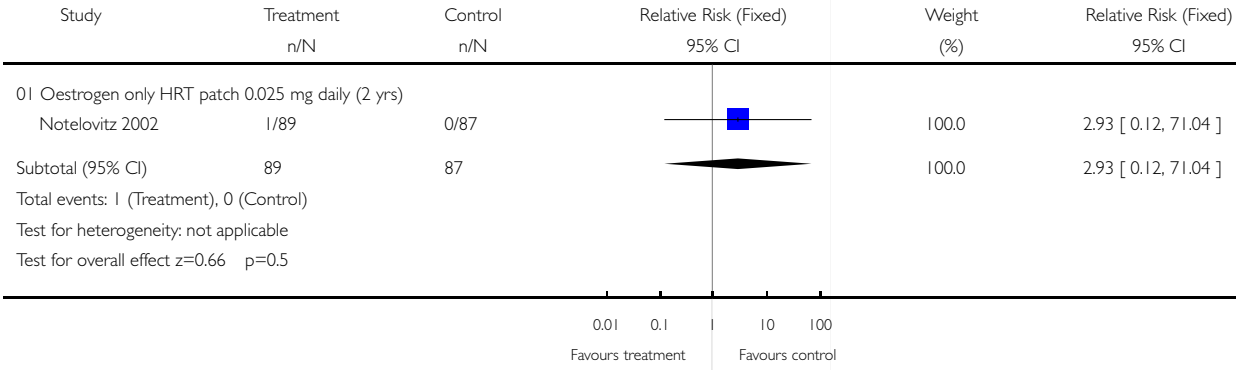


Analysis 05.01. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 01 Breast cancer: Oestrogen-only HT (low dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 01 Breast cancer: Oestrogen-only HT (low dose)



Analysis 05.02. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 02 Breast cancer: Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 02 Breast cancer: Oestrogen-only HT (moderate dose)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Oestradiol 1mg for 2 yrs					
EPAT 2001	0/111	1/111		100.0	0.33 [0.01, 8.10]
Subtotal (95% CI)	111	111		100.0	0.33 [0.01, 8.10]
Total events: 0 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					
02 CEE 0.625 for 2.8 - 3.2 yrs					
ERA 2000	1/100	0/105		24.6	3.15 [0.13, 76.39]
PEPI 1995	1/175	1/174		50.6	0.99 [0.06, 15.77]
WAVE 2002	1/60	0/62		24.8	3.10 [0.13, 74.59]
Subtotal (95% CI)	335	341		100.0	2.05 [0.38, 11.04]
Total events: 3 (Treatment), 1 (Control)					
Test for heterogeneity chi-square=0.40 df=2 p=0.82 I^2 =0.0%					
Test for overall effect z=0.83 p=0.4					
03 CEE 0.625 mg for 6.8 yrs					
WHI 1998	94/5310	124/5429		100.0	0.78 [0.59, 1.01]
Subtotal (95% CI)	5310	5429		100.0	0.78 [0.59, 1.01]
Total events: 94 (Treatment), 124 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.88 p=0.06					

Analysis 05.03. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 03 Breast cancer: Oestrogen-only HT (mod/high dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 03 Breast cancer: Oestrogen-only HT (mod/high dose)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Oestradiol patch 0.075mg for 2 yrs					
Notelovitz 2002	1/89	0/87		100.0	2.93 [0.12, 71.04]
Subtotal (95% CI)	89	87		100.0	2.93 [0.12, 71.04]
Total events: 1 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.66 p=0.5					
02 Oestradiol valerate 2 mg for 2 yrs					
ESPRIT 2002	4/513	4/504		100.0	0.98 [0.25, 3.91]
Subtotal (95% CI)	513	504		100.0	0.98 [0.25, 3.91]
Total events: 4 (Treatment), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.03 p=1					

Analysis 05.04. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 04 Breast cancer: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 04 Breast cancer: Combined continuous HT (moderate dose oestrogen)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg + MPA 2.5 mg for 1 yr					
WHI 1998	12/8506	19/8102		100.0	0.60 [0.29, 1.24]
Subtotal (95% CI)	8506	8102		100.0	0.60 [0.29, 1.24]
Total events: 12 (Treatment), 19 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.38 p=0.2					
02 CEE 0.625 mg + MPA 2.5 mg for 2 yrs					
WHI 1998	38/8506	51/8102		100.0	0.71 [0.47, 1.08]
Subtotal (95% CI)	8506	8102		100.0	0.71 [0.47, 1.08]
Total events: 38 (Treatment), 51 (Control)					
Test for heterogeneity: not applicable					

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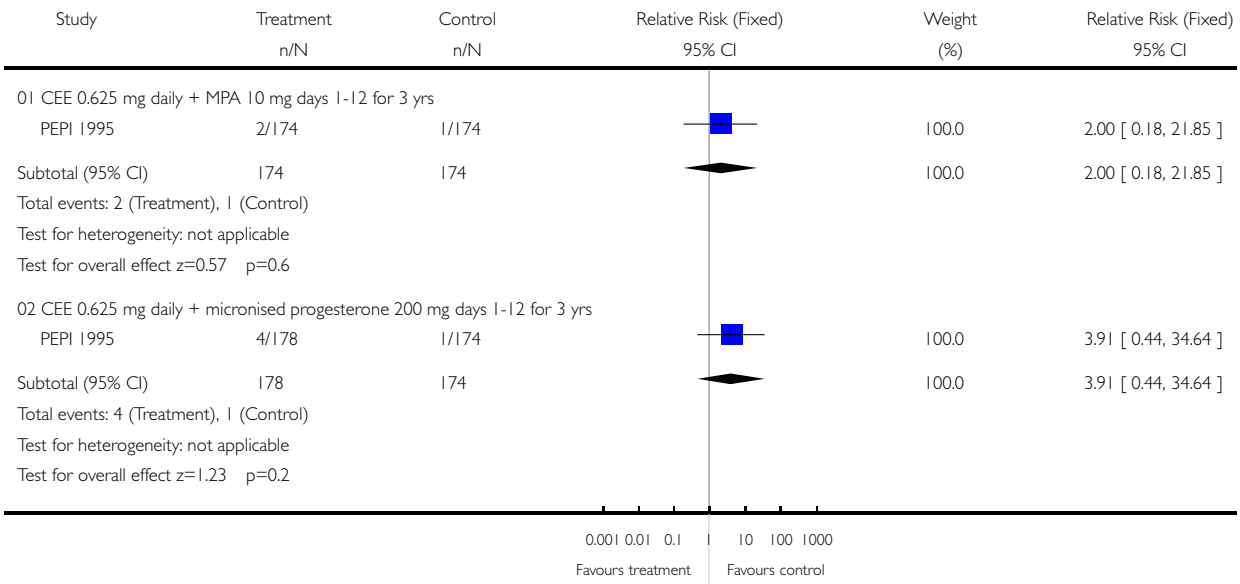
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=1.60 p=0.1					
03 CEE 0.625 mg + MPA 2.5 mg for 2.8 - 3.2 yrs					
PEPI 1995	0/174	1/174		2.0	0.33 [0.01, 8.13]
WHI 1998	65/8506	70/8102		98.0	0.88 [0.63, 1.24]
Subtotal (95% CI)	8680	8276		100.0	0.87 [0.63, 1.22]
Total events: 65 (Treatment), 71 (Control)					
Test for heterogeneity chi-square=0.35 df=1 p=0.55 I^2 =0.0%					
Test for overall effect z=0.80 p=0.4					
04 CEE 0.625 mg + MPA 2.5 mg for 4 yrs					
HERS 1998	34/1380	25/1383		100.0	1.36 [0.82, 2.27]
Subtotal (95% CI)	1380	1383		100.0	1.36 [0.82, 2.27]
Total events: 34 (Treatment), 25 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.19 p=0.2					
05 CEE 0.625 mg + MPA 2.5 mg for mean 5.6 yrs					
WHI 1998	199/8506	150/8102		100.0	1.26 [1.02, 1.56]
Subtotal (95% CI)	8506	8102		100.0	1.26 [1.02, 1.56]
Total events: 199 (Treatment), 150 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.19 p=0.03					
06 CEE 0.625 mg + MPA 2.5 mg for 4-7 yrs UNBLINDED					
HERS 1998	15/1156	14/1165		100.0	1.08 [0.52, 2.23]
Subtotal (95% CI)	1156	1165		100.0	1.08 [0.52, 2.23]
Total events: 15 (Treatment), 14 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.21 p=0.8					

Analysis 05.05. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 05 Breast cancer: Combined sequential HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 05 Breast cancer: Combined sequential HT (moderate dose oestrogen)

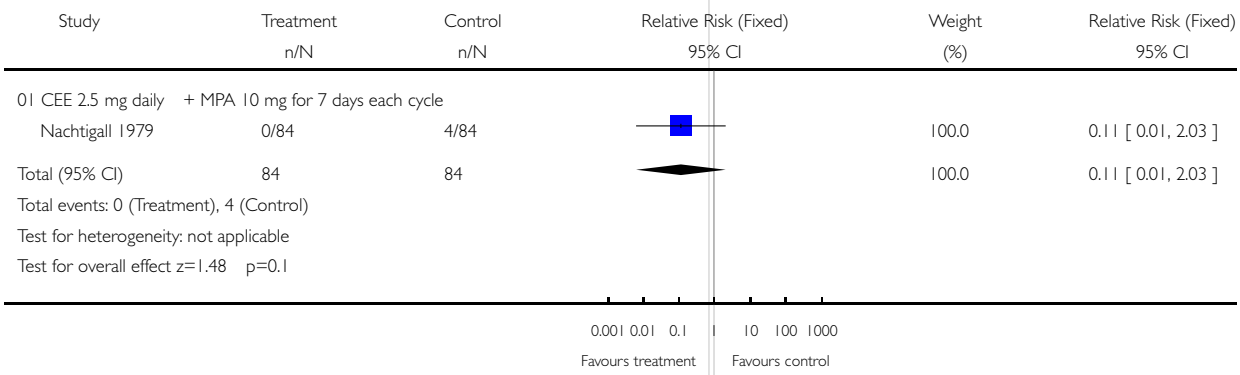


Analysis 05.06. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 06 Breast cancer: Combined sequential HT (high dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 06 Breast cancer: Combined sequential HT (high dose oestrogen)

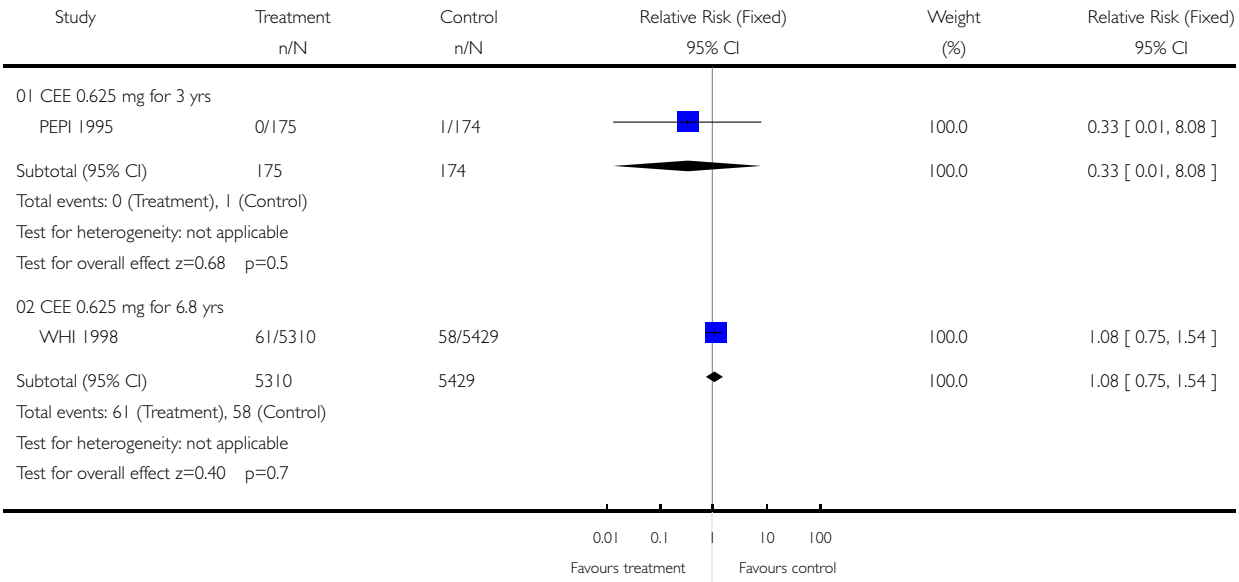


Analysis 05.07. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 07 Colorectal cancer: Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 07 Colorectal cancer: Oestrogen-only HT (moderate dose)

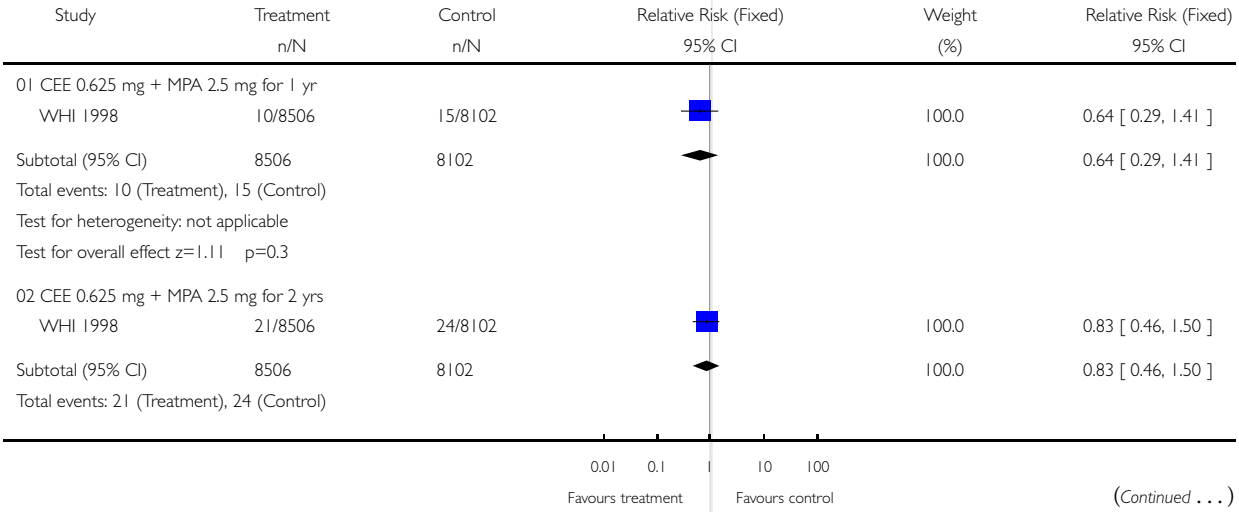


Analysis 05.08. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 08 Colorectal cancer: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 08 Colorectal cancer: Combined continuous HT (moderate dose oestrogen)



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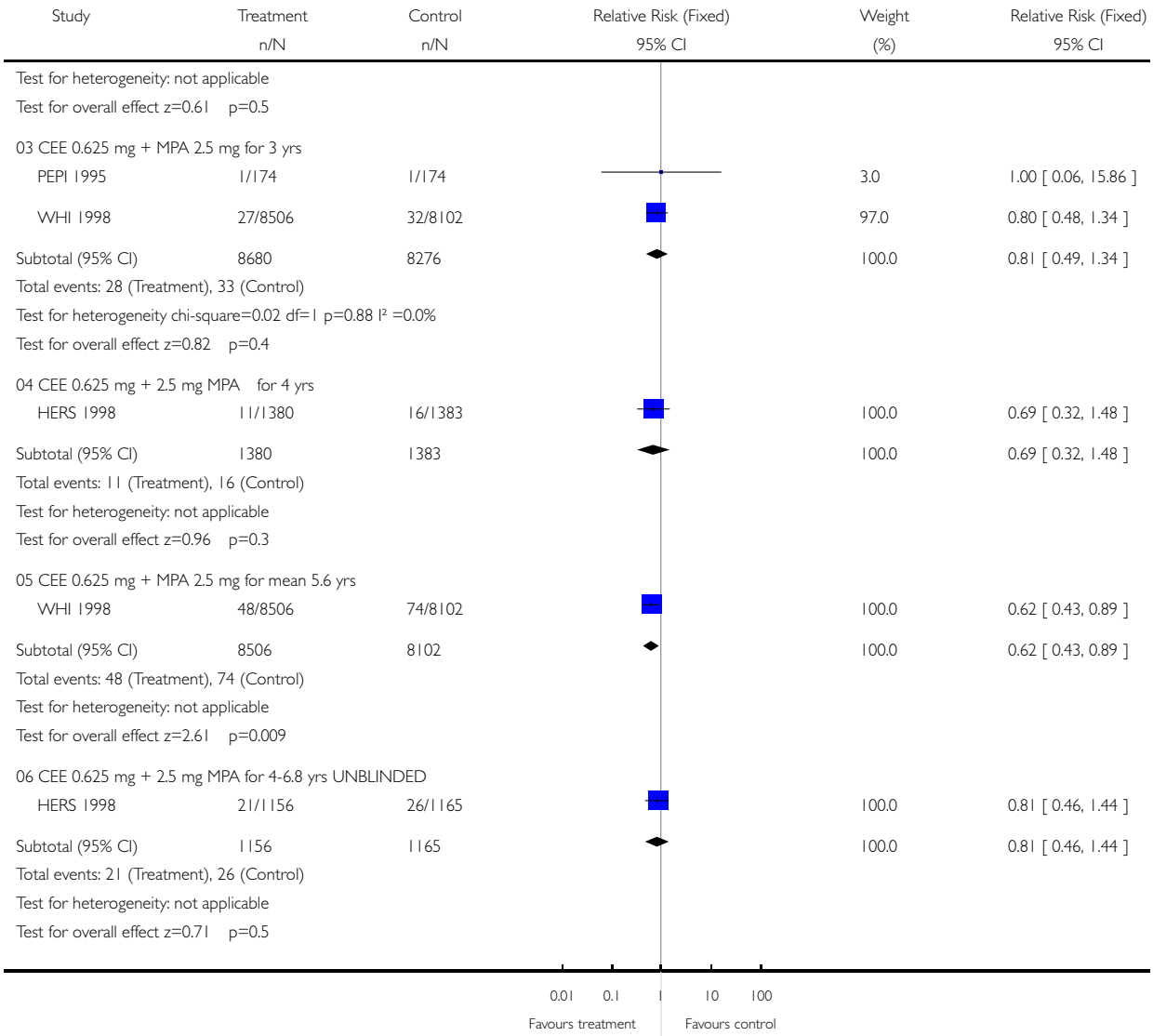
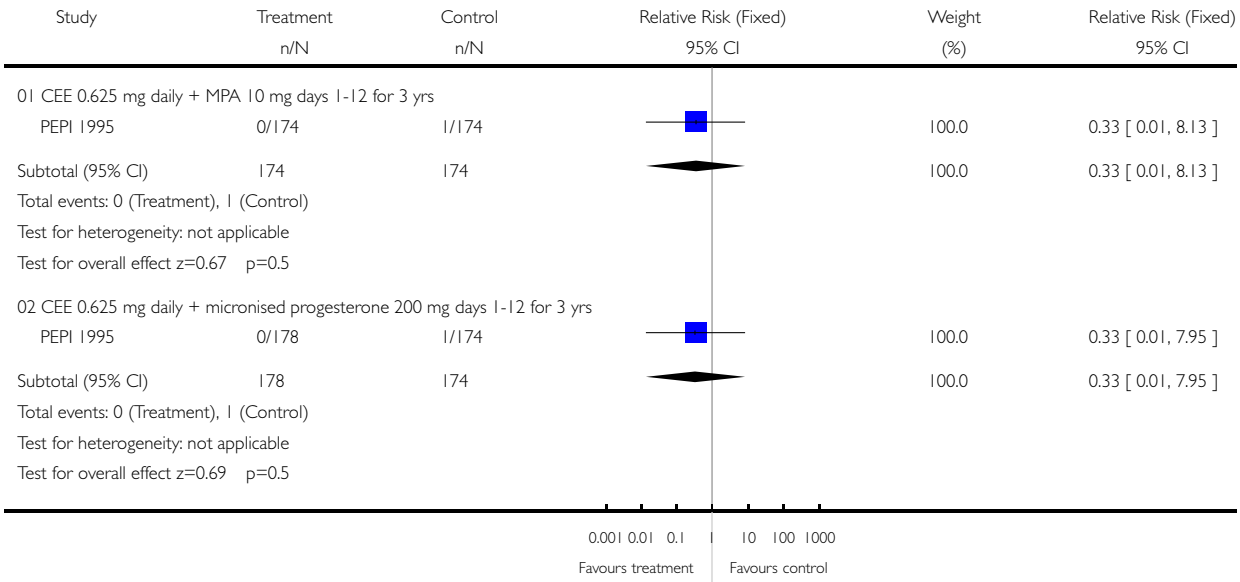


Analysis 05.09. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 09 Colorectal cancer: Combined sequential HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 09 Colorectal cancer: Combined sequential HT (moderate dose oestrogen)

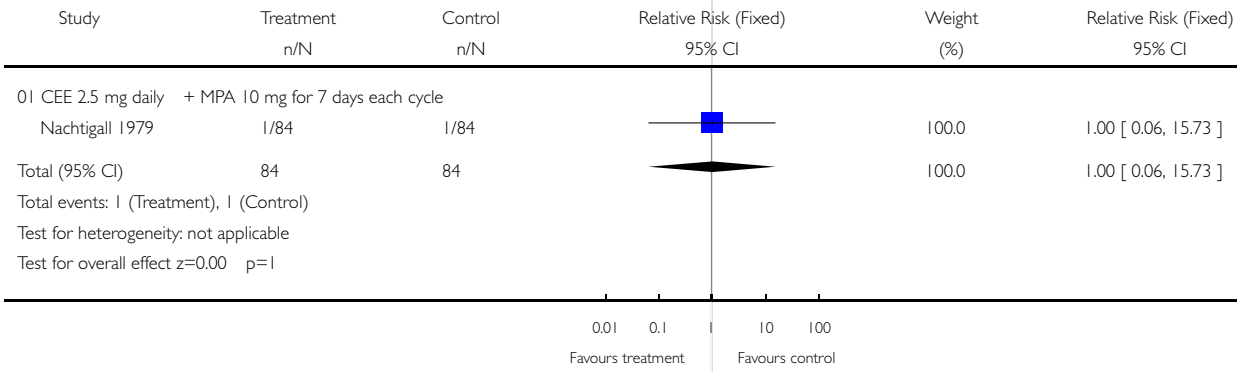


Analysis 05.10. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 10 Colorectal cancer: Combined sequential HT (high dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 10 Colorectal cancer: Combined sequential HT (high dose oestrogen)

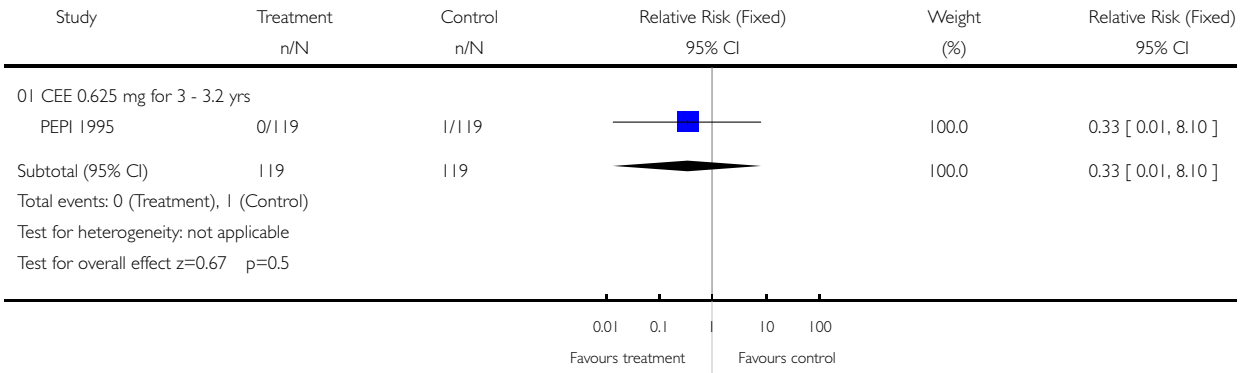


Analysis 05.11. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 11 Endometrial cancer: Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 11 Endometrial cancer: Oestrogen-only HT (moderate dose)

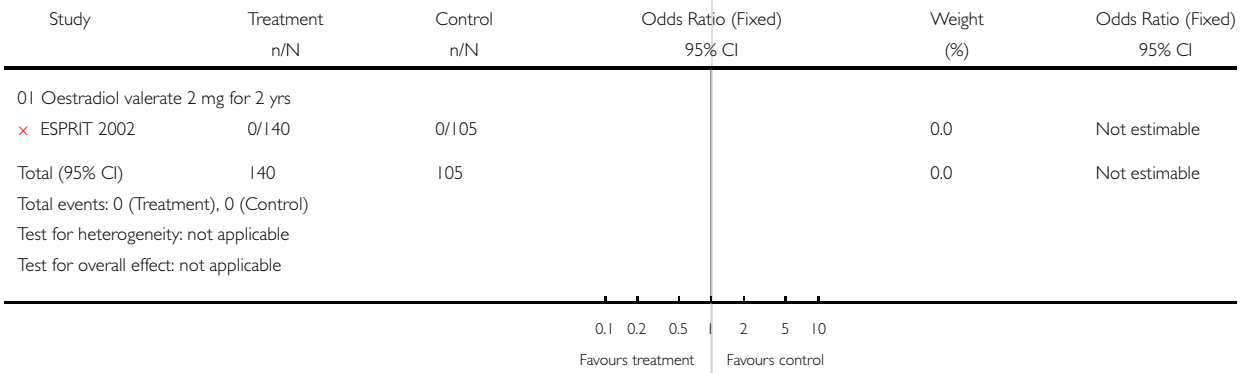


Analysis 05.12. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 12 Endometrial cancer: Oestrogen only HT (mod/high dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 12 Endometrial cancer: Oestrogen only HT (mod/high dose)

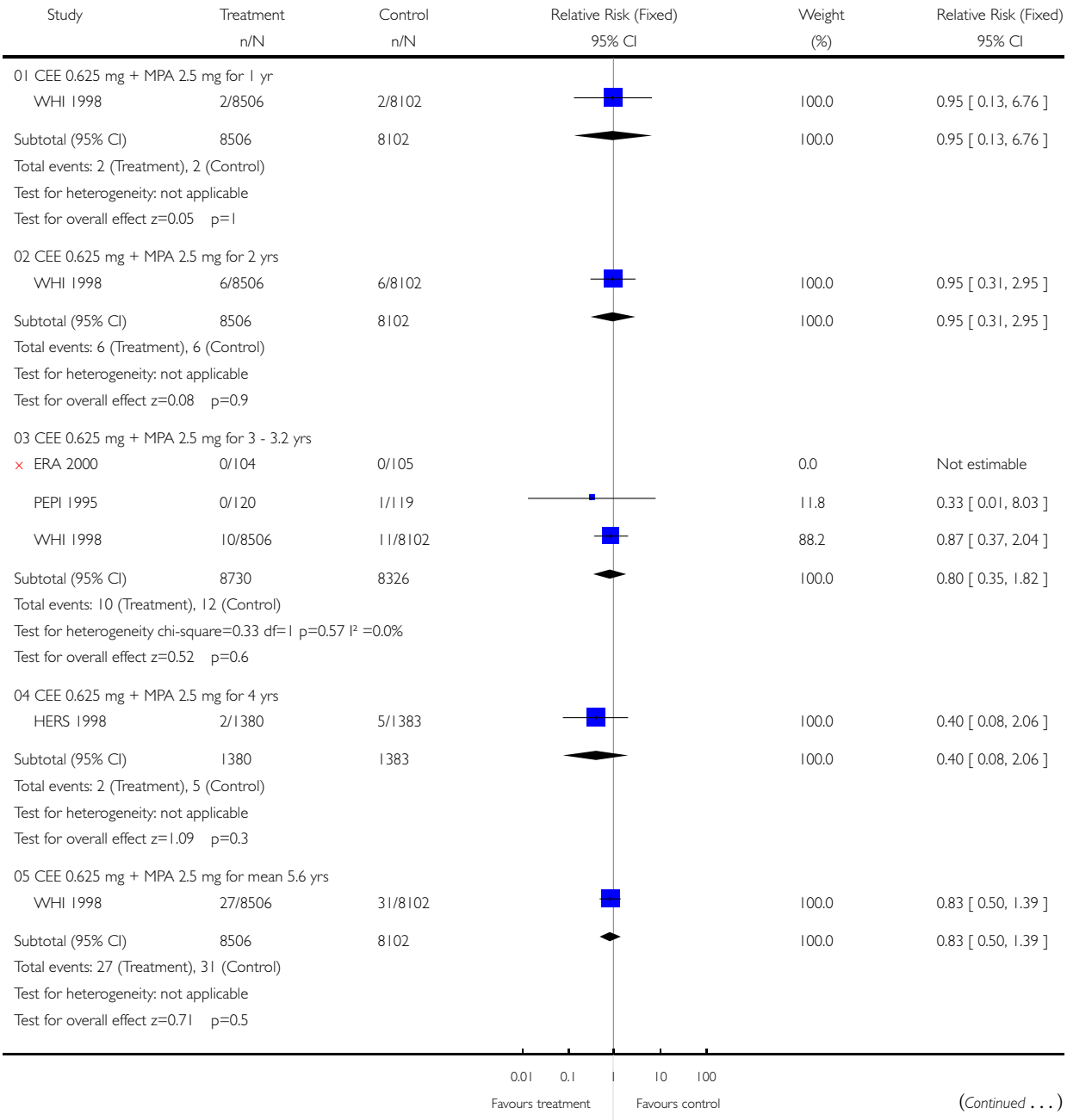


Analysis 05.13. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 13 Endometrial cancer: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 13 Endometrial cancer: Combined continuous HT (moderate dose oestrogen)



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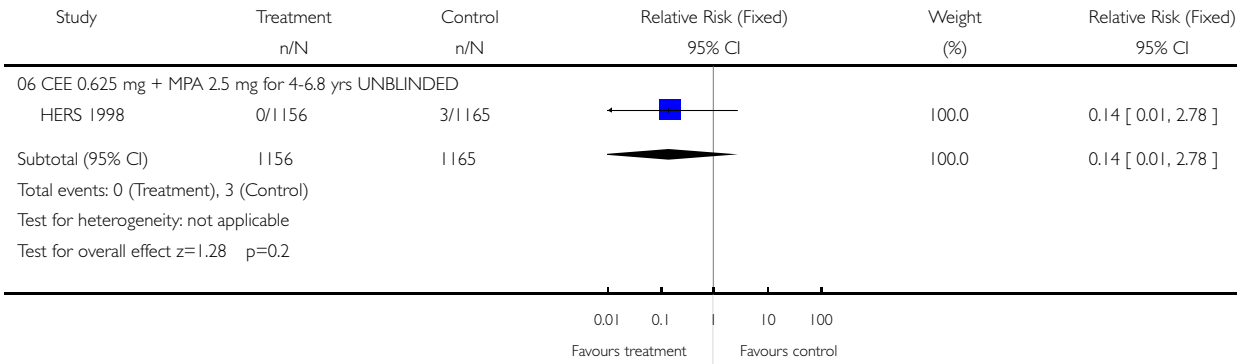
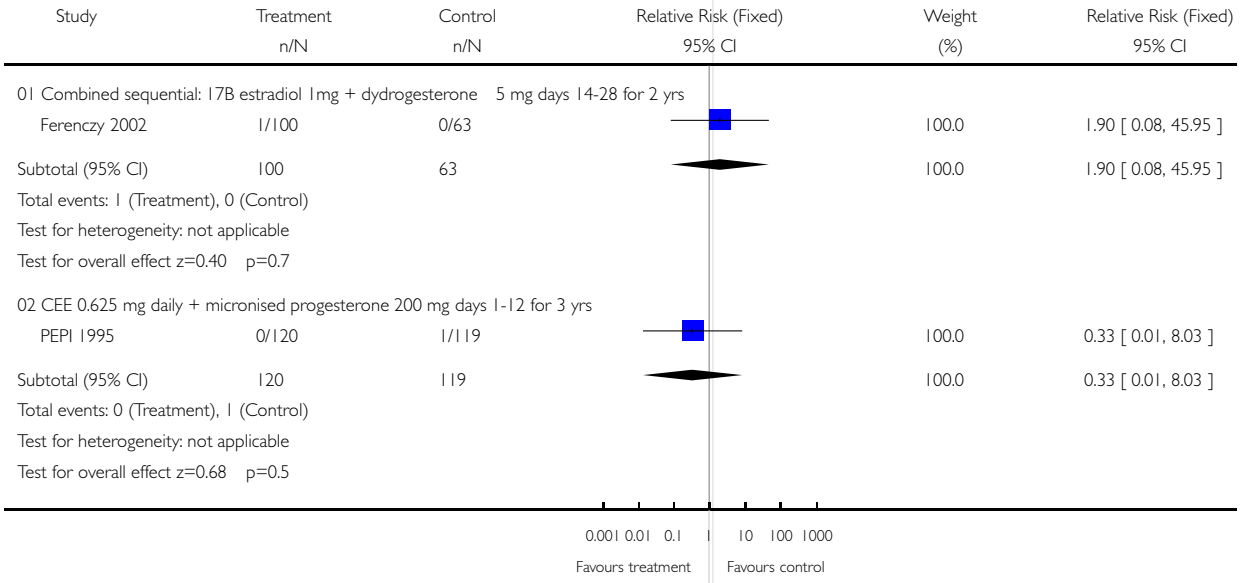


Analysis 05.14. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 14 Endometrial cancer: Combined sequential HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 14 Endometrial cancer: Combined sequential HT (moderate dose oestrogen)

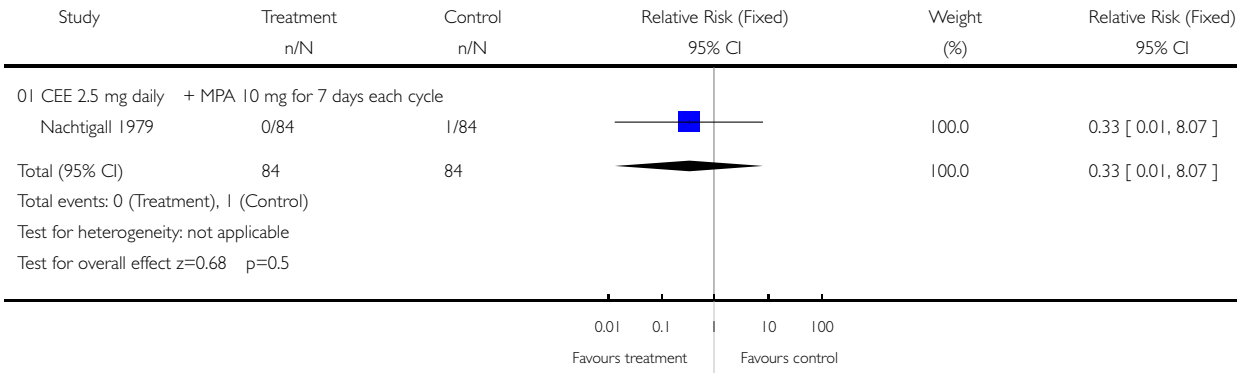


Analysis 05.15. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 15 Endometrial cancer: Combined sequential HT (high dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 15 Endometrial cancer: Combined sequential HT (high dose oestrogen)

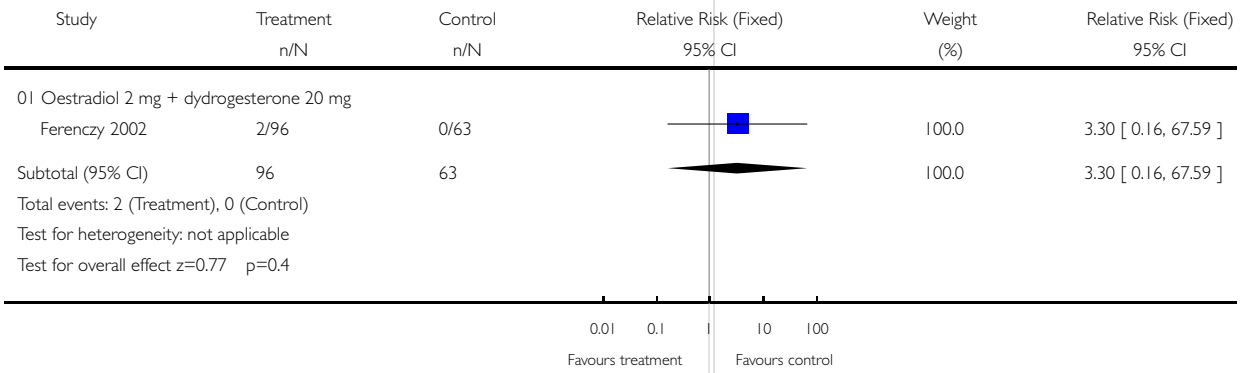


Analysis 05.16. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 16 Endometrial cancer: Combined sequential HT (mod/high dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 16 Endometrial cancer: Combined sequential HT (mod/high dose oestrogen)

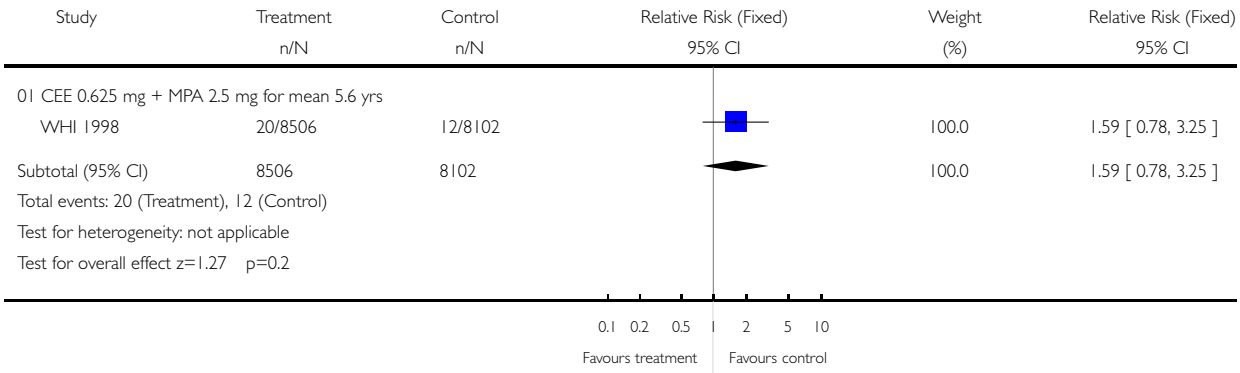


Analysis 05.17. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 17 Ovarian cancer: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 17 Ovarian cancer: Combined continuous HT (moderate dose oestrogen)

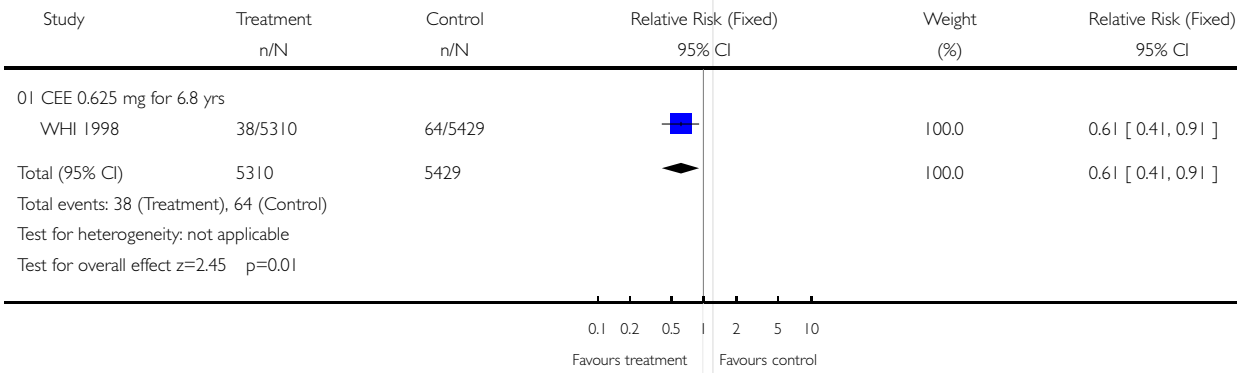


Analysis 05.18. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 18 Hip fractures: Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 18 Hip fractures: Oestrogen-only HT (moderate dose)

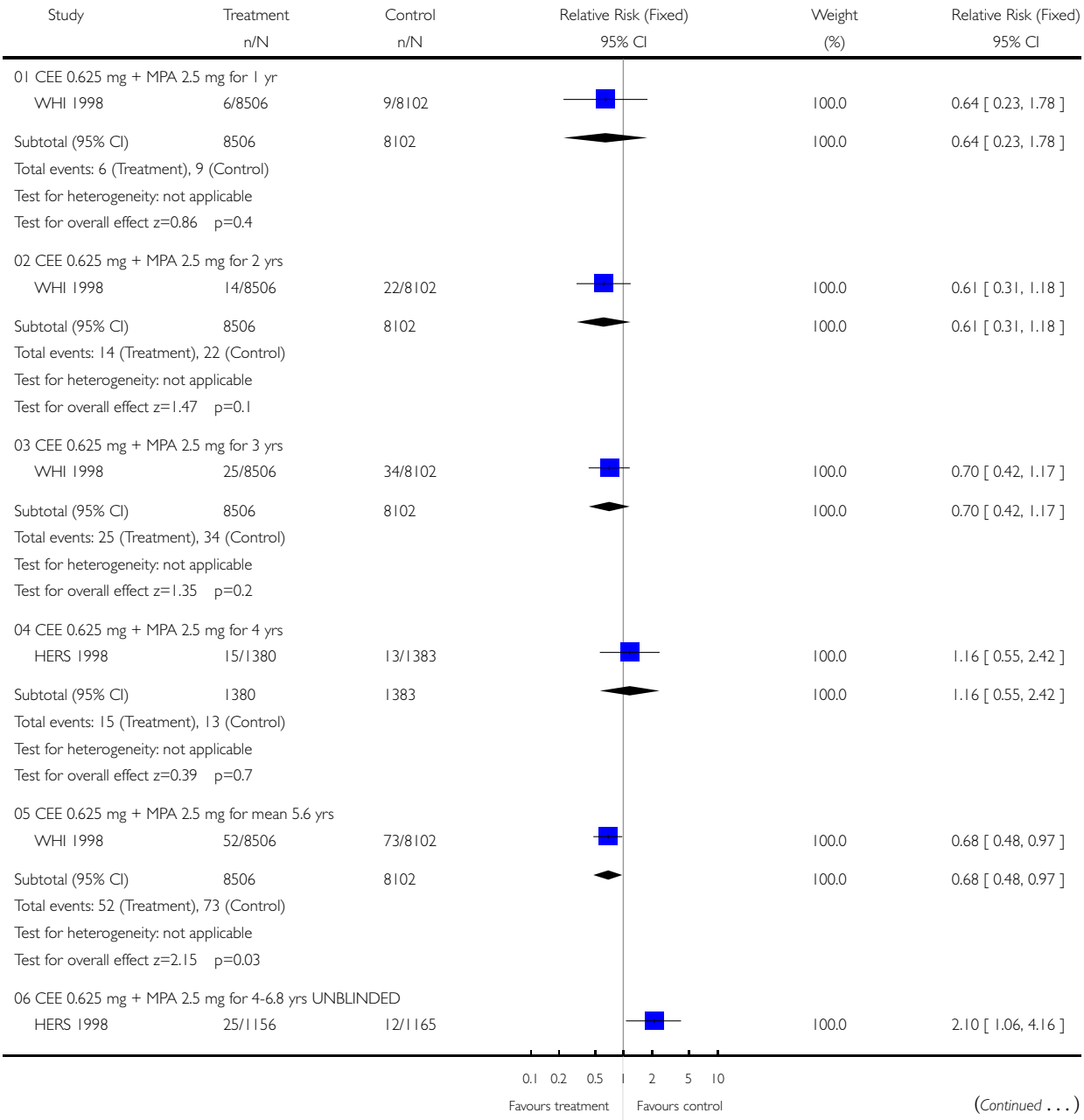


Analysis 05.19. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 19 Hip fractures: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 19 Hip fractures: Combined continuous HT (moderate dose oestrogen)



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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	1156	1165		100.0	2.10 [1.06, 4.16]
Total events: 25 (Treatment), 12 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.13 p=0.03					

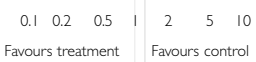
Analysis 05.20. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 20 Vertebral fractures: Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 20 Vertebral fractures: Oestrogen-only HT (moderate dose)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg for 6.8 yrs					
WHI 1998	39/5310	64/5429		100.0	0.62 [0.42, 0.93]
Total (95% CI)	5310	5429		100.0	0.62 [0.42, 0.93]
Total events: 39 (Treatment), 64 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.34 p=0.02					

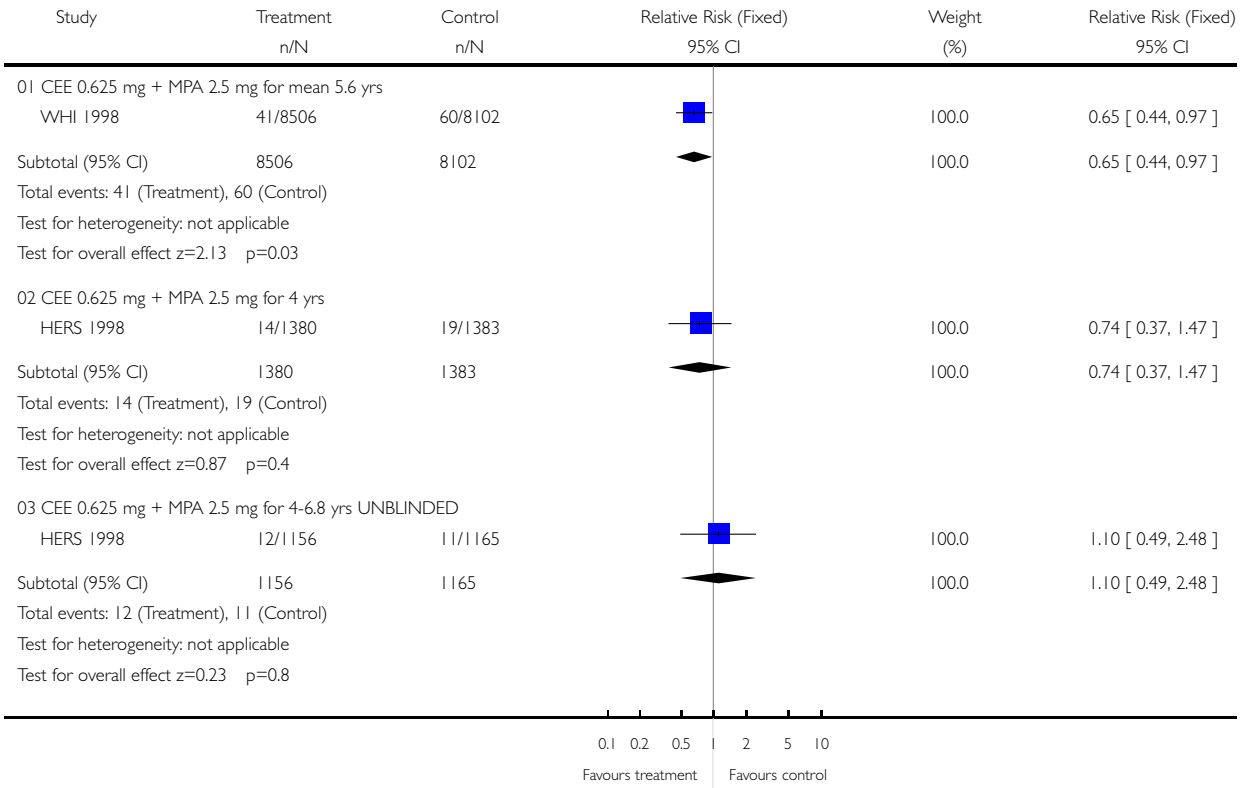


Analysis 05.21. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 21 Vertebral fractures: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 21 Vertebral fractures: Combined continuous HT (moderate dose oestrogen)

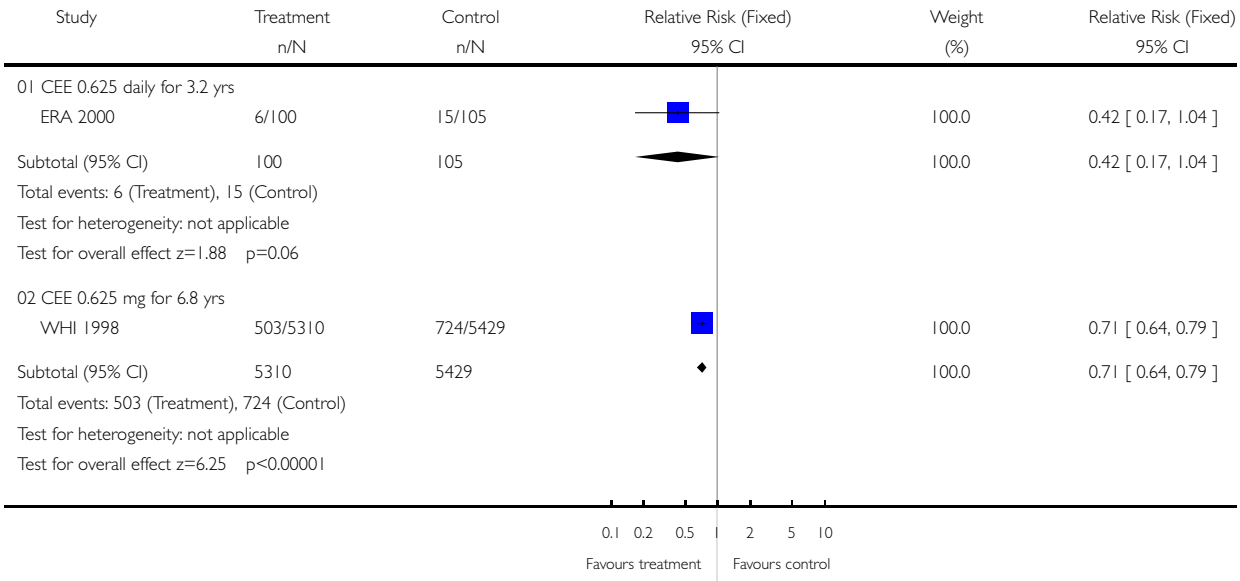


Analysis 05.22. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 22 All clinical fractures: Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 22 All clinical fractures: Oestrogen-only HT (moderate dose)

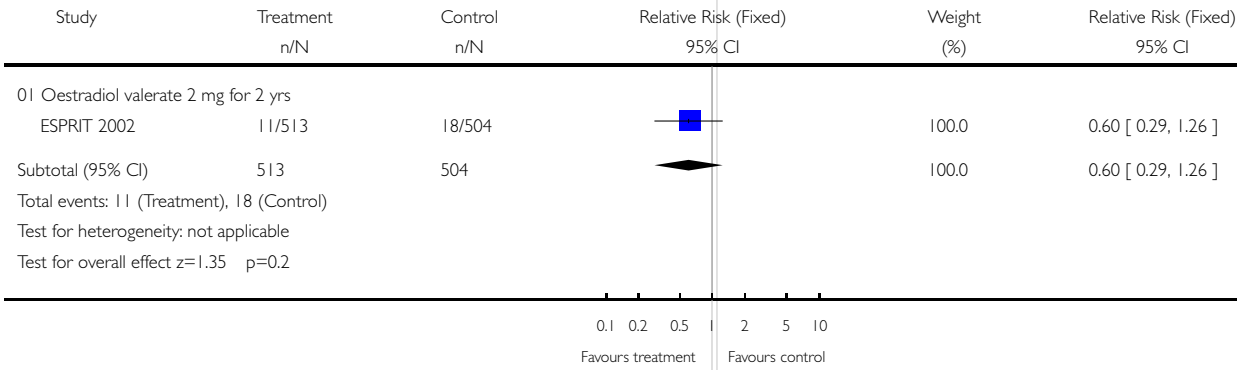


Analysis 05.23. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 23 All clinical fractures: Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 23 All clinical fractures: Oestrogen-only HT (moderate dose)

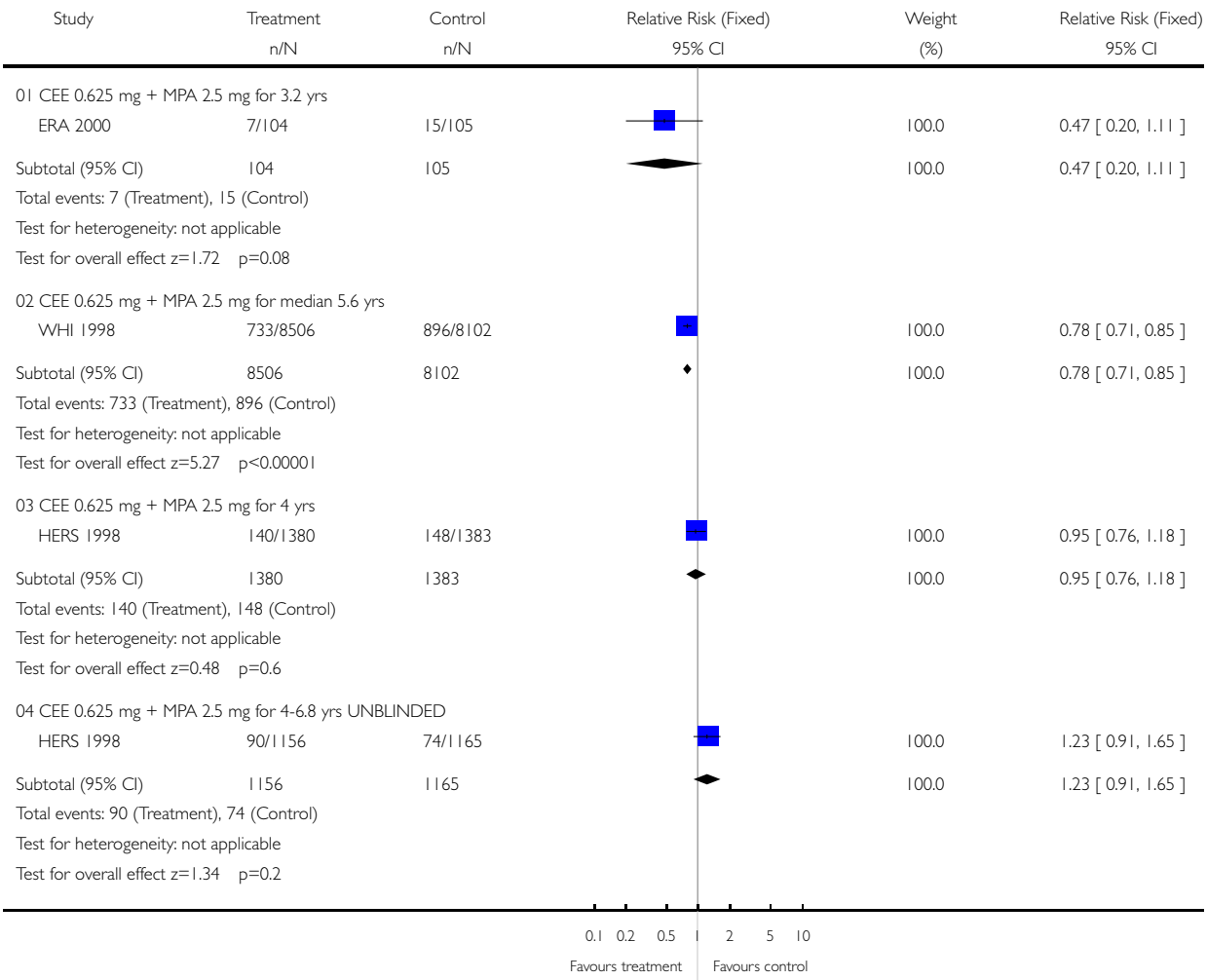


Analysis 05.24. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 24 All clinical fractures: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 24 All clinical fractures: Combined continuous HT (moderate dose oestrogen)



Analysis 05.25. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 25 Gallbladder disease requiring surgery: Oestrogen-only HT (moderate dose)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 25 Gallbladder disease requiring surgery: Oestrogen-only HT (moderate dose)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg for 3 - 3.2 yrs					
ERA 2000	2/100	2/105		1.7	1.05 [0.15, 7.31]
PEPI 1995	1/175	2/174		1.7	0.50 [0.05, 5.43]
Subtotal (95% CI)	275	279		3.4	0.77 [0.17, 3.39]
Total events: 3 (Treatment), 4 (Control)					
Test for heterogeneity chi-square=0.23 df=1 p=0.63 I^2 =0.0%					
Test for overall effect z=0.35 p=0.7					
02 CEE O.625 mg for 7.1 yrs					
WHI 1998	197/4141	113/4235		96.6	1.78 [1.42, 2.24]
Subtotal (95% CI)	4141	4235		96.6	1.78 [1.42, 2.24]
Total events: 197 (Treatment), 113 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.99 p<0.00001					
Total (95% CI)	4416	4514		100.0	1.75 [1.40, 2.19]
Total events: 200 (Treatment), 117 (Control)					
Test for heterogeneity chi-square=1.36 df=2 p=0.51 I^2 =0.0%					
Test for overall effect z=4.88 p<0.00001					

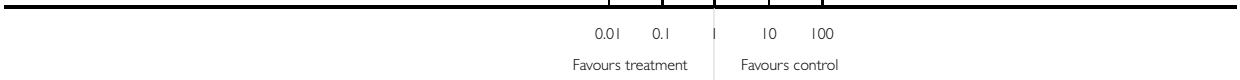
Analysis 05.26. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 26 Gallbladder disease requiring surgery: Combined continuous HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 26 Gallbladder disease requiring surgery: Combined continuous HT (moderate dose oestrogen)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 CEE 0.625 mg + 2.5 mg MPA for 3 yrs					
ERA 2000	4/104	2/105		49.9	2.02 [0.38, 10.79]
PEPI 1995	4/174	2/174		50.1	2.00 [0.37, 10.78]
Subtotal (95% CI)	278	279		100.0	2.01 [0.61, 6.59]
Total events: 8 (Treatment), 4 (Control)					
Test for heterogeneity chi-square=0.00 df=1 p=0.99 I^2 =0.0%					
Test for overall effect z=1.15 p=0.2					
02 CEE 0.625 mg + 2.5 mg MPA for 4 yrs					
HERS 1998	85/1135	62/1118		100.0	1.35 [0.98, 1.85]
Subtotal (95% CI)	1135	1118		100.0	1.35 [0.98, 1.85]
Total events: 85 (Treatment), 62 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.86 p=0.06					
03 CEE 0.625 mg + 2.5 mg MPA for 5.6 yrs					
WHI 1998	196/7308	113/6895		100.0	1.64 [1.30, 2.06]
Subtotal (95% CI)	7308	6895		100.0	1.64 [1.30, 2.06]
Total events: 196 (Treatment), 113 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.21 p=0.00003					



Analysis 05.27. Comparison 05 All women (Selected outcomes: cancer, cholecystic disease, fractures), Outcome 27 Gallbladder disease requiring surgery: Combined sequential HT (moderate dose oestrogen)

Review: Long term hormone therapy for perimenopausal and postmenopausal women

Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)

Outcome: 27 Gallbladder disease requiring surgery: Combined sequential HT (moderate dose oestrogen)