National Institute for Health and Care Excellence

Draft for consultation

Menopause (update)

[H] All-cause mortality

NICE guideline number tbc

Evidence reviews underpinning the first two bullet points of recommendation 1.6.1

November 2023

Draft for consultation

These evidence reviews were developed by NICE

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ISBN:

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All-cause mortality

Review question

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

Introduction

Hormone replacement therapy is an option available to treat menopausal symptoms. There is uncertainty surrounding the effects of taking hormone replacement therapy on risks of various conditions, and subsequently all-cause mortality. This review aims to investigate the effects, if any, on taking hormone replacement therapy and the incidence of all-cause mortality.

Summary of the protocol

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

Table 1: Summary of the protocol (PICO table)

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

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

Comparison	• Placebo • No HRT
Outcome	**Critical** • All-cause mortality **Important** • None

HRT: Hormone replacement therapy.

For further details see the review protocol in Appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document (Supplement 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Six publications were included for this review: four randomised controlled trials (RCTs) (Chlebowski 2017, Mulnard 2000, Os 2000; PEPI 1995) and two systematic reviews of RCTs (Kim 2020 and Nudy 2019).

For the systematic reviews, individual RCT data which matched the protocol was extracted and meta-analysed (see Appendix E). The individual RCTs incorporated from the systematic reviews are listed below:

- From Kim 2020 data from 11 RCTs were individually extracted: Cherry 2014, Collins 2006, Herrington 2000, Hulley 2002, Hodis 2003, Hodis 2016, Manson 2017, Tierney 2009, Veerus 2006, Vickers 2007, Viscoli 2001.
- From Nudy 2019 data from 11 RCTs were individually extracted: Angerer 2000, Giske 2002, Guidozzi 1999, Hall 1998, Harmann 2014, Hodis 2001, Jirapinyo 2003, Komulainen 1999, Kyllonen 1998, Nachtigall 1979, Samaras 1999.

Manson 2017 reported results from the same trial as Chlebowski 2017 however different subgroups were reported in each publication.

Combined effect estimates from the systematic review were not used as there was overlap with the RCT data from the two systematic reviews. The systematic reviews were primarily used to aid data extraction and risk of bias assessment. Therefore, effect estimates were reported separately for the individual RCTs and meta-analysed as appropriate according to the criteria set out in the protocol of this review.

The included studies are summarised in Table 2, please refer to the systematic review extraction tables in Appendix D for details of the incorporated RCTs.

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

Excluded studies

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

Summary of included studies

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

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes
Chlebowski 2017 RCT US	N=9700 post menopausal women Age at screening – years, mean (SD) White ethnicity: Oestrogen:	Oestrogen-only	Placebo	• All-cause mortality Subgroup information: Ethnicity Women's Health Initiative main results reported in Manson 2017 – subgroup

Study	Population	Intervention	Comparison	Outcomes
	64.3 (7.2) Placebo: 64.3 (7.3) Black ethnicity: Oestrogen: 61.7 (7.0) Placebo: 61.5 (7.1) No underlying health condition			analysis publication only Duration of follow-up: 7.2 years
Kim 2020 Systematic Review Australia, Canada, Denmark, Estonia, New Zealand, UK, US	Number of studies = 11 (Cherry 2014; Collins 2006; Herrington 2000; Hulley 2002; Hodis 2003; Hodis 2016; Manson 2017; Tierney 2009; Veerus 2006; Vickers 2007; Viscoli 2001) Oestrogen-only and placebo: N=21664 Oestrogen + Progesterone and placebo: N=31422 Underlying cardiovascular disease (Cherry 2014; Collins 2006; Herrington 2000; Hodis, 2003; Hulley 2002; Viscoli 2001) No underlying health conditions: (Hodis 2016; Manson 2017; Tierney 2009;	Oestrogen-only Oestrogen + Progesterone: • continuous combined)	Placebo or no HRT	• All-cause mortality Subgroup information: time since menopause; age at first use; constituent Duration of follow-up: Cherry 2014 14.1 years Collins 2006 0.7 (median) Herrington 2000 3.2 years Hulley 2002 6.8 years Hodis 2003 3.3 years Hodis 2016 7.5 years Manson 2017 18 years (median) Tierney 2009 2 years Veerus 2006 3.43 years Vickers 2007 1.03 years

Study	Population	Intervention	Comparison	Outcomes
	Veerus 2006; Vickers 2007)			Viscoli 2001 2.8 years
Mulnard 2000 RCT US	N=120 women older than 60 Age, year - mean (range): High dose Oestrogen: 74.2 (56-89) Low dose Oestrogen: 76.8 (60-91) Placebo: 74.1 (62-87) Diagnosis or probable Alzheimer disease	Oestrogen-only	Placebo	• All-cause mortality Subgroup information: age at first use; constituent Duration of follow-up: 15 months
Nudy 2019 Systematic Review Australia, Finland, Germany, South Africa Sweden, Thailand, US	Number of studies = 11 (Angerer 2000; Giske 2002; Guidozzi 1999; Hall 1998; Harman 2014; Hodis 2001; Jirapinyo 2003; Komulainen 1999; Kyllonen 1998; Nachtigall 1979; Samaras 1999) Oestrogen-only and placebo: N=1245 Oestrogen + Progesterone and placebo: N=1365 Underlying cardiovascular diseases (Angerer	Oestrogen-only Oestrogen + Progesterone: • Sequential combined • Continuous combined	Placebo or no HRT	• All-cause mortality Subgroup information: age at first use; constituent; length of cycle for sequential Duration of follow-up: Angerer 2000 0.92 years Giske 2002 2 years Guidozzi 1999 4 years Hall 1998 1 year Harman 2014 4 years Hodis 2001 2 years Jirapinyo 2003 1 years Komulainen 1999 5 years

Study	Population	Intervention	Comparison	Outcomes
	2000; Hall 1998; Samaras 1999) Diagnosis with cancer (Guidozzi 1999) No underlying health conditions (Giske 2002; Harman 2014; Hodis 2001; Jirapinyo 2003; Komulainen 1999; Kyllonen 1998; Nachtigall 1979)			Kyllonen 1998 2 years Nachtigall 1979 10 years Samaras 1999 1 year
Os 2000 RCT Norway	N=118 postmenopausal women Age, year - mean (range): Oestrogen + Progestin: 63 (59-68) Control: 66 (60-71) No underlying health conditions	Oestrogen + Progesterone: • Sequential combined	No HRT	• All-cause mortality Subgroup information: age at first use; constituent; length of cycle for sequential Duration of follow-up: 12 months
PEPI Trial 1995 RCT US	N=875 postmenopausal women Age at randomisation for total women (per arm not reported), year – mean (SD): 56.1 (SD not reported) No underlying health	Oestrogen-only Oestrogen + Progesterone: • Sequential combined	Placebo	• All-cause mortality Subgroup information: age at first use; constituent; length of cycle for sequential Duration of follow-up: 3 years

Study	Population	Intervention	Comparison	Outcomes
	condition			

BMI: Body mass index; HRT: Hormone replacement therapy; PEPI: Postmenopausal Estrogen/Progestin Interventions; RCT: randomised controlled trial; SD: standard deviation

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

Summary of the evidence

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

Comparison 1: Oestrogen + progesterone (any combination) versus placebo or no HRT

For the comparison oestrogen plus progesterone versus placebo or no HRT, high quality evidence showed no important difference in overall all-cause mortality. However, there were some differences when analysed by subgroup. Low to high quality evidence showed there were no important differences for the progestogenic constituents synthetic progestins, medroxyprogesterone and noresthisterone acetate on all-cause mortality. When looking at the subgroup age at first use, high quality evidence showed there was no important difference if age at first use was 50-59, 60-69 or over 69. Some of the evidence of very low to low quality was analysed separately due to low event numbers, and there was no important difference for all the subgroups for these studies.

Comparison 2: Sequential combined oestrogen + progesterone versus placebo or no HRT

There were relatively few studies contributing to sequential combined regimens and very low to low quality evidence showed no important difference for all subgroups.

Comparison 3: Continuous combined oestrogen + progesterone versus placebo or no HRT

Most of the evidence for oestrogen plus progesterone combined was in a continuous combined regimen, and was of moderate to high quality. The evidence showed that there were no important differences between oestrogen plus progesterone and placebo or no HRT, overall and for all the subgroups. Some of the evidence of very low to low quality, was analysed separately due to low event numbers, and there was no important difference for all the subgroups for these studies.

Comparison 4: Oestrogen-only versus placebo or no HRT

For the comparison oestrogen-only versus placebo or no HRT, high quality evidence showed no important difference in overall all-cause mortality. The evidence showed no important differences for most of the subgroups. For constituent, moderate to high quality evidence showed there was no important difference for all-cause mortality with oestradiol, or equine oestrogen. High quality evidence showed there was no important difference if age at first use was 60-69 years or more than 69 years, but moderate quality evidence showed an important benefit for oestrogen-only when compared to placebo or no HRT on all-cause mortality. Low quality evidence showed there was no important difference between arms for black ethnicity and high quality evidence showed no important difference for white ethnicity. Some of the evidence of very low to low quality was analysed separately due to low event numbers, and there was no important difference for all the subgroups for these studies.

See Appendix F for full GRADE tables.

Economic evidence

Included studies

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

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

Excluded studies

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

Summary of included economic evidence

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

Economic model

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

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The critical outcome was all-cause mortality. This was chosen because HRT could have a variety of different positive and negative effects on health, but any serious overall positive or negative effect should be apparent as a difference in overall mortality.

The quality of the evidence

The quality of the evidence for outcomes was assessed with GRADE and was rated as very low to high. Where the evidence was downgraded, there were mainly concerns around imprecision when 95% confidence intervals crossed 1 or more decision-making thresholds. Findings were also downgraded due to risk of bias for example around deviations for the intended intervention, as prescription registries or women's self-reporting may indicate the use of HRT, but it cannot be fully confirmed that they took the HRT. The evidence was not downgraded for inconsistency or indirectness.

Benefits and harms

The committee discussed that some of the evidence was from people with underlying health conditions which may have impacted on the results. They also noted that the length of follow-up was relatively short in many of the studies and there may not have been sufficient time for a difference in mortality to become apparent. However, they noted that the study findings from the Women's Health Initiative trial were given most weight and this included a population without underlying health conditions, and a longer follow-up period of 18 years. The committee discussed that overall high quality evidence showed no difference in mortality, with either oestrogen-only, or combined HRT.

The committee looked at the analysis by subgroup and noted that for most of the subgroups there was no difference between HRT user and placebo. Whilst they noted that there was a statistically significant decreased rate of all-cause mortality in a subgroup of people starting

oestrogen-only HRT between 50 and 59, they noted that the confidence intervals in all age groups overlapped meaning that there were no differences between subgroups by age. There was no such difference in the combined HRT analysis by age group of starting HRT.

The committee discussed some of the specific aspects of the Women's Health Initiative. They considered that the regimen in the Women's Health Initiative included a dose of equine oestrogen that is no longer used in practice, and that the route of administration was oral, whereas transdermal is more commonly used in practice. They discussed that the results were therefore specific to these characteristics of HRT. However, the committee agreed that there was high quality evidence to support a recommendation that would help to counsel a person who is considering HRT, and the results of the trial were still important.

The committee recommended that, when discussing HRT as a treatment option, it should be explained to people that HRT is unlikely to increase or decrease their life expectancy. This recommendation was based on the evidence which showed no important differences in risk of death from any cause with either oestrogen-only or combined HRT. The committee agreed that people should be aware of this when deciding whether or not to start or continue HRT, and that it would help them make a more informed decision. Though HRT treatment does not affect overall life-expectancy, the committee agreed that discussions should aim to establish the best balance between effectively treating symptoms and alleviating risks from the treatment (see Tables 1 and 2 in the NICE guideline), taking into account the person's age, symptoms, medical history, preferences and personal circumstances. See also the section on discussing treatment options (see evidence review D) which highlights what should be discussed and taken into account in relation to HRT treatment.

In the absence of any good evidence to suggest that different types of progestogen have different effects on all-cause mortality, it was assumed that the findings could be generalised to all HRT.

There was also a lack of evidence on how HRT treatment in trans men and non-binary people can affect the risk all-cause mortality (or any other health outcomes). The committee assumed that the existing evidence discussed above could be generalised to transgender men and non-binary people who have never taken gender affirming hormone therapy. However, there was uncertainty about transgender people or non-binary people who have taken gender affirming hormone therapy in the past. The committee also noted that there was no evidence from people from minority ethnic family backgrounds. They agreed to make research recommendations for these groups to fill this evidence gap. The descriptions of the research recommendations can be found in appendix K of evidence report C.

Other factors the committee took into account

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

Cost effectiveness and resource use

No previous economic evidence was identified for this topic.

The recommendations made for this review topic centre around the impact of HRT on the risk of mortality. Whilst recommendations in this area will lead to people being better informed about treatment decisions, it is unclear how such information will change the treatment decisions made and how these will impact overall resource use. It would however

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

Recommendations supported by this evidence review

This evidence review supports the first two bullet points of recommendation 1.6.1. It also supports an overarching recommendation related to trans-men and non-binary people registered female at birth who have taken cross-sex hormones in the past (recommendation 1.4.5 – see evidence review C).

Additionally, there are overarching research recommendations related to all health outcomes addressed in this guideline update (including dementia), for:

- trans-men and non-binary people registered female at birth who have taken cross-sex hormones in the past
- people from ethnic minority family backgrounds

For details refer to appendix K in evidence review C.

References – included studies

Effectiveness

Chlebowski 2017

Chlebowski, Rowan T, Barrington, Wendy, Aragaki, Aaron K et al. (2017) Oestrogen alone and health outcomes in black women by African ancestry: a secondary analyses of a randomized controlled trial. Menopause (New York, N.Y.) 24(2): 133-141

Kim 2020

Kim, Ji-Eun, Chang, Jae-Hyuck, Jeong, Min-Ji et al. (2020) A systematic review and meta-analysis of effects of menopausal hormone therapy on cardiovascular diseases. Scientific reports 10(1): 20631

Mulnard 2000

Mulnard RA, Cotman CW, Kawas C et al. (2000) Oestrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. JAMA 283(8): 1007-1015

Nudy 2019

Nudy, Matthew; Chinchilli, Vernon M; Foy, Andrew J (2019) A systematic review and meta-regression analysis to examine the 'timing hypothesis' of hormone replacement therapy on mortality, coronary heart disease, and stroke. International journal of cardiology. Heart & vasculature 22: 123-131

Os 2000

Os, I, Hofstad, A E, Brekke, M et al. (2000) The EWA (oestrogen in women with atherosclerosis) study: a randomized study of the use of hormone replacement therapy in women with angiographically verified coronary artery disease. Characteristics of the study population. Effects on lipids and lipoproteins. Journal of internal medicine 247(4): 433-41

PEPI 1995

PEPI (1995) Effects of oestrogen or oestrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Oestrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA 273(3): 199-208

RCTs included from systematic reviews (Kim 2020 and Nudy 2019)

Angerer 2000

Angerer, P, Kothny, W, Stork, S et al. (2000) Hormone replacement therapy and distensibility of carotid arteries in postmenopausal women: a randomized, controlled trial. Journal of the American College of Cardiology 36(6): 1789-96

Cherry 2014

Cherry, N, McNamee, R, Heagerty, A et al. (2014) Long-term safety of unopposed oestrogen used by women surviving myocardial infarction: 14-year follow-up of the ESPRIT randomised controlled trial. BJOG: an international journal of obstetrics and gynaecology 121(6): 700-705

Collins 2006

Collins, Peter, Flather, Marcus, Lees, Belinda et al. (2006) Randomized trial of effects of continuous combined HRT on markers of lipids and coagulation in women with acute coronary syndromes: WHISP Pilot Study. European heart journal 27(17): 2046-53

Giske 2002

Giske, L E, Hall, G, Rud, T et al. (2002) The effect of 17beta-estradiol at doses of 0.5, 1 and 2 mg compared with placebo on early postmenopausal bone loss in hysterectomized women. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 13(4): 309-16

Guidozzi 1999

Guidozzi, F and Daponte, A (1999) Oestrogen replacement therapy for ovarian carcinoma survivors: A randomized controlled trial. Cancer 86(6): 1013-8

Hall 1998

Hall, G, Pripp, U, Schenck-Gustafsson, K et al. (1998) Long-term effects of hormone replacement therapy on symptoms of angina pectoris, quality of life and compliance in women with coronary artery disease. Maturitas 28(3): 235-42

Harman 2014

Harman, S Mitchell, Black, Dennis M, Naftolin, Frederick et al. (2014) Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. Annals of internal medicine 161(4): 249-60

Herrington 2000

Herrington, D M, Reboussin, D M, Brosnihan, K B et al. (2000) Effects of oestrogen replacement on the progression of coronary-artery atherosclerosis. The New England journal of medicine 343(8): 522-9

Hodis 2001

Hodis, H N, Mack, W J, Lobo, R A et al. (2001) Oestrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. Annals of internal medicine 135(11): 939-53

Hodis 2003

Hodis, Howard N, Mack, Wendy J, Azen, Stanley P et al. (2003) Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. The New England journal of medicine 349(6): 535-45

Hodis 2016

Hodis, Howard N, Mack, Wendy J, Henderson, Victor W et al. (2016) Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol. The New England journal of medicine 374(13): 1221-31

Hulley 2002

Hulley, Stephen, Furberg, Curt, Barrett-Connor, Elizabeth et al. (2002) Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Oestrogen/progestin Replacement Study follow-up (HERS II). JAMA 288(1): 58-66

Jirapinyo 2003

Jirapinyo, Mayuree, Theppisai, Urusa, Manonai, Jittima et al. (2003) Effect of combined oral oestrogen/progestogen preparation (Kliogest) on bone mineral density, plasma lipids and postmenopausal symptoms in HRT-naive Thai women. Acta obstetricia et gynecologica Scandinavica 82(9): 857-66

Komulainen 1999

Komulainen, M, Kroger, H, Tuppurainen, M T et al. (1999) Prevention of femoral and lumbar bone loss with hormone replacement therapy and vitamin D3 in early postmenopausal women: a population-based 5-year randomized trial. The Journal of clinical endocrinology and metabolism 84(2): 546-52

Kyllonen 1998

Kyllonen, E S, Heikkinen, J E, Vaananen, H K et al. (1998) Influence of oestrogen-progestin replacement therapy and exercise on lumbar spine mobility and low back symptoms in a healthy early postmenopausal female population: a 2-year randomized controlled trial. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 7(5): 381-6

Manson 2017

Manson, JoAnn E, Aragaki, Aaron K, Rossouw, Jacques E et al. (2017) Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. JAMA 318(10): 927-938

Nachtigall 1979

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

Samaras 1999

Samaras, K, Hayward, C S, Sullivan, D et al. (1999) Effects of postmenopausal hormone replacement therapy on central abdominal fat, glycemic control, lipid metabolism, and vascular factors in type 2 diabetes: a prospective study. Diabetes care 22(9): 1401-7

Tierney 2009

Tierney, Mary C, Oh, Paul, Moineddin, Rahim et al. (2009) A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women. Psychoneuroendocrinology 34(7): 1065-74

Veerus 2006

Veerus, Piret, Hovi, Sirpa-Liisa, Fischer, Krista et al. (2006) Results from the Estonian postmenopausal hormone therapy trial [ISRCTN35338757]. Maturitas 55(2): 162-73

Vickers 2007

Vickers, Madge R, MacLennan, Alastair H, Lawton, Beverley et al. (2007) Main morbidities recorded in the women's international study of long duration oestrogen after menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women. BMJ (Clinical research ed.) 335(7613): 239

Viscoli 2001

Viscoli, C M, Brass, L M, Kernan, W N et al. (2001) A clinical trial of oestrogen-replacement therapy after ischemic stroke. The New England journal of medicine 345(17): 1243-9

Appendices

Appendix A Review protocols

Review protocol for review question: What are the effects of hormone replacement therapy for menopausal symptoms on all-cause mortality?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022362357
1.	Review title	Effects of hormone replacement therapy for menopausal symptoms on all-cause mortality
2.	Review question	What are the effects of hormone replacement therapy for menopausal symptoms on all-cause mortality?
3.	Objective	To identify the effects, if any, of HRT on all-cause mortality
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE, MEDLINE ePub Ahead-of-Print and MEDLINE-in-Process • Epistemonikos • HTA via CRD • INAHTA Searches will be restricted by: • English language • Human studies The full search strategies will be published in the final review.

5.	Condition or domain being studied	Menopause
6.	Population	Women, non-binary and trans people with menopause (including perimenopause and postmenopause)

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

8.	Comparator/Reference standard/Confounding factors	• Placebo • No HRT
9.	Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
10.	Other exclusion criteria	• People with premature ovarian insufficiency • People with early menopause (aged 40 to 44) If any study or systematic review includes <1/3 of women with the above characteristics/ who received care in the above setting, it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness.
11.	Context	This guideline will partly update the following: Menopause NG23
12.	Primary outcomes (critical outcomes)	• All-cause mortality

13.	Secondary outcomes (important outcomes)	
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • Cochrane RoB tool v.2 for cluster-randomized trials
16.	Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Minimally important differences:

		All-cause mortality: statistical significance Serious intervention-related adverse effects: statistical significance Validated scales/continuous outcomes: published MIDs where available All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes ; +/- 0.5x control group SD for continuous outcomes How the evidence included in NG23 will be incorporated with the new evidence: Studies meeting the current protocol criteria and previously included in the NG23 will be included in this update. The methods for quantitative analysis (data extraction, risk of bias, strategy for data synthesis, and analysis of subgroups) will be the same as for the new evidence and as outlined in this protocol.
17.	Analysis of sub-groups	Evidence will be stratified (in 2 layers) by: • Recency of HRT use (current users, < 5 years, 5-9 years, ≥ 10 years since last use) by duration of HRT use (<1 year, 1-4 years, 5-9 years, 10-14 years, ≥ 15 years) Additional stratification will be done only for a single specified duration and recency of HRT use (for example: only current HRT users with 5 to 14 years of use) and will only be possible if evidence is reported in this way. Evidence will be stratified by: • Age at first use (45-50 years, 50-59 years, 60-69 years, >69 years) • Time since menopause at first use (<1 year, 1-4 years, 5-9 years, >10 years) • Constituent (equine oestrogen, oestradiol) • Mode of administration (oral, transdermal) • Progestogenic constituent (for combined HRT only: (Levo)norgestrel, Norethisterone acetate, Medroxyprogesterone acetate, Micronised progesterone, any synthetic progestin) • Length of cycle (for sequential combined HRT only: Sequential long cycle [3 monthly], Sequential 30 day cycle) • By surgical menopause (surgical menopause, no surgical menopause) • BMI (<18.5, 18.5 to 24.9, ≥25) By factors identified in the equalities section of the scope: • Ethnicity (White British, Asian/Asian British, Black/African/Caribbean/Black British, Mixed/Multiple ethnic groups) • Disability (disability, no disability) • Socioeconomic group (deprived, non deprived) • Non-binary and trans people Where evidence is stratified or subgrouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence

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

24.	Named contact	5a. Named contact 5b Named contact e-mail menopause@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) [Note it is essential to use the template text here to enable PROSPERO to recognise this as a NICE protocol]
25.	Review team members	• Senior Systematic Reviewer • Systematic Reviewer
26.	Funding sources/sponsor	This systematic review is being completed by NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	None
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022362357
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts

		• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Hormone replacement therapy; all-cause mortality	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

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

Appendix B Literature search strategies

Literature search strategies for review question: What are the effects of hormone replacement therapy for menopausal symptoms on all-cause mortality?

There was a combined literature search strategies for review questions:

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

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

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

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

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

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

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

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

Clinical searches

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

Date of last search: 03/10/2022

#	Searches	
1	Climacteric/	4935
2	Menopause/ or Perimenopause/ or Postmenopause/	56226
3	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	103042
4	("change of life" or life change?).ti,ab.	3175
5	or/1-4	117224
6	exp Hormone Replacement Therapy/	26181

#	Searches	
7	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	48129
8	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	87130
9	exp *Oestrogens/	97369
10	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	91850
11	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	110232
12	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	8328
13	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	161
14	or/6-13	300800
15	5 and 14	38439
16	exp Breast Neoplasms/	331829
17	exp "Neoplasms, Ductal, Lobular, and Medullary"/	45099
18	exp breast/ and exp neoplasms/	31705
19	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	412638
20	exp uterine neoplasms/	143954
21	Endometrial Hyperplasia/	3751
22	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	71639
23	exp Ovarian Neoplasms/	92941
24	Fallopian Tube Neoplasms/	3090
25	Peritoneal Neoplasms/	16848
26	Pelvic Neoplasms/	7356
27	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	134115
28	((epithelial or germ cell) adj5 ovar*).ti,ab.	18696
29	exp Dementia/	195885
30	(amentia* or dementia* or lewy body).ti,ab.	131539
31	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	172723
32	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	212540
33	Death/ or exp Mortality/	438343
34	(death or dying or die* or dead or mortality or fatal*).ti,ab.	2676396
35	exp Cardiovascular Diseases/	2652417
36	exp Stroke/	164004
37	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	265024
38	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	391497
39	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	237740
40	(stroke or strokes).ti,ab.	293720
41	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	177232
42	TIA.ti,ab.	9584
43	(myocardial adj2 infarct*).ti,ab.	215115
44	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	85723
45	atrial flutter*.ti,ab.	6330
46	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	150990
47	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).ti,ab,kw,kf.	23385
48	pulmonary embolism/ or thromboembolism/ or venous thromboembolism/ or venous thrombosis/ or upper extremity deep vein thrombosis/	98814

#	Searches	
49	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	110885
50	exp osteoporosis/	61247
51	fractures, bone/ or osteoporotic fractures/	76201
52	exp Bone Remodeling/ or Bone Density/	118506
53	exp radius fractures/ or spinal fractures/ or hip fractures/	45889
54	(osteoporo* or osteop?en*).ti,ab.	91147
55	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab.	136427
56	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab.	76474
57	exp Muscle Strength/ or Muscle Contraction/ or Muscle, Skeletal/ or Muscle weakness/	275399
58	exp Muscular Atrophy/	20100
59	(sarcop?en* or dynap?eni*).ti,ab.	12753
60	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	89183
61	exp Diabetes Mellitus, Type 2/	162254
62	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	178683
63	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	3367
64	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	1079
65	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	11970
66	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	52630
67	or/16-66	7071734
68	15 and 67	24780
69	animals/ not humans/	5018518
70	exp Animals, Laboratory/	944064
71	exp Animal Experimentation/	10221
72	exp Models, Animal/	633340
73	exp Rodentia/	3486788
74	(rat or rats or mouse or mice).ti.	1413148
75	or/69-74	6058843
76	68 not 75	22173
77	limit 76 to english language	19974
78	Climacteric/	4935
79	Menopause/ or Perimenopause/ or Postmenopause/	56226
80	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	103042
81	("change of life" or life change?).ti,ab.	3175
82	or/78-81	117224
83	exp Hormone Replacement Therapy/	26181
84	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	48129
85	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	87130
86	exp *Oestrogens/	97369
87	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	91850
88	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	110232
89	((combin* or sequen* or continu*) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	6337
90	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	161
91	or/83-90	300359
92	82 and 91	38419
93	animals/ not humans/	5018518
94	exp Animals, Laboratory/	944064
95	exp Animal Experimentation/	10221
96	exp Models, Animal/	633340

#	Searches	
97	exp Rodentia/	3486788
98	(rat or rats or mouse or mice).ti.	1413148
99	or/93-98	6058843
100	92 not 99	34708
101	limit 100 to english language	30818
102	randomized controlled trial.pt.	578276
103	controlled clinical trial.pt.	95066
104	pragmatic clinical trial.pt.	2153
105	randomi#ed.ab.	690521
106	placebo.ab.	232230
107	randomly.ab.	392671
108	Clinical Trials as topic.sh.	200427
109	trial.ti.	271569
110	or/102-109	1520899
111	COMPARATIVE STUDIES/	1911627
112	FOLLOW-UP STUDIES/	687669
113	TIME FACTORS/	1228326
114	reviewed.tw.	604810
115	prospective$.tw.	826138
116	retrospective$.tw.	951729
117	baseline.tw.	681295
118	cohort.tw.	716940
119	case series.tw.	96297
120	or/111-119	5840666
121	COHORT STUDIES/	319704
122	FOLLOW-UP STUDIES/	687669
123	LONGITUDINAL STUDIES/	160686
124	PROSPECTIVE STUDIES/	640096
125	RETROSPECTIVE STUDIES/	1062925
126	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.	990520
127	(incidence? adj (stud* or research or analys*)).tw.	2167
128	(longitudinal* adj1 (survey* or evaluat*)).tw.	8189
129	(prospective* adj method*).tw.	492
130	(retrospective* adj design*).tw.	2556
131	Case-Control Studies/	323880
132	"nested case control".ti,ab.	10276
133	or/121-132	2937576
134	110 or 120 or 133	7274173
135	101 and 134	16133
136	77 or 135	25292

1

2 Database: Embase <1974 to 2022 September 30>

3 Date of last search: 03/10/2022

#	Searches	
1	climacterium/ or "menopause and climacterium"/	8994
2	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	134540
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	148870
4	("change of life" or life change?).tw.	4281
5	or/1-4	184584
6	exp hormone substitution/	61182

#	Searches	
7	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	70813
8	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	118537
9	exp *oestrogen/	126164
10	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	99068
11	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	134303
12	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	9843
13	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	261
14	or/6-13	401114
15	5 and 14	58995
16	exp breast tumor/	610160
17	exp medullary carcinoma/	11738
18	exp breast/ and exp neoplasm/	81181
19	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	580028
20	exp uterus cancer/	178703
21	endometrium hyperplasia/	8475
22	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	94083
23	exp ovary tumor/	165879
24	uterine tube tumor/	1128
25	exp peritoneum tumor/	32297
26	exp pelvis tumor/	8687
27	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	189064
28	((epithelial or germ cell) adj5 ovar*).ti,ab.	26375
29	exp dementia/	414481
30	(amentia* or dementia* or lewy body).ti,ab.	188972
31	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	233156
32	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	296024
33	death/ or fatality/ or exp mortality/	1565750
34	(death or dying or die* or dead or mortality or fatal*).ti,ab.	3638723
35	exp cardiovascular disease/	4653676
36	exp cerebrovascular accident/	278318
37	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	395575
38	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	582395
39	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	388936
40	(stroke or strokes).ti,ab.	467280
41	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	248980
42	TIA.ti,ab.	21167
43	(myocardial adj2 infarct*).ti,ab.	308381
44	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	151993
45	atrial flutter*.ti,ab.	10322
46	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	225615
47	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).ti,ab,kw,kf.	38407
48	pulmonary embolism/ or lung embolism/ or thromboembolism/ or venous thromboembolism/ or venous thrombosis/ or vein thrombosis/ or upper extremity deep vein thrombosis/	238572

#	Searches	
49	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	173070
50	exp osteoporosis/	144975
51	exp fracture/	333661
52	bone remodeling/ or bone density/	136963
53	(osteoporo* or osteop?en*).ti,ab.	139235
54	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab.	184524
55	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab.	105447
56	muscle strength/ or muscle contraction/ or skeletal muscle/ or muscle weakness/	298183
57	exp muscle atrophy/	53010
58	(sarcop?en* or dynap?eni*).ti,ab.	19831
59	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	123477
60	diabetes mellitus/ or non insulin dependent diabetes mellitus/	903538
61	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	274466
62	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	4587
63	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	1729
64	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	13941
65	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	87957
66	or/16-65	10247056
67	15 and 66	41567
68	animal/ not human/	1164743
69	nonhuman/	7043049
70	exp Animal Experiment/	2901019
71	exp Experimental Animal/	776639
72	animal model/	1589792
73	exp Rodent/	3873528
74	(rat or rats or mouse or mice).ti.	1563613
75	or/68-74	9201242
76	67 not 75	35048
77	limit 76 to english language	30447
78	climacterium/ or "menopause and climacterium"/	8994
79	menopause/ or early menopause/ or postmenopause/ or exp menopause related disorder/	134540
80	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	148870
81	("change of life" or life change?).tw.	4281
82	or/78-81	184584
83	exp hormone substitution/	61182
84	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	70813
85	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	118537
86	exp *oestrogen/	126164
87	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	99068
88	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	134303
89	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	9843
90	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	261
91	or/83-90	401114
92	82 and 91	58995
93	animal/ not human/	1164743
94	nonhuman/	7043049
95	exp Animal Experiment/	2901019

#	Searches	
96	exp Experimental Animal/	776639
97	animal model/	1589792
98	exp Rodent/	3873528
99	(rat or rats or mouse or mice).ti.	1563613
100	or/93-99	9201242
101	92 not 100	50424
102	limit 101 to english language	43215
103	random*.ti,ab.	1840480
104	factorial*.ti,ab.	44821
105	(crossover* or cross over*).ti,ab.	120165
106	((doubl* or singl*) adj blind*).ti,ab.	261774
107	(assign* or allocat* or volunteer* or placebo*).ti,ab.	1196283
108	crossover procedure/	71600
109	single blind procedure/	47754
110	randomized controlled trial/	730322
111	double blind procedure/	199308
112	or/103-111	2737481
113	CONTROLLED STUDY/	9111478
114	TREATMENT OUTCOME/	935485
115	MAJOR CLINICAL STUDY/	4618747
116	CLINICAL TRIAL/	1046476
117	reviewed.tw.	873307
118	baseline.tw.	1157267
119	(compare$ or compara$).tw.	7021464
120	or/113-119	16140633
121	COHORT ANALYSIS/	901841
122	FOLLOW UP/	1902143
123	LONGITUDINAL STUDY/	179050
124	PROSPECTIVE STUDY/	798586
125	RETROSPECTIVE STUDIES/	1035839
126	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.	1497898
127	(incidence? adj (stud* or research or analys*)).tw.	2924
128	(longitudinal* adj1 (survey* or evaluat*)).tw.	10476
129	(prospective* adj method*).tw.	1417
130	(retrospective* adj design*).tw.	4171
131	case control study/	193429
132	"nested case control".ti,ab.	13700
133	or/121-132	4296161
134	112 or 120 or 133	17894341
135	102 and 134	30379
136	77 or 135	39104
137	(conference abstract or conference paper or conference proceeding or "conference review").pt.	5322870
138	136 not 137	30760

1

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

3 Date of last search: 03/10/2022

#	Searches	
1	menopause/ or life changes/	9242
2	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	7061
3	("change of life" or life change?).ti,ab.	2938

#	Searches	
4	or/1-3	15066
5	hormone therapy/	2262
6	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	2942
7	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	13552
8	exp *oestrogens/	5657
9	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	4482
10	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	6993
11	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	528
12	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	12
13	or/5-12	24383
14	4 and 13	2373
15	breast neoplasms/	11017
16	Breast/ and exp neoplasms/	300
17	((breast* or mammar*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab.	15213
18	uterus/ and exp neoplasms/	43
19	((endometr* or uter* or womb) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan* or hyperplas*)).ti,ab.	457
20	ovaries/ and exp neoplasms/	444
21	((ovar* or fallopian or peritoneal* or peritoneum or pelvi*) adj5 (neoplas* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or malignan*)).ti,ab.	1347
22	((epithelial or germ cell) adj5 ovar*).ti,ab.	58
23	exp dementia/ or exp alzheimer's disease/	87977
24	(amentia* or dementia* or lewy body).ti,ab.	72463
25	(alzheimer* or alzeimer* or (cortical adj4 sclerosis)).ti,ab.	67104
26	((memory or remember* or cognitiv* or brain* or hippocamp*) adj3 (loss* or declin* or function* or atroph*)).ti,ab.	120339
27	exp "death and dying"/	45080
28	(death or dying or die* or dead or mortality or fatal*).ti,ab.	218375
29	exp Cardiovascular Disorders/ or Cerebrovascular Accidents/	68930
30	((cardiovascular or cardio vascular) adj3 (event* or disease* or outcome* or symptom*)).ti,ab.	14620
31	((coronary or peripheral vascular or heart or peripheral arter* or cardiac) adj3 (disease* or event* or outcome* or symptom*)).ti,ab.	16319
32	((heart or cardiac) adj3 (failure or attack* or infarct* or rhythm*)).ti,ab.	6390
33	(stroke or strokes).ti,ab,mh.	38668
34	((cerebro* or cerebral* or brain or cerebell* or intracran* or intracerebral or subarachnoid) adj2 (accident* or apoplexy or haemorrhag* or hemorrhag* or haematoma* or hematoma* or bleed* or ischemi* or ischaemi* or infarct* or thrombo* or emboli* or vasc* or occlus*)).ti,ab.	14812
35	TIA.ti,ab.	993
36	(myocardial adj2 infarct*).ti,ab.	4538
37	((atrial or auricular or atrium) adj3 fibrillat*).ti,ab.	1391
38	atrial flutter*.ti,ab.	27
39	(arrhythmia* or tachyarrhythmia* or tachycardia* or dysrhythmia*).ti,ab.	4960
40	((sudden or unexpected) adj3 (cardiac or heart) adj3 (death* or arrest*)).mp.	709
41	embolisms/ or thromboses/	1323
42	(((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj4 (emboli* or embolus or thromboembolism))).ti,ab.	1179
43	osteoporosis/	1165
44	bones/ and (accidents/ or injuries/ or falls/)	117
45	(osteoporo* or osteop?en*).ti,ab.	2275

#	Searches	
46	(bone* adj4 (turnover or turn over* or densit* or break* or broke* or loss* or remode* or re mode* or fractur*)).ti,ab,mh.	2050
47	(fractur* adj4 (osteop* or fragil* or vertebra* or spine or spinal or wrist* or radial or radius or femur* or hip* or lumbar)).ti,ab,mh.	1936
48	muscle contractions/	2056
49	muscular atrophy/	752
50	(sarcop?en* or dynap?eni*).ti,ab.	357
51	((muscle* or muscular*) adj2 (mass or function or strength* or loss or lost or declin* or atroph*)).ti,ab.	5464
52	exp type 2 diabetes/	5494
53	(Type* adj3 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).ti,ab.	9348
54	((Matur* or adult* or slow*) adj4 onset* adj3 (diabete* or diabetic*)).ti,ab.	75
55	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).ti,ab.	28
56	((Non-insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).ti,ab.	265
57	(NIDDM or T2D or T2DM or TIID or DM2 or DMII).ti,ab.	2147
58	or/15-57	522743
59	14 and 58	1116
60	animal.po.	432218
61	(rat or rats or mouse or mice).ti.	123700
62	60 or 61	436853
63	59 not 62	872
64	limit 63 to english language	849
65	menopause/ or life changes/	9242
66	(menopau* or postmenopau* or perimenopau* or climacteri*).ti,ab.	7061
67	("change of life" or life change?).ti,ab.	2938
68	or/65-67	15066
69	hormone therapy/	2262
70	(hormon* adj2 (replac* or therap* or substitut*)).ti,ab.	2942
71	(HRT or HT or MHT or ERT or EPRT or SEPRT).ti,ab.	13552
72	exp *oestrogens/	5657
73	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ti.	4482
74	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*).ab. /freq=2	6993
75	((combin* or sequen* or continu* or plus) adj4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)).ti,ab.	528
76	(("body identical*" or bio-identical* or bioidentical*) adj2 hormon*).ti,ab.	12
77	or/69-76	24383
78	68 and 77	2373
79	animal.po.	432218
80	(rat or rats or mouse or mice).ti.	123700
81	79 or 80	436853
82	78 not 81	1974
83	limit 82 to english language	1898
84	clinical trial.md.	34832
85	clinical trial.md.	34832
86	Clinical trials/	12104
87	Randomized controlled trials/	913
88	Randomized clinical trials/	383
89	assign*.ti,ab.	106838
90	allocat*.ti,ab.	35101
91	crossover*.ti,ab.	8375
92	cross over*.ti,ab.	3251
93	((doubl* or singl*) adj blind*).ti,ab.	28070
94	factorial*.ti,ab.	21909

#	Searches	
95	placebo*.ti,ab.	42984
96	random*.ti,ab.	229145
97	volunteer*.ti,ab.	41704
98	trial?.ti,ab.	203614
99	or/84-98	512268
100	FOLLOWUP STUDY/	0
101	followup study.md.	86839
102	TREATMENT OUTCOMES/	38539
103	treatment outcome.md.	22898
104	CLINICAL TRIALS/	12104
105	clinical trial.md.	34832
106	reviewed.tw.	93954
107	prospective$.tw.	78083
108	retrospective$.tw.	50502
109	baseline.tw.	133530
110	cohort.tw.	81269
111	case series.tw.	4679
112	(compare$ or compara$).tw.	719207
113	or/100-112	1088229
114	COHORT ANALYSIS/	1643
115	LONGITUDINAL STUDIES/ or longitudinal study.md.	188660
116	FOLLOWUP STUDIES/ or followup study.md.	87168
117	PROSPECTIVE STUDIES/ or prospective study.md.	49600
118	RETROSPECTIVE STUDIES/ or retrospective study.md.	34340
119	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.	141639
120	(incidence? adj (stud* or research or analys*)).tw.	614
121	(longitudinal* adj1 (survey* or evaluat*)).tw.	5386
122	(prospective* adj method*).tw.	156
123	(retrospective* adj design*).tw.	489
124	or/114-123	307794
125	99 or 113 or 124	1485971
126	83 and 125	1056
127	64 or 126	1411

1

2 Database: Cochrane Database of Systematic Reviews (CDSR) Issue 10 of 12, October
3 2022

4 Date of last search: 03/10/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1625
3	MeSH descriptor: [Perimenopause] this term only	172
4	MeSH descriptor: [Postmenopause] this term only	4992
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	28112
6	("change of life" or "life change*"):ti,ab	175
7	{or #1-#6}	28696
8	MeSH descriptor: [Hormone Replacement Therapy] explode all trees	3018
9	(hormon* NEAR/2 (replac* or therap* or substitut*)):ti,ab	9032
10	(HRT or HT or MHT or ERT or EPRT or SEPRT):ti,ab	7486
11	MeSH descriptor: [Oestrogens] explode all trees	1958
12	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ti	7138

#	Searches	
13	(oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*):ab	17513
14	((combin* or sequen* or continu* or plus) NEAR/4 (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)):ti,ab	2443
15	(("body identical*" or bio-identical* or bioidentical*) NEAR/2 hormon*):ti,ab	29
16	{or #8-#15}	31472
17	#7 AND #16	11025
18	"conference":pt or (clinicaltrials or trialsearch):so	641065
19	#17 NOT #18	8124
20	#19 in Cochrane Reviews	56

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

Date of last search: 03/10/2022

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

Database: Epistemonikos

Date of last search: 27/07/2022

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

#	Searches	
3	1 AND 2	7537

Database: HTA via CRD

Date of last search: 03/10/2022

#	Searches	
1	MeSH DESCRIPTOR Climacteric	9
2	MeSH DESCRIPTOR Menopause	117
3	MeSH DESCRIPTOR Perimenopause	7
4	MeSH DESCRIPTOR Postmenopause	209
5	((menopau* or postmenopau* or perimenopau* or climacteri*))	957
6	(("change of life" or "life change" or "life changes"))	38
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	994
8	MeSH DESCRIPTOR Hormone Replacement Therapy EXPLODE ALL TREES	191
9	((hormon* AND (replac* or therap* or substitut*)))	1577
10	((HRT or HT or MHT or ERT or EPRT or SEPRT))	435
11	MeSH DESCRIPTOR Oestrogens EXPLODE ALL TREES	136
12	((oestrogen* or oestrogen* or oestradiol* or estradiol* or estrone* or oestrone* or estriol* or oestriol*))	670
13	(((combin* or sequen* or continu* or plus) AND (progest* or gestagen* or gestogen* or medroxyprogesterone* or norgestrel* or drospirenone* or norethisterone* or dydrogesterone* or levonorgestrel*)))	291
14	((("body identical*" or bio-identical* or bioidentical*) AND hormon*))	3
15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	2314
16	#7 AND #15	473
17	(#7 AND #15) IN HTA	71

Database: INAHTA

Date of last search: 03/10/2022

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

Economic searches

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

1 Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	4935
2	Menopause/ or Perimenopause/ or Postmenopause/	55972
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	102310
4	("change of life" or life change?).tw.	3141
5	or/1-4	116452
6	limit 5 to english language	103660
7	limit 6 to yr="2012 -Current"	41579
8	letter/	1188475
9	editorial/	613156
10	news/	213557
11	exp historical article/	408665
12	Anecdotes as Topic/	4746
13	comment/	973045
14	case report/	2282504
15	(letter or comment*).ti.	179095
16	or/8-15	4782431
17	randomized controlled trial/ or random*.ti,ab.	1466248
18	16 not 17	4751747
19	animals/ not humans/	4997958
20	exp Animals, Laboratory/	942090
21	exp Animal Experimentation/	10205
22	exp Models, Animal/	631246
23	exp Rodentia/	3472512
24	(rat or rats or mouse or mice).ti.	1407073
25	or/18-24	10620565
26	7 not 25	34368
27	Economics/	27455
28	Value of life/	5793
29	exp "Costs and Cost Analysis"/	259348
30	exp Economics, Hospital/	25612
31	exp Economics, Medical/	14359
32	Economics, Nursing/	4013
33	Economics, Pharmaceutical/	3074
34	exp "Fees and Charges"/	31172
35	exp Budgets/	14034
36	budget*.ti,ab.	33535
37	cost*.ti.	136425
38	(economic* or pharmaco?economic*).ti.	56592
39	(price* or pricing*).ti,ab.	48567
40	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.	191586
41	(financ* or fee or fees).ti,ab.	145674
42	(value adj2 (money or monetary)).ti,ab.	2817
43	or/27-42	689907
44	exp models, economic/	16130
45	*Models, Theoretical/	64214
46	*Models, Organizational/	6490
47	markov chains/	15758
48	monte carlo method/	31445
49	exp Decision Theory/	12940
50	(markov* or monte carlo).ti,ab.	79077
51	econom* model*.ti,ab.	4760
52	(decision* adj2 (tree* or analy* or model*)).ti,ab.	31806
53	or/44-52	210296

#	Searches	
54	43 or 53	865352
55	26 and 54	849

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2 Database: Embase <1974 to 2022 July 27>

3 Date of last search: 28/07/2022

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

#	Searches	
47	monte carlo method/	46995
48	(markov* or monte carlo).ti,ab.	87061
49	econom* model*.ti,ab.	7134
50	(decision* adj2 (tree* or analy* or model*)).ti,ab.	43807
51	or/41-50	225433
52	38 or 51	1266430
53	24 and 52	2248

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

3 Date of last search: 01/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	444
7	{or #1-#6}	28529
8	MeSH descriptor: [Economics] this term only	45
9	MeSH descriptor: [Value of Life] this term only	32
10	MeSH descriptor: [Costs and Cost Analysis] explode all trees	11515
11	MeSH descriptor: [Economics, Hospital] explode all trees	736
12	MeSH descriptor: [Economics, Medical] explode all trees	62
13	MeSH descriptor: [Economics, Nursing] explode all trees	13
14	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65
15	MeSH descriptor: [Fees and Charges] explode all trees	259
16	MeSH descriptor: [Budgets] explode all trees	32
17	budget*:ti,ab	1284
18	cost*:ti,ab	75603
19	(economic* or pharmaco?economic*):ti,ab	21792
20	(price* or pricing*):ti,ab	2632
21	(financ* or fee or fees or expenditure* or saving*):ti,ab	22897
22	(value near/2 (money or monetary)):ti,ab	347
23	resourc* allocat*:ti,ab	4633
24	(fund or funds or funding* or funded):ti,ab	20420
25	(ration or rations or rationing* or rationed):ti,ab	713
26	{or #8-#25}	120278
27	MeSH descriptor: [Models, Economic] explode all trees	371
28	MeSH descriptor: [Models, Theoretical] this term only	744
29	MeSH descriptor: [Models, Organizational] this term only	180
30	MeSH descriptor: [Markov Chains] this term only	288
31	MeSH descriptor: [Monte Carlo Method] this term only	203
32	MeSH descriptor: [Decision Theory] explode all trees	174
33	(markov* or monte carlo):ti,ab	2214
34	econom* model*:ti,ab	7061
35	(decision* near/2 (tree* or analy* or model*)):ti,ab	2140
36	{or #27-#35}	11044
37	#26 or #36	123649
38	#7 and #37	1179
39	#7 and #37 with Cochrane Library publication date Between Jan 2012 and Aug 2022, in Cochrane Reviews	37

Database: Cochrane Central Register of Controlled Trials (CENTRAL) Issue 7 of 12, July 2022

Date of last search: 01/08/2022

#	Searches	
1	MeSH descriptor: [Climacteric] this term only	335
2	MeSH descriptor: [Menopause] this term only	1622
3	MeSH descriptor: [Perimenopause] this term only	168
4	MeSH descriptor: [Postmenopause] this term only	4982
5	(menopau* or postmenopau* or perimenopau* or climacteri*):ti,ab	27681
6	("change of life" or "life change" or "life changes"):ti,ab	444
7	{or #1-#6}	28529
8	MeSH descriptor: [Economics] this term only	45
9	MeSH descriptor: [Value of Life] this term only	32
10	MeSH descriptor: [Costs and Cost Analysis] explode all trees	11515
11	MeSH descriptor: [Economics, Hospital] explode all trees	736
12	MeSH descriptor: [Economics, Medical] explode all trees	62
13	MeSH descriptor: [Economics, Nursing] explode all trees	13
14	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65
15	MeSH descriptor: [Fees and Charges] explode all trees	259
16	MeSH descriptor: [Budgets] explode all trees	32
17	budget*:ti,ab	1284
18	cost*:ti,ab	75603
19	(economic* or pharmaco?economic*):ti,ab	21792
20	(price* or pricing*):ti,ab	2632
21	(financ* or fee or fees or expenditure* or saving*):ti,ab	22897
22	(value near/2 (money or monetary)):ti,ab	347
23	resourc* allocat*:ti,ab	4633
24	(fund or funds or funding* or funded):ti,ab	20420
25	(ration or rations or rationing* or rationed):ti,ab	713
26	{or #8-#25}	120278
27	MeSH descriptor: [Models, Economic] explode all trees	371
28	MeSH descriptor: [Models, Theoretical] this term only	744
29	MeSH descriptor: [Models, Organizational] this term only	180
30	MeSH descriptor: [Markov Chains] this term only	288
31	MeSH descriptor: [Monte Carlo Method] this term only	203
32	MeSH descriptor: [Decision Theory] explode all trees	174
33	(markov* or monte carlo):ti,ab	2214
34	econom* model*:ti,ab	7061
35	(decision* near/2 (tree* or analy* or model*)):ti,ab	2140
36	{or #27-#35}	11044
37	#26 or #36	123649
38	#7 and #37	1179
39	"conference":pt or (clinicaltrials or trialsearch):so	608941
40	#38 not #39 with Publication Year from 2012 to 2022, in Trials	326

Database: EconLit <1886 to July 21, 2022>

Date of last search: 28/07/2022

#	Searches	
1	Climacteric/	0
2	Menopause/ or Perimenopause/ or Postmenopause/ or exp Menopause Related Disorder/	0

#	Searches	
3	(menopau* or postmenopau* or perimenopau* or climacteri*).tw.	70
4	("change of life" or life change?).tw.	92
5	or/1-4	162
6	limit 5 to yr="2012 -Current"	69

Database: CRD HTA

Date of last search: 28/07/2022

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

Database: INAHTA

Date of last search: 28/07/2022

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

Database: EED

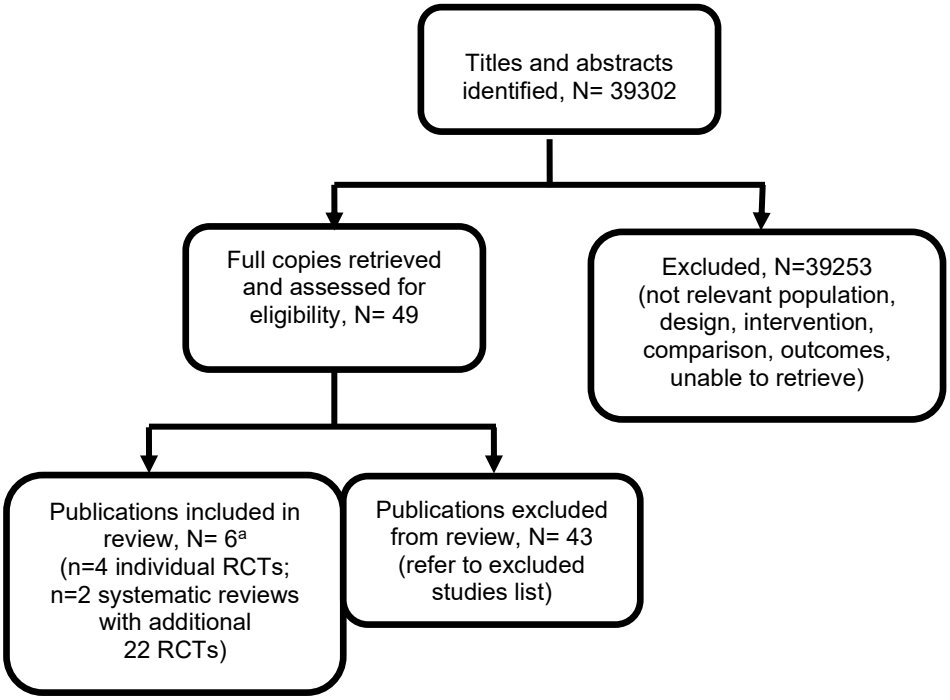
Date of last search: 28/07/2022

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

Appendix C Effectiveness evidence study selection

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

Figure 1: Study selection flow chart



[a]Six publications were included in this review, however 2 of those publications are systematic reviews that included 22 RCTs between them.

Appendix D Evidence tables

Evidence tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on all-cause mortality?

Please note that for the systematic reviews Kim 2020 and Nudy 2019, details for the included individual RCTs have been extracted within the systematic review extraction table.

Table 4: Evidence tables

Chlebowski, 2017

Bibliographic Reference	Chlebowski, Rowan T; Barrington, Wendy; Aragaki, Aaron K; Manson, JoAnn E; Sarto, Gloria; O'Sullivan, Mary J; Wu, Daniel; Cauley, Jane A; Qi, Lihong; Wallace, Robert L; Prentice, Ross L; Oestrogen alone and health outcomes in black women by African ancestry: a secondary analyses of a randomized controlled trial.; Menopause (New York, N.Y.); 2017; vol. 24 (no. 2); 133-141

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial
Study dates	1993-2005
Inclusion criteria	Postmenopausal women between 50–79 years of age with anticipated survival > three years without a breast cancer history
Exclusion criteria	Not reported
Patient characteristics	**Age at screening – years, mean (SD)** White ethnicity Oestrogen: 64.3 (7.2) Placebo: 64.3 (7.3)

	Black ethnicity Oestrogen: 61.7 (7.0) Placebo: 61.5 (7.1) **BMI (kg/m2) – median (IQR)** White Oestrogen: 29.0 (25.3, 33.3) Placebo: 28.7 (25.4, 32.9) Black Oestrogen: 31.2 (27.4, 35.9) Placebo: 30.9 (27.5, 35.8)
Intervention(s)/control	**Intervention** Daily conjugated oestrogen (0.625 mg/d) **Control** Placebo
Duration of follow-up	Median follow-up: 7.2 years
Sources of funding	Novartis, Amgen, Genentech Genomic Health Pfizer and Novo Nordisk Educational Concepts Group
Sample size	N= 9700 Oestrogen: n= 4790 Placebo: n= 4910 **By race:**

	White: N = 8084 Oestrogen: n=4009 Placebo: n=4075 Black: N=1616 Oestrogen: n= 781 Placebo: n= 835

1 **Outcomes**

2 **Outcome**

Outcome	**Oestrogen, N = 4790**	**Placebo, N = 4910**
All-cause mortality – Black population No of events	n = 98	n = 99
All-cause mortality – Black population Sample size	n = 781	n = 835
All-cause mortality – White population No of events	n = 565	n = 574
All-cause mortality – White population Sample size	n = 4009	n = 4075

3 **Hazard ratio**

Outcome	**Oestrogen vs Placebo**
All-cause mortality – Black population	

Outcome	Oestrogen vs Placebo
Hazard ratio/95% CI	1.04 (0.79 to 1.38)
All-cause mortality – White population	
Hazard ratio/95% CI	1.01 (0.9 to 1.13)

1 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants were randomised with no differences at baseline.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Blinded trial with appropriate analysis.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for nearly all participants randomised.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate measurements of outcomes used.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Data analysed according to trial protocol.)*
Overall bias and directness	Risk of bias judgement	Low
Overall bias and directness	Overall directness	Directly applicable

2 **Kim, 2020**

Bibliographic Kim, Ji-Eun; Chang, Jae-Hyuck; Jeong, Min-Ji; Choi, Jaesung; Park, JooYong; Baek, Chaewon; Shin, Aesun; Park, Sang Min;

Reference Kang, Daehee; Choi, Ji-Yeob; A systematic review and meta-analysis of effects of menopausal hormone therapy on cardiovascular diseases.; Scientific reports; 2020; vol. 10 (no. 1); 20631

1 **Study details**

Country/ies where study was carried out	Cherry 2014 United Kingdom Collins 2006 United Kingdom Herrington 2000 United States Hulley 2002 United States Hodis 2003 United States Hodis 2016 United States Manson 2017 United States Tierney 2009 Canada Veerus 2006 Estonia Vickers 2007 Australia, New Zealand, United Kingdom Viscoli 2001 United States
Study type	Systematic review of randomised controlled trials
Study dates	Extracted from individual RCTs

	Cherry 2014 July 1996 -December 2010 Collins 2006 October 1999 to October 2001 Herrington 2000 January 1995 and December 1996 Hulley 2002 1993 to 2000 Hodis 2003 June 1995 to October 2000 Hodis 2016 Not reported Manson 2017 1993 to 1998 Tierney 2009 April 2000 to January 2004 Veerus 2006 1999 to 2001 Vickers 2007 2000 to 2002 Viscoli 2001 December 1993 to May 1998
Inclusion criteria	Extracted from individual RCT Cherry 2014 • Women aged 50–69 years admitted to coronary care units or general medical wards • Meeting the diagnostic criteria for myocardial infarction • Discharged alive from hospital within 31 days of admission

	• No previous documented myocardial infarction Collins 2006 • Postmenopausal women – defined as amenorrhoea for >12 months, or women with a hysterectomy >12 months, or aged >55 • More than 48 hours, or less than 28 days after admission for a myocardial infarction or unstable angina • Informed consent Herrington 2000 • Postmenopausal • No receiving oestrogen-replacement treatment • one or more epicardial coronary stenoses of at least 30 percent of the luminal diameter. Hodis 2003 • Postmenopausal – defined as serum estradiol level below 20 pg per milliter • 75 years of younger • low-density lipoprotein cholesterol level of 100 to 250 mg per deciliter (2.59 to 6.46 mmol per liter) • total triglyceride level of less than 400 mg per deciliter (4.52 mmol per liter) • had at least 1 coronary-artery lesion occluding 30% or more of the luminal diameter (or 20% if they have undergone percutaneous transluminal coronary angioplasty, or coronary-artery bypass). Hodis 2016 • healthy postmenopausal women without diabetes and without clinical evidence of cardiovascular disease • no regular menses for at least 6 months or who had surgically induced menopause • serum estradiol level lower than 25 pg per milliliter Hulley 2002 • Postmenopausal • Younger than 80 • Baseline coronary artery disease • No prior hysterectomy Manson 2017

	• postmenopausal • aged 50-59 • with a uterus Tierney 2009 • 60 or older • Last menstrual cycle 12 or more months before screening • Normal to below normal scores of screening instrument – short-delay recall Veerus 2006 • Aged 50-64 at time of sampling • 12 months or more since last period Vickers 2007 • Women aged 50-69 • Postmenopausal in the past 12 months Viscoli 2001 • Postmenopausal women older than 44 • Within 90 days of a qualifying ischaemic stroke or transient ischaemic attack
Exclusion criteria	Extracted from individual RCT Cherry 2014 • Women who reported a history of cancer or use of hormone replacement therapy in the previous 12 months • Use of HRT or vaginal bleeding in the 12 months before admission • History of breast, ovarian, or endometrial carcinoma • Active thrombophlebitis • History of deep-vein thrombosis or pulmonary embolism • Acute or chronic liver disease • Rotor syndrome

	• Dubin-Johnson syndrome • Severe renal disease Collins 2006 • Women for whom acute coronary syndrome diagnosis not confirmed at time of randomisation • Use of HRT within previous 12 months • Any contraindications for long-term HRT • Increased risk of thromboembolism • History of deep vein thromboembolism or pulmonary embolus • BMI >32 kg/m2 • Prolonged immobility or bed rest • Known breast cancer or endometrial cancer • Post-menopausal bleeding that has not been adequately investigated • Non-cardiac conditions influencing survival Herrington 2000 • Known or suspected breast or endometrial carcinoma • previous or planned coronary-artery bypass surgery • history of deep-vein thrombosis or pulmonary embolism • symptomatic gallstones • serum aspartate aminotransferase level more than 1.5 times the normal value • triglyceride level of more than 400 mg per deciliter (4.52 mmol per liter) while fasting, a serum creatinine level of more than 2.0 mg per deciliter (176.8 µmol per liter) • more than 70 percent stenosis of the left main coronary artery • uncontrolled hypertension • uncontrolled diabetes. Hulley 2002

	• History of deep vein thrombosis or pulmonary embolism • History of breast cancer • Endometrial hyperplasia or cancer • Abnormal Papanicolaou results • Hormone use within the last 3 months • Disease judged to be fatal with 4 years Hodis 2003 • Smoked more than 15 cigarettes per day • Diagnosis of breast of gynaecological cancers within 5 years before screening • life-threatening disease • projected survival of less than 5 years • diastolic blood pressure of more than 110 mm Hg • fasting serum glucose of more than 200 mg per deciliter • thyroid disease • serum creatinine level more than 2.5mg per deciliter • congestive heart failure • more than 5 hot flashes a day that interfered with daily activities • plans to undergo coronary-artery revascularisation within 6 months of first screening visit • baseline coronary angiogram that had been obtained before or less than 6 months after revascularisation • arbamazep infarction less than 6 weeks before screening visit. Hodis 2016 • indeterminate time since menopause • history of breast cancer • current postmenopause hormone therapy within 1 month of screening Manson 2017

	• Not reported Tierney 2009 • met criteria for dementia • clinical history of a neurological systemic or psychiatric condition that would affect cognition • conditions that were considered to be exacerbated by estrogen including history of breast and endometrial cancer • cardiovascular conditions • history of thromboembolic event in the last 6 months Veerus 2006 • use of hormone therapy during the past 6 months • untreated endometrial adenomatosis or atypical hyperplasia of the endometrium • history of breast, endometrial or ovarian cancer • any other cancer treated in last 5 years • cardiovascular or liver conditions Vickers 2007 • history of breast cancer • any other cancer in the past 10 years except basal and squamous cell skin cancer • endometriosis or endometrial hyperplasia • venous thromboembolism • gall bladder disease in women who had not had a cholecystectomy • myocardial infarction, unstable angina, cerebrovascular accident, subarachnoid haemorrhage, transient ischaemic attack • use of hormone replacement therapy within the past six months Viscoli 2001 • history of breast or endometrial cancer • venous thromboembolic event while receiving estrogen-replacement therapy

	• had a neurologic or psychiatric disease that could complicate the evaluation of end points • coexisting condition that limited their life expectancy.
Patient characteristics	Age extracted from systematic review, other characteristics extracted from individual RCTs. **Cherry 2014** **Age - mean (range)** 62.6 (50-69) (not reported for each arm) **Age at last menstrual period – mean (SD)** Estradiol valerate: 46.3 (5.8) Placebo: 46.6 (5.7) **BMI kg/m2 – mean (SD)** Estradiol valerate: 26.8 (5.1) Placebo: 26.7 (5.3) **Use of HRT >12 months before admission – n (%)** Estradiol valerate: 62 (12%) Placebo: 51 (10%) **Collins 2006** **Age – years** 69 (>55+) (SD not reported, each arm not reported) **BMI kg/m2 – mean (SD)** HRT: 26.0 (3.9) Placebo: 26.4 (4.7) **Time since menopause, median (IQR)** HRT: 21.6 (15.8 to 29.9) Placebo: 23.9 (13.8 to 30.5) **Herrington 2000** **Age – years (range)**

	65.8 (41-79) (not reported for each arm) **Ethnicity, number (%)** White: Estrogen: 81 (81) Estrogen plus MPA: 87 (84) Placebo: 85 (81) Black: Estrogen: 14 (14) Estrogen plus MPA: 15 (14) Placebo: 14 (13) Other: Estrogen: 5 (5) Estrogen plus MPA: 2 (2) Placebo: 6 (6) **Hulley 2002** **Age – years** 67 (SD not reported, each arm not reported) **White ethnicity %** *HERS* Hormone: 88 Placebo: 90 *HERS II* Hormone: 89 Placebo: 91 **BMI kg/m2, mean (SD)** *HERS* Hormone: 29 (6) Placebo: 29 (6) *HERS II* Hormone: 29 (5) Placebo: 29 (5)

Age at last menstrual period, mean (SD), years
HERS
Hormone: 49 (5)
Placebo: (49 (5)
HERS II
Hormone: 49 (5)
Placebo: 49 (5)

Estrogen past use %
HERS
Hormone: 24
Placebo: 23
HERS II
Hormone: 25
Placebo: 23

Hodis 2003

Age – years (range)
63.5 (48-75) (each arm not reported)

Race or ethnic group, number (%)
Non-Hispanic white:
Control: 21 (28)
Oestrogen-only: 16 (21)
Oestrogen + Progestin: 32 (43)

Non-Hispanic black:
Control: 11 (14)
Oestrogen-only: 17 (22)
Oestrogen + Progestin: 10 (14)

Hispanic:
Control: 40 (53)
Oestrogen-only: 32 (42)
Oestrogen + Progestin: 28 (38)
Asian:

	Control: 4 (5) Oestrogen-only: 11 (14) Oestrogen + Progestin: 4 (5) **BMI kg/m2, mean (SD)** Control: 30.0 (5.4) Oestrogen-only: 30.6 (5.6) Oestrogen + Progestin: 30.2 (5.6) **Time since menopause – years, mean (SD)** Control: 18.3 (10.5) Oestrogen-only: 16.7 (10.3) Oestrogen + Progestin: 19.7 (10.5) **Hodis 2016** **Age** (SD not reported, each arm not reported) *early post-menopause:* 53.4 *late post-menopause:* 63.6 **BMI kg/m2, median (IQR)** *early post-menopause:* Placebo: 26 (23.2-29.7) Estradiol: 26.2 (23.3–30.6) *late post-menopause:* Placebo: 26.4 (23.1–29.6) Estradiol: 27.2 (23.2–31.2) **Ethnicity, number (%)** White, non-Hispanic *early post-menopause:* Placebo: 73 (59.3) Estradiol: 88 (70.4) *late post-menopause:* Placebo: 127 (72.2) Estradiol: 127 (73.8) Black, non-Hispanic

	early post-menopause: Placebo: 14 (11.4) Estradiol: 7 (5.6) *late post-menopause:* Placebo: 14 (8.0) Estradiol: 17 (9.9) Hispanic *early post-menopause:* Placebo: 20 (16.3) Estradiol: 16 (12.8) *late post-menopause:* Placebo: 23 (13.1) Estradiol: 20 (11.6) Asian *early post-menopause:* Placebo: 16 (13.0) Estradiol: 14 (11.2) *late post-menopause:* Placebo: 12 (6.8) Estradiol: 8 (4.7) **Previous hormone use, number (%)** *early post-menopause:* Placebo: 60 (48.8) Estradiol: 66 (52.8) *late post-menopause:* Placebo: 150 (85.2) Estradiol: 155 (90.1) **Manson 2017** **Age (range)** 50-79 (SD not reported, each arm not reported) **BMI kg/m2, median (IQR)** *Estrogen + MPA:*

	Active: 27.5 (24.2-31.7) Placebo: 27.5 (24.3-31.7) *Estrogen only:* Active: 29.2 (25.7-33.7) Placebo: 29.2 (25.7-33) **Ethnicity, number (%)** White *Estrogen + MPA:* Active: 7141 (84.0) Placebo: 6805 (84.0) *Estrogen only:* Active: 4009 (75.5) Placebo: 4075 (75.1) Black *Estrogen + MPA:* Active: 548 (6.4) Placebo: 574 (7.1) *Estrogen only:* Active: 781 (14.7) Placebo: 835 (15.4) Hispanic *Estrogen + MPA:* Active: 471 (5.5) Placebo: 415 (5.1) *Estrogen only:* Active: 319 (6.0) Placebo: 332 (6.1) American Indian *Estrogen + MPA:* Active: 25 (0.3) Placebo: 30 (0.4) *Estrogen only:* Active: 41 (0.8)

	Placebo: 34 (0.6) Asian/Pacific Islander *Estrogen + MPA:* Active: 194 (2.3) Placebo: 169 (2.1) *Estrogen only:* Active: 86 (1.6) Placebo: 78 (1.4) Unknown *Estrogen + MPA:* Active: 127 (1.5) Placebo: 109 (1.3) *Estrogen only:* Active: 74 (1.4) Placebo: 75 (1.4) **Tierney 2009** **Age, (range)** (SD not reported, each arm not reported) 75 (61-87) **BMI kg/m2, mean (SD)** HRT: 27 (5.2) Placebo: 26.6 (5.4) **Ethnicity, number (%)** White HRT: 67 (95.7) Placebo: 65 (90.3) Black HRT: 2 (2.9) Placebo: 4 (5.6) Asian: HRT: 1 (1.4) Placebo: 3 (4.2)

	Prior HRT use, number (%) HRT: 22 (31.4) Placebo: 17 (23.6) **Veerus 2006** **Age (SD not reported, each arm not reported)** 58.8 **BMI kg/m2, mean (SD)** Open HT: 27.2 (4.5) Control: 26.9 (4.6) Blind HT: 27.0 (4.8) Placebo: 26.9 (4.2) **Age at menopause, mean (SD)** Open HT: 50.2 (3.9) Control: 50.5 (4.0) Blind HT: 50.4 (3.8) Placebo: 50.3 (3.9) Vickers 2007 **Age, (range) (each arm not reported)** 62.8 (50-69) **BMI kg/m2, number (%)** <25 Combined HRT: 629 (29) Placebo: 659 (30) 25-29 Combined HRT: 934 (43) Placebo: 848 (39) >=30 Combined HRT: 623 (28) Placebo: 675 (31)

	Ever used HRT at screening, duration of use, median (IQR) Combined: 3.8 (0.8 to 8) Placebo: 4 (0.9 to 8) **Viscoli 2001** **Age (SD not reported, each arm not reported)** 71 (46-91) **BMI kg/m2, mean (SD)** Estradiol: 28 (7) Placebo: 28 (5) **Ethnicity %** White Estradiol: 84 Placebo: 83 Black Estradiol: 13 Placebo: 13 Other Estradiol: 3 Placebo: 4 **Previous estrogen-replacement therapy (%)** Estradiol: 28 Placebo: 31
Intervention(s)/control	**Cherry 2014** Intervention: E only: 2 mg estradiol valerate (*taken daily for 2 years – continuous) Control: Placebo **Collins 2006** Intervention: Combined EP: 1 mg 17b-estradiol + 0.5mg norethisterone acetate (*taken daily – continuous)

	Control: Placebo **Herrington 2000** Intervention: Oestrogen-only: 0.625 mg conjugated equine oestrogen (*daily) Combined EP: 0.625 mg conjugated equine oestrogen + 2.5 mg medroxyprogesterone acetate (*daily) Control: Placebo **Hulley 2002** Intervention: Combined EP: 0.625 mg conjugated oestrogen, 2.5 mg medroxyprogesterone acetate Control: Placebo **Hodis 2003** Intervention: Combined EP: 1 mg 17β-estradiol + 5 mg medroxyprogesterone acetate (*12 consecutive days of every month) Oestrogen: 1 mg 17β-estradiol (*daily) Control: Placebo **Hodis 2016** Intervention: Oestrogen: 1 mg 17ß-estradiol (women with a uterus also received 45 mg micronized progesterone (as a 4% vaginal gel) (*not excluded a vaginal progesterone not considered systemic) Control: Placebo **Manson 2017** Intervention: Combined EP: 0.625 mg conjugated oestrogen + 2.5 mg medroxyprogesterone acetate Oestrogen: 0.625 mg conjugated equine oestrogen Control: Placebo **Tierney 2009** Intervention: Combined EP: 1 mg 17β-estradiol micronized + 0.35 mg norethindrone Control: Placebo **Veerus 2006** Intervention:

	Combined EP: 0.625 mg conjugated equine oestrogen +2.5 mg (or 5 mg) medroxyprogesterone acetate Control: Placebo **Vickers 2007** Intervention: Combined EP: 0.625 mg conjugated equine oestrogen + 2.5 mg medroxyprogesterone acetate Control: Placebo **Viscoli 2001** Intervention: Oestrogen:1 mg 17ß-estradiol Control: Placebo
Duration of follow-up	**Mean, years** Cherry 2014 14.1 years Collins 2006 0.7 (median) Herrington 2000 3.2 years Hulley 2002 6.8 years Hodis 2003 3.3 years Hodis 2016 7.5 years Manson 2017 18 years (median) Tierney 2009 2 years Veerus 2006 3.43 years

	Vickers 2007 1.03 years Viscoli 2001 2.8 years
Sources of funding	Not reported
Sample size	**Cherry 2014** N=1017 Oestrogen: n=513 Placebo: n=504 **Collins 2006** N=100 Oestrogen + Progesterone: n=49 Placebo: n=51 **Herrington 2000** N=309 Oestrogen: n=100 Oestrogen + Progesterone: n=104 Placebo: n=105 **Hulley 2002** N=2763 Oestrogen + Progesterone: n=1380 Placebo: n=1383 **Hodis 2003** N=226 Oestrogen: n=76 Oestrogen + Progesterone: n=74 Placebo: n=76 **Hodis 2016** N=643

	Oestrogen-only: 323 Placebo:320 **Manson 2017** N=40878 Oestrogen-only: n=5310 Placebo: n=13531 Oestrogen + Progesterone: n=8506 **Tierney 2009** N=142 Oestrogen: n=70 Placebo: n=72 **Veerus 2006** N=1778 Oestrogen + Progesterone: n=898 Placebo: n=880 **Vickers 2007** N=4385 Oestrogen + Progesterone: n=2196 Placebo: n=2189 **Viscoli 2001** N=664 Oestrogen-only: n=337 Placebo: n=327

1 **Outcomes**

2 **All-cause mortality**

Outcome	Oestrogen-only	Oestrogen + Progestin	Placebo or No HRT
Cherry 2014 No of events	n = 214	*NA*	n = 204

Outcome	Oestrogen-only	Oestrogen + Progestin	Placebo or No HRT
Cherry 2014 Sample size	n = 513	*NA*	n = 504
50-59 age group No of events	n = 46	*NA*	n = 39
50-59 age group Sample size	n = 167	*NA*	n = 134
60-69 age group No of events	n = 168	*NA*	n = 165
60-69 age group Sample size	n = 346	*NA*	n = 370
Collins 2006 No of events	*NA*	n = 1	n = 2
Collins 2006 Sample size	*NA*	n = 49	n = 51
Herrington 2000 No of events	n = 8	n = 3	n = 6
Herrington 2000 Sample size	n = 100	n = 104	n = 105

Outcome	Oestrogen-only	Oestrogen + Progestin	Placebo or No HRT
Hulley 2002 No of events	*NA*	n = 261	n = 239
Hulley 2002 Sample size	*NA*	n = 1380	n = 1383
Hodis 2003 No of events	n = 2	n = 3	n = 4
Hodis 2003 Sample size	n = 76	n = 74	n = 76
Hodis 2016 No of events	n = 1	*NA*	n = 1
Hodis 2016 Sample size	n = 323	*NA*	n = 320
Hodis 2016 - <6 years since menopause No of events	n = 0	*NA*	n = 1
Hodis 2016 - <6 years since menopause Sample size	n = 137	*NA*	n = 134
Hodis 2016: >=10 years since menopause No of events	n = 1	*NA*	n = 0

Outcome	Oestrogen-only	Oestrogen + Progestin	Placebo or No HRT
Hodis 2016: >=10 years since menopause Sample size	n = 186	*NA*	n = 186
Manson 2017 (18 year cumulative follow up) No of events	n = 1505	n = 2244	n = 3740
Manson 2017 (18 year cumulative follow up) Sample size	n = 5310	n = 8506	n = 13531
Manson 2017 – Age group 50-59 (18 year cumulative follow up) No of events	n = 170	*NA*	n = 218
Manson 2017 – Age group 50-59 (18 year cumulative follow up) Sample size	n = 1639	*NA*	n = 1674
Manson 2017 – Age group 50-59 (18 year cumulative follow up) No of events	*NA*	n = 307	n = 294
Manson 2017 – Age group 50-59 (18 year cumulative follow up) Sample size	*NA*	n = 2837	n = 2683
Manson 2017 – Age group 60-69	n = 650	*NA*	n = 694

Outcome	Oestrogen-only	Oestrogen + Progestin	Placebo or No HRT
(18 year cumulative follow up) No of events			
Manson 2017 – Age group 60-69 (18 year cumulative follow up) Sample size	n = 2386	*NA*	n = 2465
Manson 2017 – Age group 60-69 (18 year cumulative follow up) No of events	*NA*	n = 964	n = 919
Manson 2017 – Age group 60-69 (18 year cumulative follow up) Sample size	*NA*	n = 3854	n = 3655
Manson 2017 – Age group 70-79 (18 year cumulative follow up) No of events	n = 685	*NA*	n = 718
Manson 2017 – Age group 70-79 (18 year cumulative follow up) Sample size	n = 1285	*NA*	n = 1290
Manson 2017 – Age group 70-79 (18 year cumulative follow up) No of events	*NA*	n = 973	n = 897
Manson 2017 – Age group 70-79 (18 year cumulative follow up)	*NA*	n = 1815	n = 1764

Outcome	Oestrogen-only	Oestrogen + Progestin	Placebo or No HRT
Sample size			
Tierney 2009 No of events	n = 2	*NA*	n = 2
Tierney 2009 Sample size	n = 70	*NA*	n = 72
Veerus 2006 No of events	*NA*	n = 3	n = 4
Veerus 2006 Sample size	*NA*	n = 898	n = 880
Vickers 2007 No of events	*NA*	n = 8	n = 5
Vickers 2007 Sample size	*NA*	n = 2196	n = 2189
Viscoli 2001 No of events	n = 48	*NA*	n = 41
Viscoli 2001 Sample size	n = 337	*NA*	n = 327

Mortality – Hazard ratios

Outcome	Oestrogen-only vs Placebo or No HRT	Oestrogen + Progestin vs Placebo or No HRT
Cherry 2014 Hazard ratio/95% CI	1.07 (0.88 to 1.29)	*NA*
Cherry 2014 – 50-59 years Hazard ratio/95% CI	0.9 (0.59 to 1.38)	*NA*
Cherry 2014 – 60-69 years Hazard ratio/95% CI	1.11 (0.9 to 1.38)	*NA*
Hulley 2002 Hazard ratio/95% CI	*NA*	1.1 (0.92 to 1.31)
Manson 2017 (18 year cumulative follow up) Hazard ratio/95% CI	0.94 (0.88 to 1.01)	1.02 (0.96 to 1.08)
Manson 2017 50-59 (18 year cumulative follow up) Hazard ratio/95% CI	0.79 (0.64 to 0.96)	0.97 (0.83 to 1.14)
Manson 2017 60-69 (18 year cumulative follow up) Hazard ratio/95% CI	0.97 (0.88 to 1.08)	0.98 (0.90 to 1.08)
Manson 2017 70-79 (18 year cumulative follow up) Hazard ratio/95% CI	0.97 (0.87 to 1.07)	1.07 (0.98 to 1.18)
Vickers 2007 Hazard ratio/95% CI	*NA*	1.6 (0.52 to 4.89)

1 **Critical appraisal – NGA Critical appraisal – ROBIS checklist**

Section	Question	Answer

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low *(No potential concerns were identified.)*
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	High *(Some eligible studies are likely to be missing from the review. Only English text papers were included and there is insufficient information regarding the process of selecting studies.)*
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Unclear *(Although 2 reviewers were responsible for data extraction and critical appraisal, no information is provided on how this was conducted.)*
Synthesis and findings	Concerns regarding the synthesis and findings	Low *(The synthesis is unlikely to produce biased results, because any limitations in the data were overcome)*
Overall study ratings	Overall risk of bias	High *(SR was rated as high risk as there was insufficient information regarding identification and selection.)*
Overall study ratings	Applicability as a source of data	Partially applicable

1 **Mulnard, 2000**

Bibliographic Reference Mulnard RA; Cotman CW; Kawas C; van Dyck CH; Sano M; Doody R; Koss E; Pfeiffer E; Jin S; Gamst A; Grundman M; Thomas R; Thal LJ; Oestrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study.; JAMA; 2000; vol. 283 (no. 8)

2 **Study details**

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	Recruitment: October 1995 – January 1999

Inclusion criteria	Diagnosis or probable Alzheimer disease in the mild to moderate range Female sex Previous hysterectomy Age older than 60 years Absence of major clinical depressive disorder Normal gynaecological breasts and mammography results
Exclusion criteria	Myocardial infarction within 1 year History of thromboembolic disease or hypercoagulable state Hyperlipidemia Use of excluded medications
Patient characteristics	**Age, year – mean (range)** High dose Oestrogen: 74.2 (56-89) Low dose Oestrogen: 76.8 (60-91) Placebo: 74.1 (62-87) **Weight, kg mean (range)** High dose Oestrogen: 66 (41-109) Low dose Oestrogen: 60.3 (44-86) Placebo: 64.8 (40-104) **Serum estradiol levels mean (SD)** High dose Oestrogen: 3.2 (3.0) Low dose Oestrogen: 3.4 (4) Placebo: 3.8 (4)
Intervention(s)/control	**Intervention** Conjugated equine oestrogen 1.25mg/d: 2 oestrogen 0.625mg/d tablets daily Conjugated equine oestrogen 0.625mg/d: 1 oestrogen 0.625mg/d tablet + a placebo tablet daily **Control** 2 placebo tablets daily

Duration of follow-up	15 months
Sources of funding	National Institute on Aging National Institutes of Health
Sample size	N=120 Intervention: n=81 Placebo: n=39
Other information	Data available for subgroup analysis for age at first use taken from age at randomisation and constituent available from intervention description

1 **Outcomes**

Outcome	**Oestrogen, N= 81**	**Placebo, N= 39**
All-cause mortality No of events	n = 2	n = 0

2 **Critical appraisal**

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Concealed randomisation process with no differences at baseline found.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double blinded study with appropriate analysis used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for nearly all participants and intention to treat analysis used.)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measures used.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(No trial protocol available)*
Overall bias and directness	Risk of bias judgement	Some concerns *(Study had some concerns in one domain due to missing trial protocol.)*
Overall bias and directness	Overall directness	Directly applicable

1 **Nudy, 2019**

Bibliographic Reference Nudy, Matthew; Chinchilli, Vernon M; Foy, Andrew J; A systematic review and meta-regression analysis to examine the 'timing hypothesis' of hormone replacement therapy on mortality, coronary heart disease, and stroke.; International journal of cardiology. Heart & vasculature; 2019; vol. 22; 123-131

2 **Study details**

Country/ies where study was carried out	Extracted from individual RCT Angerer 2000 Germany Giske 2002 Sweden Guidozzi 1999 South Africa Hall 1998 Sweden Harman 2014 US Hodis 2001 US

	Jirapinyo 2003 Thailand Komulainen 1999 Finland Kyllonen 1998 Finland Nachtigall 1979 US Samaras 1999 Australia
Study type	Systematic review of randomised controlled trials
Study dates	Extracted from individual RCT **Angerer 2000** Recruitment: March 1995 and September 1996 **Giske 2002** Not reported **Guidozzi 1999** Recruitment: January 1987 – June 1994 **Hall 1998** Not reported **Harman 2014** Recruitment: July 2005 – June 2008 **Hodis 2001** Not reported **Jirapinyo 2003** Not reported **Komulainen 1999** 1989-1991

	Kyllonen 1998 Not reported **Nachtigall 1979** Not reported **Samaras 1999** Not reported
Inclusion criteria	Extracted from individual RCT **Angerer 2000** Between 40 and 70 years of age Had passed natural or surgical menopause for at least one year or had follicle stimulating hormone (FSH) levels >40 IU/liter in case they were hysterectomized Had more than 1 mm IMT in at least one of the predefined segments of the carotid arteries Gave written informed consent. **Giske 2002** Healthy, peri- and postmenopausal women with follicle stimulating hormone (FSH) levels above 20 IU/l Not been taking any hormones for at least 3 months before joining the study **Guidozzi 1999** Patients younger than 59 years with invasive epithelial ovarian carcinoma who had their primary management at the respective hospital **Hall 1998** Postmenopausal women with coronary artery disease aged 44–75 years **Harman 2014** Women aged 42 to 58 years who were between 6 and 36 months from their last menses Plasma follicle-stimulating hormone levels of 35 IU/L or greater Estradiol (E2) levels less than 147 pmol/L **Hodis 2001** Postmenopausal (serum estradiol level , 73.4 pmol/L [,20 pg/mL]) 45 years of age or older Low-density lipoprotein (LDL) cholesterol level of 3.37 mmol/L or greater ($130 mg/dL)

	Jirapinyo 2003 Aged between 45 and 65 years Intact uterus Amenorrhoeic for at least 1 year Never received HRT **Komulainen 1999** Recently postmenopausal Without contraindications to HRT **Kyllonen 1998** Postmenopausal Aged 49–55 years **Nachtigall 1979** Last menstrual period 2 or more years ago Never have taken HRT Elevated follicle stimulating hormone levels (>105.5 mU Total urinary oestrogen levels <10 pg/ml **Samaras 1999** None specified
Exclusion criteria	Extracted from individual RCT Angerer 2000 • Myocardial infarction within the last six months • CHD that required treatment for angina • Any other contraindication against HRT • Women with conditions requiring HRT Giske 2002 • Women using phosphates, vitamin D or calcium for osteoporosis

- Women with osteoporosis

Guidozzi 1999

- Patients with ovarian carcinoma of low malignant potential
- Patients who had ever taken conjugated oestrogens

Hall 1998

- Not reported

Harman 2014

- Women with a history of clinical CVD, including myocardial infarction, angina, congestive heart failure, stroke, transient ischemic attack, or thromboembolic disease,

Hodis 2001

- Breast or gynecologic cancer which had been diagnosed in the past 5 years or if these cancers were identified during screening
- Previous usage of HRT for more than 10 years or usage of HRT within 1 month of the first screening visit
- Five or more hot flushes daily that interfered with daily activity and precluded randomization
- Diastolic blood pressure greater than 110 mm Hg
- Untreated thyroid disease
- Life-threatening disease with a survival prognosis of less than 5 years
- Total triglyceride level of 4.52 mmol/L or greater ($400 mg/dL)
- High-density lipoprotein (HDL) cholesterol level less than 0.78 mmol/L (,30 mg/dL)
- Serum creatinine concentration greater than 221 mmol/L (.2.5 mg/dL)
- Current smoker

Jirapinyo 2003

- Any history of breast carcinoma

	• Endometrial carcinoma • Liver disease, where liver function tests have failed to return to normal • Deep venous thrombosis • Thromboembolic disorders • Cerebral vascular accidents • Abnormal genital bleeding of unknown etiology • Cardiac dysfunction • Presence of uncontrolled diabetes mellitus • Intake of any steroid hormones during the 6-month period prior to study • Current treatment with liver enzyme-inducing medication (e.g. barbiturates, phenytoin, rifampicin, arbamazepine) • Porphyria and known or suspected allergy to trial product or related products • On concomitant medications that affect bone metabolism or with a large amount of vitamin D treatment (>1000 U/day) Komulainen 1999 • History of breast or endometrial cancer • Thromboembolic diseases • Medication-resistant hypertension Kyllonen 1998 • Not reported Nachtigall 1979 • Acute heart disease • Hypertension of recordings larger than 160/94

	• Any apparent malignancy • Prior hysterectomy Samaras 1999 • Menopause duration of more than 10 years • HRT in the preceding 2 years • cardiac disease • Weight loss of more than 3kg in the preceding 6 months • Postural drop in blood pressure of more than 30 mmHg • Symptoms of autonomic neuropathy • Fasting triglycerides of more than 4,0 mmol/L • Vitamin supplementation • Severe concomitant illness
Patient characteristics	Extracted from individual RCT- except age **Angerer 2000** **Age – mean (SD)** 59.2 (4.2) **BMI (kg/m2)** HRT1: 25.9 ± 4.2 HRT2: 25.5 ± 4.1 No-HRT: 25.6 ± 4.4 **Diabetes Mellitus (n)** HRT1: 3

	HRT2: 2 No-HRT: 5 **Hypertension (n)** HRT1: 20 HRT2: 28 No-HRT: 21 **CHD (n)** HRT1: 1 HRT2: 1 No-HRT: 5 **Giske 2002** **Age – mean (SD)** 49.5 **BMI (kg/m2) – mean (range)** 0.5mg Estradiol: 24.5 (17.7-31.2) 1mg Estradiol: 24.7 (18.0-35.8) 2mg Estradiol: 24.7 (19.8-33.1) Placebo: 25.6 (18.7-37.6) **Blood pressure (mmHg) – mean (range)** 0.5mg Estradiol: 122/80 (100–150/60–90) 1mg Estradiol: 122/80 (95–160/60–90) 2mg Estradiol: 120/80 (90–140/50–90)

	Placebo: 130/80 (100–150/70–90) **Hemoglobin (g/L) – mean (range)** 0.5mg Estradiol: 130/80 (100–150/70–90) 1mg Estradiol: 139 (112–159) 2mg Estradiol: 137 (96–161) Placebo: **Guidozzi 1999** **Under 59 years (mean age not provided)** **Cancer stages (n)** I: HRT: 7 No HRT: 9 II: HRT: 9 No HRT: 4 III: HRT: 38 No HRT: 46 IV: HRT: 5 No HRT: 7

	Hall 1998 **Age – mean (SD)** 59.4 (6.6) **BMI (kg/m2) – mean (SD)** 25.9 (4.9) **Years after menopause – mean (SD)** 11.4 (6.9) Harman 2014 **Age – mean (SD)** 52.7 (2.6) **BMI (kg/m2) – mean (SD)** 26.2 (4.3) **Hodis 2001** **Age – mean (SD)** 62.2 (6.9) **BMI (kg/m2) – mean (SD)** Estradiol: 28.7 (5.5) Placebo: 29.0 (5.3) **Jirapinyo 2003** **Age – mean (SD)** 54.3 (4.4)

	BMI (kg/m2) – mean (SD) HRT: 23.9 (3.5) Placebo: 24.3 (3.3) **Komulainen 1999** **Age – mean (SD)** 52.8 **BMI (kg/m2) – mean (range)** HRT: 26.9 (26.1–27.7) HRT+Vitamin D: 26.8 (26.0–27.6) Vitamin D: 27.1 (26.4–27.9) Placebo: 27.1 (26.4–27.9) **Time since menopause in years – mean (range)** HRT: 1.1 (1.0–1.2) HRT+Vitamin D: 1.1 (1.0–1.2) Vitamin D: 1.1 (1.0–1.2) Placebo: 1.1 (1.0–1.2) **Previous HRT use in years – mean (range)** HRT: 0.8 (0.5–1.1) HRT+Vitamin D: 0.6 (0.3–0.9) Vitamin D: 0.6 (0.3–0.8) Placebo: 0.4 (0.2–0.5)

	Kyllonen 1998 **Age – mean (SD)** 52.6 (1.5) **BMI (kg/m2) – mean (SD)** 25.6 (3.5) **Time since last menstruation in years – mean (SD)** 2.37 (1.12) Nachtigall 1979 **Age – mean** 55 **Years since last menstruation – mean** HRT: 4.7 No HRT: 4.5 **Samaras 1999** **Age – mean (SD)** 57.5 (5.6) **BMI (kg/m2) – mean (SD)** 29.7 (1.3)
Intervention(s)/control	**Angerer 2000** Intervention (combined) • 1 mg 17β-estradiol plus 0.025 mg gestodene for 12 days per month • 1 mg 17β-estradiol plus 0.025 mg gestodene for 12 days every 3rd month

- subgroups: estradiol constituent; synthetic progestin constituent

Control

- No HRT

Giske 2002 (oestrogen-only)

Intervention

- 0.5 mg mg/day of 17β-estradiol
- 1 mg mg/day of 17β-estradiol
- 2 mg mg/day of 17β-estradiol
- subgroup: estradiol constituent

Control

- Placebo

Guidozzi 1999 (oestrogen-only)

Intervention

- 0.625 mg/day of conjugated equine oestrogen

subgroup: equine constituent

Control

- No HRT

Hall 1998 (combined)

Intervention

- 50 µg/day transdermal 17β-estradiol followed by 10 days of medroxyprogesterone acetate
- Oral 0.625 mg/day of conjugated oestrogen with MPA
- subgroup: estradiol constituent; medroxyprogestrone acetate constituent

Control

- Placebo

Harman 2014 (oestrogen-only)

Intervention

- 0.45 mg/day of oral conjugated equine oestrogen
- 50 µg/day of transdermal 17β-estradiol each with 200 mg of oral progesterone for 12 days/month

- subgroup: equine constituent

Control

- Placebo

Hodis 2001 (oestrogen-only)

Intervention

- 1 mg/day of 17β-estradiol
- subgroup: estradiol constituent

Control

- Placebo

Jirapinyo 2003 (combined)

Intervention

- 2 mg/day of 17β-estradiol plus 1 mg/day norethisterone acetate
- subgroups: estradiol constituent; noethisterone acetate constituent

Control

- Placebo

Komulainen 1999 (sequential combined)

Intervention

- 2 mg/day of estradiol valerate plus 1 mg of cyproterone acetate or 300 IU/day of vitamin D plus 2 mg/day of estradiol valerate plus 1 mg of cyproterone acetate (estradiol valerate days 1-21, cyproterone acetate days 12-21, treatment free 22-28)
- 300 IU/day of vitamin D
- subgroups: estradiol constituent; synthetic progestin constituent; 30 day cycle

Control

- Placebo

Kyllonen 1998 (sequential combined)

Intervention

- 2 mg/day estradiol valerate with 10 mg/day of medroxyprogesterone acetate (estradiol valerate for 11 days, progesterone for 10 days, placebo for 7 days)
- subgroups: estradiol constituent; medroxyprogesterone acetate constituent; 30 day cycle

	Control • Placebo **Nachtigall 1979 (combined)** Intervention • 2.5 mg/day of conjugated equine oestrogen and 10 mg/day of medroxyprogesterone • subgroups: equine constituent; medroxyprogesterone constituent Control • Placebo **Samaras 1999 (combined)** Intervention • 2 months of conjugated equine oestrogen 0.625 mg/day followed by 4 months of CEE plus medroxyprogesterone 5 mg daily • subgroups: equine constituent; medroxyprogesterone constituent Control • No HRT
Duration of follow-up	Angerer 2000 0.92 years Giske 2002 2 years Guidozzi 1999 4 years Hall 1998 1 year Harman 2014 4 years Hodis 2001 2 years Jirapinyo 2003 1 years

	Komulainen 1999 5 years Kyllonen 1998 2 years Nachtigall 1979 10 years Samaras 1999 1 year
Sources of funding	Extracted from individual RCT **Angerer 2000** Muenchener Universitaetsgesellschaft, Muenchen, Germany, made possible by Schering AG, Berlin, Germany **Giske 2002** Novo Nordisk A/S **Guidozzi 1999** Not reported **Hall 1998** Swedish Heart and Lung Foundation The Swedish Medical Research Council Ciba Geigy, Switzerland **Harman 2014** Aurora Foundation Pfizer Pharmaceuticals Bayer HealthCare and Abbott Pharmaceuticals

	Hodis 2001 Mead Johnson Laboratories Pharmacia & Upjohn Company Bristol-Myers Squibb Company Merck & Co., Inc Parke-Davis Novartis Pharmaceuticals Corp **Jirapinyo 2003** Novo Nordisk Asia Pacific Pte Ltd **Komulainen 1999** Leiras Oy, Finland and Schering AG **Kyllonen 1998** Deaconess Institute of Oulu Orion Corporation, Orion Pharma, Helsinki, Finland **Nachtigall 1979** Not reported **Samaras 1999** St Vincent's Clinic Foundation
Sample size	Angerer 2000 N= 321 Giske 2002 N= 166

	Guidozzi 1999 N= 130 Hall 1998 N= 200 Harman 2014 N= 727 Hodis 2001 N= 222 Jirapinyo 2003 N= 120 Komulainen 1999 N= 464 Kyllonen 1998 N= 78 Nachtigall 1979 N= 168 Samaras 1999 N= 14

1 **Outcomes**

2 **All-cause mortality**

Outcome	Oestrogen	Oestrogen + Progestin	Placebo or no HRT
Angerer 2000 No of events	*NA*	n = 1	n = 0
Angerer 2000 Sample size	*NA*	n = 119	n = 54

Outcome	Oestrogen	Oestrogen + Progestin	Placebo or no HRT
Giske 2002 No of events	n = 1	*NA*	n = 0
Giske 2002 Sample size	n = 108	*NA*	n = 31
Guidozzi 1999 No of events	n = 32	*NA*	n = 41
Guidozzi 1999 Sample size	n = 62	*NA*	n = 68
Hall 1998 No of events	*NA*	n = 0	n = 1
Hall 1998 Sample size	*NA*	n = 40	n = 20
Hall 1998 – transdermal No of events	*NA*	n = 0	n = 1
Hall 1998 – transdermal Sample size	*NA*	n = 20	n = 20
Hall 1998 – oral No of events	*NA*	n = 0	n = 1

Outcome	Oestrogen	Oestrogen + Progestin	Placebo or no HRT
Hall 1998 – oral Sample size	*NA*	n = 20	n = 20
Harman 2014 No of events	n = 1	*NA*	n = 0
Harman 2014 Sample size	n = 552	*NA*	n = 275
Hodis 2001 No of events	n = 0	*NA*	n = 1
Hodis 2001 Sample size	n = 111	*NA*	n = 111
Jirapinyo 2003 No of events	*NA*	n = 1	n = 0
Jirapinyo 2003 Sample size	*NA*	n = 50	n = 53
Komulainen 1999 No of events	*NA*	n = 2	n = 1
Komulainen 1999 Sample size	*NA*	n = 231	n = 227

Outcome	Oestrogen	Oestrogen + Progestin	Placebo or no HRT
Kyllonen 1998 No of events	*NA*	n = 1	n = 0
Kyllonen 1998 Sample size	*NA*	n = 52	n = 26
Nachtigall 1979 No of events	*NA*	n = 3	n = 7
Nachtigall 1979 Sample size	*NA*	n = 87	n = 84
Samaras 1999 No of events	*NA*	n = 0	n = 1
Samaras 1999 Sample size	*NA*	n = 7	n = 7

1 **Critical appraisal – NGA Critical appraisal – ROBIS checklist – 2.6 mortality**

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Unclear *(SR did not provide sufficient information regarding eligibility criteria.)*
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	High *(Only one database was searched with English language restriction.)*
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low *(Risk of bias was assessed using appropriate criteria, data extraction and*

Section	Question	Answer
		risk of bias assessment involved two reviewers,)
Synthesis and findings	Concerns regarding the synthesis and findings	Low *(The synthesis is unlikely to produce biased results, because any limitations in the data were overcome.)*
Overall study ratings	Overall risk of bias	Unclear *(There was insufficient information provided regarding the selection and identification process of studies.)*
Overall study ratings	Applicability as a source of data	Fully applicable

1 **Os, 2000**

Bibliographic Reference Os, I; Hofstad, A E; Brekke, M; Abdelnoor, M; Nesheim, B I; Jacobsen, A F; Birkeland, K; Larsen, A; Midtbo, K; Westheim, A; The EWA (oestrogen in women with atherosclerosis) study: a randomized study of the use of hormone replacement therapy in women with angiographically verified coronary artery disease. Characteristics of the study population. Effects on lipids and lipoproteins.; Journal of internal medicine; 2000; vol. 247 (no. 4); 433-41

2 **Study details**

Country/ies where study was carried out	Norway
Study type	Randomised controlled trial
Study dates	Recruitment: May 1995 and January 1997
Inclusion criteria	• less than 71 years of age • no natural menses for at least 1 year • postmenopausal status verified with elevated follicle stimulating hormone (FSH) and luteinizing hormone (LH)
Exclusion criteria	• previously prescribed HRT (previous use of oestriol was permitted; had been used by two women) • venous thromboembolism during pregnancy or during use of contraceptive pills, without predisposing cause or family history of venous thromboembolism

	• previous gynaecological cancer or breast cancer • alcoholism or other drug abuse • serious psychiatric disorder intervening with compliance and ability to attend study visits
Patient characteristics	**Age, year - mean (range)** Oestrogen + Progestin: 63 (59-68) Control: 66 (60-71) **Height, cm mean (range)** Oestrogen + Progestin: 163 (159-166) Control: 165 (160-167) **Weight, kg mean (range)** Oestrogen + Progestin: 69 (61-79) Control: 65 (60-75)
Intervention(s)/control	**Intervention** Transdermal patches of 17- b estradiol (Estraderm) 50 mg for 24 hours, changed twice weekly. 17-b estradiol was given unopposed for 3 months, followed for 14 days with 5 mg o.d. of medroxyprogesterone acetate (Provera). Subgroup: estradiol constituent, medroxyprogesterone acetate constituent, long cycle. **Control** No treatment
Sample size	N=118 Oestrogen + Progestin: n=60 Control: n=58
Duration of follow-up	12 months
Sources of funding	The Norwegian Research Council The Johan Throne Holst Medical Research Fund

Other information	Data available for subgroup analysis for age at first use taken from age at randomisation. Constituent and length of cycle for sequential available from intervention description.

1 **Outcomes**

2 **Outcomes**

Outcome	Oestrogen + Progestin, N = 60	Control, N = 58
All-cause mortality No of events	n = 2	n = 1

3 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation was concealed and no differences at baseline between groups were found.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(No information regarding analysis provided.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	High *(Unclear if outcome data is available for all participants randomised, with unclear use of analysis.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low *(Appropriate outcome measure used with examiners unaware of intervention assignment.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Some concerns *(Unable to obtain trial protocol)*
Overall bias and directness	Risk of bias judgement	High *(Study had high risk of bias in 2 domains due to missing information regarding analysis and number of*

Section	Question	Answer
		participants analysed.)
Overall bias and directness	Overall directness	Indirectly applicable

1

2 **PEPI 1995**

Bibliographic Reference	Effects of oestrogen or oestrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Oestrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial.; JAMA; 1995; vol. 273 (no. 3)

3 **Study details**

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	Recruitment: December 1989 and February 1991
Inclusion criteria	Women aged 45 to 64 years Naturally or surgically menopausal At least 1 year, but not greater than 10 years past their last menstrual period If surgically menopausal, at least 2 months after hysterectomy and with a follicle stimulating hormone level greater than or equal to 40 IU/L. Normal baseline results of mammography and endometrial biopsy
Exclusion criteria	Severe menopausal symptoms were excluded Having used oestrogens or progestins within 3 months Being treated with thyroid hormone and not been taking a stable dose for at least 3 months

	Serious illness (eg, myocardial infarction within 6 months, congestive heart failure, stroke, transient ischemic attack) or contraindications to oestrogen, including prior breast or endometrial cancer. LDL-C level of 4.91 mmol/L or more (>190 mg/ dL) Triglyceride level of 12.93 mmol/L or more (>500 mg/dL) Body mass index greater than or equal to 40 Blood pressure greater than or equal to 160 mm Hg systolic or 95 mm Hg diastolic Fasting plasma glucose level of 7.7 mmol/L or more (>140 mg/dL)
Patient characteristics	**Age, year - mean** 56.1 (SD not reported) (per arm not reported) **Weight, kg mean (SD)** Oestrogen: 70.1 (1) Oestrogen + Progestin: 69 (1) Placebo: 70.2 (3.4)
Intervention(s)/control	**Intervention** Oestrogen: conjugated equine oestrogen (CEE) 0.625 mg/d Oestrogen and Progestin: 1) CEE, 0.625 mg/d, plus medroxyprogesterone acetate (MPA), 10 mg/d for the first 12 days; 2) CEE, 0.625 mg/d, plus MPA, 2.5 mg/d; 3) CEE, 0.625 mg/d, plus MP, 200 mg/d for the first 12 days subgroup: equine constituent; medroxyprogesterone acetate constituent; 30 day cycle **Control** Placebo
Duration of follow-up	3 years

Sources of funding	Not reported
Sample size	N= 875 Intervention: n= 701 Placebo: n= 174
Other information	Data available for subgroup analysis for age at first use taken from age at randomisation. Constituent and length of cycle for sequential available from intervention description.

1 **Outcomes**

2

Outcome	Oestrogen, N = 175	Oestrogen + Progestin, N = 526	Placebo, N = 174
All-cause mortality No of events	n = 0	n = 3	n = 0

3 **Critical appraisal**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants were randomised with no differences at baseline found.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Majority of participants (94%) was blinded to treatment. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low *(Data available for nearly all participants and intention to treat analysis used.)*
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the	Low

Section	Question	Answer
	outcome	*(Appropriate outcome measures used.)*
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Data analysed according to trial protocol.)*
Overall bias and directness	Risk of bias judgement	Low *(Study had no concerns in any domain)*
Overall bias and directness	Overall directness	Directly applicable

1
2

Appendix E Forest plots

Forest plots for review question: What are the effects of hormone replacement therapy for menopausal symptoms on all-cause mortality?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in Appendix F. RCT data taken from the systematic reviews included in this review have been cited with the RCT reference within the forest plots, please see figure footnotes for further details. Combined effect estimates from the systematic reviews are not reported in the forest plots to avoid double counting.

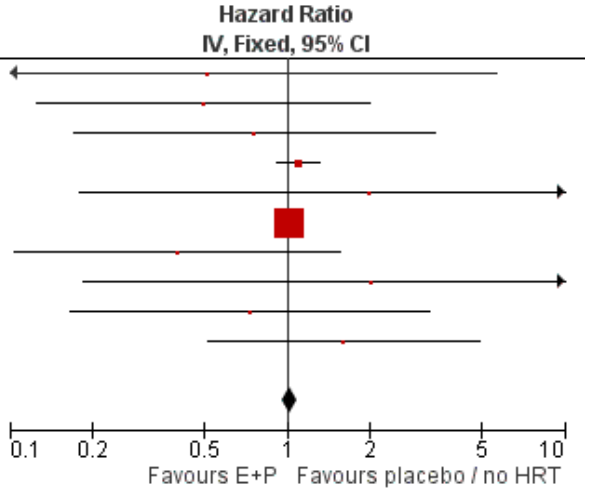
Comparison 1: Oestrogen plus progesterone (any combined) versus placebo or no HRT

Hazard ratio

Figure 2: All-cause mortality - overall

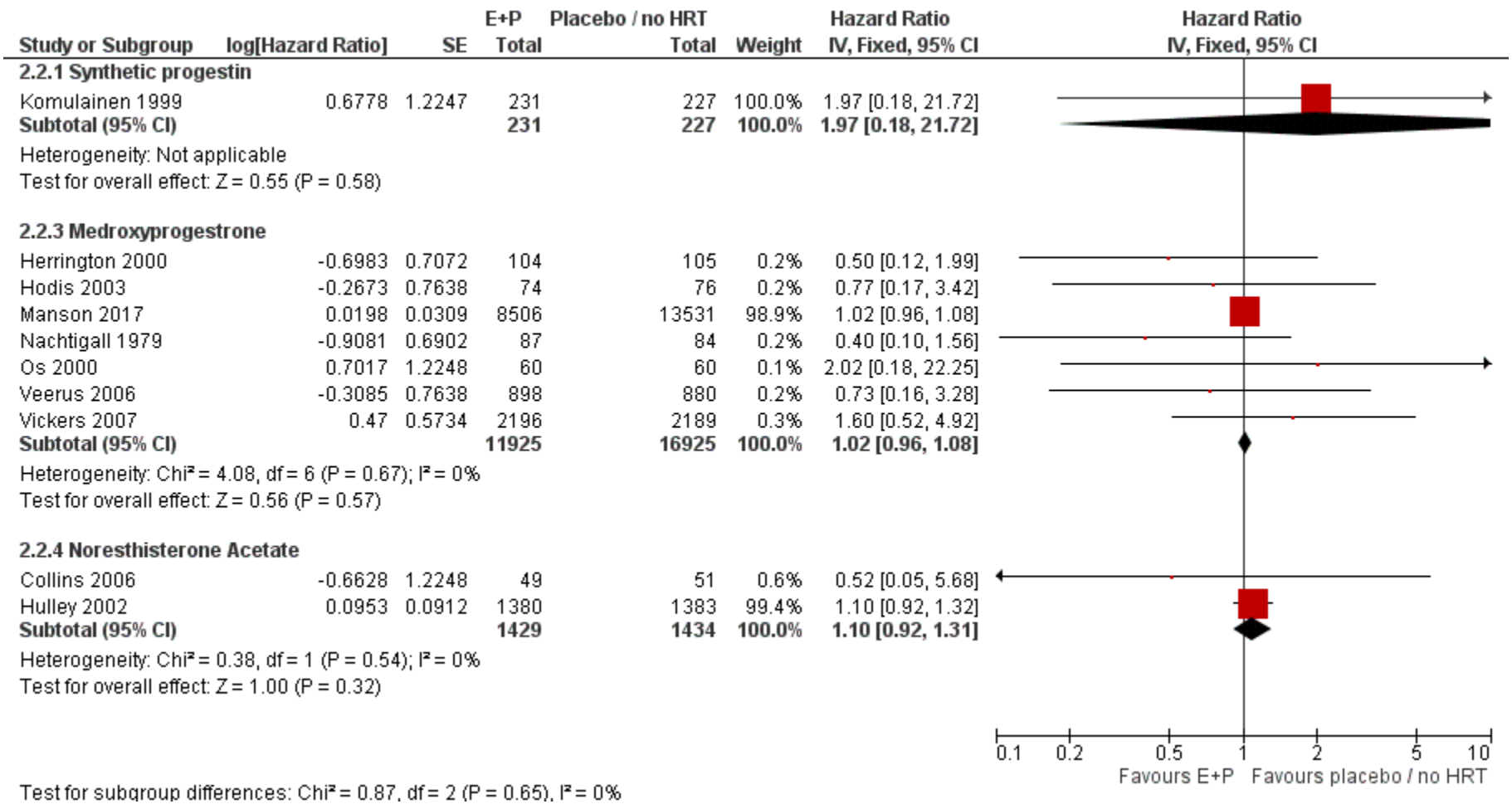
Study or Subgroup	log[Hazard Ratio]	SE	E+P Total	Placebo / no HRT Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Collins 2006	-0.6628	1.2248	49	51	0.1%	0.52 [0.05, 5.68]
Herrington 2000	-0.6983	0.7072	104	105	0.2%	0.50 [0.12, 1.99]
Hodis 2003	-0.2673	0.7638	74	76	0.1%	0.77 [0.17, 3.42]
Hulley 2002	0.0953	0.0912	1380	1383	10.2%	1.10 [0.92, 1.32]
Komulainen 1999	0.6778	1.2247	231	227	0.1%	1.97 [0.18, 21.72]
Manson 2017	0.0198	0.0309	8506	13531	88.7%	1.02 [0.96, 1.08]
Nachtigall 1979	-0.9081	0.6902	87	84	0.2%	0.40 [0.10, 1.56]
Os 2000	0.7017	1.2248	60	60	0.1%	2.02 [0.18, 22.25]
Veerus 2006	-0.3085	0.7638	898	880	0.1%	0.73 [0.16, 3.28]
Vickers 2007	0.47	0.5734	2196	2189	0.3%	1.60 [0.52, 4.92]
Total (95% CI)			**13585**	**18586**	**100.0%**	**1.03 [0.97, 1.09]**

Heterogeneity: Chi² = 5.34, df = 9 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.39)



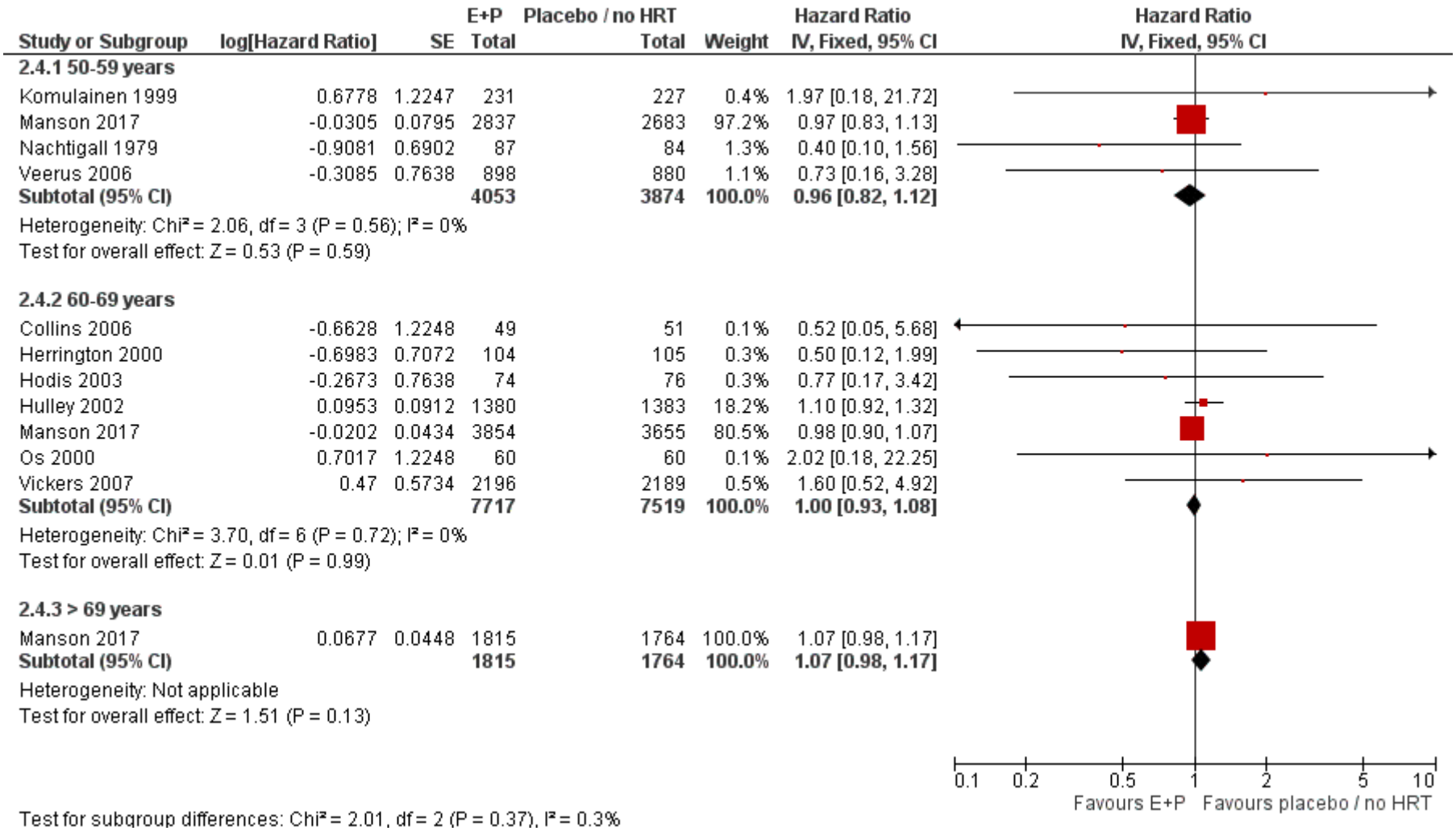
Collins 2006, Herrington 2000, Hulley 2002, Hodis 2003, Manson 2017, Veerus 2006 and Vickers 2007 have been extracted from the systematic review Kim 2020; Komulainen 1999 and Nachtigall 1979 have been extracted from the systematic review Nudy 2019.

Figure 3: All-cause mortality - by progestogenic constituent



Collins 2006, Herrington 2000, Hulley 2002, Hodis 2003, Manson 2017, Veerus 2006 and Vickers 2007 have been extracted from the systematic review Kim 2020; Komulainen 1999 and Nachtigall 1979, have been extracted from the systematic review Nudy 2019.

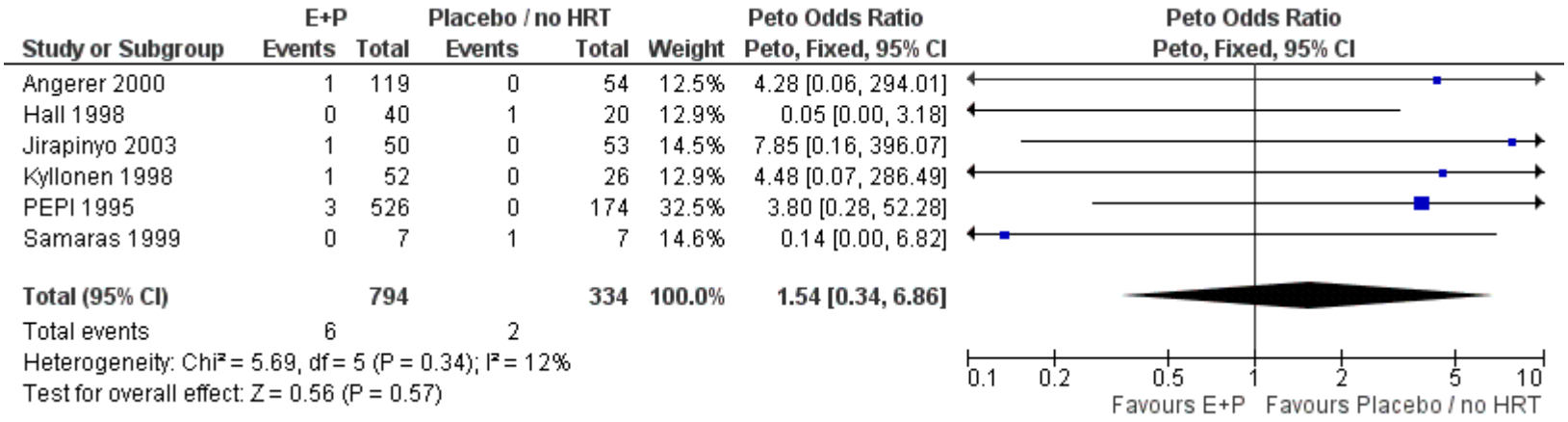
Figure 4: All-cause mortality - by age at first use



Collins 2006, Herrington 2000, Hulley 2002, Hodis 2003, Manson 2017, Veerus 2006 and Vickers 2007 have been extracted from the systematic review Kim 2020; Komulainen 1999 and Nachtigall 1979 have been extracted from the systematic review Nudy 2019.

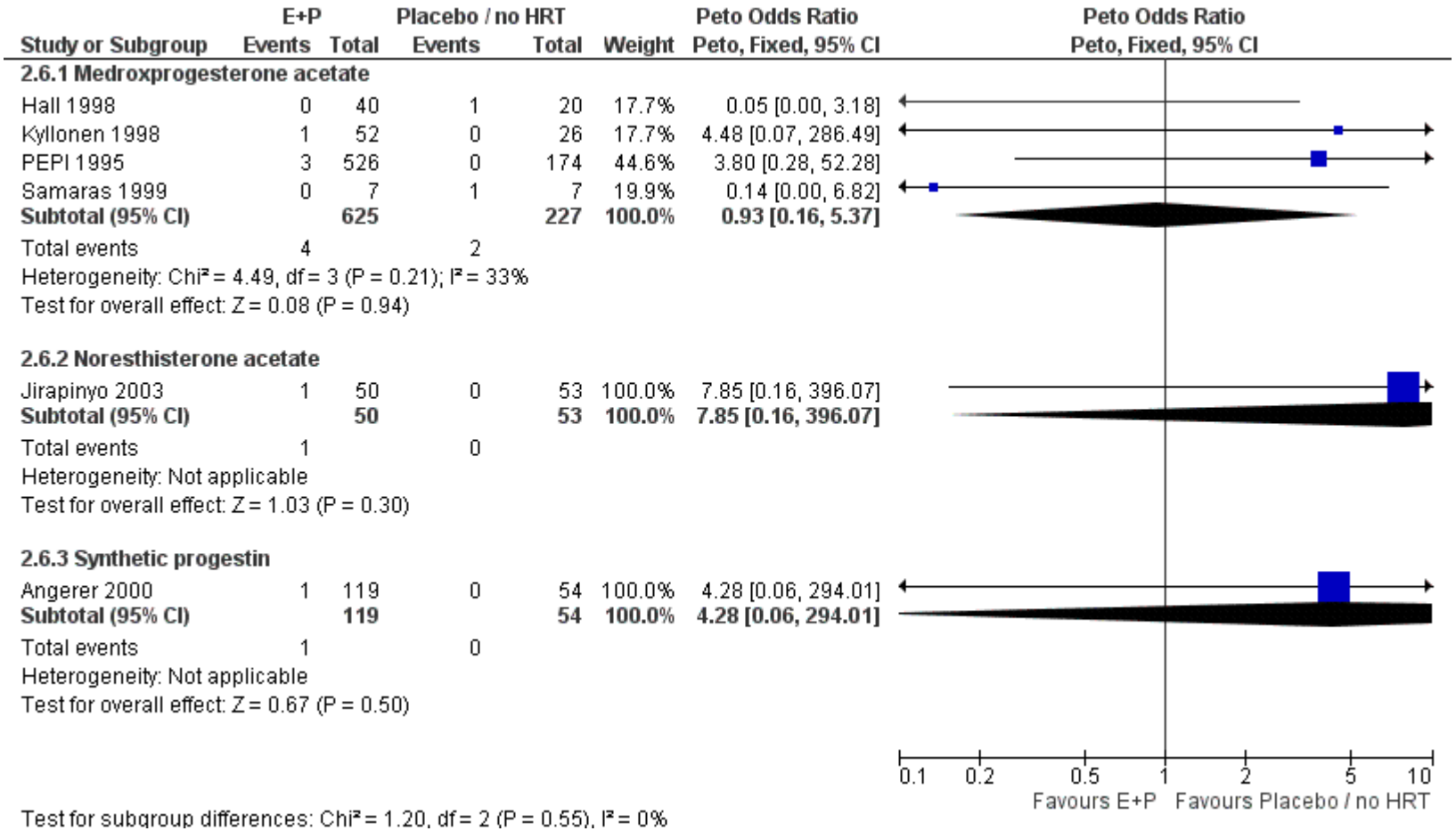
Peto odds ratio

Figure 5: All-cause mortality - overall



Angerer 2000, Hall 1998, Jirapinyo 2003, Kyllonen 1998 and Samaras 1999 have been extracted from the systematic review Nudy 2019.

Figure 6: All-cause mortality - by progestogenic constituent



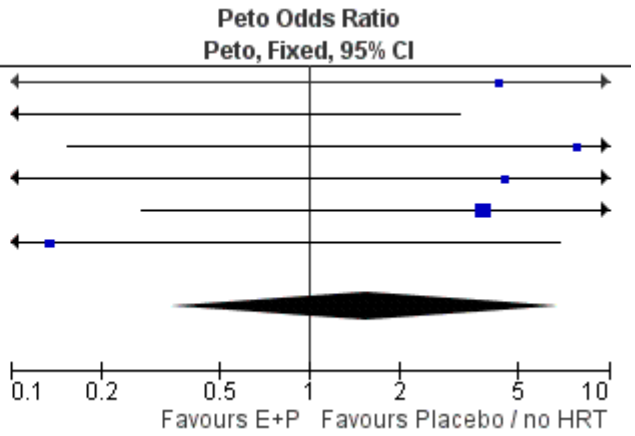
Test for subgroup differences: Chi² = 1.20, df = 2 (P = 0.55), I² = 0%

Angerer 2000, Hall 1998, Jirapinyo 2003, Kyllonen 1998 and Samaras 1999 have been extracted from the systematic review Nudy 2019.

Figure 7: All-cause mortality - by age at first use – 50-59 years

Study or Subgroup	E+P Events	E+P Total	Placebo / no HRT Events	Placebo / no HRT Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Angerer 2000	1	119	0	54	12.5%	4.28 [0.06, 294.01]
Hall 1998	0	40	1	20	12.9%	0.05 [0.00, 3.18]
Jirapinyo 2003	1	50	0	53	14.5%	7.85 [0.16, 396.07]
Kyllonen 1998	1	52	0	26	12.9%	4.48 [0.07, 286.49]
PEPI 1995	3	526	0	174	32.5%	3.80 [0.28, 52.28]
Samaras 1999	0	7	1	7	14.6%	0.14 [0.00, 6.82]
Total (95% CI)		**794**		**334**	**100.0%**	**1.54 [0.34, 6.86]**
Total events	6		2			

Heterogeneity: Chi² = 5.69, df = 5 (P = 0.34); I² = 12%
Test for overall effect: Z = 0.56 (P = 0.57)



Angerer 2000, Hall 1998, Jirapinyo 2003, Kyllonen 1998, Samaras 1999 have been extracted from the systematic review Nudy 2019.

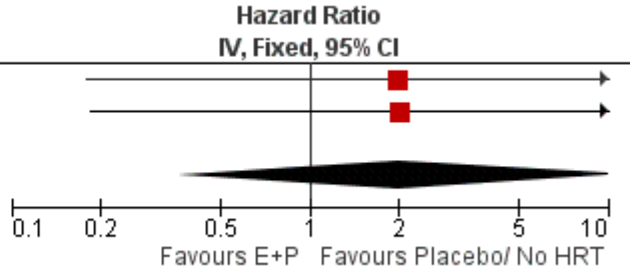
Comparison 2: Sequential combined oestrogen and progesterone versus placebo or no HRT

Hazard ratio

Figure 8: All-cause mortality - overall

Study or Subgroup	log[Hazard Ratio]	SE	E+P Total	Placebo/ no HRT Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Komulainen 1999	0.6778	1.2247	231	227	50.0%	1.97 [0.18, 21.72]
Os 2000	0.7017	1.2248	60	60	50.0%	2.02 [0.18, 22.25]
Total (95% CI)			**291**	**287**	**100.0%**	**1.99 [0.37, 10.88]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.80 (P = 0.43)



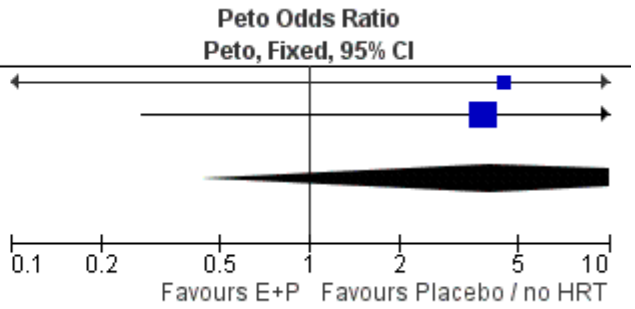
Komulainen 1999 has been extracted from the systematic review Nudy 2019.

Peto odds ratio

Figure 9: All-cause mortality - Overall (age at first use 50-59; medroxyprogesterone acetate, 30 day)

Study or Subgroup	E+P Events	E+P Total	Placebo / no HRT Events	Placebo / no HRT Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kyllonen 1998	1	52	0	26	28.5%	4.48 [0.07, 286.49]
PEPI 1995	3	526	0	174	71.5%	3.80 [0.28, 52.28]
Total (95% CI)		**578**		**200**	**100.0%**	**3.98 [0.43, 36.58]**
Total events	4		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)



Kyllonen 1998 has been extracted from the systematic review Nudy 2019.

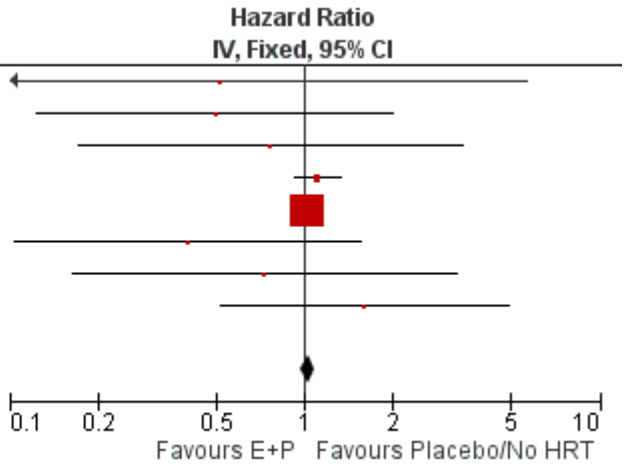
Comparison 3: Continuous combined oestrogen plus progesterone versus placebo or no HRT

1 ***Hazard ratio***

Figure 10: All-cause mortality - Overall

Study or Subgroup	log[Hazard Ratio]	SE	E+P Total	Placebo/ No HRT Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Collins 2006	-0.6628	1.2248	49	51	0.1%	0.52 [0.05, 5.68]
Herrington 2000	-0.6983	0.7072	104	105	0.2%	0.50 [0.12, 1.99]
Hodis 2003	-0.2673	0.7638	74	76	0.1%	0.77 [0.17, 3.42]
Hulley 2002	0.0953	0.0912	1380	1383	10.2%	1.10 [0.92, 1.32]
Manson 2017	0.0198	0.0309	8506	13531	88.8%	1.02 [0.96, 1.08]
Nachtigall 1979	-0.9081	0.6902	87	84	0.2%	0.40 [0.10, 1.56]
Veerus 2006	-0.3085	0.7638	898	880	0.1%	0.73 [0.16, 3.28]
Vickers 2007	0.4675	0.5701	2196	2189	0.3%	1.60 [0.52, 4.88]
Total (95% CI)			**13294**	**18299**	**100.0%**	**1.02 [0.97, 1.09]**

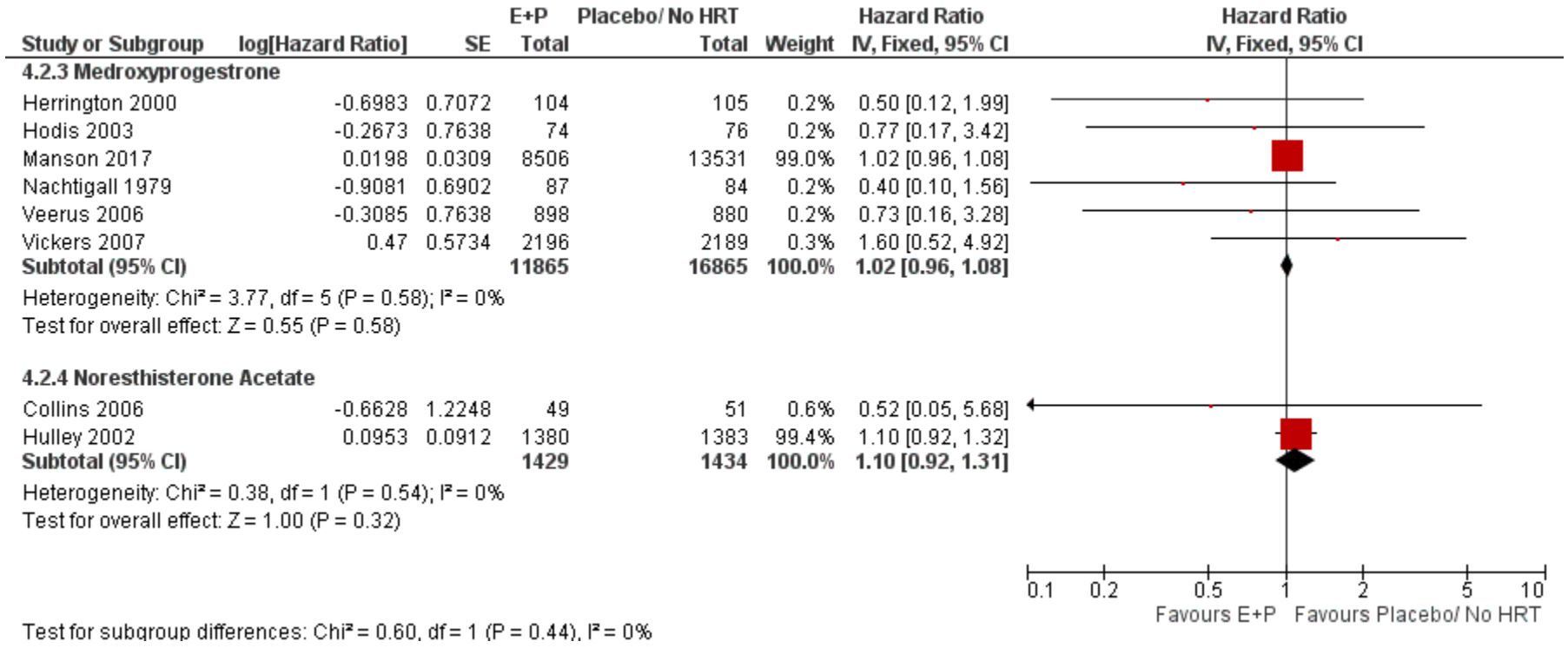
Heterogeneity: Chi² = 4.75, df = 7 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)



Collins 2006, Herrington 2000, Hulley 2002, Hodis 2003, Manson 2017, Veerus 2006 and Vickers 2007 have been extracted from the systematic review Kim 2020; Nachtigall 1979 has been extracted from Nudy 2019

2

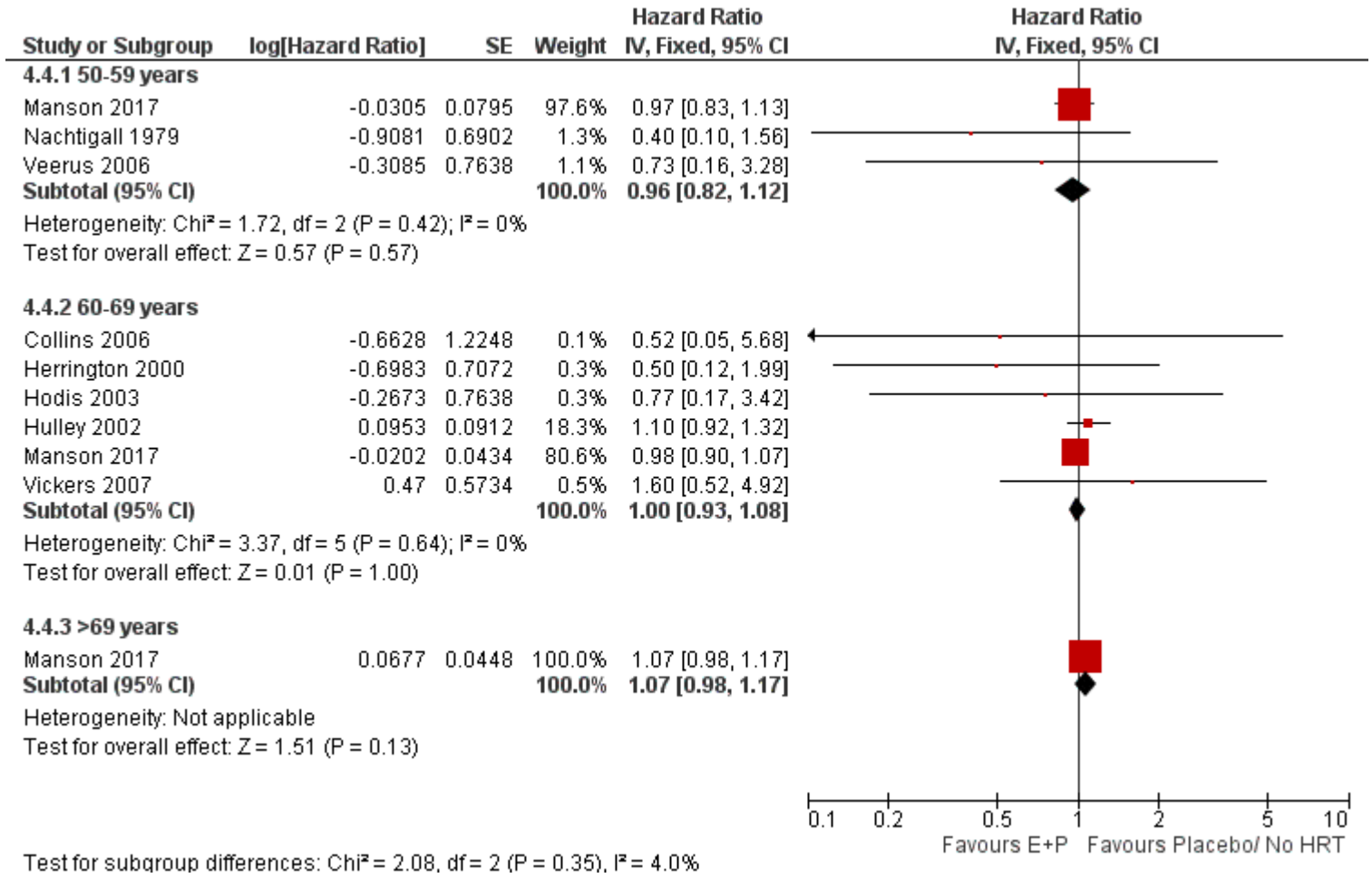
Figure 11: All-cause mortality - by progestogenic constituent



Collins 2006, Herrington 2000, Hulley 2002, Hodis 2003, Manson 2017, Veerus 2006 and Vickers 2007 have been extracted from the systematic review Kim 2020; Nachtigall 1979 has been extracted from the systematic review Nudy 2019.

1

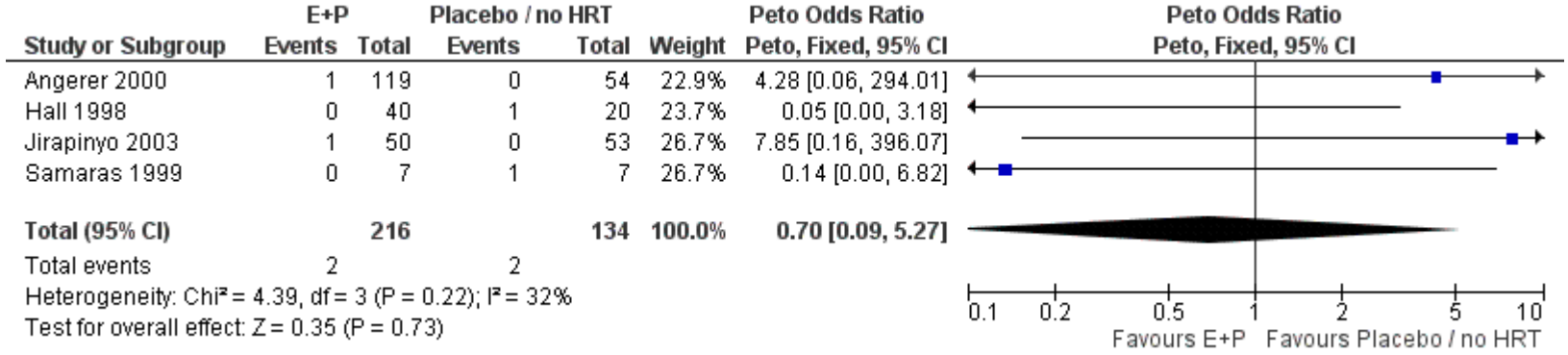
Figure 12: All-cause mortality - by age at first use



Collins 2006, Herrington 2000, Hulley 2002, Hodis 2003, Manson 2017, Veerus 2006 and Vickers 2007 have been extracted from the systematic review Kim 2020; Nachtigall 1979 have been extracted from the systematic review Nudy 2019.

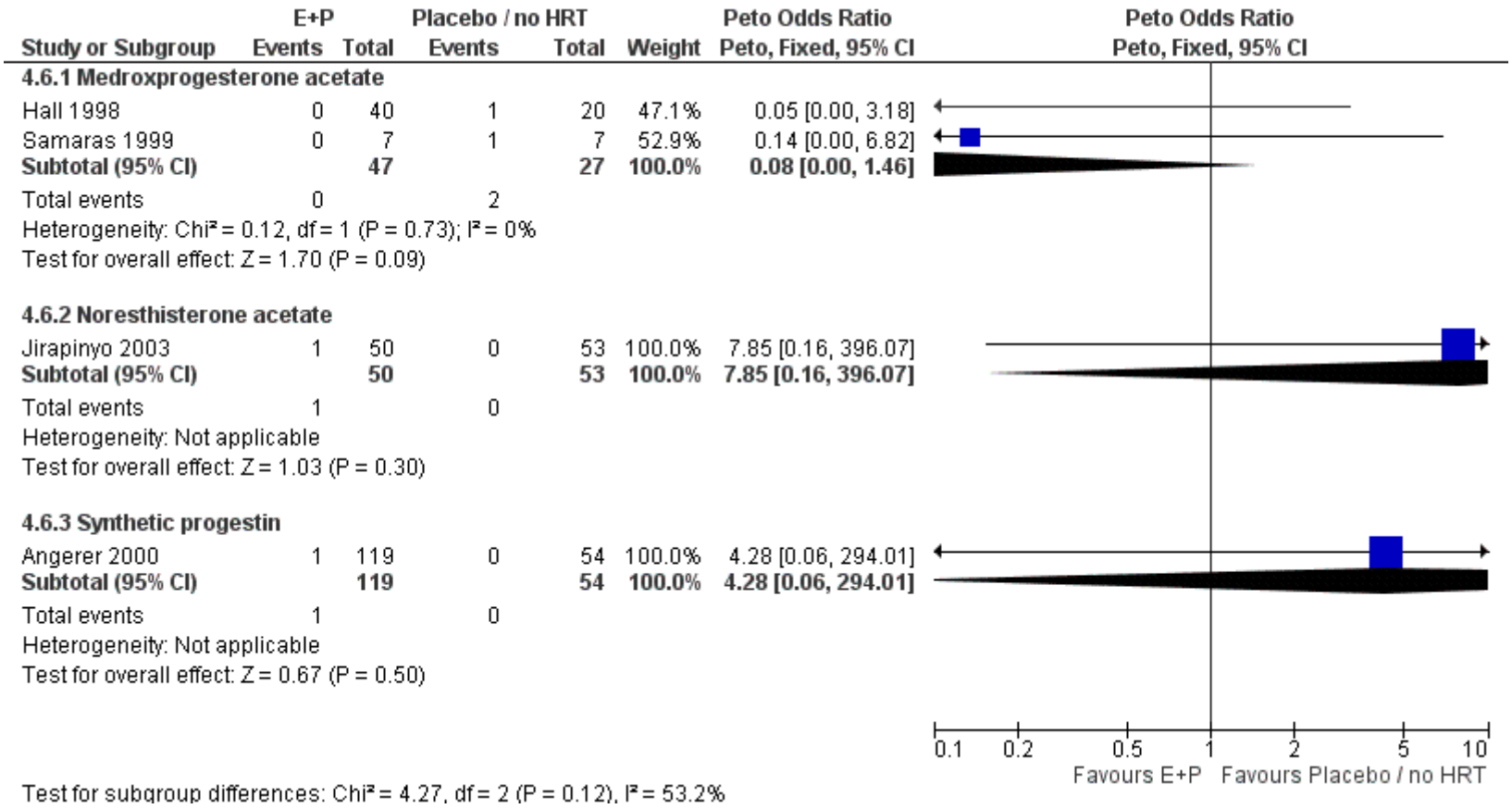
Peto odds ratio

Figure 13: All-cause mortality – overall (age at first use 50-59)



Angerer 2000, Hall 1998, Jirapinyo 2003 and Samaras 1999 have been extracted from the systematic review Nudy 2019.

Figure 14: All-cause mortality - by constituent



1 Angerer 2000, Hall 1998, Jirapinyo 2003 and Samaras 1999 have been extracted from the systematic review Nudy 2019

2

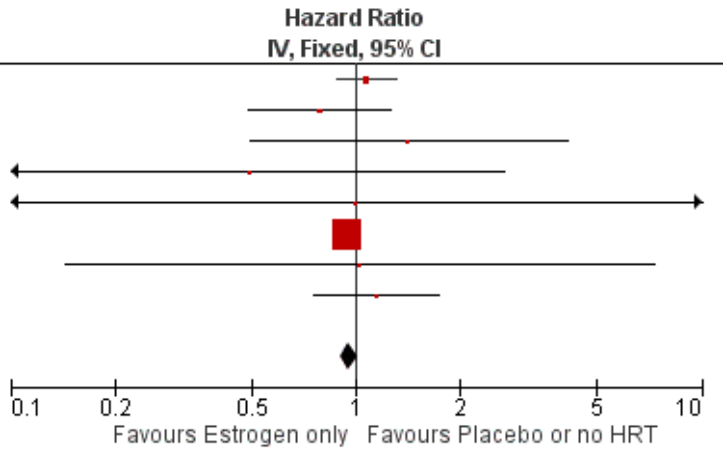
Comparison 4: Oestrogen-only versus Placebo or No HRT

Hazard ratio

Figure 15: All-cause mortality (overall)

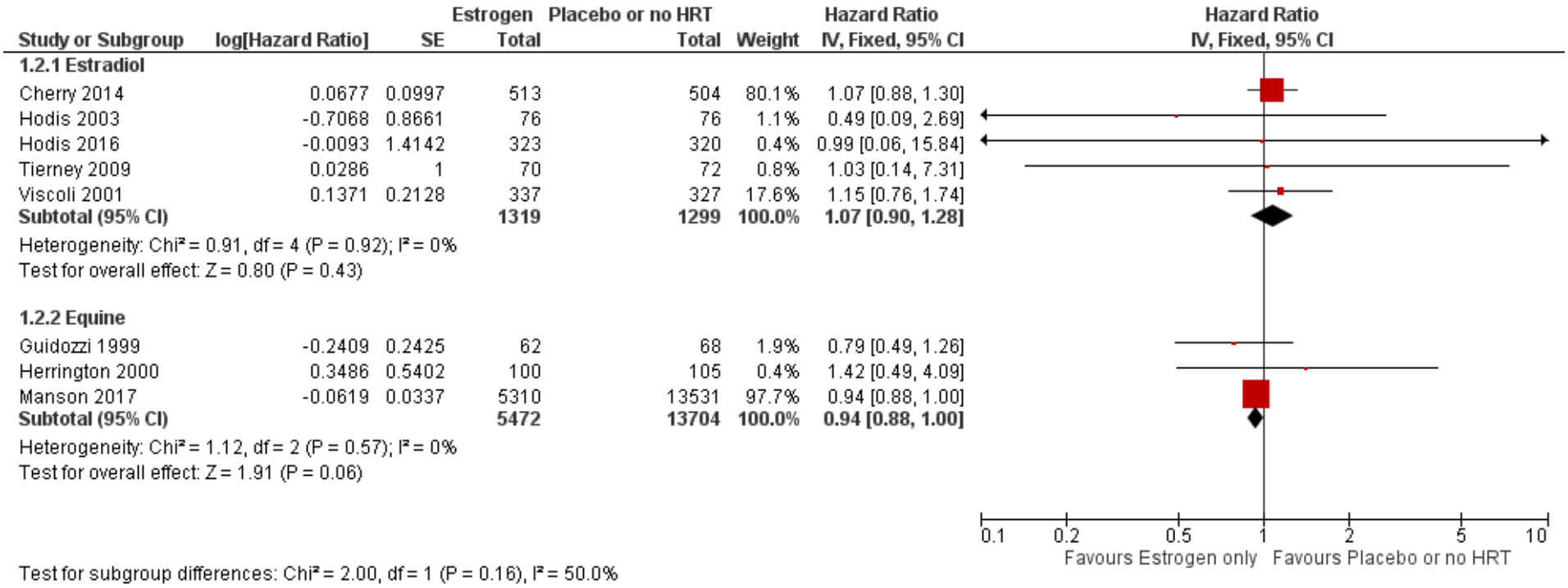
Study or Subgroup	log[Hazard Ratio]	SE	Estrogen Total	Placebo or no HRT Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Cherry 2014	0.0677	0.0997	513	504	9.8%	1.07 [0.88, 1.30]
Guidozzi 1999	-0.2409	0.2425	62	68	1.7%	0.79 [0.49, 1.26]
Herrington 2000	0.3486	0.5402	100	105	0.3%	1.42 [0.49, 4.09]
Hodis 2003	-0.7068	0.8661	76	76	0.1%	0.49 [0.09, 2.69]
Hodis 2016	-0.0093	1.4142	323	320	0.0%	0.99 [0.06, 15.84]
Manson 2017	-0.0619	0.0337	5310	13531	85.8%	0.94 [0.88, 1.00]
Tierney 2009	0.0286	1	70	72	0.1%	1.03 [0.14, 7.31]
Viscoli 2001	0.1371	0.2128	337	327	2.2%	1.15 [0.76, 1.74]
Total (95% CI)			**6791**	**15003**	**100.0%**	**0.95 [0.90, 1.01]**

Heterogeneity: Chi² = 4.03, df = 7 (P = 0.78); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)



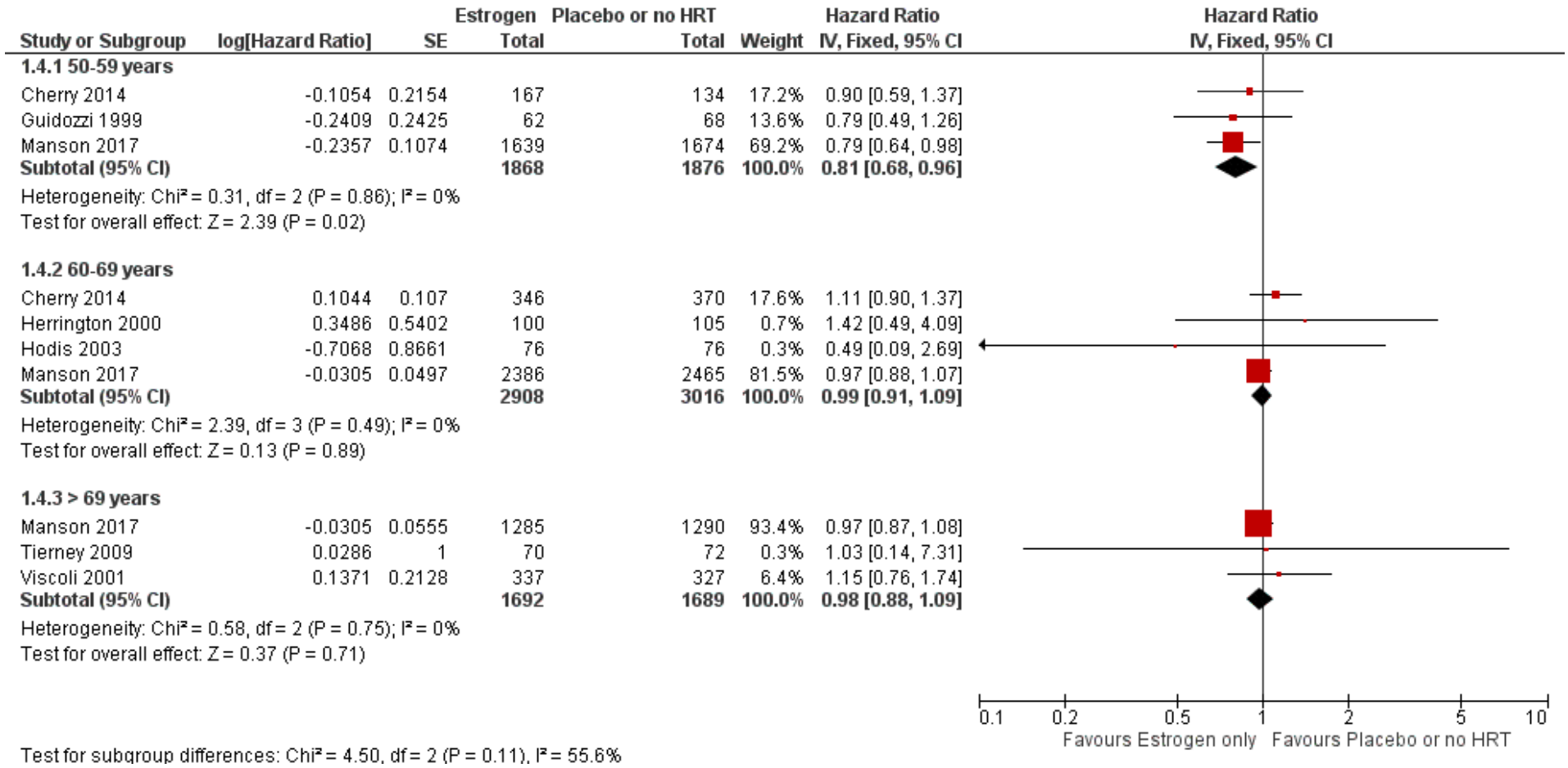
Cherry 2014, Herrington 2000, Hodis 2003, Hodis 2016, Manson 2017, Tierney 2009 and Viscoli 2001 have been extracted from the systematic review Kim 2020; Guidozzi 1999 has been extracted from the systematic review Nudy 2019.

Figure 16: All-cause mortality - by constituent



Cherry 2014, Herrington 2000, Hodis 2003, Hodis 2016, Manson 2017, Tierney 2009 and Viscoli 2001 have been extracted from the systematic review Kim 2020; Guidozzi 1999 has been extracted from the systematic review Nudy 2019.

Figure 17: All-cause mortality - by age at first use



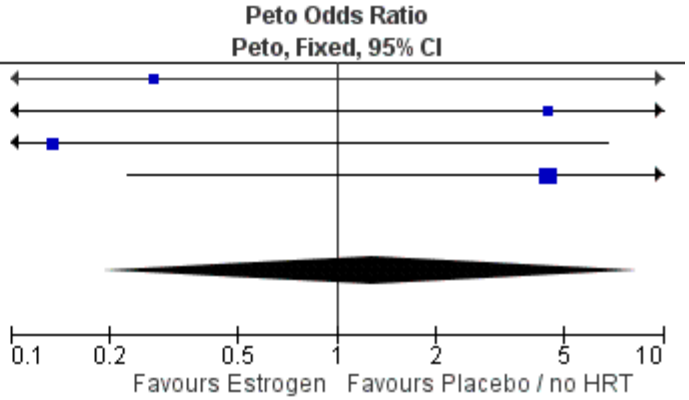
Cherry 2014, Herrington 2000, Hodis 2003, Manson 2017, Tierney 2009 and Viscoli 2001 have been extracted from the systematic review Kim 2020; Guidozzi 1999 has been extracted from the systematic review Nudy 2019.

1 ***Peto odds ratio***

Figure 18: All-cause mortality (overall)

Study or Subgroup	Estrogen Events	Estrogen Total	Placebo or no HRT Events	Placebo or no HRT Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Giske 2002	0	31	1	108	16.0%	0.28 [0.00, 30.61]
Harman 2014	1	552	0	275	20.5%	4.47 [0.07, 286.70]
Hodis 2001	0	111	1	111	23.1%	0.14 [0.00, 6.82]
Mulnard 2000	2	81	0	39	40.3%	4.46 [0.23, 86.97]
PEPI 1995	0	175	0	174		Not estimable
Total (95% CI)		**950**		**707**	**100.0%**	**1.27 [0.19, 8.38]**
Total events	3		2			

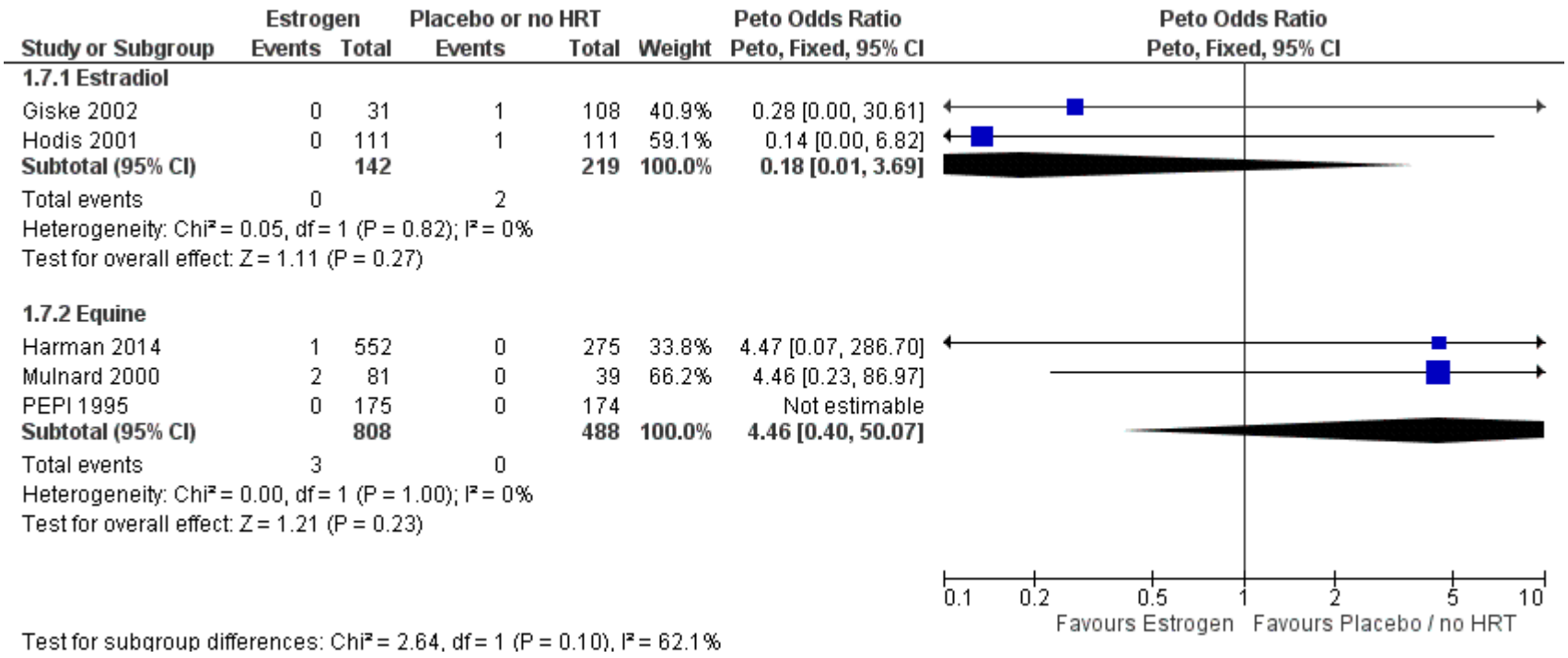
Heterogeneity: Chi² = 2.69, df = 3 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)



Giske 2002, Harman 2014 and Hodis 2001 have been extracted from the systematic review Nudy 2019.

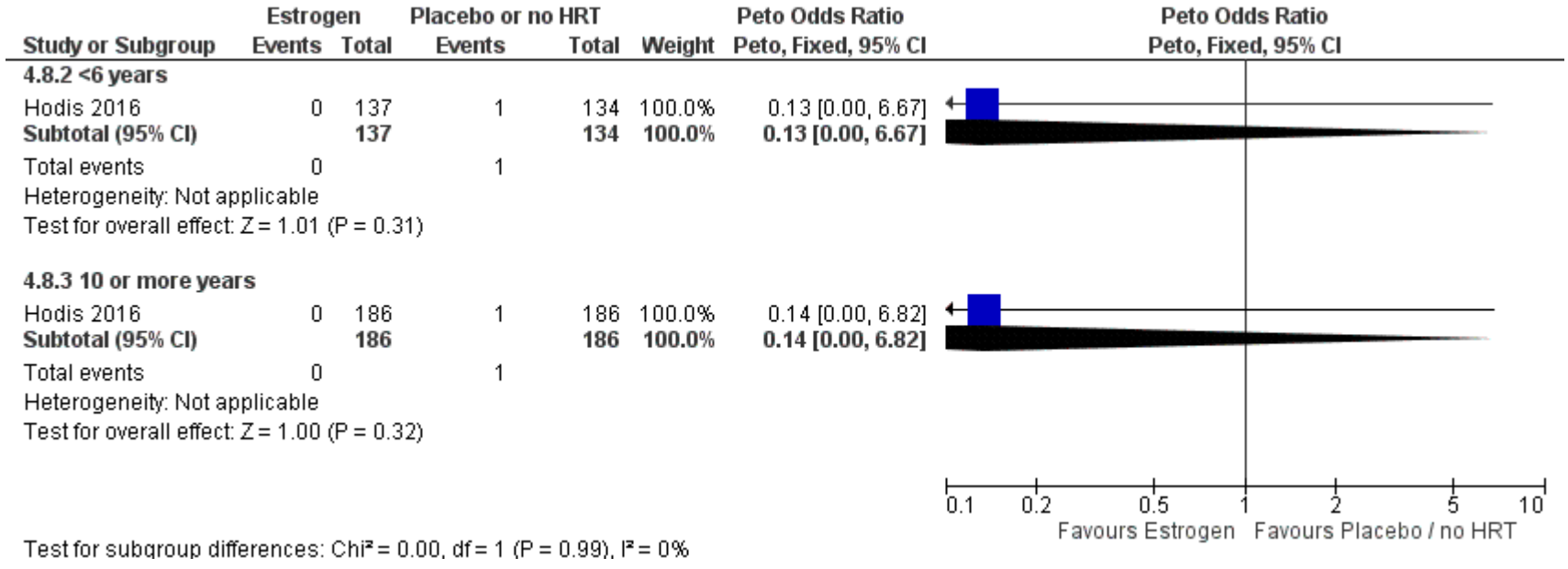
2

Figure 19: All-cause mortality – by constituent



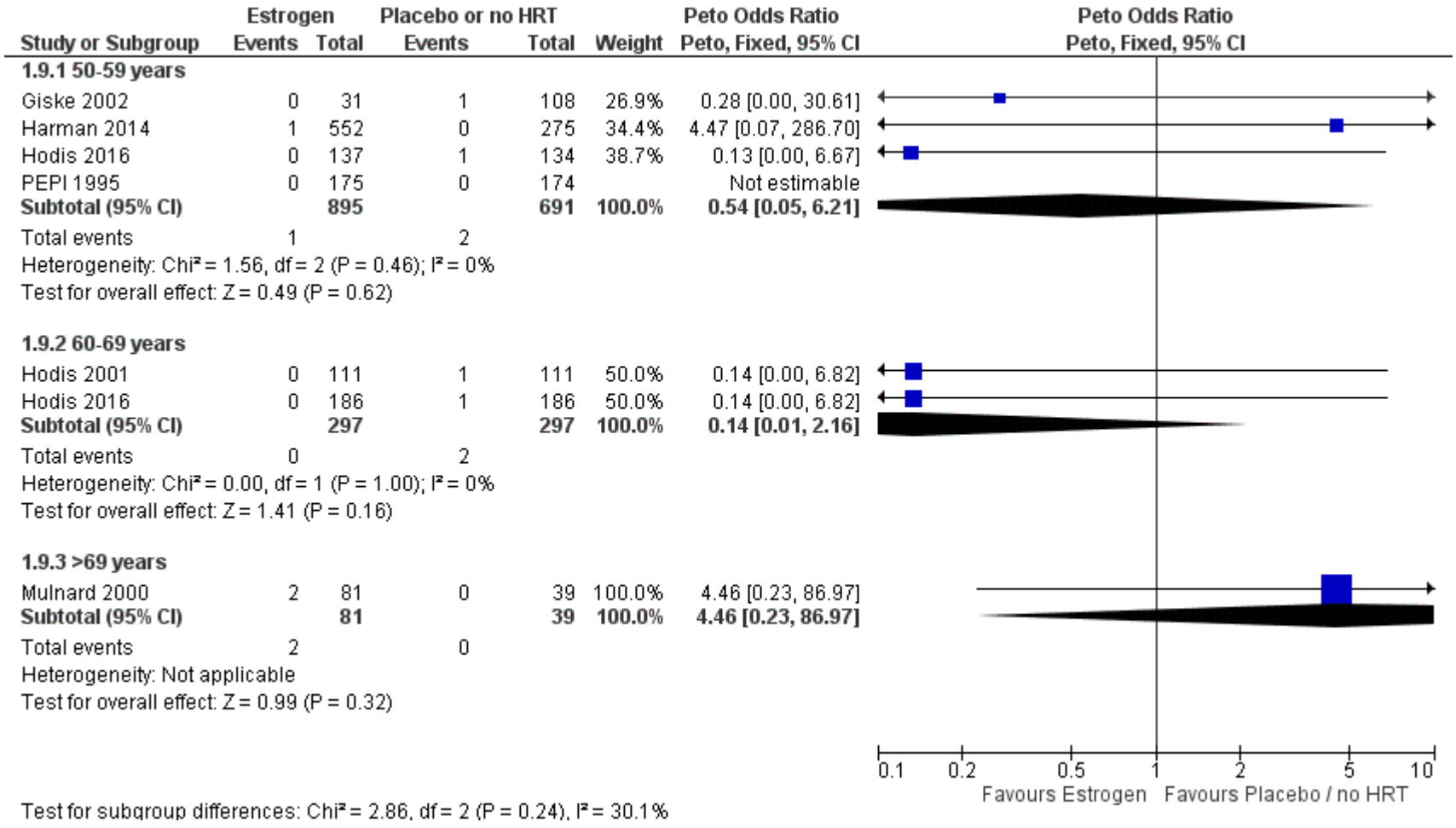
1 Giske 2002, Harman 2014 and Hodis 2001 have been extracted from the systematic review Nudy 2019.

Figure 20: All-cause mortality – by time since menopause



Hodis 2016 has been extracted from the systematic review Kim 2020.

Figure 21: All-cause mortality - by age at first use



Hodis 2016 has been extracted from the systematic review Kim 2020 and Giske 2002; Harman 2014 and Hodis 2001 have been extracted from the systematic review Nudy 2019.

Appendix F GRADE tables

GRADE tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on all-cause mortality?

RCT data taken from the systematic reviews included in this review have been cited with the RCT reference within the tables, please see table footnotes for further details. Combined effect estimates from the systematic reviews are not reported in the GRADE tables to avoid double counting.

Table 5: Comparison 1: Oestrogen + progesterone (any combination) versus Placebo or No HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + Progesterone (any combination)	Placebo/ No HRT	Relative (95% CI)	Absolute		
All-cause mortality (overall) (hazard ratio)												
10[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2530/13585 (18.6%)	4009/18586 (21.6%)	HR 1.03 (0.97 to 1.09)	Not calculable	HIGH	CRITICAL
All-cause mortality - by progestogenic constituent - Synthetic progestin (hazard ratio)												
1 (Komulainen 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/231 (0.87%)	1/227 (0.44%)	HR 1.97 (0.18 to 21.72)	Not calculable	LOW	CRITICAL
All-cause mortality - by progestogenic constituent – Medroxyprogestrone (hazard ratio)												
7[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2266/11925 (19%)	3767/16925 (22.3%)	HR 1.02 (0.96 to 1.08)	Not calculable	HIGH	CRITICAL
All-cause mortality - by progestogenic constituent - Noresthisterone Acetate (hazard ratio)												
2[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	262/1429 (18.3%)	241/1434 (16.8%)	HR 1.1 (0.92 to 1.31)	Not calculable	MODERATE	CRITICAL
All-cause mortality - by age at first use - 50-59 years (hazard ratio)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + Progesterone (any combination)	Placebo/ No HRT	Relative (95% CI)	Absolute		
4[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	315/4053 (7.8%)	306/3874 (7.9%)	HR 0.96 (0.82 to 1.12)	Not calculable	HIGH	CRITICAL
All-cause mortality - by age at first use - 60-69 years (hazard ratio)												
7[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1242/7717 (16.1%)	1176/7519 (15.6%)	HR 1.00 (0.93 to 1.08)	Not calculable	HIGH	CRITICAL
All-cause mortality - by age at first use - >69 years (hazard ratio)												
1 (Manson 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	973/1815 (53.6%)	897/1764 (50.9%)	HR 1.07 (0.98 to 1.17)	Not calculable	HIGH	CRITICAL
All-cause mortality (overall) (Peto odds ratio)												
6[8]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/794 (0.76%)	2/334 (0.6%)	POR 1.54 (0.34 to 6.86)	3 more per 1000 (from 4 fewer to 35 more)	VERY LOW	CRITICAL
All-cause mortality -by progestogenic constituent - Medroxprogesterone acetate (Peto odds ratio)												
4[10]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/625 (0.64%)	2/227 (0.88%)	POR 0.93 (0.16 to 5.37)	1 fewer per 1000 (from 7 fewer to 39 more)	VERY LOW	CRITICAL
All-cause mortality -by progestogenic constituent - Noresthisterone acetate (Peto odds ratio)												
1 (Jirapinyo 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	1/50 (2%)	0/53 (0%)	POR 7.85 (0.16 to 396.07)	20 more per 1000 (from 30 fewer to 70 more)[11]	LOW	CRITICAL
All-cause mortality -by progestogenic constituent - Synthetic progestin (Peto odds ratio)												
1 (Angerer 2000)	randomised trials	very serious[12]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/119 (0.84%)	0/54 (0%)	POR 4.28 (0.06 to 294.01)	10 more per 1000 (from 20 fewer to 40 more)[11]	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen + Progesterone (any combination)	Placebo/ No HRT	Relative (95% CI)	Absolute		
All-cause mortality - by age at first use - 50-59 years (Peto odds ratio)												
6[13]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/794 (0.76%)	2/334 (0.6%)	POR 1.54 (0.34 to 6.86)	3 more per 1000 (from 4 fewer to 35 more)	VERY LOW	CRITICAL

CI; confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; POR: Peto odds ratio
Collins 2006, Herrington 2000, Hulley 2002, Hodis 2003, Manson 2017, Veerus 2006 and Vickers 2007 have been extracted from the systematic review Kim 2020; Angerer 2000, Hall 1998, Jirapinyo 2003, Komulainen 1999, Kyllonen 1998, Nachtigall 1979, and Samaras 1999 have been extracted from the systematic review Nudy 2019.
1 Collins 2006; Herrington 2000; Hodis 2003; Hulley 2002; Komulainen 1999; Manson 2017; Nachtigall 1979; Os 2000; Veerus 2006; Vickers 2007
2 95% CI crosses 2 MIDs
3 Herrington 2000; Hodis 2003; Manson 2017; Nachtigall 1979; Os 2000; Veerus 2006; Vickers 2007
4 Collins 2006; Hulley 2002
5 95% CI crosses 1 MID
6 Komulainen 1999; Manson 2017; Nachtigall 1979; Veerus 2006
7 Collins 2006; Herrington 2000; Hodis 2003; Hulley 2002; Manson 2017; Os 2000; Vickers 2007
8 Angerer 2000; Hall 1998; Jirapinyo 2003; Kyllonen 1998; PEPI 1995; Samaras 1999
9 Serious risk of bias in the evidence contributing to outcomes as per RoB2 and Nudy 2019
10 Hall 1998; Kyllonen 1998; PEPI 1995; Samaras 1999
11 Calculated from risk difference
12 Very serious risk of bias in the evidence contributing to outcomes as per assessment in Nudy 2019
13 Angerer 2000; Hall 1998; Jirapinyo 2003; Kyllonen 1998; PEPI 1995; Samaras 1999

Table 6: Comparison 2: Sequential combined oestrogen + progesterone versus Placebo or no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential combined oestrogen + progesterone	Placebo / no HRT	Relative (95% CI)	Absolute		
All-cause mortality (overall) (hazard ratio)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/291 (1.4%)	2/287 (0.7%)	HR 1.99 (0.37 to 10.88)	Not calculable	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential combined oestrogen + progesterone	Placebo / no HRT	Relative (95% CI)	Absolute		
All-cause mortality - by progestogenic constituent - Synthetic progestin, length of cycle 30 days (hazard ratio)												
1 (Komulainen 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	2/231 (0.87%)	1/227 (0.44%)	HR 1.97 (0.18 to 21.72)	4 more per 1000 (from 4 fewer to 87 more)	LOW	CRITICAL
All-cause mortality - by progestogenic constituent – Medroxyprogestrone acetate, long cycle (hazard ratio)												
1 (Os 2000)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/60 (3.3%)	1/60 (1.7%)	HR 2.02 (0.18 to 22.25)	17 more per 1000 (from 14 fewer to 295 more)	VERY LOW	CRITICAL
All-cause mortality (overall) / (age at first use 50-59; Medroxyprogesterone acetate, 30 day) (Peto odds ratio)												
2[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	4/578 (0.69%)	0/200 (0%)	POR 3.98 (0.43 to 36.58)	10 more per 1000 (from 10 fewer to 20 more)[6]	LOW	CRITICAL

CI; confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; POR: Peto odds ratio
Komulainen 1999 has been extracted from the systematic review Nudy 2019.
1 Komulainen 1999; Os 2000
2 Serious risk of bias in the evidence contributing to outcomes as per RoB2 and assessment by Nudy 2019
3 95% CI crosses 2 MIDs
4 Very serious risk of bias in the evidence contributing to outcomes as per RoB2
5 Kyllonen 1998; PEPI 1995
6 Calculated from risk difference

Table 7: Comparison 3: Continuous combined oestrogen + progesterone versus placebo or no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous combined oestrogen + progesterone	Placebo / No HRT	Relative (95% CI)	Absolute		

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous combined oestrogen + progesterone	Placebo / No HRT	Relative (95% CI)	Absolute		
All-cause mortality - (overall) (hazard ratio)												
8[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2526/13294 (19%)	4007/18299 (21.9%)	HR 1.02 (0.97 to 1.09)	4 more per 1000 (from 6 fewer to 17 more)	HIGH	CRITICAL
All-cause mortality - by progestogenic constituent – Medroxyprogestrone (hazard ratio)												
6[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2264/11865 (19.1%)	3766/16865 (22.3%)	HR 1.02 (0.96 to 1.08)	4 more per 1000 (from 8 fewer to 16 more)	HIGH	CRITICAL
All-cause mortality - by progestogenic constituent - Noresthisterone acetate (hazard ratio)												
2[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	262/1429 (18.3%)	241/1434 (16.8%)	HR 1.1 (0.92 to 1.31)	15 more per 1000 (from 12 fewer to 46 more)	MODERATE	CRITICAL
All-cause mortality - by age at first use - 50-59 years (hazard ratio)												
3[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	313/3822 (8.2%)	305/3647 (8.4%)	HR 0.96 (0.82 to 1.12)	3 fewer per 1000 (from 15 fewer to 10 more)	HIGH	CRITICAL
All-cause mortality - by age at first use - 60-69 years (hazard ratio)												
6[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1240/7657 (16.2%)	1175/7459 (15.8%)	HR 1.00 (0.93 to 1.08)	0 fewer per 1000 (from 10 fewer to 11 more)	HIGH	CRITICAL
All-cause mortality - by age at first use - >69 years (hazard ratio)												
1 (Manson 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	973/1815 (53.6%)	897/1764 (50.9%)	HR 1.07 (0.98 to 1.17)	24 more per 1000 (from 7 fewer to 56 more)	HIGH	CRITICAL
All-cause mortality (overall) (age at first use 50-59) (Peto odds ratio)												
4[7]	randomised	very	no serious	no serious	very serious[9]	none	2/216	2/134	POR 0.7	4 fewer per 1000		CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continuous combined oestrogen + progesterone	Placebo / No HRT	Relative (95% CI)	Absolute		
	trials	serious[8]	inconsistency	indirectness			(0.93%)	(1.5%)	(0.09 to 5.27)	(from 14 fewer to 64 more)	VERY LOW	
All-cause mortality -by progestogenic constituent - Medroxprogesterone acetate (Peto odds ratio)												
2[10]	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	0/47 (0%)	2/27 (7.4%)	POR 0.08 (0 to 1.46)	68 fewer per 1000 (from 74 fewer to 34 more)	VERY LOW	CRITICAL
All-cause mortality -by progestogenic constituent - Noresthisterone acetate (Peto odds ratio)												
1 (Jirapinyo 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	1/50 (2%)	0/53 (0%)	POR 7.85 (0.16 to 396.07)	20 more per 1000 (from 30 fewer to 70 more)[11]	LOW	CRITICAL
All-cause mortality -by progestogenic constituent - Synthetic progestin (Peto odds ratio)												
1 (Angerer 2000)	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	1/119 (0.84%)	0/54 (0%)	POR 4.28 (0.06 to 294.01)	10 more per 1000 (from 20 fewer to 40 more)[11]	VERY LOW	CRITICAL

CI; confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; POR: Peto odds ratio
Collins 2006, Herrington 2000, Hulley 2002, Hodis 2003, Manson 2017, Veerus 2006 and Vickers 2007 have been extracted from the systematic review Kim 2020; Angerer 2000, Hall 1998, Jirapinyo 2003 and Nachtigall 1979 have been extracted from Nudy 2019
1 Collins 2006; Herrington 2000; Hodis 2003; Hulley 2002; Manson 2017; Nachtigall 1979; Veerus 2006; Vickers 2007
2 Herrington 2000; Hodis 2003; Manson 2017; Nachtigall 1979; Veerus 2006; Vickers 2007
3 Collins 2006; Hulley 2002
4 95% CI crosses 1 MID
5 Manson 2017; Nachtigall 1979; Veerus 2006
6 Collins 2006; Herrington 2000; Hodis 2003; Hulley 2002; Manson 2017; Vickers 2007
7 Angerer 2000; Hall 1998; Jirapinyo 2003; Samaras 1999
8 Very serious risk of bias in the evidence contributing to the outcomes assessed by Nudy 2019
9 95% CI crosses 2 MIDs
10 Hall 1998; Samaras 1999
11 Calculated from risk difference

Table 8: Comparison 4: Oestrogen-only versus placebo or no HRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen	No HRT/placebo	Relative (95% CI)	Absolute		
All-cause mortality (overall) (hazard ratio)												
8[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1812/6791 (26.7%)	4039/15003 (26.9%)	HR 0.95 (0.9 to 1.01)	Not calculable	HIGH	CRITICAL
All-cause mortality - by constituent – Estradiol (hazard ratio)												
5[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	267/1319 (20.2%)	252/1299 (19.4%)	HR 1.07 (0.9 to 1.28)	Not calculable	MODERATE	CRITICAL
All-cause mortality - by constituent – Equine (hazard ratio)												
3[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1545/5472 (28.2%)	3787/13704 (27.6%)	HR 0.94 (0.88 to 1)	Not calculable	HIGH	CRITICAL
All-cause mortality - by age at first use - 50-59 years (hazard ratio)												
3[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	248/1868 (13.3%)	298/1876 (15.9%)	HR 0.81 (0.68 to 0.96)	Not calculable	MODERATE	CRITICAL
All-cause mortality - by age at first use - 60-69 years (hazard ratio)												
4[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	828/2908 (28.5%)	869/3016 (28.8%)	HR 0.99 (0.91 to 1.09)	Not calculable	HIGH	CRITICAL
All-cause mortality - by age at first use - > 69 years (hazard ratio)												
3[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	735/1692 (43.4%)	761/1689 (45.1%)	HR 0.98 (0.88 to 1.09)	Not calculable	HIGH	CRITICAL
All-cause mortality - ethnicity – Black (hazard ratio)												
1 (Chlebowski 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	98/781 (12.5%)	99/835 (11.9%)	HR 1.04 (0.79 to 1.37)	Not calculable	LOW	CRITICAL
All-cause mortality - ethnicity – White (hazard ratio)												
1 (Chlebowski 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	565/4009 (14.1%)	574/4075 (14.1%)	HR 1.01 (0.9 to 1.13)	Not calculable	HIGH	CRITICAL
All-cause mortality (overall) (Peto odds ratio)												
5[9]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	3/950 (0.32%)	2/707 (0.28%)	POR 1.27 (0.19 to 8.38)	1 more per 1000 (from 2 fewer to 21 more)	LOW	CRITICAL
All-cause mortality - by constituent – Estradiol (Peto odds ratio)												
2[10]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[8]	none	0/142 (0%)	2/219 (0.91%)	POR 0.18 (0.01 to 3.69)	7 fewer per 1000 (from 9 fewer to 25 more)	VERY LOW	CRITICAL
All-cause mortality - by constituent – Equine (Peto odds ratio)												
3[12]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	3/808 (0.37%)	0/488 (0%)	POR 4.46 (0.4 to 50.07)	0 more per 1000 (from 0 more to 10 more)[13]	LOW	CRITICAL
All-cause mortality - by time since menopause - <6 years (Peto odds ratio)												
1 (Hodis 2016)	randomised	serious[11]	no serious	no serious	very serious[8]	none	0/137	1/134	POR 0.13 (0	6 fewer per 1000		CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oestrogen	No HRT/placebo	Relative (95% CI)	Absolute		
	trials		inconsistency	indirectness			(0%)	(0.75%)	to 6.67)	(from 7 fewer to 42 more)	VERY LOW	
All-cause mortality - by time since menopause - 10 or more years (Peto odds ratio)												
1 (Hodis 2016)	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[8]	none	0/186 (0%)	1/186 (0.54%)	POR 0.14 (0 to 6.82)	5 fewer per 1000 (from 5 fewer to 31 more)	VERY LOW	CRITICAL
All-cause mortality - by age at first use - 50-59 years (Peto odds ratio)												
4[14]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[8]	none	1/895 (0.11%)	2/691 (0.29%)	POR 0.54 (0.05 to 6.21)	1 fewer per 1000 (from 3 fewer to 15 more)	VERY LOW	CRITICAL
All-cause mortality - by age at first use - 60-69 years (Peto odds ratio)												
2[15]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[8]	none	0/297 (0%)	2/297 (0.67%)	POR 0.14 (0.01 to 2.16)	6 fewer per 1000 (from 7 fewer to 8 more)	VERY LOW	CRITICAL
All-cause mortality - by age at first use - >69 years (Peto odds ratio)												
1 (Mulnard 2000)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	2/81 (2.5%)	0/39 (0%)	POR 4.46 (0.23 to 86.97)	20 more per 1000 (from 30 fewer to 80 more)[13]	LOW	CRITICAL

CI; confidence interval; HR: hazard ratio; HRT: hormone replacement therapy; POR: Peto odds ratio
Cherry 2014, Herrington 2000, Hodis 2003, Hodis 2016, Manson 2017, Tierney 2009 and Viscoli 2001 have been extracted from the systematic review Kim 2020; Giske 2002, Guidozzi 1999, Harman 2014 and Hodis 2001 have been extracted from the systematic review Nudy 2019.
1 Cherry 2014; Guidozzi 1999; Herrington 2000; Hodis 2003; Hodis 2016; Manson 2017; Tierney 2009; Viscoli 2001
2 Cherry 2014; Hodis 2003; Hodis 2016; Tierney 2009; Viscoli 2001
3 95% CI crosses 1 MID
4 Guidozzi 1999; Herrington 2000; Manson 2017
5 Cherry 2014; Guidozzi 1999; Manson 2017
6 Cherry 2014; Herrington 2000; Hodis 2003; Manson 2017
7 Manson 2017; Tierney 2009; Viscoli 2001
8 95% CI crosses 2 MIDs
9 Giske 2002; Harman 2014; Hodis 2001; Mulnard 2000; PEPI 1995
10 Giske 2002; Hodis 2001
11 Serious risk of bias in the evidence contributing to the outcomes assessed by Nudy 2019 or Kim 2020
12 Harman 2014; Mulnard 2000; PEPI 1995
13 Calculated from risk difference
14 Giske 2002; Harman 2014; Hodis 2016; PEPI 1995
15 Hodis 2001; Hodis 2016

Appendix G Economic evidence study selection

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

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

Appendix H Economic evidence tables

Economic evidence tables for review question: What are the effects of hormone replacement therapy for menopausal symptoms on all-cause mortality?

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

Appendix I Economic model

Economic model for review question: What are the effects of hormone replacement therapy for menopausal symptoms on all-cause mortality?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What are the effects of hormone replacement therapy for menopausal symptoms on all-cause mortality?

Excluded effectiveness studies

Table 9: Excluded studies and reasons for their exclusion

Study	Reason
Anderson, Garnet L, Chlebowski, Rowan T, Aragaki, Aaron K et al. (2012) Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. The Lancet. Oncology 13(5): 476-86	- More recent follow-up study available (Manson 2017)
Arrenbrecht, S and Boermans, A J M (2002) Effects of transdermal estradiol delivered by a matrix patch on bone density in hysterectomized, postmenopausal women: a 2-year placebo-controlled trial. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 13(2): 176-83	- Outcomes - reported outcomes do not match the review protocols - exclude as paper doesn't clearly report mortality or any death and no information on if Nudy 2019 contacted Arrenbrech for this information
Bae, Jong-Myon and Yoon, Byung-Koo (2018) The Role of Menopausal Hormone Therapy in Reducing All-cause Mortality in Postmenopausal Women Younger than 60 Years: An Adaptive Meta-analysis. Journal of menopausal medicine 24(3): 139-142	- Study design Systematic review with insufficient information on each study. Potentially relevant studies have been checked against the protocol and all are included
Benkhadra, Khalid, Mohammed, Khaled, Al Nofal, Alaa et al. (2015) Menopausal Hormone Therapy and Mortality: A Systematic Review and Meta-Analysis. The Journal of clinical endocrinology and metabolism 100(11): 4021-8	- Study design - Systematic review. Potentially relevant studies have been checked against the protocol and included if relevant
Bhupathiraju, Shilpa N, Grodstein, Francine, Rosner, Bernard A et al. (2017) Hormone Therapy Use and Risk of Chronic Disease in the Nurses' Health Study: A Comparative Analysis With the Women's Health Initiative. American journal of epidemiology 186(6): 696-708	- Study design - not a systematic review or randomised controlled trial
Binder, E F, Williams, D B, Schechtman, K B et al. (2001) Effects of hormone replacement therapy on serum lipids in elderly women. a randomized, placebo-controlled trial. Annals of internal medicine 134(9pt1): 754-60	- Intervention- oestrogen-only & combined HRT not reported separately
Cherry, Nicola, Gilmour, Kyle, Hannaford, Philip et al. (2002) Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. Lancet (London, England) 360(9350): 2001-8	- More recent follow-up study available (Cherry 2014)
Clarke, S C, Kelleher, J, Lloyd-Jones, H et al. (2002) A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT atherosclerosis study. BJOG : an international journal of obstetrics and gynaecology 109(9): 1056-62	- Intervention- oestrogen-only & combined HRT not reported separately
Fahlen, M., Fornander, T., Johansson, H. et al. (2013) Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial. European Journal of Cancer 49(1):	- Intervention- oestrogen-only & combined HRT not reported separately

Study	Reason
52-59	
Grady, D, Wenger, N K, Herrington, D et al. (2000) Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Oestrogen/progestin Replacement Study. Annals of internal medicine 132(9): 689-96	- Outcomes - reported outcomes do not match the review protocols
Grady, Deborah, Herrington, David, Bittner, Vera et al. (2002) Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Oestrogen/progestin Replacement Study follow-up (HERS II). JAMA 288(1): 49-57	- More recent follow-up study available (Hulley 2002)
Greenspan, S.L.; Resnick, N.M.; Parker, R.A. (2005) The effect of hormone replacement on physical performance in community-dwelling elderly women. American Journal of Medicine 118(11): 1232-1239	- Intervention - HRT not oestrogen-only, or combined oestrogen and progestogen - Outcome not reported separately for oestrogen-only and combined oestrogen and progesterone
Guidozzi, F (1999) Oestrogen replacement therapy in breast cancer survivors. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 64(1): 59-63	- Outcomes no relevant outcomes reported.
Hall, G M, Daniels, M, Doyle, D V et al. (1994) Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. Arthritis and rheumatism 37(10): 1499-505	- Comparison - Calcium supplementation, which is neither placebo nor no HRT
Henderson, V.W., St John, J.A., Hodis, H.N. et al. (2016) Cognitive effects of estradiol after menopause. Neurology 87(7): 699-708	- Outcomes - no relevant outcomes reported
Herrington, D M, Fong, J, Sempos, C T et al. (1998) Comparison of the Heart and Oestrogen/Progestin Replacement Study (HERS) cohort with women with coronary disease from the National Health and Nutrition Examination Survey III (NHANES III). American heart journal 136(1): 115-24	- Outcomes - no relevant outcomes reported
Herrington, David M, Vittinghoff, Eric, Lin, Feng et al. (2002) Statin therapy, cardiovascular events, and total mortality in the Heart and Oestrogen/Progestin Replacement Study (HERS). Circulation 105(25): 2962-7	- Intervention – HRT not oestrogen-only, or combined oestrogen and progestogen
Hodis, Howard N, Mack, Wendy J, Shoupe, Donna et al. (2015) Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. Menopause (New York, N.Y.) 22(4): 391-401	- Outcomes - no relevant outcomes reported
Holm, M, Olsen, A, Au Yeung, S L et al. (2019) Pattern of mortality after menopausal hormone therapy: long-term follow up in a population-based cohort. BJOG : an international journal of obstetrics and gynaecology 126(1): 55-63	- Study design - not a systematic review or randomised controlled trial
Hulley, S, Grady, D, Bush, T et al. (1998) Randomized trial of oestrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Oestrogen/progestin Replacement Study (HERS) Research Group. JAMA 280(7): 605-13	- More recent follow-up available
Johnson, Bruce E and Johnson, Cynda Ann (2018) Pooled RCTs: In postmenopausal women, hormone therapy for 6 to 7 years did not affect mortality at 18 years. Annals of internal medicine 168(2): jc4	- Study design - not a systematic review or randomised controlled trial
Karim, Roksana, Mack, Wendy J, Lobo, Roger A et al. (2005) Determinants of the effect of oestrogen on the progression of	- Outcomes - no relevant

Study	Reason
subclinical atherosclerosis: Oestrogen in the Prevention of Atherosclerosis Trial. Menopause (New York, N.Y.) 12(4): 366-73	outcomes reported
Lindsay, R, Hart, D M, Aitken, J M et al. (1976) Long-term prevention of postmenopausal osteoporosis by oestrogen. Evidence for an increased bone mass after delayed onset of oestrogen treatment. Lancet (London, England) 1(7968): 1038-41	- Outcomes - no relevant outcomes reported
MacDonald, A G, Murphy, E A, Capell, H A et al. (1994) Effects of hormone replacement therapy in rheumatoid arthritis: a double blind placebo-controlled study. Annals of the rheumatic diseases 53(1): 54-7	- Intervention - HRT not oestrogen-only, or combined oestrogen and progestogen
Manson, J.E., Chlebowski, R.T., Stefanick, M.L. et al. (2014) Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials. Obstetrical and Gynecological Survey 69(2): 83-85	- More recent follow-up studies available (Manson 2017 and 2019)
Manson, JoAnn E, Aragaki, Aaron K, Bassuk, Shari S et al. (2019) Menopausal Oestrogen-Alone Therapy and Health Outcomes in Women With and Without Bilateral Oophorectomy: A Randomized Trial. Annals of internal medicine 171(6): 406-414	- Cohort already included - Manson 2017 includes the same cohort with the same subgroups matching the protocol, for the same duration of follow-up. This publication only includes a further subgroup of participants with known oophorectomy status, which does not fall under the subgroups specified for this review
Manson, JoAnn E, Chlebowski, Rowan T, Stefanick, Marcia L et al. (2013) Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 310(13): 1353-68	- More recent follow-up available
Marjoribanks, Jane, Farquhar, Cindy, Roberts, Helen et al. (2017) Long-term hormone therapy for perimenopausal and postmenopausal women. The Cochrane database of systematic reviews 1: cd004143	Systematic review - individual papers have been checked and included if relevant
Mijatovic, V, Netelenbos, C, van der Mooren, M J et al. (1998) Randomized, double-blind, placebo-controlled study of the effects of raloxifene and conjugated equine oestrogen on plasma homocysteine levels in healthy postmenopausal women. Fertility and sterility 70(6): 1085-9	- Outcomes – no relevant outcomes reported
Mosekilde, L, Beck-Nielsen, H, Sorensen, O H et al. (2000) Hormonal replacement therapy reduces forearm fracture incidence in recent postmenopausal women - results of the Danish Osteoporosis Prevention Study. Maturitas 36(3): 181-93	- Intervention - HRT not oestrogen-only, or combined oestrogen and progestogen
Nair, G V and Herrington, D M (2000) The ERA trial: findings and implications for the future. Climacteric : the journal of the International Menopause Society 3(4): 227-32	- Outcomes - no relevant outcomes reported
Padula, Amy M, Pressman, Alice R, Vittinghoff, Eric et al. (2012) Placebo adherence and mortality in the Heart and Oestrogen/Progestin Replacement Study. The American journal of medicine 125(8): 804-10	- Outcomes - no relevant outcomes reported (outcome is mortality in the placebo group)
Perez-Jaraiz, M D, Revilla, M, Alvarez de los Heros, J I et al. (1996) Prophylaxis of osteoporosis with calcium, oestrogens	- Outcomes - reported outcomes do not match the

Study	Reason
and/or eelcatonin: comparative longitudinal study of bone mass. Maturitas 23(3): 327-32	review protocols
Prentice, Ross L, Aragaki, Aaron K, Chlebowski, Rowan T et al. (2021) Randomized Trial Evaluation of the Benefits and Risks of Menopausal Hormone Therapy Among Women 50-59 Years of Age. American journal of epidemiology 190(3): 365-375	- Cohort already included Mortality data for this subgroup of women is already included in Manson 2017.
Ravn, P, Bidstrup, M, Wasnich, R D et al. (1999) Alendronate and oestrogen-progestin in the long-term prevention of bone loss: four-year results from the early postmenopausal intervention cohort study. A randomized, controlled trial. Annals of internal medicine 131(12): 935-42	- Outcomes - reported outcomes do not match the review protocols
Salpeter, Shelley R, Cheng, Ji, Thabane, Lehana et al. (2009) Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. The American journal of medicine 122(11): 1016-1022e1	- More recent systematic review included with all studies judged to be relevant
Salpeter, Shelley R, Walsh, Judith M E, Greyber, Elizabeth et al. (2004) Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. Journal of general internal medicine 19(7): 791-804	- More recent systematic review included with all studies judged to be relevant
Schierbeck, Louise Lind, Rejnmark, Lars, Tofteng, Charlotte Landbo et al. (2012) Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ (Clinical research ed.) 345: e6409	- Intervention- oestrogen-only & combined HRT not reported separately
Simin, Johanna, Khodir, Habiba, Fornes, Romina et al. (2022) Association between menopausal hormone therapy use and mortality risk: a Swedish population-based matched cohort study. Acta oncologica (Stockholm, Sweden) 61(5): 632-640	- Study design - not a systematic review or randomised controlled trial
Veerus, Piret, Fischer, Krista, Hovi, Sirpa-Liisa et al. (2008) Symptom reporting and quality of life in the Estonian Postmenopausal Hormone Therapy Trial. BMC women's health 8: 5	- Outcomes - reported outcomes do not match the review protocols
Vickers, Madge R, Martin, Jeannett, Meade, Tom W et al. (2007) The Women's international study of long-duration oestrogen after menopause (WISDOM): a randomised controlled trial. BMC women's health 7: 2	- Outcomes – no relevant outcomes reported.
Waters, David D, Alderman, Edwin L, Hsia, Judith et al. (2002) Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. JAMA 288(19): 2432-40	- Intervention - HRT not oestrogen-only, or combined oestrogen and progestogen
Watts, N B, Nolan, J C, Brennan, J J et al. (2000) Esterified oestrogen therapy in postmenopausal women. Relationships of bone marker changes and plasma estradiol to BMD changes: a two-year study. Menopause (New York, N.Y.) 7(6): 375-82	- Outcomes – no relevant outcomes reported

Excluded economic studies

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

Appendix K Research recommendations – full details

Research recommendations for review question: What are the effects of hormone replacement therapy for menopausal symptoms on all-cause mortality?

There are overarching research recommendations related to all health outcomes addressed in this guideline update (including all-cause mortality), for:

- trans-men and non-binary people registered female at birth who have taken cross-sex hormones in the past
- people from ethnic minority family backgrounds

For details refer to appendix K in evidence review C.