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Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: An Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Background: Menopausal hormone therapy plays an important role in the clinical management of menopausal symptoms. Because of an increased risk of harms, menopausal hormone therapy is currently not recommended for the primary prevention of chronic conditions.

Purpose: To update evidence on the effectiveness of hormone therapy in reducing risks for chronic conditions, its adverse effects, and differences among population subgroups for the U.S. Preventive Services Task Force.

Data Sources: We searched MEDLINE, the Cochrane Library, and Embase for English-language articles (through August 1, 2016). We conducted searches for unpublished literature by searching ClinicalTrials.gov, HSRProj, the World Health Organization's International Clinical Trials Registry Platform, and NIH Reporter. In addition, we reviewed reference lists of pertinent review articles and studies meeting our inclusion criteria.

Study Selection: We dually reviewed the literature and included randomized, placebo-controlled trials that provided information on the primary prevention of chronic conditions with hormone therapy and reported health outcomes.

Data Extraction: We abstracted details about participants, study design, analysis, followup, and results; study quality and strength of evidence were rated using established criteria.

Data Synthesis: Seventeen fair-quality trials met eligibility criteria. The Women's Health Initiative (WHI) was the largest study and most applicable to the target population.

Results of our review indicate differences in the risk-benefit profiles between treatment formulations. Women using estrogen only had statistically significantly lower risks (per 10,000 women over 6.8 to 7.2 years) for diabetes (137 fewer cases) and fractures (382 fewer cases) than women taking placebo. However, risks (per 10,000 women over 5.4 to 7.1 years) were statistically significantly increased for gallbladder disease (378 more cases), stroke (79 more cases), and venous thromboembolism (78 more cases). The risk for urinary incontinence (1,261 more cases per 10,000 women) was increased during a followup of 1 year.

Women using estrogen plus progestin therapy experienced statistically significantly lower risks (per 10,000 women during 5.0 to 5.6 years) for colorectal cancer (33 fewer cases), diabetes (77 fewer cases), and fractures (222 fewer cases) than those on placebo. Risks (per 10,000 women over 4 to 5.6 years) for invasive breast cancer (52 more cases), coronary heart disease (41 more cases), probable dementia (88 more cases), gallbladder disease (259 more cases), stroke (53 more cases), and venous thromboembolism (120 more cases) were statistically significantly increased compared with women taking placebo. The risk for urinary incontinence (876 more cases per 10,000 women) was increased during a followup of 1 year.

Some subgroup analyses indicate that time since menopause and age might modify the cardiovascular effects of hormone therapy. Younger women on estrogen only had lower risks for

myocardial infarction than older women relative to women using placebo. Younger women on estrogen only also had a reduced risk for all-cause mortality, while older women had an increased risk. Women who initiated estrogen plus progestin therapy closer to menopause did not have the elevated risk for myocardial infarction that women experienced who started this therapy more than 20 years after menopause.

Limitations: Few trials or subgroup analyses were powered for prevention outcomes. No comparative evidence on type, dose, and mode of delivery of hormone therapy is available. The applicability of results to younger women who initiate hormone therapy for the management of menopausal symptoms and to women with nonwhite ethnic backgrounds might be limited.

Conclusions: Women undergoing hormone therapy for the primary prevention of chronic conditions experience some beneficial effects but also an increase of risks for harms. Although some evidence suggests that timing of the start of hormone therapy can modify the risk-benefit profiles, particularly those for cardiovascular events, the available evidence is contradictory and insufficient to draw firm conclusions.

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Chapter 1. Introduction

Scope and Purpose

The U.S. Preventive Services Task Force (USPSTF) will use this report to update its 2012 recommendation on use of menopausal hormone therapy for postmenopausal women to prevent chronic health conditions such as cardiovascular disease,[1] types of cancer, and osteoporotic fractures. In 2012, the USPSTF recommended against the use of estrogen plus progestin for the prevention of chronic conditions in postmenopausal women (Grade D recommendation) and against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy (Grade D recommendation).[1] These recommendations do not apply to women younger than 50 years who have had surgical menopause.

The purposes of this report are to update evidence about the benefits and harms of hormone therapy for preventing chronic conditions and to examine whether outcomes vary among women in different subgroups. Use of hormone therapy for treating women with menopausal symptoms, such as vasomotor hot flashes or vulvovaginal complaints (e.g., dryness or dyspareunia), or for other indications is outside the scope of this review.

Condition Definition

Menopause is the cessation of the menstrual cycle and the end of a woman's reproductive years; it is defined retrospectively, 12 months after the final menstrual period.[2] Natural menopause results from the relative depletion of ovarian follicles responsive to the gonadotropins and the consequent decline in estrogen and progesterone concentration. The Stages of Reproductive Aging Workshop describes menopause as a series of four stages along a reproductive continuum.[3] Early perimenopause results from anovulatory menstrual cycles and is characterized by irregularity in menstrual cycle length and duration. Late perimenopause is marked by progressive menstrual irregularity. Early postmenopause is the interval within 4 years of the final menstrual period, and late postmenopause is 5 or more years after the final menstrual period.

In the past, menopause was viewed as a risk factor for several chronic conditions attributable primarily to two (related) bodies of evidence: (1) large observational studies showing an increased risk of chronic conditions in relationship to age at natural menopause[4, 5] (as well as increased incidence of biomarkers associated with chronic conditions, such as elevated lipid levels[6]) and (2) observational data showing that estrogen may have a positive effect on both the incidence of chronic conditions[7, 8] and intermediate outcomes related to the risk of chronic conditions (e.g., increase in arterial wall thickness).

"Chronic conditions" refers to common, preventable diseases and conditions treated in primary care settings. These can include heart disease, osteoporosis (and subsequent fractures), cognitive impairment, some types of cancers, and others. These conditions all have multiple risk factors, such as lack of physical activity, poor nutrition, tobacco use, and others. Before 2002, hormone therapy was believed to help prevent these conditions based on evidence from observational

studies,[8, 9] and it was commonly prescribed for primary prevention in women with and without menopausal symptoms.

Prevalence and Burden

Natural menopause occurs at a median age of 51.3 years.[10] Surgery (bilateral oophorectomy), chemotherapy, or radiation can induce premature menopause (defined as menopause that occurs before the age of 40). In the absence of a known cause (e.g., radiation), menopause before age 40 years is considered to be abnormal and is referred to as primary ovarian insufficiency.[11] In some women, menopause is associated with its own morbidity. Approximately 85 percent of women transitioning through menopause report experiencing symptoms such as vasomotor symptoms (hot flashes, sleep disturbances, psychological symptoms [depressive symptoms, anxiety, or mood disturbances]), urogenital problems, and sexual dysfunction.[10, 12]

The prevalence and incidence of most chronic diseases increase with age, and the average U.S. woman who reaches menopause is expected to live another 30 years.[13] However, the excess risk that can be attributed to menopause alone is uncertain for at least two reasons: (1) the hormone events associated with natural menopause and aging do not happen in isolation[12] and (2) chronic conditions are multifactorial. The evidence supporting menopause as a risk factor for chronic disease is strongest for cardiovascular disease and osteoporosis. Currently, the American College of Cardiology/American Heart Association Guidelines[14] recognize the postmenopausal state as a risk factor for cardiovascular disease, assigning it the same weight as male sex. However, data are conflicting on whether the type of menopause (surgical or natural) affects cardiovascular risk; in a large cohort of U.S. women (N=121,700), bilateral oophorectomy, but not natural menopause, was associated with an increased risk of cardiovascular disease.[15]

Interventions

Hormone Therapy

Currently, hormone therapy is approved by the U.S. Food and Drug Administration[16, 17] only for treatment of menopausal symptoms and prevention and treatment of osteoporosis, with the advice that "estrogens and progestins should be used at the lowest doses for the shortest duration to reach treatment goals, although it is not known at what dose there may be less risk of serious side effects."[17] Hormone therapy includes the use of various forms, doses, and regimens of estrogen with or without progestin.[18] Hormone therapy can be taken orally, vaginally, or intranasally or as an implant, skin patch, cream, or gel. Women who have not had previous hysterectomies use a combination therapy of estrogen plus progestin (sometimes denoted combined hormone therapy, but hereafter in this report specified as estrogen plus progestin) to prevent endometrial proliferation and endometrial cancer, whereas women with previous hysterectomies use only estrogen (estrogen-only hormone therapy). Products approved for use in the United States are listed in **Table 1**.

Formulations of oral estrogen may include estradiol (derived from Mexican yam), estradiol

valerate (a pro-drug for estradiol), synthetic conjugated estrogen, ethinyl estradiol, or conjugated equine estrogen (derived from horse mare urine).[19] The progestogens include synthetic derivatives of progesterone or progestins (e.g., norethindrone, norethindrone acetate, levornorgstrel, drosperinone, norgestimate, and medroxyprogesterone acetate) and natural progesterones derived from plants (e.g., orally administered micronized progesterone). Natural progesterones are identical to the steroid produced by the corpus luteum.

For estrogen plus progestin therapy, progestin can be taken either every day (continuous combined therapy) or cyclically with estrogens taken daily and progestins taken for part of the month (sequentially combined hormone therapy). Progestins and natural progesterones differ in their metabolic action and risk of harms such as adverse effects on blood lipids, breast tenderness, or headaches.[19]

A recent Agency for Healthcare Quality and Research–supported review synthesized evidence from 283 randomized controlled trials, published through January 2014, analyzing the effectiveness of treatments for menopausal symptoms. Symptoms of interest included vasomotor, psychological, and urogenital symptoms; quality of life; sexual function; and sleep disturbance.[20] The authors concluded that although estrogens are the most effective treatment for vasomotor symptom relief and confer the greatest improvement in quality-of-life measures, they are also associated with potential long-term harms. Potential harms of long-term hormone therapy include increased risk of venous thromboembolism, stroke, breast cancer, and others. Finally, the authors concluded that compared with placebo, nonhormonal treatments show similar effects as estrogens for other common symptoms, such as psychological, urogenital, and sleep disturbance.[20]

Current Clinical Practice

The number of women using hormone therapy has declined significantly in recent years.[21] Between 1988 and 1994, an estimated 44 percent of postmenopausal women in the United States reported current or past use of at least one form of hormone therapy.[22] Results from the Women's Health Initiative (WHI),[23, 24] a large U.S.-based randomized controlled trial of hormone therapy versus placebo, were first released in 2002; findings indicated that hormone therapy use is associated with important adverse health effects. Between 2003 and 2004, use of all formulations of hormone therapy decreased to 11.9 percent among non-Hispanic white women; however, among non-Hispanic black and Hispanic women, prevalence did not decline substantially until 2005 to 2006. In 2010, the prevalence of hormone therapy use was estimated at 4.7 percent overall—2.7 percent for estrogen only and 1.7 percent for estrogen plus progestin.[25]

Despite the results of the Women's Health Initiative (WHI) and an overall decline in hormone therapy use, current recommendations by professional societies are inconsistent. Some guidelines recommend hormone therapy for women at increased risk of osteoporosis and fracture.[26, 27] Data also suggest that the overall net benefit of hormone therapy use may be increased for women who initiate treatment during the menopause transition or early postmenopause rather than late postmenopause. This approach is often referred to as the "timing hypothesis" (i.e., a critical window for favorable outcomes of hormone therapy treatment).[28] The hypothesis proposes that

hormone therapy given at or soon after menopause reduces the risk of cardiovascular disease but the potential beneficial effects will be attenuated or not experienced when hormone therapy is initiated several years after menopause.[29]

The timing hypothesis arose initially from data of the Framingham study, which indicated that natural menopause increases the risk of cardiovascular disease. Studies in female monkeys[30] and large observational studies in women[8, 31, 32] corroborated the hypothesis that early commencement of hormone therapy prevents the progression of atherosclerosis. The purported health benefits of early hormone therapy have been extended to lower mortality,[33] reduced risk of dementia, and better cognition.[34] Most of these claims are based on observational studies; post-hoc subgroup analyses of the WHI also reported benefits of an early commencement of hormone therapy.[35]

Summary of Guidelines From Other Groups

Several organizations have issued clinical practice guidelines related to using hormone therapy in postmenopausal women for the prevention of chronic conditions (**Table 2**). No current guidelines recommend the routine use of hormone therapy for primary or secondary prevention of heart disease, and most recommend against the use of hormone therapy for prevention of any chronic conditions. Both the American Congress of Obstetricians and Gynecologists (ACOG) guidelines[26] and the American Association of Clinical Endocrinologists guidelines[27] note that hormone therapy is approved for women at increased risk of osteoporosis and fracture. The ACOG guidelines also mention the uncertainty about whether the potential cardiovascular benefits for women may differ based on early versus late initiation of hormone therapy.[26, 36] The North American Menopause Society guidelines[37] focus primarily on considerations for women with symptoms; they note that the balance of potential health benefits and risks should be weighed individually for each woman.

Chapter 2. Methods

The methods for this review follow the guidance provided in the USPSTF Procedure Manual.[38]

Key Questions and Analytic Framework

The investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers developed the scope, Key Questions (KQs), and analytic framework (**Figure 1**) that guided our literature search and review. Specifically, our KQs are:

1. What are the benefits of menopausal hormone therapy when used for the primary prevention of chronic conditions?
2. What are the harms of menopausal hormone therapy when used for the primary prevention of chronic conditions?
3. Do the benefits and harms of menopausal hormone therapy differ by subgroup (race or ethnicity; women with premature menopause; women with surgical menopause; age during hormone therapy use; duration of use; type, dose, and mode of delivery of hormone therapy; and comorbid condition) or by timing of intervention (initiation of hormone therapy during perimenopause vs. postmenopause)?

We will also answer the following contextual questions:

1. What is the average treatment duration of hormone therapy in women who initiate its use for the treatment of menopausal symptoms?
2. Does the use of hormone therapy differ by subgroup?

Apart from the introduction above, this methods chapter, and the results and discussion chapters to follow, this report has several appendices. They include **Appendix A**, which documents our various search strategies; **Appendix B**, which lists the inclusion and exclusion criteria based on relevant populations, interventions, comparators, outcomes, timing, and settings (PICOTS) and other elements such as study designs; **Appendix C**, which gives the criteria for rating the quality of randomized controlled trials according to the USPSTF approach; **Appendix D**, which is the flowchart for the literature review, based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance; **Appendix E**, which lists all studies that we excluded at the full-text review stage; **Appendix F**, which documents our critical appraisal decisions, specifically the ratings for each domain of the quality ratings for each trial; **Appendix G**, which contains outcome-specific tables containing all data reported for a given outcome from the included trials used for our main analyses; and **Appendix H**, which includes forest plots for outcomes with sufficient data to complete meta-analysis.

Search Strategies

We searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-

language articles published from June 1, 2011, through August 1, 2016. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, interventions, comparators, outcomes, timing, and settings. **Appendix A** describes all the search strategies.

We conducted targeted searches for unpublished literature by searching ClinicalTrials.gov, HSRProj, the World Health Organization's International Clinical Trials Registry Platform, and NIH Reporter. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.

Study Selection

We selected hormone therapy studies on the basis of inclusion and exclusion criteria developed for each KQ based on the PICOTS approach for identifying populations, interventions, comparators, outcomes, timing, settings, and study designs. The basic criteria are described below, and **Appendix B** provides more details. We imported all citations identified through searches and other sources into EndNote v.7.

Two investigators independently reviewed titles and abstracts. We then dually and independently reviewed the full text of all articles that either reviewer marked for potential inclusion. We resolved disagreements by discussion and consensus; if necessary, we sought adjudication of conflicts from other experienced members of the review team. **Appendix E** lists studies that we excluded at the full-text review stage.

In addition to the searches for the updated literature, we incorporated all included citations from the previous report, which covered the publication period of January 2002 through November 2011.[39] Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed all included citations from three recent systematic reviews[19, 40, 41] and included all relevant citations that met our criteria for fair or good quality.

Populations

We included studies of generally healthy perimenopausal and postmenopausal women who were eligible for menopausal hormone therapy. Women with and without menopausal symptoms were included if the focus of the analysis was either on the primary prevention of chronic conditions or on harms of hormone therapy. In some cases, we included studies that may have had populations for which hormone therapy use was intended for secondary prevention (e.g., slowing the progression of coronary-artery atherosclerosis). We excluded postmenopausal women with contraindications for hormone therapy use.

Interventions

We searched for studies that examined the use of systemic therapy with estrogen-only formulations or combination preparations of estrogen plus progestin for the primary prevention of chronic conditions. We limited our evaluation to medications that have been approved by the U.S. Food and Drug Administration for this purpose and that are available for use in the United States. **Table 1** lists the drugs in these two classes by generic name and gives the brand names, the type of product (e.g., patch or pill), and information on dosage. We focused our analysis on studies that present the effect of the intervention by type of hormone therapy (i.e., estrogen only or estrogen plus progestin). We included studies that do not differentiate between type of hormone therapy in the evidence tables, but we do not discuss them in detail in the results.

Comparators

We included placebo-controlled trials and studies with inactive treatments as a comparator.

Outcomes

Because of the main focus on primary prevention of chronic conditions, we included trials that measured various metrics for the following array of such diagnoses or events: several cancers (breast, cervical, endometrial, ovarian, colorectal, and lung), coronary heart disease, stroke, and thromboembolism. We also included trials that assessed cognitive functioning and dementia, diabetes (new diagnoses requiring medication), fractures, gallbladder disease (cholecystitis and cholelithiasis), and urinary incontinence (stress, urge, and overall). Finally, we included studies that measured all-cause mortality. If we encountered studies for the secondary prevention of, for instance, myocardial infarction, we still included them for other primary outcomes (e.g., fractures) but not for the specific secondary prevention target.

With respect to harms, we sought information on adverse events, unanticipated negative consequences, or side effects attributable to hormone therapy.

Our analysis prioritized outcomes that were prespecified. We generally do not present the full results for multiple measures of a single construct (e.g., for cognitive function), unless the results were statistically significant. We also elected to prioritize individual rather than composite outcomes, when both were available.

Timing

We searched for studies that reported on outcomes of 1 year or more of hormone therapy for the outcomes outlined above (duration of the intervention). We also evaluated the effect of the timing of the intervention relative to menopause when such data were available but did not base inclusion or exclusion decisions on this criterion.

Settings

For all KQs, we included trials done in all primary care or primary care-like settings but not in inpatient, hormone specialist, or institutional settings such as nursing homes or similar facilities. With respect to geography, we searched for studies conducted in the United States or in countries designated by the United Nations Development Programme as having a very high Human Development Index (HDI).[42]

Study Designs

In our searches, we included the following study designs: randomized controlled trials, controlled trials, and systematic reviews. We also included large controlled cohort studies (>10,000 women) for outcomes for which we had no evidence from trials or systematic reviews. We included data from long-term followup studies of trials if they provided information on how elevated or reduced risks changed after women had stopped hormone therapy. We present these findings in the context of results from the randomized trials.

Because we had sufficient evidence from randomized trials, we did not use any observational studies to address the KQs. Systematic reviews were used only to identify studies (from their reference lists) that we might otherwise have missed.

Data Abstraction and Quality Rating

We abstracted pertinent information from each included study; details included methods and populations, interventions, comparators, outcomes, timing, and settings. A second investigator checked all data abstractions for completeness and accuracy. We resolved differences by consensus or adjudication by a third senior investigator.

Using predefined criteria developed by the USPSTF, two investigators independently assessed the quality of each study as good, fair, or poor.[43] The USPSTF criteria appear in **Appendix C**; **Appendix F** lists our ratings for each domain for each eligible study. Disagreements were resolved by discussion and consensus. We rated trials with fatal flaws as poor quality (i.e., high risk of bias). Fatal flaws that resulted in poor-quality ratings included initially assembled groups that were not close to being comparable or were not maintained throughout the study, overall attrition of at least 20 percent or differential attrition of at least 15 percentage points between groups, and use of unreliable or invalid measurement instruments or unequal application among groups (including not masking outcome assessment). For randomized controlled trials, the lack of intention-to-treat analysis was also a reason for rating a trial as poor quality.

Data Synthesis and Analysis

We qualitatively synthesized findings for each KQ by summarizing the characteristics and results of included studies in tabular or narrative format. To determine whether meta-analyses were appropriate, we assessed both the number of trials available and their clinical and methodological

heterogeneity following established guidance.[44] To do this, we qualitatively assessed the populations, similarities and differences in treatments used, and similarities in outcomes and timing of outcomes assessed.

When at least three similar trials were available, we conducted quantitative synthesis of studies with random-effects models using the inverse-variance weighted method (DerSimonian and Laird).[45]

For all quantitative syntheses, we calculated the chi-squared statistic and the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity rather than due to chance) to assess statistical heterogeneity in effects between studies.[46, 47] An I^2 from 0 to 40 percent might not be important, 30 percent to 60 percent may represent moderate heterogeneity, 50 percent to 90 percent may represent substantial heterogeneity, and 75 percent or greater represents considerable heterogeneity.[48] The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g., p-value from the chi-squared test or a confidence interval [CI] for I^2). However, as precision and the number of subjects increase, I^2 may become inflated toward 100 percent and may not reflect clinically relevant heterogeneity.[49]

We conducted all the quantitative analyses using Comprehensive Meta-Analysis Version 3 (Biostat Inc., Englewood, NJ, USA).

We rated the strength of evidence (SOE) for each major outcome for each KQ using the domains set out in the AHRQ guidance:[50] study limitations,[51] consistency,[52] precision,[53] directness,[54] and reporting bias.[55] We also considered other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect).[56]

Two reviewers assessed each SOE domain for each key outcome and developed the overall SOE grades. The reviewers were two senior members of the review team (including at least one subject matter expert and one methodologist); they resolved any differences by consensus discussion.

SOE grades reflect the confidence that the reviewers have that various estimates of effect are close to true effects with respect to the KQs in a systematic review. A high grade indicates confidence that the estimate of effect lies close to the true effect for this outcome, the body of evidence has few or no deficiencies, and the findings are stable. A moderate grade suggests that although the estimate of effect lies close to the true effect for this outcome, the body of evidence has some deficiencies and some doubt persists as to the stability of the findings. A low grade suggests limited confidence about the estimate of effect, with the need for additional studies. Insufficient evidence means that we have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome.

Expert Review and Public Comment

This draft report was reviewed by content experts, USPSTF members, and AHRQ Medical Officers before it was posted for public comment. We will revise it, as appropriate, based on public comments and additional any additional comments received from content experts, USPSTF members, and AHRQ Medical Officers.

USPSTF Involvement

This review was funded by AHRQ. AHRQ staff and members of the USPSTF participated in developing the scope of the work and reviewed draft manuscripts, but the authors are solely responsible for the content.

Chapter 3. Results

This chapter begins with the results of our literature searches and a general description of the included trials that form the basis of our analyses and findings. As noted, we used systematic reviews only for finding trials of menopausal hormone therapy that our searches might have missed. Furthermore, because we had adequate evidence based on trials, we do not present information on controlled cohort studies.

Following those sections, we present a summary of the available trial evidence regarding benefits and harms (KQ 1 and KQ 2) and differences of effects in subgroups (KQ 3). We then document the evidence in more detail for each outcome of interest stratified by the hormone therapy treatment (estrogen only or estrogen plus progestin).

Because results of the Women's Health Initiative (WHI) have been published in multiple publications, we chose articles that focused on specific outcomes (e.g., gallbladder disease, urinary incontinence) over more general publications, when available.

Results of Literature Searches

The update of this report identified 2,241 citations. Of these, 1,989 abstracts were excluded and investigators reviewed 252 full-text articles. We retained 17 articles reporting on 13 trials that met inclusion criteria given in **Appendix B**. Overall, 68 articles from the previous review and this update represented a total of 18 good- or fair-quality trials.[39] **Appendix D** documents the disposition of the articles identified from searches (i.e., the flow chart of the literature). **Appendix E** lists articles excluded at full-text review.

Description of Trials

Included articles provided data on 40,058 peri- and postmenopausal women comparing the effects of estrogen, either alone or in combination with progestin, against placebo for the prevention of chronic conditions. These trials specifically were the following:[57, 58] Estrogen Memory Study (EMS),[59] Estrogen in the Prevention of Atherosclerosis Trial (EPAT),[60] Estonian Postmenopausal Hormone Therapy Trial (EPHT),[61] Estrogen Replacement and Atherosclerosis Study (ERA),[62] Oestrogen in the Prevention of Reinfarction Trial (ESPRIT),[63, 64] Greenspan et al., 2005,[65] Heart and Estrogen Replacement Study (HERS),[66-72] Kronos Early Estrogen Prevention Study–Cognitive and Affective Study (KEEPS-Cog),[73] Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial,[74] STOP-IT,[75] Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA),[76-79] Women's Angiographic Vitamin and Estrogen (WAVE) Trial,[80] the WHI estrogen plus progestin trial,[23, 35, 81-104] WHI estrogen-only trial,[24, 35, 82, 88, 94, 98, 99, 102, 104-113] WHI Memory Study (WHIMS),[114-118] WHI Memory Study of Younger Women (WHIMSY),[119] WHI Study of Cognitive Aging (WHISCA),[120-122] and Women's International Study of Long Duration Oestrogen After Menopause (WISDOM).[123]

Of the 18 included trials, 13 were conducted in the United States. The remaining trials were conducted in Australia, Canada, Estonia, New Zealand, and the United Kingdom. The duration of followup in the trials averaged 3.5 years. The mean age of women participating in trials ranged from 53 (KEEPS-Cog) to 79 years (EMS). The majority of women were white; the proportions of nonwhite women ranged from 1 percent (WISDOM)) to 41 percent (EPHT). The proportions of women with previous or current hormone therapy use ranged from 2 percent to 54.5 percent. A range of 3.7 percent to 58 percent of women in the trials were current smokers.

Of the 18 included studies, the WHI trials were the only studies powered to assess the effectiveness of hormone therapy for the primary prevention of various chronic conditions. They enrolled generally healthy postmenopausal women ages 50 to 79 years and compared oral conjugated equine estrogen, 0.625 mg/d with or without medroxyprogesterone 2.5 mg/d with placebo. The WHI trials also had the longest durations of followup among included trials (median of 7.2 years for the estrogen-only trial and 5.6 years for the estrogen plus progestin trial).

Table 3 summarizes the main characteristics and quality ratings of the eligible trials named above. Of these, all but five were rated fair quality. We rated four trials as poor quality and do not include them in these tables or analyses.[57, 124-126] Three trials (which are described in **Table 3**) met eligibility criteria but did not stratify results by regimen (i.e., whether women used estrogen-only or estrogen plus progestin).[65, 75, 80] **Table 4** presents baseline characteristics of participants in included trials. Outcomes data from included trials appear in **Appendix G**.

Summary of Evidence

Eighteen fair- and good-quality trials met eligibility criteria. The WHI reported most of the results and was most applicable to the target population. This summary section provides an overview of results. More detailed findings by chronic condition and regimen follow the summary.

Figures 2 and **3** depict the absolute risk reductions or increases for various outcomes of interest for women who received hormone therapy for 5 to 7 years compared with those on placebo. Results are depicted as point estimates (fewer or more events per 10.000 women) with 95 percent CIs based on meta-analyses of included trials or, if meta-analyses were not feasible, based on results from the largest and most reliable trial (usually the WHI).

Figures 2 and **3** also present the relative risks and the strength of evidence for each outcome. We calculated relative risks based primarily on the latest publication summarizing results of the WHI trials.[102] Therefore, effect estimates might differ slightly from hazard ratios (HRs) reported in WHI publications. We chose relative risks because they are more intuitive to interpret than HR.

For several outcomes of interest we did not find any statistically significant differences between women using hormone therapy and women on placebo. For estrogen-only therapy, outcomes that were not statistically significant include probable dementia, breast cancer, colorectal cancer, lung cancer, coronary heart disease, quality of life, and all-cause mortality. For estrogen plus

progestin therapy, we did not find statistically significant differences for cervical cancer, endometrial cancer, lung cancer, ovarian cancer, quality of life, and all-cause mortality.

Some of these nonstatistically significant outcomes, however, had wide CIs that encompassed both clinically relevant benefits and harms leading to inconclusive results. Specifically for cervical cancer, endometrial cancer, lung cancer, and ovarian cancer, event rates in studies were too low to draw firm conclusions about differences in benefits and harms.

KQ 1. What Are the Benefits of Menopausal Hormone Therapy When Used for Primary Prevention of Chronic Conditions?

Overall, trials reported several statistically significant benefits for women using hormone therapy. For women using estrogen only, risks for fractures (382 fewer cases per 10,000 women over 7.2 years [95% CI, 283 to 495 fewer]) and diabetes (137 fewer cases per 10,000 women over 7.1 years [95% CI, 21 to 248 fewer]) were statistically significantly reduced compared with women taking placebo (Figure 2). The risk of breast cancer was numerically reduced but did not reach statistical significance (HR, 0.79; 95% CI, 0.61 to 1.02).[102] Women on estrogen plus progestin therapy experienced statistically significantly reduced risks for colorectal cancer (33 fewer cases per 10,000 women over 5.6 years [95% CI, 8 to 52 fewer]), fractures (222 fewer cases per 10,000 women over 5.0 years [95% CI, 67 to 354 fewer]), and diabetes (77 fewer cases per 10,000 women over 5.6 years [95% CI, 21 to 206 fewer]) compared with women in the placebo groups (Figure 3).

Long-term followup studies of the WHI showed that most beneficial effects dissipated after stopping hormone therapy. An exception was the risk of invasive breast cancer in women who received estrogen-only therapy. Specifically, 3.9 years after women stopped hormone therapy treatment, the risk remained numerically (but not statistically) lower for women who had been treated with estrogen only during the trial phase (HR, 0.75; 95% CI, 0.51 to 1.09).[112] We did not find any evidence on functional capacity.

KQ 2. What Are the Harms of Menopausal Hormone Therapy When Used for Primary Prevention of Chronic Conditions?

Results of trials and our meta-analyses indicate several important harms for hormone therapy. They differ by treatment formulation (i.e., estrogen only or estrogen plus progestin).

Women on estrogen-only therapy had statistically significantly increased risks for gallbladder disease (378 more cases per 10,000 women over 7.1 years [95% CI, 236 to 538 more]), stroke (79 more cases per 10,000 women over 7.1 years [95% CI, 14 to 160 more]), urinary incontinence (1261 more cases per 10,000 women over 1 year [95% CI, 880 to 1,689 more]), and venous thromboembolism (78 more cases per 10,000 women over 7.1 years [95% CI, 20 to 153 more]; see Figure 2). Likewise, for women on estrogen plus progestin therapy, risks for invasive breast cancer (52 more cases per 10,000 women over 5.6 years [95% CI, 6 to 107 more]), coronary heart disease (41 more cases per 10,000 women over 5.1 years [95% CI, 0 to 93 more]), probable dementia (88 more cases per 10,000 women over 4 years [95% CI, 15 to 213 more]),

gallbladder disease (259 more cases per 10,000 women over 5.6 years [95% CI, 167 to 366 more]), stroke (53 more cases per 10,000 women over 5.6 years [95% CI, 12 to 104 more]), urinary incontinence (876 more cases per 10,000 women over 1 year [95% CI, 606 to 1,168 more]), and venous thromboembolism (120 more cases per 10,000 women over 5.6 years [95% CI, 68 to 185 more]) were statistically significantly increased compared with women taking placebo (see Figure 3). We did not find any evidence on other harms or on the impact of harms on functional capacity.

KQ 3. Do the Benefits and Harms of Menopausal Hormone Therapy Differ by Subgroup or by Timing of Intervention?

Subgroups specified for this KQ included the following: race or ethnicity; women with premature menopause; women with surgical menopause; age of use; duration of use; types, doses, and modes of delivery of hormone therapy; and presence of comorbidities. Trials did not report results for most of these subgroups. Post hoc subgroup analyses of trial results based on these characteristics were restricted to age and a limited number of coexisting conditions or risk factors.

Some subgroup analyses indicate that time since menopause and age might modify the cardiovascular effects of hormone therapy. Younger women on estrogen only had lower risks for myocardial infarction than older women relative to women using placebo (p=0.02). Younger women on estrogen only had also a reduced risk for all-cause mortality while older women had an increased risk (p=0.04). Women who initiated estrogen plus progestin therapy closer to menopause did not have the elevated risk for myocardial infarction that women experienced who started therapy more than 20 years after menopause (p=0.01).

Findings also indicated an increased risk of breast cancer in women on estrogen plus progestin who initiated therapy within 5 years of menopause (p=0.03). Older women had an increased risk attributable to estrogen-only hormone therapy for colorectal cancer. Some of these subgroup differences, however, are based on relatively few events and need to be interpreted cautiously. We did not find any evidence on functional capacity.

Detailed Presentation of the Evidence

In the sections below, we present benefits and harms first for estrogen-only hormone therapy and then for estrogen plus progestin by outcome of interest. Although data from the four trials that did not stratify results by treatment regimen are not analyzed in this report, they are included in **Appendix G**. We specifically comment on the various cancers (breaking out the gynecologic cancers by specific type, such as cervical or ovarian) and then turn to the various other condition-specific outcomes. Evidence about all-cause mortality comes last. We also address differences of effects by subgroups and by the timing of the intervention, when such data were available. In one instance (on the effect of timing of the intervention on cardiovascular outcomes), we present information from two trials that were not eligible for our report because they focused on intermediate outcomes. However, they are the only available evidence directly addressing this question.

Table 3 describes the main characteristics of eligible trials, including the various types and levels of estrogen only (top panel) or estrogen plus progestin (bottom panel) used. **Appendix G** presents results of individual trials for each outcome in more detail.

Because the two WHI trials were the largest studies, we summarize results on outcomes of interest at the end of the intervention phase of the WHI trials according to treatment (estrogen only or estrogen plus progestin) in **Table 5**. **Tables 6–8** are summary-of-findings tables presenting the available evidence, effect estimates, and strength of evidence ratings for each outcome by treatment. Effect estimates are based on meta-analyses of included trials or, if meta-analyses were not feasible, based on results from the largest and most reliable trial (usually the WHI).

Estrogen Only: Cancers

Breast Cancer

Benefits and Harms of Hormone Therapy

Five randomized controlled trials (WHI [N=10,739],[24, 98, 102, 104, 105, 112] ESPRIT [N=1,017],[63, 64] EPAT [N=222],[60] ERA [N=205],[62] and PEPI [N=349][74]) comparing estrogen only to placebo reported on breast cancer incidence (see **Appendix G Table 1**). We did not pool trial results primarily because of heterogeneity in study duration and outcome measures. Only two trials followed women for more than 3 years (WHI and ESPRIT), and only the WHI reported on risk of invasive breast cancer (versus any breast cancer).

In the WHI, women assigned to estrogen alone had a nonsignificant decrease in invasive breast cancer risk compared with placebo during the 7.2-year (median) intervention phase (2.0% vs. 2.5%; HR, 0.79; 95% CI, 0.61 to 1.02).[102, 112] The risk remained numerically lower during the 6.6-year (median) postintervention phase after the trial had been stopped.[102] The difference between groups was statistically significant during cumulative (trial and postintervention phase, median 13 years) followup (HR, 0.79; 95% CI, 0.65 to 0.97).[102]

In the ESPRIT trial, postmenopausal women 50 to 69 years of age who survived a first myocardial infarction were randomized to estrogen only or placebo. The risk of breast cancer in women randomized to estrogen only and placebo during the 2-year intervention period was similar (0.8% vs. 0.8%; RR, 0.98; 95% CI, 0.25 to 3.91).[63]

Three other trials reported on breast cancer incidence over 2 to 3 years, the EPAT,[60] ERA,[62] and PEPI trials;[74] results were inconclusive. Only four cases of breast cancer were reported across the trials (two each in the estrogen-only and placebo groups).

Differences in Treatment Effects Based on Subgroups

In the WHI, no difference in breast cancer risk by subgroups based on age at randomization could be detected.[102] Biennial analyses of invasive breast cancer risk during the intervention phase of the WHI demonstrated no evidence of a trend over time since randomization (p for

trend=0.29).[104]

Differences in Treatment Effects Based on Timing of the Intervention

Risk of invasive breast cancer in the WHI trial was similar in women who initiated estrogen soon after menopause (<5 years) versus later (≥5 years).[98]

Cervical Cancer

Benefits and Harms of Hormone Therapy

One trial (ESPRIT[64] [N = 1,017]) reported one incident case of cervical cancer, identified via data linkage to United Kingdom cancer records, over a mean followup of 12.6 years, among women who received placebo, and zero incident cases of cervical cancer among women who received estrogen-only hormone therapy (**Appendix G Table 2**). None of the other trials reported on cervical cancer.

Differences in Treatment Effects Based on Subgroups

We found no evidence about differences in treatment effects by subgroups.

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence about differences in treatment effects based on timing of the intervention.

Colorectal Cancer

Benefits and Harms of Hormone Therapy

One trial (WHI [N=10,739]) estimated the incidence of colorectal cancer among 5,310 women with previous hysterectomy who received estrogen-only hormone therapy and 5,429 women with previous hysterectomy who received placebo (**Appendix G Table 3**).[24, 98, 102, 112, 113]

During the WHI intervention phase, 1.2 percent of women who received estrogen-only hormone therapy and 1.1 percent of women who received placebo developed colorectal cancer (HR, 1.15; 95% CI, 0.81 to 1.64).[102]

Differences in Treatment Effects Based on Subgroups

In the WHI intervention phase, younger women had statistically significantly lower risks of developing colorectal cancer than older women (p for interaction=0.02). Among women 50 to 59 years and 60 to 69 years of age at randomization, there were no statistically significant differences in the risk of colorectal cancer between women on estrogen-only hormone therapy and placebo (HRs of 0.71 and 0.88; 95% CIs of 0.30 to 1.67 and 0.53 to 1.47, respectively). The risk of colorectal cancer among women 70 to 79 years was significantly higher for those on estrogen-only therapy than for women on placebo (HR, 2.24; 95% CI, 1.16 to 4.30). The

significant interaction with age at randomization was no longer present after a median cumulative followup of 13.0 years.[102]

The WHI did not detect any statistically significant subgroup effects regarding race or ethnic groups, diabetes status, previous use of menopausal hormones, or bilateral oophorectomy status after a mean of 7.1 years.[113]

Differences in Treatment Effects Based on Timing of the Intervention

No statistically significant differences in incidence of colorectal cancer emerged between women who received estrogen-only hormone therapy and those who received placebo according their years since menopause (i.e., <10 years, 10 to <20 years, and ≥20 years since menopause) in the WHI.[102] The effect of hormone therapy on the risk of invasive colorectal cancer did not differ significantly between women who initiated hormone therapy within the first 5 years after menopause and those who initiated combined hormone therapy after 5 years following menopause.[98]

Endometrial Cancer

Benefits and Harms of Hormone Therapy

Five trials (ERA [N=205],[62] EPAT [N=222],[60] ESPRIT [N=1,017],[63, 64] PEPI [N=349],[74] and ULTRA [N=417][77]) provided data on endometrial cancer among women who received estrogen-only hormone therapy or placebo. We present results in **Appendix G Table 4** but do not discuss them here because of the well-known risk of endometrial hyperplasia and cancer associated with unopposed estrogen use.

Differences in Treatment Effects Based on Subgroups

We found no evidence about differences in treatment effects by subgroups.

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence about differences in treatment effects based on timing of the intervention.

Lung Cancer

Benefits and Harms of Hormone Therapy

One trial (WHI [N=10,739]) estimated the incidence of lung cancer among 5,310 women with previous hysterectomy who received estrogen-only hormone therapy and 5,429 women with previous hysterectomy who received placebo (**Appendix G Table 5**).[102, 108]

No statistically significant differences in lung cancer incidence emerged between women who received estrogen-only hormone therapy and women who received placebo. Only 1.2% of women who received estrogen-only hormone therapy and 1.1% of women who received placebo

developed lung cancer during the WHI intervention phase over a median followup period of 7.2 years (HR, 1.05; CI, 0.74 to 1.49).[102] During the postintervention followup period (mean duration=6.8 years), risks between treatment groups remained similar.[102]

Differences in Treatment Effects Based on Subgroups

The WHI reported no statistically significant differences in risks for women based on age at randomization.[102]

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence about differences in treatment effects based on timing of the intervention.

Ovarian Cancer

Benefits and Harms of Hormone Therapy

One trial (ESPRIT [N=1,017]) of women with previously documented myocardial infarction provided the incidence of ovarian cancer among women who received estrogen-only hormone therapy or placebo during the trial's 2-year intervention (**Appendix G Table 6**).[64] The authors do not report ovarian cancer incidence at the end of the intervention phase.[63] During long-term followup (average: 12.6 years) that included both the trial phase and the posttrial observational phase, there was no statistically significant difference in the incidence of ovarian cancer between the two groups; 0.78 percent of women in the estrogen-only group and 0.20 percent in the placebo group developed ovarian cancer.[64]

Differences in Treatment Effects Based on Subgroups

We found no evidence about differences in treatment effects by subgroups.

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence about differences in treatment effects based on timing of the intervention.

Estrogen Only: Other Chronic Conditions

Coronary Heart Disease

Benefits and Harms of Hormone Therapy

Four trials (EPAT [N=222],[60] PEPI [N=349],[74] WHI [N=10,739],[111] and ERA [N=205][62]) provided data on the risk of coronary heart disease in women who used estrogen only (**Appendix G Table 7**).

Of these, three trials (EPAT,[60] PEPI,[74] WHI[111]) were similar enough to be combined in a meta-analysis. We did not include the ERA study in the meta-analysis because only women with an

elevated cardiovascular risk were eligible for enrollment.[62] Studies in the meta-analysis provide information about the prevention of coronary heart disease with estrogen only based on data for 11,310 women who had previously undergone hysterectomy. Treatment durations ranged from 2 to 7.1 years. The WHI and the EPAT trial defined coronary heart disease as nonfatal myocardial infarction or coronary death;[111] the definition that the PEPI trial used was unclear.[74]

A meta-analysis of these three trials rendered no statistically significant difference in coronary events between women on estrogen therapy and those on placebo (relative risk [RR], 0.95; 95% CI, 0.79 to 1.14). In the meta-analysis, 3.6 percent of women receiving estrogen-only therapy and 3.8 percent of those on placebo experienced a coronary event during a mean followup of 6.8 years. A sensitivity analyses including ERA rendered similar results.

A long-term followup study of the WHI reported that 3.9 years after stopping the randomized treatment, the cardiovascular risk was still similar between women on hormone therapy during the trial and those who were randomized to placebo (HR, 0.97; 95% CI, 0.75 to 1.25).[112]

Differences in Treatment Effects Based on Subgroups

In the WHI trial, no statistically significant difference in risk of coronary heart disease attributable to hormone therapy could be detected between subgroups based on age, race, or ethnicity, hypertension, diabetes, high cholesterol requiring medication, coronary risk factors, years since bilateral oophorectomy, years since hysterectomy, or body mass index.[35, 102, 111] However, risk increased numerically with age. The HR for women ages 50 to 59 years was 0.60 (95% CI, 0.35 to 1.04) in favor of hormone therapy. By comparison, the HRs for women 60 to 69 years and 70 to 79 years at baseline were 0.95 (95% CI, 0.72 to 1.24) and 1.09 (95% CI, 0.80 to 1.49), respectively (p for trend=0.08).[102] Analyses that focused just on myocardial infarction showed that younger women on estrogen only had lower risks for myocardial infarction than older women relative to women using placebo (p=0.02). Findings, however, need to be viewed cautiously because only 48 women in the 50- to 59-year age group experienced a myocardial infarction.[102]

Differences in Treatment Effects Based on Timing of the Intervention

In the WHI, time since menopause did not have a statistically significant impact on the risk of coronary heart disease.[102] Likewise, an analysis of WHI data that took the first use of hormone therapy (before enrollment into the WHI) into consideration to assess the effect of timing of hormone therapy did not find an effect of early initiation on the risk of coronary heart disease (p=0.40).[98]

The onset of menopause in women who had undergone hysterectomy without oophorectomy, however, cannot always be determined with certainty. Results, therefore, have to be interpreted cautiously.

Cognitive Function and Dementia

Benefits and Harms of Hormone Therapy

The WHI trials evaluated dementia or mild cognitive impairment (**Appendix G Table 8**). The WHIMS trial (N=2,947) was a subset of the WHI trial, limited to women 65 to 79 years of age at baseline, free of probable dementia, and recruited from 39 of 40 WHI trial centers. Participants in WHIMS were followed for approximately 5.2 years. WHISCA was a subset (N=434 in the estrogen arm, N=452 in the placebo arm) of the WHIMS trial, limited to 14 of the 39 trial centers and designed to evaluate changes in cognitive function over time, with the first assessment occurring 3 years after the start of treatment (because WHISCA was an ancillary trial to WHIMS).[127] Participants in WHISCA were followed for approximately 3.6 years during the trial, and a further subset of WHISCA, in an extension study, was followed for 2.4 years after treatment. Neither WHIMS nor WHISCA found an elevated risk of probable dementia or mild cognitive impairment for women on hormone therapy.[117, 121] When using a composite outcome measure (probable dementia or mild cognitive impairment), the study found a statistically significantly higher risk of women treated with estrogen-only therapy compared with women on placebo (6.4% vs. 4.7%; cumulative HR, 1.38; 95% CI, 1.01 to 1.89).[117]

Three trials (WHIMS [N=4,344],[115] WHISCA [N=1,213],[120] and ULTRA [N=417][79]) measured global cognitive function using the Modified Mini-Mental Status Examination (3MSE); heterogeneity in timing precluded meta-analysis. The WHIMS and WHISCA trials are described above. The ULTRA trial randomized women to estrogen-only or placebo transdermal patches. Additionally, all participants received 400 mg of calcium twice daily and 400 IU of vitamin D once daily.[79] The ULTRA trial followed participants for 2 years. The WHI trials found cognitive deficits during the trial period (difference in 3MSE score at 3.6 years during WHISCA trial: -0.092; p=0.02;[120] change in 3MSE score at 5.4 years at the end of the WHIMS trial[115]: -0.26; 95% CI -0.542 to 0; p=0.04). In a long-term extension of the WHISCA trial, with outcomes measured at 2.4 years after trial termination, these differences were not sustained.[120] The ULTRA study found no differences.[79]

Three trials (WHISCA [N=1,213],[120, 121] WHIMSY [N=1,326],[119] and ULTRA [N=417][79]) evaluated other measures of cognitive function (e.g., spatial ability, verbal knowledge, verbal fluency, verbal memory, figural memory, attention, and working memory); heterogeneity in outcome measures precluded meta-analysis. The WHISCA and ULTRA trials are described above. The WHIMSY trial was an extension of the WHI trial, limited to enrolled active participants in the WHI trials who were ages 50 to 55 years at enrollment and agreed to be contacted for recruitment (N=1,326 assessed, N by treatment regimen not reported). The WHIMSY trial followed women for 7.2 years after the end of the trial. All three trials found no differences in groups as randomized for the majority of outcomes.

Differences in Treatment Effects Based on Subgroups

The WHIMS study reported no difference in the hazard rate for probable dementia by race or history of diabetes, stroke, hypertension, or cardiovascular disease.[117]

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence on differences in treatment effects based on timing of the intervention.

Diabetes

Benefits and Harms of Hormone Therapy

The WHI (N=9,917)[102, 106] was the only trial that provided information about the prevention of diabetes with estrogen only among women not receiving treatment for diabetes at baseline (**Appendix G Table 9**). Incident diabetes was self-reported and defined as a new diagnosis of diabetes by a physician followed by treatment with oral hypoglycemic drugs or insulin.[106]

During a median of 7.2 years of followup, 9.2 percent of women receiving estrogen therapy and 10.5 percent of those on placebo reported a new diabetes diagnosis. The difference in risks between these groups did reach statistical significance (HR, 0.86; 95% CI, 0.76 to 0.98).[102] When the analysis focused on women who adhered to medication (took ≥80% of study pills or began open-label therapy), the difference in risks increased further (HR, 0.73; 95% CI, 0.60 to 0.88).[106] The overall reduction in diabetes risk was no longer observed 6.6 years postintervention (HR, 1.07; 95% CI, 0.92 to 1.25).[102]

Differences in Treatment Effects Based on Subgroups

A test for interaction did not detect any statistically significant subgroup effects with respect to race/ethnicity, age at screening, hypertension, or metabolic syndrome at baseline among women in the WHI.[106]

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence on differences in treatment effects based on timing of the intervention.

Fractures

Benefits and Harms of Hormone Therapy

The WHI (N=10,739) found a reduced risk of total osteoporotic fractures in the estrogen-only arm when compared with placebo during the trial (10.2% vs. 14.1%; HR, 0.72; 95% CI, 0.64 to 0.80)[102] as did the ERA trial[62] (**Appendix G Table 10**). The difference (for hip fractures) was no longer statistically significant in the postintervention phase of the WHI study (through 10.7.years).[112] The ERA randomized women to the same treatment regimen as the WHI study and followed them for 3.2 years. The study found fewer fractures at all sites (6% vs. 14.3%) in the estrogen-only arm, but the relative risk was not statistically significant (calculated RR, 0.42; 95% CI, 0.17 to 1.04).[62]

Differences in Treatment Effects Based on Subgroups

A test for interaction did not detect any statistically significant subgroup effects with respect to age among women in the WHI.[81]

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence on differences in treatment effects based on timing of the intervention.

Gallbladder Disease

Benefits and Harms of Hormone Therapy

Two trials (PEPI [N=349][74] and WHI [N=8,376][88]) provided information about the prevention of gallbladder disease with estrogen only based on data for 8,725 women with gallbladders and without gallbladder disease (**Appendix G Table 11**). Treatment duration among women in PEPI was 3 years and an average of 7.1 years among those in the WHI. Although the definition of gallbladder disease used in PEPI is unclear, it included cholecystitis and calculi in the WHI.[74, 88] Gallbladder procedures, including biliary tract procedures such as cholecystectomies, were also reported for women in the WHI.[88]

The larger of the two trials, WHI, reported gallbladder events (disease or procedure) during followup for 5.5 percent of women receiving estrogen therapy and 3.4 percent of those taking placebo.[88] The difference in gallbladder events between these groups was statistically significant (HR, 1.67; 95% CI, 1.35 to 2.06).[88] However, risk of gallbladder disease neutralized 6.6 years postintervention (HR, 0.98; 95% CI, 0.68 to 1.41).[102]

The PEPI trial had few cases of gallbladder disease and reported inconclusive results.[74]

Differences in Treatment Effects Based on Subgroups

Risk of gallbladder events attributable to estrogen therapy among women in the WHI increased with age but did not reach statistical significance.[88] No other evidence is available in the included studies on subgroups of interest.

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence about differences in treatment effects based on timing of the intervention.

Stroke

Benefits and Harms of Hormone Therapy

Three trials (WHI [N=10,739],[102, 112] EPAT [N=222],[60] and ERA [N=205][62]) reported on risk of stroke (**Appendix G Table 12**). We did not pool trial results because of heterogeneity in study duration and outcome measures.

During the WHI 7.2-year (median) intervention phase, women on estrogen only had a statistically significantly higher risk of stroke compared with those on placebo (3.2% vs. 2.4%; HR, 1.35; 95% CI, 1.07 to 1.70).[102] During the postintervention period (3.9 years after stopping therapy), the risks between the two treatment groups became similar again; cumulatively (at 10.7 years of followup), stroke risk was higher in the estrogen-only group compared with the placebo group (4.4% vs. 3.8%; HR, 1.15; 95% CI, 0.97 to 1. 37).[102, 112]

The two smaller trials (EPAT[60] and ERA[62]) reported on stroke risk among women randomized to estrogen or placebo; few events occurred overall and results were inconclusive. In the EPAT trial, one participant (randomized to placebo) had a cerebrovascular accident at 2 years.[60] In the ERA trial, the risk of stroke or transient ischemic attack was similar in the estrogen-only and placebo groups (5 vs. 6 events, respectively).[62]

Differences in Treatment Effects Based on Subgroups

In the WHI estrogen-only trial, no differences in stroke risk by subgroups, including race or ethnicity, age, prior cardiovascular disease, hypertension, diabetes, could be detected.[110]

Differences in Treatment Effects Based on Timing of the Intervention

Risk of stroke in the WHI was similar in women who initiated estrogen soon after menopause (<5 years) versus later (≥ 5 years).[98]

Urinary Incontinence

Benefits and Harms of Hormone Therapy

Two trials (WHI [N=3,073 continent][94] and ULTRA [N=239 continent][78]) provided results on incident urinary incontinence (self-reported; **Appendix G Table 13**). The WHI followed continent women through year 1 and then evaluated incontinence at year 2. The ULTRA study followed participants for 2 years.[79] Both studies found higher risks of urinary incontinence in the treatment arms for all time points, but the only statistically significant risk was at 1 year (WHI trial, 36.5% vs. 23.8%; RR, 1.53; 95% CI, 1.37 to 1.71).[94, 102] Results drawing on smaller samples at 2 years (ULTRA trial, 39.0% vs. 36.8%; OR, 1.2; 95% CI, 0.7 to 2.2)[78] and 3 years of treatment did not show any statistically significant differences (WHI trial, 28.1% vs. 19.1%; RR, 1.47; 95% CI, 0.92 to 2.36).[94]

Differences in Treatment Effects Based on Subgroups

We found no evidence on differences in treatment effects by subgroups.

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence on differences in treatment effects based on timing of the intervention.

Venous Thromboembolism

Benefits and Harms of Hormone Therapy

Two trials (WHI [N=10,739][102, 112] and EPAT [N=222][60]) reported on risk of thromboembolism (**Appendix G Table 14**). In the WHI, women randomized to estrogen alone had an increased risk of deep vein thrombosis compared with placebo during the 7.1-year (mean) intervention phase (1.6% vs. 1.0%; HR, 1.48; 95% CI, 1.06 to 2.07);[102] the risk of pulmonary embolus was also higher in the estrogen group than placebo, but results were not significant (0.98% vs. 0.72%; HR, 1.35; 95% CI, 0.89 to 2.05).[102] There was no difference between groups for risk of deep vein thrombosis or pulmonary embolus 3.9 years after stopping therapy in the postintervention period.[112] The EPAT trial reported no venous thromboembolic events in either group during 2 years of followup.[60]

Differences in Treatment Effects Based on Subgroups

The WHI reported no differences for subgroups by race or ethnicity, age, or history of cardiovascular disease.[109]

Differences in Treatment Effects Based on Timing of the Intervention

Risk of venous thromboembolism in the WHI was similar in women who initiated estrogen soon after menopause (<5 years) versus later (≥ 5 years).[98]

Health-Related Quality of Life

Benefits and Harms of Hormone Therapy

The WHI (N=10,739)[102] was the only trial that reported on health-related quality of life (**Appendix G Table 15**). It used the RAND-36 form, which assesses physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. Women in both groups had similar scores on all items except for emotional role and social functioning for which women on placebo had statistically significantly better scores than women on estrogen-only therapy (p=0.04 and p=0.01, respectively).

Differences in Treatment Effects Based on Subgroups

We found no evidence on differences in treatment effects by subgroups.

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence on differences in treatment effects based on timing of the intervention.

All-Cause Mortality

Benefits and Harms of Hormone Therapy

Three trials (ERA [N=205],[62] ESPRIT [N=1,017],[63] and WHI [N=10,739][112]) provided information about the risk of death due to any cause among 11,961 women receiving estrogen therapy (**Appendix G Table 16**). The treatment duration of these trials ranged from an average of 2 years to 7.1 years.[62, 63, 112] A meta-analysis of these trials rendered no statistically significant difference in all-cause mortality between women receiving estrogen therapy and those on placebo (RR, 1.01; 95% CI, 0.88 to 1.17) during a mean followup of 6.8 years.

The WHI, the largest of the three trials, reported an HR of 1.04 (95% CI, 0.89 to 1.22), with deaths among 5.6 percent and 5.5 percent of women in the active and placebo groups, respectively.[112] The difference in risk between the two groups remained similar at followup 3.9 years after stopping the randomized treatment (HR, 1.00; 95% CI, 0.84 to 1.18).[112]

Differences in Treatment Effects Based on Subgroups

Interaction with age reached statistical significance, with a lower risk of death in younger women on estrogen therapy compared with younger women in the placebo group (p=0.04).[112] The HR was 0.73 (95% CI, 0.53 to 1.00) in favor of estrogen therapy among women ages 50 to 59 compared with 1.04 (95% CI, 0.88 to 1.24) among women ages 60 to 69 and 1.12 (95% CI, 0.94 to 1.33) among women ages 70 to 79.

Differences in Treatment Effects Based on Timing of the Intervention

An analysis of WHI data considered the time between menopause and the first use of hormone therapy (before enrollment into the WHI).[98] The effect of estrogen-only therapy on all-cause mortality did not differ significantly between women who initiated hormone therapy within the first 5 years after menopause and those who initiated hormone therapy after 5 years following menopause.[98]

Estrogen Plus Progestin: Cancers

Breast Cancer

Benefits and Harms of Hormone Therapy

Six trials (WHI [N=16,608],[23, 84, 85, 90, 92, 98, 102, 104] HERS [N=2,763],[68] PEPI [N=700],[74] EPHT [N=777],[61] ERA [N=209],[62] and WISDOM [N=4,385])[123] comparing estrogen plus progestin with placebo reported on breast cancer incidence (**Appendix G Table 1**). We did not pool trial results because of heterogeneity in study duration and outcome measures. Only two trials followed women for more than 4 years (WHI and HERS), and only the WHI reported on the risk of invasive breast cancer (versus any breast cancer).

The WHI is the largest trial; during the intervention phase (median 5.6 years), women assigned

to estrogen plus progestin had a significantly increased risk of invasive breast cancer compared with women on placebo (2.4% vs. 1.9%; HR, 1.24; 95% CI, 1.01 to 1.53).[102] The risk of invasive breast cancer in women who took estrogen plus progestin remained significantly increased compared with the risk of women on placebo during a median postintervention followup of 8.2 years (HR, 1.32; 95% CI, 1.08 to 1.61).[102] In the HERS trial, more women randomized to estrogen plus progestin developed breast cancer during the 4.1-year intervention phase than did the women receiving placebo, but the results were not statistically significant (2.5% vs. 1.8%; HR, 1.38; 95% CI, 0.82 to 2.31).[68]

Four other trials reported on breast cancer incidence.[61, 62, 74, 128] In three small trials, ERA, PEPI and EPHT, few cases occurred overall and risk of breast cancer incidence was similar between groups randomized to estrogen plus progestin and placebo over 3 to 4 years (zero cases overall in ERA and 3 vs. 3 cases, respectively, across PEPI and EPHT); few cases of breast cancer were reported overall.[61, 62, 74] The fourth trial, WISDOM (N=4,385), was stopped after 1 year because of the WHI results that indicated excess breast cancer risk in women receiving estrogen plus progestin; breast cancer incidence was similar between groups at 1 year (5 vs. 7 cases, respectively).[123]

Differences in Treatment Effects Based on Subgroups

In the WHI estrogen plus progestin trial, incidence of invasive breast cancer did not differ based on age at randomization.[102] Biennial analyses of invasive breast cancer risk during the intervention phase of the WHI provided evidence of a trend over time (p for trend=0.008). The risk of invasive breast cancer increased numerically with time since randomization (2 years after: HR, 0.71; 95% CI, 0.47 to 1.08; 4 years after: HR, 1.36; 95% CI, 0.95 to 1.94; 6 years after: HR, 1.65; 95% CI, 1.17 to 2.32).[104]

Differences in Treatment Effects Based on Timing of the Intervention

In the WHI estrogen plus progestin trial, invasive breast cancer risk decreased with an increasing gap in time since menopause (p for interaction=0.03).[98]

Cervical Cancer

Benefits and Harms of Hormone Therapy

The WHI (N=16,608) evaluated the incidence of cervical cancer among women with an intact uterus who received either estrogen plus progestin or placebo (**Appendix G Table 2**).[81] The incidence of cervical cancer did not differ significantly between women who received estrogen plus progestin hormone therapy and women who received placebo (HR, 1.44; 95% CI, 0.47 to 4.42) during a median followup period of 5.6 years; 0.09 percent of women receiving hormone therapy and 0.06 percent of women receiving placebo were diagnosed with cervical cancer.[81] WHI investigators did not provide cervical cancer incidence from the postintervention and postintervention extension phases.

Differences in Treatment Effects Based on Subgroups

We found no evidence about differences in treatment effects by subgroups.

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence about differences in treatment effects based on timing of the intervention.

Colorectal Cancer

Benefits and Harms of Hormone Therapy

Four trials (WHI [N=16,608],[23, 87, 92, 98, 102] EMS [N=142],[59] HERS [N= 2,763],[68] and WISDOM [N=4,385][123]) reported on the incidence of colorectal cancer (**Appendix G Table 3**). In the WHI intervention phase, women receiving estrogen plus progestin were less likely to develop colorectal cancer than women in the placebo group (HR, 0.62; 95% CI, 0.43 to 0.89); 0.59 percent of women in the estrogen plus progestin therapy group and 0.93 percent of women in the placebo group developed colorectal cancer over a median followup period of 5.6 years.[102] Over the entire median followup period of 13.2 years, the colorectal cancer risk remained lower in the hormone therapy arm (HR, 0.80; 95% CI, 0.63 to 1.01).[102] In the HERS trial, there was a numeric decrease in the risk of colorectal cancer with estrogen plus progestin use (HR, 0.69; 95% CI, 0.32 to 1.49) over a mean 4.1 years.[68]

The EMS and WISDOM trials reported no statistically significant differences in risks of colorectal cancer. Event rates in these studies, however, were low (zero events in EMS and four events in WISDOM), and very short followup time periods (i.e., <2 years) precluded them from being combined with the WHI and HERS trial data in meta-analysis.

Differences in Treatment Effects Based on Subgroups

In the WHI intervention phase, the incidence of colorectal cancer did not differ significantly between women who received estrogen plus progestin hormone therapy and women who received placebo according to the following variables: age,[102] race or ethnicity, and family history of colorectal cancer.[87]

Differences in Treatment Effects Based on Timing of the Intervention

The incidence of colorectal cancer in the WHI did not differ significantly between women who received hormone therapy and women who received placebo according to their years since menopause (i.e., <10 years, 10 to <20 years, and ≥20 years since menopause) in the WHI intervention phase.[102] The effect of estrogen plus progestin on the risk of invasive colorectal cancer did not differ significantly between women who initiated hormone therapy within the first 5 years after menopause and those who initiated it after 5 years following menopause.[98]

Endometrial Cancer

Benefits and Harms of Hormone Therapy

Two trials (WHI [N=16,608][23, 81, 92, 98, 102, 103, 108] and HERS[68] [N=2,763]) estimated the incidence of endometrial cancer among a total of 9,886 women with an intact uterus who received estrogen plus progestin hormone therapy and 9,485 women with an intact uterus who received placebo (**Appendix G Table 4**).

In both trials, the incidence of endometrial cancer did not differ significantly between women who received estrogen plus progestin hormone therapy and women who received placebo. During the WHI's intervention phase (median followup=5.6 years), 0.32 percent of women who received estrogen plus progestin and 0.37 percent of women who received placebo developed endometrial cancer (HR, 0.83; 95% CI, 0.49 to 1.40).[102] Likewise, during the HERS trial phase (mean followup=4.1 years), no statistically significant differences in risks could be detected (0.14% vs. 0.36%; HR, 0.39; 95% CI, 0.08 to 2.02).[68]

During the WHI postintervention period, statistically significantly fewer women who were randomized to hormone therapy during the trial phase developed endometrial cancer (HR, 0.58; 95% CI, 0.40 to 0.86) compared with women who had received placebo.[102]

Two additional trials (ERA [N=209][62] and PEPI [N=700][74]) reported zero endometrial cancer cases as adverse events over a period of 3 years; the trials were too small and short in duration to draw inferences on differences in risks or to combine in meta-analysis with the WHI and HERS.

Differences in Treatment Effects Based on Subgroups

The WHI reported no significant differences among 10-year age groups at randomization in the incidence of endometrial cancer between women who received estrogen plus progestin hormone therapy and those who received placebo.[102]

Differences in Treatment Effects Based on Timing of the Intervention

The effect of estrogen plus progestin on the risk of invasive endometrial cancer in the WHI did not differ significantly between women who started estrogen plus progestin hormone therapy within the first 5 years after menopause and women who began it after 5 years following menopause.[98]

Lung Cancer

Benefits and Harms of Hormone Therapy

Two trials (WHI [N=16,608][86, 102] and HERS [N=2,763][68]) estimated the incidence of lung cancer among a total of 9,886 women with an intact uterus who received estrogen plus progestin and 9,485 women with an intact uterus who received placebo (**Appendix G Table 5**).

In both the WHI and HERS, lung cancer incidence did not differ significantly between women who received estrogen plus progestin and those who received placebo. In the WHI intervention phase (median followup=5.6 years), 0.92 percent of women who received estrogen plus progestin and 0.86 percent of women who received placebo developed lung cancer (HR, 1.05; 95% CI, 0.76 to 1.45).[102] In the HERS trial phase (mean followup=4.1 years), 1.74 percent of women who received estrogen plus progestin and 1.37 percent of women who received placebo developed lung cancer (HR, 1.28; 95% CI, 0.70 to 2.33).[68]

The risks between groups remained similar during the postintervention followup.[68, 102]

A small trial (EMS [N=142][59]) reported only a single lung cancer case among women receiving estrogen plus progestin and zero cases among women receiving placebo during a comparatively short 2-year trial period, precluding it from being combined with the WHI and HERS in meta-analysis.[59]

Differences in Treatment Effects Based on Subgroups

In the WHI, no significant differences in the incidence of lung cancer emerged among 10-year age groups at randomization between women who received estrogen plus progestin and women who received placebo.[102]

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence about differences in treatment effects based on timing of the intervention.

Ovarian Cancer

Benefits and Harms of Hormone Therapy

The WHI (N=16,608) evaluated the incidence of invasive ovarian cancer among women with an intact uterus who received either estrogen plus progestin hormone therapy or placebo (**Appendix G Table 6**).[81, 102] The incidence of invasive ovarian cancer did not differ significantly between groups (HR, 1.41; 95% CI, 0.75 to 2.66); 0.28 percent of women who received estrogen plus progestin and 0.20 percent of women who received placebo developed invasive ovarian cancer over a median followup of 5.6 years during the intervention phase.[102]

Risk remained similar during the postintervention followup (median followup of 8.2 years; HR, 1.12; 95% CI, 0.65 to 1.90).[102]

Differences in Treatment Effects Based on Subgroups

In the WHI, there were no significant differences in the incidence of invasive ovarian cancer among 10-year age groups at randomization between women who received estrogen plus progestin and those who received placebo.[102]

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence on differences in treatment effects based on timing of the intervention.

Estrogen Plus Progestin: Other Chronic Conditions

Coronary Heart Disease

Benefits and Harms of Hormone Therapy

Overall, six trials (EMS [N=142],[59] EPHT [N=777)],[61] PEPI [N=700],[74] WHI [N=16,608],[23] WISDOM [N=4,385],[123] and ERA [N=209][62]) provided information about preventing coronary heart disease with estrogen plus progestin (**Appendix G Table 7**).

Of these, three trials (EPHT,[61] PEPI,[74] and WHI[23]) were similar enough to be combined in a meta-analysis. We did not include the ERA study, which enrolled only women with an elevated cardiovascular risk,[62] the EMS trial[59] because its definition of cardiovascular events also included deep vein thrombosis and cerebrovascular events, and the WISDOM trial because it had a followup time of only 1 year.[123] Trials included in the meta-analysis provided data on 18,081 women with treatment durations of 2 to 5.2 years. Results of the meta-analysis showed a statistically significantly higher risk of coronary events in women treated with hormone therapy than in those on placebo (2.1% vs. 1.7%; RR, 1.23; 95% CI, 1.00 to 1.52) during a mean followup of 5 years. Sensitivity analyses including ERA, EMS, and WISDOM rendered similar results.

The WHI reported a HR of 1.18 (95% CI, 0.95 to 1.45) for coronary events.[102] Long-term followup of women in the WHI showed that 2.4 years after stopping the randomized hormone therapy, the cardiovascular risk was similar between women who took this hormone therapy during the trial and those who received placebo (HR, 1.04; 95% CI, 0.89 to 1.21).[92]

The WISDOM trial was prematurely closed because of findings of the WHI. However, after 1 year of followup (6,498 women years), women on estrogen plus progestin had a statistically significantly higher risk of cardiovascular events (0.3% vs. 0.0%; p=0.016) than women on placebo.[123]

Differences in Treatment Effects Based on Subgroups

WHI subgroup analyses indicated no significant differences in subgroups based on race or ethnic group, age, years since menopause, hypertension, diabetes, or cardiovascular disease at baseline.[102]

Differences in Treatment Effects Based on Timing of the Intervention

Subgroup analysis in the WHI indicated that women who had started hormone therapy closer to menopause (within 10 years of menopause) did not have the same elevated risk of coronary heart disease as women who had initiated hormone therapy later. The HR for coronary heart disease in

women with less than 10 years of menopause was 0.90 (95% CI, 0.56 to 1.45). In women with more than 20 years of menopause, the HR was 1.52 (95% CI, 1.07 to 2.17) (p for trend=0.08).[102] When the analyses focused just on myocardial infarction, women who initiated estrogen plus progestin therapy closer to menopause did not have the elevated risk for myocardial infarction that women experienced who started therapy more than 20 years after menopause (p=0.01). Findings, however, need to be viewed cautiously because only 67 women who initiated hormone therapy within 10 years of menopause experienced a myocardial infarction.[102]

An additional analysis based on WHI data took into consideration the time between menopause and the first use of hormone therapy (before enrollment into the WHI) to assess the effect of timing.[98] This analysis, therefore, addresses the effect of timing better than analyses that focus exclusively on the time between menopause and randomization. The effect of estrogen plus progestin on the risk of cardiovascular events did not differ significantly between women who initiated hormone therapy within the first 5 years after menopause and those who started it after 5 years following menopause (for interaction, p=0.42).[98]

Two other trials did not meet our eligibility criteria because they assessed only surrogate endpoints for cardiovascular disease. They did, however, address the timing hypothesis. Specifically, the KEEPS (Kronos Early Estrogen Prevention) and ELITE (Early versus Late Intervention Trial with Estradiol) trials used change in carotid artery intima-media thickness as the primary outcome.[29, 129] Secondary endpoints included changes in markers of cardiovascular risk. KEEPS and ELITE enrolled women free from cardiovascular disease and stratified them according to time since menopause.

KEEPS enrolled healthy women age 42 to 58 years within 3 years of menopause. It compared women receiving low-dose daily oral conjugated equine estrogen (0.45 mg/day) or transdermal estrogen (17β-estradiol, 50 mcg/day), both with cyclic progesterone (200 mg for 12 days) treatment, with women receiving placebo. After 4 years of followup, investigators did not detect any statistically significant differences in the primary endpoint and found only mixed results for secondary endpoints.[129]

By contrast, ELITE used a higher oral estrogen dose (17β-estradiol, 1 mg/day) than KEEPS and vaginal micronized progesterone (45 mg/day for 10 days) for 5 years. Compared with placebo, hormone therapy resulted in a significantly lower rate of atherosclerosis progression among early postmenopausal women (fewer than 6 years since menopause) but not among late postmenopausal women (more than 10 years since menopause). The clinical significance of this difference, however, is unclear.

Cognitive Functioning and Dementia

Benefits and Harms of Hormone Therapy

One WHI trial (WHIMS [N=4,532][118]) evaluated the risk of probable dementia or mild cognitive impairment among women taking estrogen plus progestin (**Appendix G Table 8**). WHIMS was a subset of the WHI trial; it was limited to women who were 65 to 79 years of age at baseline, free of probable dementia, and recruited from 39 of 40 WHI trial centers. Participants in WHIMS

were followed for approximately 5.4 years. Women using estrogen plus progestin had a higher risk of probable dementia than those on placebo (1.8% vs. 0.9%; HR, 2.05; 95% CI, 1.21 to 3.48). The trial did not find an elevated risk of mild cognitive impairment.[118]

Three studies (HERS, KEEPS-Cog, and WHI) comprising four trials (HERS [N=1,328],[72] KEEPS-Cog [N=693],[73] WHIMS [N=4,532],[115, 116] and WHISCA [N=1,213][120]) measured global cognitive functioning using the Modified Mini-Mental Status Examination (MMSE). The HERS trial had a treatment regimen similar to that used in the WHI studies. It included 662 women randomized to estrogen plus progestin and 666 women randomized to placebo; participants were followed for 4.2 years. HERS found no cognitive deficits through 4 years of followup.[72]

WHISCA was a subset (N=690 in the estrogen plus progestin arm, N=726 in the placebo arm) of the WHIMS trial. It was limited to 14 of the 39 trial centers and designed to evaluate changes in cognitive functioning over time; the first assessment occurred 3 years after the start of treatment.[127] Participants in WHISCA were followed for approximately another 2 years; a further subset of WHISCA, in an extension study, were followed for 4 years after treatment. Deficits in cognitive functioning measured during the trial period (2 years) among WHIMS participants for the active arm were not sustained for women in WHISCA.[120]

KEEPS-Cog is an ancillary study to KEEPS, comprising women who consented to participate in a study of cognitive function. Women were 52.6 years on average and 1.4 years past their last menstrual period. The study randomized women to either oral or transdermal estrogen plus progestin or placebo pills and patches. The study found no differences between women randomized to estrogen plus progestin therapy and those randomized to placebo in changes in the 3MSE over a 4-year period of observation. Four trials (EMS [N=142],[59] HERS [N=1,328],[72] WHISCA [N=1,416],[122] and WHIMSY [N=1,326][119]) evaluated other measures of cognitive functioning; heterogeneity in outcome measures precluded meta-analysis. The HERS and WHISCA trials are described above. The WHIMSY trial was an extension of the WHI trial, limited to 1,326 enrolled active participants in treatment or placebo arms in the WHI trials who were 50 to 55 years of age at enrollment and agreed to be contacted for recruitment (N=1,326 assessed, N by treatment regimen not reported). The WHIMSY trial followed women for 7.2 years after the end of the trials. The EMS trial randomized 70 women to estrogen plus progestin and 72 women to placebo and followed them for 2 years. Women in HERS were followed for 4.2 years. All trials found no differences in groups as randomized for the majority of outcomes.

Differences in Treatment Effects Based on Subgroups

WHIMS found no difference in possible dementia by history of diabetes,[118] stroke,[118] hypertension,[117] cardiovascular disease,[117] or race.[117] It also found no difference in the rate of change in three MMSE scores by race, BMI, history of cardiovascular disease, hypertension, diabetes, or length of use.[116]

Differences in Treatment Effects Based on Timing of the Intervention

WHIMS found no difference in the rate of change in three MMSE scores by time to initiation of hormone therapy after the last menstrual period.[116]

Diabetes

Benefits and Harms of Hormone Therapy

Two trials (HERS [N=2,029][70] and WHI [N=15,874][97, 102]) provided information about the prevention of diabetes with estrogen plus progestin among 17,903 nondiabetic women or women not receiving treatment for diabetes at baseline (**Appendix G Table 9**). Incident diabetes was defined for women in HERS as having a fasting glucose level of ≥6.9 mmol/L (≥126 mg/dL), self-report of new diabetes or diabetes-related complications (diabetic neuropathy, diabetic retinopathy, diabetic foot ulcer, diabetic renal disease, or hypoglycemia if reported by a woman taking an antidiabetic medication), or initiation of hypoglycemic medication; this analysis was conducted post hoc and should be considered cautiously.[70] In the WHI, incident diabetes was limited to self-reported new diagnoses of diabetes by a physician followed by treatment with oral hypoglycemic drugs or insulin.[97]

Estrogen plus progestin therapy protected against incident diabetes among women in HERS (mean 4.1 years followup; HR, 0.65; (95% CI, 0.48 to 0.89) and WHI (mean 5.6 years followup; HR, 0.81; 95% CI, 0.70 to 0.94).[70, 97] In the WHI, the larger trial of the two, new diabetes diagnoses were reported during followup by 4.0 percent of women randomized to active treatment and 4.8 percent of those on placebo.[97, 102] However, this reduction in diabetes risk was no longer observed 8.2 years postintervention (HR, 1.19, 95% CI, 1.05 to 1.34).[102]

Differences in Treatment Effects Based on Subgroups

A test for interaction did not detect any statistically significant subgroup effects with respect to race or ethnicity, age at screening, or hypertension at baseline for women in the WHI.[97]

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence on differences in treatment effects based on timing of the intervention.

Fractures

Benefits and Harms of Hormone Therapy

Five trials (EMS [N=142],[59] EPHT [N=777],[61] ERA [N=209],[62] HERS [N=2,763],[68] and WHI [N=16,608][23, 83, 92, 102]) provided information on the rate of fractures (**Appendix G Table 10**). These trials spanned reporting periods from 2 through 5.2 years. The studies varied widely in sample size, from a total of 142 patients in the smallest study (EMS) to 16,608 in the largest (WHI). Studies defined fractures in varying ways; some specified hip or vertebral fractures only, while others included all osteoporotic or all fractures, regardless of site.

A random-effects meta-analysis of these five trials measuring outcomes during or at the end of the trial period (N=20,499) yielded a relative risk of 0.80 (95% CI, 0.68 to 0.94). In the meta-analysis, 8.6% of women on estrogen plus progestin and 10.9% of women on placebo experienced fractures.

Differences in Treatment Effects Based on Subgroups

We found no evidence on differences in treatment effects by subgroups.

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence on differences in treatment effects based on timing of the intervention.

Gallbladder Disease

Benefits and Harms of Hormone Therapy

Two trials (PEPI [N=700][74] and WHI [N=14,203][88]) provided information about the prevention of gallbladder disease with estrogen plus progestin among 14,903 women with gallbladders and without gallbladder disease (**Appendix G Table 11**). Treatment duration was 3 years for women in PEPI and 5.6 years, on average, for women in the WHI. The WHI's definition of gallbladder disease included cholecystitis and calculi; the definition used in PEPI is unclear.[74, 88] Gallbladder procedures were also reported in the WHI, which included biliary tract procedures such as cholecystectomies.[88]

The WHI, which is the larger of the two trials, reported gallbladder events (disease or procedure) during followup for 3.1 percent of women randomized to active treatment and 2.0 percent of those taking placebo; this difference was statistically significant (HR, 1.59; 95% CI, 1.28 to 1.97).[88] Risk for gallbladder disease decreased postintervention but continued to favor placebo over estrogen plus progestin therapy (mean 5.6 years intervention: HR, 1.61; 95% CI, 1.30 to 2.00;[88] median 8.2 years postintervention: HR, 1.24; 95% CI, 1.01 to 1.52[102]).

The PEPI trial had few cases of gallbladder disease and reported inconclusive results.[74]

Differences in Treatment Effects Based on Subgroups

A test for interaction did not detect any subgroup effects with respect to age of women in the WHI.[88] We found no other evidence on differences in treatment effects by subgroups.

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence on differences in treatment effects based on timing of the intervention.

Stroke

Benefits and Harms of Hormone Therapy

Three trials reported on risk of stroke (WHI [N=16,608],[24, 98, 101, 102, 112] EMS [N=142],[59] and EPHT [N=777][61]) (**Appendix G Table 12**). We did not pool trial results because of heterogeneity in study duration and outcome measures.

During the WHI intervention phase (median 5.6 years), stroke risk was significantly higher with estrogen plus progestin than with placebo (1.9% vs. 1.3%; HR, 1.37; 95% CI, 1.07 to 1.76); during postintervention followup, stroke risk was similar for these two groups (HR, 1.04; 95% CI, 0.86 to 1.26).[102] Cumulatively, stroke risk was higher in the estrogen plus progestin group compared with placebo (HR, 1.16; 95% CI, 1.00 to 1.35).[102]

The two other trials comparing estrogen plus progestin and placebo reported on the incidence of various cerebrovascular events as harms of treatment.[59, 61] In EMS, few events occurred over 2 years (three total), and the results were inconclusive.[59] In EPHT, risk of any cerebrovascular event (composite stroke, transient ischemic attack, subarachnoid hemorrhage) was higher among women randomized to estrogen plus progestin than placebo (5.7% vs. 2.4%; HR, 2.46; 95% CI, 1.14 to 5.34).[61]

Differences in Treatment Effects Based on Subgroups

No difference was seen in stroke risk in the WHI based on subgroups of women by age, race, ethnicity, or coexisting condition.[101]

Differences in Treatment Effects Based on Timing of the Intervention

Risk of stroke in the WHI was similar for women who started estrogen plus progestin soon after menopause (<5 years) and those who started later (≥5 years).[98]

Urinary Incontinence

Benefits and Harms of Hormone Therapy

Two trials (WHI [N=5,182] and HERS [N=1,208]) provided results on incident urinary incontinence (self-reported) in women who had been continent at baseline (**Appendix G Table 13**).[71, 94] The WHI followed continent women through year 1 and then evaluated incontinence at year 2 for those continent at year 1. The HERS trial had a similar treatment regimen as the WHI studies and followed women for 4.2 years. Both studies showed a consistently higher risk of urinary incontinence at all time points for the estrogen plus progestin group when compared with placebo. In the WHI, 31.2 percent of women on hormone therapy reported incident incontinence at year 1 compared with 22.5 percent of women on placebo (RR, 1.39; 95% CI, 1.27 to 1.52).[94] At year 3, the risk remained statistically significantly elevated (RR, 1.81; 95% CI, 1.16 to 2.84).[94] In the HERS trial, women on estrogen plus progestin had a higher risk of incontinence when compared with women on placebo at the 4.2-year followup (OR,1.6; 95% CI, 1.3 to 1.9).[71]

Differences in Treatment Effects Based on Subgroups

We found no evidence on differences in treatment effects by subgroups.

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence on differences in treatment effects based on timing of the intervention.

Venous Thromboembolism

Benefits and Harms of Hormone Therapy

Four trials (WHI [N=16,608],[89, 92, 98, 102] ERA [N=209],[62] EMS [N=142],[59] and EPHT [N=777][61]) reported on the incidence of venous thromboembolism (**Appendix G Table 14**). We did not pool trial because of heterogeneity in study duration and outcome measures.

In the WHI, women randomized to estrogen plus progestin had an increased risk of pulmonary embolism (1.0% vs. 0.5%; HR, 1.98; 95% CI, 1.36 to 2.87) and deep vein thrombosis (1.4% vs. 0.8%; HR, 1.87; 95% CI, 1.37 to 2.54) compared with women in the placebo group over a median followup of 5.6 years.[89, 102] The groups did not differ for deep vein thrombosis or pulmonary embolus risk during the 2.4-year postintervention period after women stopped therapy.[92]

In three smaller trials (N=142 to 777), groups did not differ in risk of venous thromboembolism among participants randomized to estrogen plus progestin or placebo over 2 to 3 years (two vs. zero events across all three trials).[59, 61, 62]

Differences in Treatment Effects Based on Subgroups

In the WHI, pulmonary embolus or deep vein thrombosis risk did not differ for the treatment and placebo groups by subgroups based on age.[102]

Differences in Treatment Effects Based on Timing of the Intervention

Risk of venous thromboembolism in the WHI was similar for women who began hormone therapy soon after menopause (<5 years) and those who started later (≥ 5 years).[98]

Health-Related Quality of Life

Benefits and Harms of Hormone Therapy

The WHI (N=16,608)[102] was the only trial that reported on health-related quality of life (**Appendix G Table 15**). It used the RAND-36 form, which assesses physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. Women in both groups had similar scores on all items except for physical functioning ($p<0.001$), physical role ($p=0.02$), bodily pain ($p<0.001$), and general health ($p=0.02$) for which women on hormone therapy had statistically significantly better scores than women on placebo.

Differences in Treatment Effects Based on Subgroups

We found no evidence on differences in treatment effects by subgroups.

Differences in Treatment Effects Based on Timing of the Intervention

We found no evidence on differences in treatment effects based on timing of the intervention.

All-Cause Mortality

Benefits and Harms of Hormone Therapy

Three trials (ERA [N=209],[62] HERS [N=2,763],[68] and WHI [N=16,608][92]) provided information about the risk of death from any cause (i.e., all-cause mortality) among 19,580 women with treatment of estrogen plus progestin (**Appendix G Table 16**). The length of treatment for these trials ranged between an average of 3.2 years and 5.6 years (weighted mean 5.2 years).[62, 68, 92] A meta-analysis of these trials yielded no statistically significant difference in all-cause mortality between women on hormone therapy and those on placebo (RR, 1.01; 95% CI, 0.88 to 1.17).

The WHI, the largest of the three trials, reported an HR of 0.97 (95% CI, 0.81 to 1.16); 2.9 percent of women in both treatment groups died.[92] The risk of death among those who had received estrogen plus progestin and those who had received placebo at followup 2.4 years after stopping hormone therapy was not significantly different (HR, 1.15; 95% CI, 0.95 to 1.39).[92] However, when the analysis focused on women in the postintervention phase without prior hormone therapy use who adhered to medication (took ≥80% of study pills), the difference in risk of death was statistically significant (HR, 1.53; 95% CI, 1.04 to 2.24).[92]

Risks of death from breast cancer (HR, 1.96 [95% CI, 1.00 to 4.04])[84] and lung cancer (HR, 1.71 [95% CI, 1.16 to 2.52])[86] were higher among women randomized to estrogen plus progestin than among those taking placebo 2.4 years after stopping hormone therapy.

Differences in Treatment Effects Based on Subgroups

We found no evidence on differences in treatment effects by subgroups.

Differences in Treatment Effects Based on Timing of the Intervention

An analysis of WHI data considered the time between menopause and the first use of hormone therapy (before enrollment into the WHI).[98] The effect of estrogen plus progestin on all-cause mortality did not differ significantly between women who initiated hormone therapy within the first 5 years after menopause and those who started it after 5 years following menopause.

Chapter 4. Discussion

This chapter begins with a summary of review findings for each KQ. Following those sections, we present limitations of the evidence and the review, and end with conclusions. Our searches also addressed two contextual questions on the duration of hormone therapy use and differences in use by subgroups (see Methods for detailed contextual questions). For both questions we did not find any studies of interest and, therefore, do not discuss contextual questions any further in this chapter.

Summary of Review Findings

Benefits and Harms of Hormone Therapy (KQs 1 and 2)

Eighteen trials (reported in 68 publications) comparing the effects of estrogen only or estrogen plus progestin against placebo for preventing chronic conditions in postmenopausal women met our eligibility criteria. **Tables 6** and **7** summarize findings, strength of evidence (SOE), and applicability for various outcomes for both KQs 1 and 2.

The Women's Health Initiative (WHI) was the only trial designed and powered to evaluate the effectiveness of hormone therapy for primary prevention of the multiple conditions that are the focus of this review. The WHI met criteria for fair quality, and it provided most of the estimates of benefits and harms. Including the post-trial phases, it had up to 13 years of followup to assess how risks for chronic conditions change after women stopped hormone therapy.

Results of our review indicate some benefits of hormone therapy regarding the prevention of chronic conditions (KQ 1). For women using estrogen only, risks for diabetes (137 fewer cases per 10,000 women over 7.1 years) and fractures (382 fewer cases per 10,000 women over 6.8 years) were statistically significantly reduced compared with women taking placebo. Women on estrogen plus progestin therapy experienced statistically significantly reduced risks for colorectal cancer (33 fewer cases per 10,000 women over 5.6 years), diabetes (77 fewer cases per 10,000 women over 5.6 years), and fractures (222 fewer cases per 10,000 women over 5.0 years) compared with women in the placebo groups.

Our review also documented several important harms of hormone therapy (KQ 2). Women on estrogen-only therapy had statistically significantly increased risks for gallbladder disease (378 more cases per 10,000 women over 7.1 years), stroke (79 more cases per 10,000 women over 7.1 years), urinary incontinence (1,261 more cases per 10,000 women over 1 year), and venous thromboembolism (78 more cases per 10,000 women over 7.1 years).

Likewise, for women on estrogen plus progestin therapy, risks for invasive breast cancer (52 more cases per 10,000 women over 5.6 years), coronary heart disease (41 more cases per 10,000 women over 5.1 years), probable dementia (88 more cases per 10,000 women over 4 years), gallbladder disease (259 more cases per 10,000 women over 5.6 years), stroke (53 more cases per 10,000 women over 5.6 years), urinary incontinence (876 more cases per 10,000 women over

1 year), and venous thromboembolism (120 more cases per 10,000 women over 5.6 years) were statistically significantly increased compared with women taking placebo.

The WHI used a global index based on beneficial and harmful events to assess the trade-offs between advantages and disadvantages of hormone therapy. Overall, estrogen plus progestin led to 20 additional adverse events per 10,000 person-years (hazard ratio [HR], 1.12; 95% CI, 1.02 to 1.24).[102] For women who were randomized to estrogen-only therapy, the global index did not show a statistically significant difference in overall beneficial or harmful events (HR, 1.03; 95% CI, 0.93 to 1.13).

Information About Subgroups of Women (KQ 3)

Subgroups (KQ 3) of interest for this report include the following characteristics: race and ethnicity; premature menopause; women with surgical menopause; age of use; duration of use; types, doses, and modes of delivery of hormone therapy; and presence of coexisting conditions. **Table 8** summarizes findings, strength of evidence, and applicability for subgroups for both treatment regimens (KQ 3).

Trials did not report results for most of these subgroups. Post hoc subgroup analyses of trial results based on these characteristics were restricted to race and ethnicity, age, and a limited number of comorbidities or risk factors. In general, tests of interactions did not detect any statistically significant subgroup effects that are of interest for this report. An exception is the influence of age on all-cause mortality and coronary heart disease. Younger women on estrogen only had lower risks for myocardial infarction than older women relative to women using placebo (p=0.02). Younger women on estrogen only also had a reduced risk for all-cause mortality (p=0.04).

These findings, however, have to be interpreted cautiously because, overall, for example, only 489 women died in the estrogen-only WHI trial, which could lead to chance findings when assessing differences in subgroups. The publications do not provide any information on how many women died in the age strata.

Recent subgroup analyses of the WHI regarding the impact of timing on risks of coronary events provide consistent findings. Time since menopause did not have a statistically significant impact on the risk of coronary heart disease in women using estrogen-only therapy. Women who initiated a combination therapy within 10 years of menopause did not have an increased coronary risk compared with those who initiated later. Early initiation in this group, however, also did not lead to any beneficial effects regarding cardiovascular risks. It remains unclear though whether a shorter time interval than 10 years might have been a more appropriate measure to assess the impact of timing. An additional subgroup analysis took hormone therapy use of women before enrollment into the WHI into consideration (e.g., about 40% of women in the estrogen-only trial used hormone therapy before enrollment) and found also no difference in coronary risks between early and late initiation of hormone therapy.

Two recent trials, the KEEPS (Kronos Early Estrogen Prevention) and ELITE (Early versus Late Intervention Trial with Estradiol) studies,[29, 129] addressed whether timing of therapy initiation

affected either benefits or harms of hormone therapy. Both trials enrolled women who were younger than participants in the WHI. Both trials assessed surrogate outcomes of cardiovascular disease (primary outcome in both trials was carotid artery intima-media thickness). They provided mixed results regarding beneficial effects of early initiation on carotid artery intima-media thickness.

A recent Cochrane review assessed the timing hypothesis by stratifying trials in a meta-analysis according to when any hormone therapy treatment was started (the review did not stratify between estrogen only and combination hormone therapy).[19] If this information was not available, they used the mean age of participants at baseline as surrogates. Results provided some support of the timing hypothesis. All-cause mortality was lower in the subgroup of studies where treatment was started within 10 years of menopause compared with studies where more than 10 years had elapsed (p=0.01). Likewise, the risk of coronary heart disease was lower in women who initiated hormone therapy early (p=0.02). Nevertheless, because of issues of potential ecological fallacy, findings of such study-level analyses have to be viewed cautiously.

Another study that is often viewed as supporting the timing hypothesis is the DOPS (Danish Osteoporosis Prevention Study).[58] We did not take this study into consideration because of poor quality due to lack of blinding of outcomes assessors. DOPS included 1,006 women who, on average, were younger than those in the WHI; it reported that hormone therapy given to early postmenopausal women reduced the risk of cardiovascular disease without any significant increase in harms after 10 years of treatment and 16 years of cumulative followup. These findings would support the timing hypothesis, but they are limited by the small number of events and the precision of the estimates. For example, during 10 years of treatment only 49 cardiovascular events took place.

To date, the evidence regarding the impact of doses and modes of delivery of hormone therapy on benefits and risks is still insufficient to draw firm conclusions. In treatment studies, progestins and natural progesterones differ in their metabolic action and risk of harms such as adverse effects on blood lipids, breast tenderness, and headaches. The risk-benefit profile of each type of progestin and progesterone for use in hormone therapy is currently still unclear.[19]

For this report, the PEPI trial was the only eligible study that used different types (regular synthetic and micronized progestins) and different regimens of progestins (continuous and sequential progestin regimens) within the same study.[74] Results reported no differences in benefits and harms between different types and regimens. The sample size of the PEPI trial (N=875) was too small to detect potential differences of outcomes that are of interest for this report. All the other studies included in this review used continuous progestin regimens.

Limitations and Future Research

In our analyses, we stratified results by regimen because findings from the WHI suggested that the risk-benefit profiles for estrogen-only treatment and for the combination of estrogen plus progestin are different. As a consequence, we were not able to include three trials in our analyses that did not report results stratified by treatment regimen.[65, 75, 80]

The WHI provided the best and most applicable information for many of our outcomes of interest. To date, more than 130 manuscripts have been published on the WHI trials. During our review, we noticed that effect estimates were not always consistent across various publications. Because it was impossible for us to discern which were the most correct estimates, in general, we relied on articles that focused on specific outcomes (e.g., publications on gallbladder disease, urinary incontinence), when available. In general, differences in effect estimates affected the magnitude of risks and benefits but never the direction of effects. For each effect estimate that we present in the report, we provide the respective citation of the WHI publication.

Low event rates also limited conclusions for some outcomes in the report. For example, in the WHI estrogen plus progestin trial, only 40 women developed ovarian cancer. Likewise, event rates for cervical and endometrial cancers were low, rendering wide CIs that encompassed clinically meaningful differences in risks. The confidence in conclusions about benefits and risks of hormone therapy regarding these outcomes is low.

A recent analysis of individual patient data of 52 epidemiological studies on more than 21,000 women with ovarian cancer detected a higher risk of ovarian cancer in women who used hormone therapy[130] (RR, 1.37; 95% CI, 1.29 to 1.46). Risks were similar between estrogen-only and estrogen plus progestin therapies. Even 10 years after stopping long-duration hormone therapy, risks for serious and endometrioid ovarian tumors were still elevated (RR, 1.25; 95% CI, 1.07 to 1.46).

Some outcomes might be affected by potential biases, such as diabetes and urinary incontinence, which relied on self-reporting, or cognitive function, which was limited by disparate adherence rates (WHIMS, 61.4% for placebo vs. 32.3% for estrogen plus progestin). Trials often used different measures for ascertaining outcomes, which limited comparisons across trials. For cognitive function, WHIMS was the only trial to use a thorough adjudication process for probable dementia and mild cognitive impairment, whereas other trials used batteries of cognitive tests. For diabetes, the WHI relied on participants' self-reports of new diagnoses or new treatment for diabetes, whereas HERS used fasting glucose levels. For urinary incontinence, all trials relied on self-reported measures.

In addition, we did not find any evidence on functional capacity.

The main limitation of our review process was that we restricted our review to trials published in English-language journals. However, we did not identify any relevant trials from English-language abstracts of non-English journals, additional citation searches, or expert reviewers. Given the large number of eligible trials for this report, the impact of potentially missed non-English publications on the overall effect estimates and conclusions is probably negligible.

Most trials had high attrition or low adherence to medications; this was true even for the WHI, in which 40 percent to 50 percent of participants discontinued their medications during the trial. Nevertheless, secondary analyses of the WHI limited to adherent women (i.e., censoring women within 6 months of reporting less than 80% compliance with study pills) were generally similar to intention-to-treat results[102] but with accentuated findings. For example, the adherence-adjusted HRs for breast cancer were 0.58 (95% CI, 0.39 to 0.84) for women on estrogen-only therapy and

1.52 (95% CI, 1.15 to 2.00) for women on estrogen plus progestin (compared with HR, 0.79 [95% CI, 0.61 to 1.02] and HR, 1.26 [95% CI, 1.02 to1.55], respectively, in the intention-to treat analyses).[102]

The applicability of our findings might be limited by three main aspects. First, most women initiate hormone therapy during perimenopause or when they have symptoms of menopause (average age of menopause is 51 years). The average age of women in the included studies ranged from 50 to 79 years. In the WHI, the average age of women was approximately 64 years. Only around 30 percent of women in the WHI were between 50 and 59 years at the time of enrollment. Although younger women who used estrogen-only therapy had reduced risks for coronary heart disease and overall mortality than women on placebo, analyses of the WHI data did not provide any clear overall benefit of initiating hormone therapy early. Second, the majority of women (around 80%) were white. Subgroup analyses, however, did not did reveal differences in beneficial or harmful effects among ethnic groups, but such analyses might have been underpowered. Third, the majority of findings came from the WHI, which tested only one dose, formulation, and route of administration of hormone therapy in each trial. The PEPI trial was the only study that directly compared different formulations of estrogen and progestin combinations.

Continuing research on long-term outcomes, such as cancer and mortality, will be important to provide a full understanding of the implications of hormone therapy. In the WHI studies, some of the risk reductions and increases disappeared after women had stopped treatment. Other risks such as invasive breast cancer maintained elevated years after women had stopped estrogen plus progestin treatment. Given that most women who use hormone therapy start treatment of menopausal symptoms during perimenopause or early postmenopause, future research needs to further explore the impact of early initiation on health outcomes and the primary prevention of chronic diseases. Future studies also need to explore the comparative benefits and harms of different formulations and treatment durations of hormone therapy.
Finally, most subgroup analyses of the WHI were probably not powered to detect clinically relevant differences between subgroups of interest. Combining individual patient data of all trials to conduct individual patient data meta-analyses could probably overcome this issue and provide more definitive answers.

Conclusions

Depending on the treatment regimen, the risk-benefit profiles of hormone therapy for the prevention of chronic conditions differ for women ages 50 to 79. Women undergoing hormone therapy experience some beneficial effects (e.g., reduced risks of fractures or diabetes) but also an increase of risks for harms (e.g., higher risks for stroke, thromboembolic events, gallbladder disease, and urinary incontinence), particularly for women over age 60. Some evidence suggests that age at the initiation of hormone therapy can modify the risk-benefit profiles, particularly those for overall mortality and cardiovascular events. To date, however, the available evidence regarding benefits and harms of early initiation of hormone therapy is contradictory.

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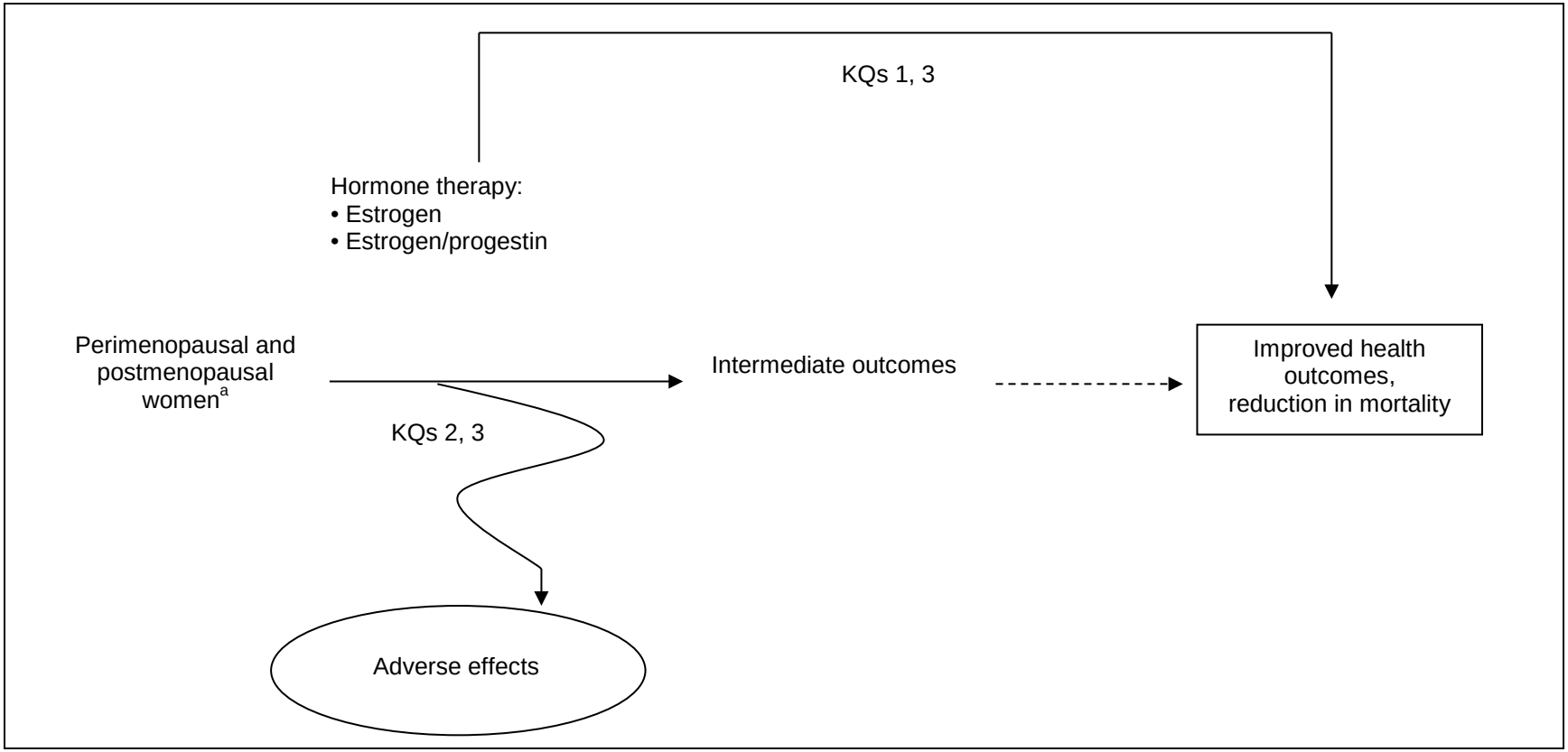
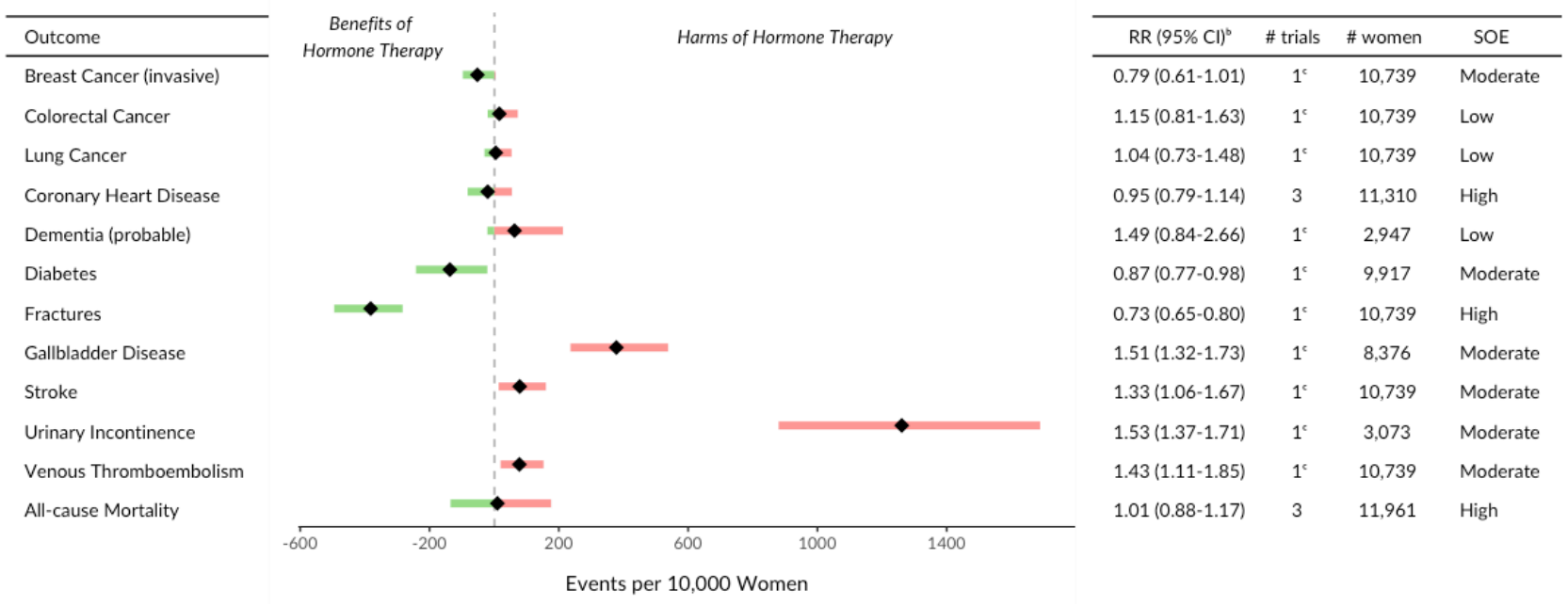
Figure 1. Analytic Framework



[a]Definitions of perimenopausal and postmenopausal women are based on STRAW+ 10 criteria (Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. Menopause. 2012;19(4):387-95).

Abbreviation: KQ = key question.

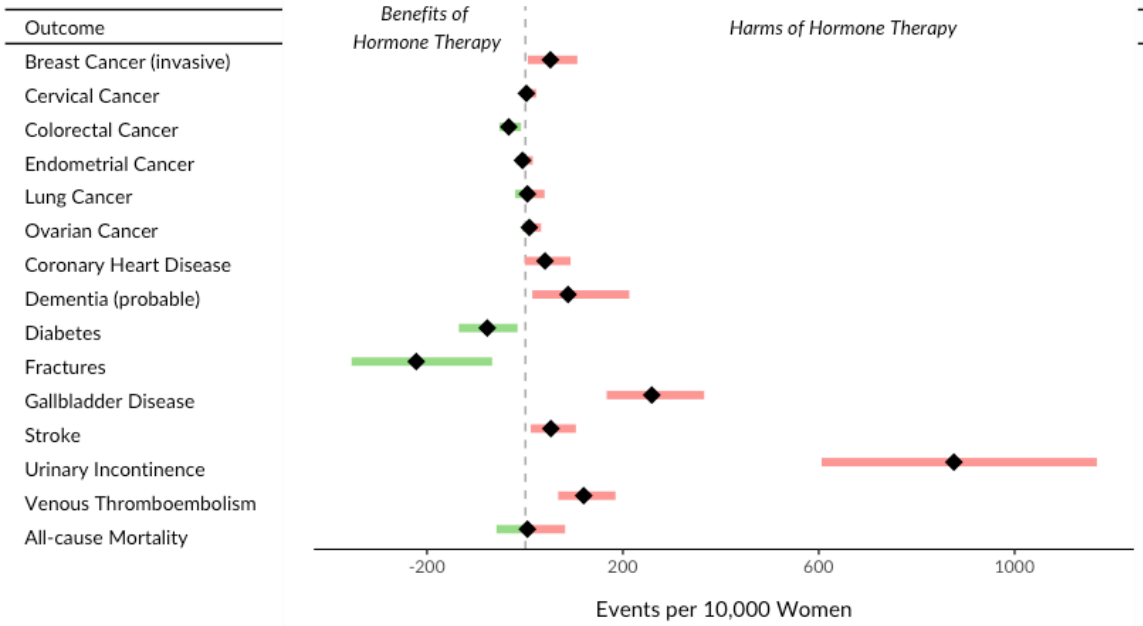
Figure 2. Absolute Risk Reductions or Increases for Women Treated With Estrogen Only[a]



[a] Followup periods for all outcomes are 7.1 years except: fractures 7.2 years; dementia 5.2 years; urinary incontinence 1 year
[b] We calculated relatives risks to determine absolute risk reductions and increases presented in this figure because it is unclear whether the proportional hazards assumption is always met in long-term hormone therapy trials. Estimates of relative risks might differ from hazard ratios of trials that are presented in the text
[c] Estimates are based on the best available single study.

Abbreviations: CL = confidence limit; DVT = deep vein thrombosis; PE = pulmonary embolism; RR = relative risk; SOE = strength of evidence.

Figure 3. Absolute Risk Reductions or Increases for Women Treated With Estrogen Plus Progestin[a]



Outcome	RR (95% CI)[b]	# trials	# women	SOE
Breast Cancer (invasive)	1.27 (1.03-1.56)	1[c]	16,608	High
Cervical Cancer	1.52 (0.50-4.66)	1[c]	16,608	Low
Colorectal Cancer	0.64 (0.44-0.91)	1[c]	16,608	Moderate
Endometrial Cancer	0.86 (0.51-1.44)	1[c]	16,608	Low
Lung Cancer	1.06 (0.77-1.46)	1[c]	16,608	Moderate
Ovarian Cancer	1.43 (0.76-2.69)	1[c]	16,608	Low
Coronary Heart Disease	1.23 (1.00-1.52)	3	18,081	High
Dementia (probable)	1.97 (1.16-3.33)	1[c]	4,532	Moderate
Diabetes	0.84 (0.72-0.97)	1[c]	15,874	Moderate
Fractures	0.80 (0.68-0.94)	5	20,499	High
Gallbladder Disease	1.56 (1.36-1.79)	1[c]	14,203	Moderate
Stroke	1.39 (1.09-1.77)	1[c]	16,608	High
Urinary Incontinence	1.39 (1.27-1.52)	1[c]	5,182	Moderate
Venous Thromboembolism	1.95 (1.54-2.47)	1[c]	16,608	Moderate
All-cause Mortality	1.01 (0.88-1.17)	3	19,580	Moderate

[a] Followup periods for all outcomes are 5.6 years except: fractures 5.0 years; coronary heart disease 5.1 years; dementia 4 years; urinary incontinence 1 year
[b] We calculated relatives risks to determine absolute risk reductions and increases presented in this figure because it is unclear whether the proportional hazards assumption is always met in long-term hormone therapy trials. Estimates of relative risks might differ from hazard ratios of trials that are presented in the text
[c] Estimates are based on the best available single study.

Abbreviations: CL = confidence limit; DVT = deep vein thrombosis; PE = pulmonary embolism; RR = relative risk; SOE = strength of evidence.

Table 1. Hormone Therapies Approved by the U.S. Food and Drug Administration[17,127]

Category of Hormone Therapy and Generic Name	Brand Name	Product Type	Dosage[a]
Estrogen-Only Formulations			
Estradiol[b]	Alora	Patch	0.025 mg–0.1 mg/24-hr twice weekly
Estradiol[b]	Climara	Patch	0.025 mg–0.1 mg/24-hr once weekly
Estradiol[b]	Estrace	Pill	0.5 mg–2 mg daily
Estradiol[b]	Estraderm	Patch	0.05 mg–0.1 mg patch continuously or cyclically
Estradiol[b]	Menostar	Patch	0.014 mg/24-hr patch once weekly
Estradiol[b]	Minivelle	Patch	0.025 mg/24 hr–0.1 mg/24-hr twice weekly
Estradiol[b]	Vivelle	Patch	0.0375 mg–0.1 mg patch daily
Estradiol[b]	Vivelle-Dot	Patch	0.025 mg–0.1 mg/24-hr twice weekly
Estradiol Acetate[b]	Femtrace	Pill	0.45 mg–1.8 mg tablets
Esterified Estrogen[b]	Menest	Pill	0.3 mg–1.25 mg/day cyclically
Estropipate[c]	Ogen	Pill	0.75 mg–3 mg daily
Conjugated Estrogens[d]	Premarin	Pill, injection	0.3 mg/day cyclically
Synthetic Conjugated Estrogens[e]	Enjuvia	Pill	0.3 mg/day
Combination Estrogen plus Progestin Formulations			
Estradiol[b] + Drospirenone[f]	Angeliq	Pill	Drospirenone 0.25 mg/estradiol 0.5 mg to drospirenone 0.5 mg/estradiol 1 mg daily
Estradiol[b] + Norethindrone Acetate[f]	Activella	Pill	Estradiol 0.5 mg/norethindrone 0.1 mg to estradiol 1 mg/norethindrone 0.1 mg
Estradiol[b] + Norgestimate[f]	Prefest	Pill	Estradiol 1 mg daily for 3 days, then estradiol 1 mg/norgestimate 0.09 mg daily for 3 days
Estradiol[b] + Levonorgestrel[f]	Climara Pro	Patch	Estradiol 0.045 mg/levonorgestrel 0.015 mg/24-hr once weekly
Estradiol[b] + Norethindrone Acetate[f]	Combipatch	Patch	Estradiol 0.05 mg/norethindrone 0.14 mg to estradiol 0.05 mg/norethindrone 0.25 mg/24-hr once weekly
Conjugated Estrogen[d] + Medroxyprogesterone Acetate[f]	Prempro	Pill	Conjugated estrogen 0.625 mg/MPA 5 mg once daily
Ethinyl Estradiol[b] + Norethindrone Acetate[f]	Femhrt	Pill	Ethinyl estradiol 0.0025 mg/norethindrone acetate 0.5 mg daily

[a] Dosages are based on the package inserts for the brand name formulations.
[b] Estradiol can be from natural sources or prepared synthetically.
[c] Natural estrogenic substance prepared from purified crystalline estrone.
[d] Conjugated estrogens, such as conjugated equine estrogens, are derived wholly or partially from the urine of pregnant mares or synthetic estrone and equilin.
[e] Synthetic conjugated estrogens are prepared using plant sources, such yams and soy, and use only synthetic resources.
[e] Synthetic progestin.

Abbreviations: hr = hour; mg = milligram; MPA = medroxyprogesterone acetate.

Table 2. Clinical Practice Guidelines and Recommendations About Use of Hormone Therapy for Prevention of Chronic Conditions

Organization, Year	Recommendations
Canadian Task Force on Preventive Health Care, 2004[132]	Recommends against the use of estrogen only and estrogen plus progestin therapy for the primary prevention of chronic diseases in menopausal women (Grade D recommendation).
American Association of Clinical Endocrinologists, 2011[133]	Recommends against the use of menopausal hormone therapy for primary or secondary prevention of cardiovascular disease (Grade D; Best Evidence Level 1). Recommends that menopausal hormone therapy should be used for the prevention and treatment of osteoporosis within the context of the overall benefit-versus-risk analysis of each patient. Recommendations note that data from multiple randomized controlled trials substantiate the efficacy of estrogens in preserving bone mass and, less consistently, preventing fractures, but nonhormonal therapeutic options for bone health exist (Grade A; Best Evidence Level 1). Hormone therapy for the prevention or treatment (or both) of dementia is not recommended (Grade D; Best Evidence Level 1). Recommendations note that menopausal hormone therapy should be prescribed to women in conjunction with a thorough discussion of the possible relationship between menopausal hormone therapy and breast cancer. Guidelines note that current evidence suggests that combination estrogen and progestational agent regimens are associated with a possible higher risk of breast cancer than is therapy with estrogen alone (Grade A; Best Evidence Level 1). Concordant with current FDA warnings, the task force recommends that women who are at increased risk of thromboembolic disease should not take estrogen-containing therapy while noting that there is evidence that transdermal estradiol may not increase this risk (Grade D; Best Evidence Level 1).
American Heart Association, 2011[134]	Recommends against the use of hormone therapy and selective estrogen-receptor modulators for primary and secondary prevention of cardiovascular disease in women (Class III, Level of Evidence A).
American Academy of Family Physicians, 2012[135]	Recommends against the use of estrogen plus progestin for the prevention of chronic conditions in postmenopausal women (Grade: D recommendation). The American Academy of Family Physicians recommends against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy (Grade: D recommendation).
American Congress of Obstetricians and Gynecologists, 2013–2014[36]	Recommends against the use of menopausal hormone therapy for primary and secondary prevention of coronary heart disease because of insufficient evidence for benefit. The guidelines also note the following consideration: Recent evidence suggests that women in early menopause who are in good cardiovascular health and are at low risk of adverse cardiovascular outcomes should be considered candidates for the use of estrogen therapy or conjugated equine estrogen plus a progestin for relief of menopausal symptoms. There is some evidence that lends support to the “timing hypothesis,” which posits that cardiovascular benefit may be derived when estrogen therapy or hormone therapy is used close to the onset of menopause, but the relationship of duration of therapy to cardiovascular outcomes awaits further study. Hormone therapy (i.e., estrogen only or estrogen plus progestin) positively affects bone health; it is approved for use in women with an increased risk of osteoporosis[136] and fracture.
American College of Physicians, 2015[137]	Recommends the U.S. Preventive Services Task Force Web site and the North American Menopause Society[138]

Abbreviation: FDA = U.S. Food and Drug Administration.

Table 3. Characteristics of Randomized Controlled Trials of Use of Menopausal Hormone Therapy

Trial Name (Acronym)	Author, Year	Intervention; Duration	Country; Participants	Quality Rating
Estrogen Memory Study (EMS)	Tierney et al., 2009[59]	17β-estradiol 1 mg/day for 4 days then 17β-estradiol 1 mg plus norethindrone 0.35 mg/day for 3 days, repeated every week (N=70) Placebo (N=72) 2 years	• Canada • Age >60 years • Last menstrual cycle >12 months before screening • Fluent in English and could read normal print and hear normal speech	Fair
Estrogen in the Prevention of Atherosclerosis (EPAT)	Hodis et al., 2011[60]	Micronized 17β-estradiol 1 mg/day (N=111) Placebo (N=111) 2 years	• United States • Postmenopausal women • Ages 45 or older • With low-density lipoprotein cholesterol level of ≥ 130 mg/dL	Fair
Estonian Postmenopausal Hormone Therapy Trial (EPHT)	Veerus et al., 2003[61]	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=404) Placebo (N=373) Mean 3.4 years	• Estonia • Ages 50–64 years • An elapsed 12 months or more since the last period at the randomization stage	Fair
Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis (ERA)	Herrington et al., 2000[62]	CEE 0.625 mg/day(N=100) CEE 0.625 mg/day plus MPA 2.5 mg/day (N=104) Placebo (N=105) 3 years	• United States • Postmenopausal women not currently receiving estrogen replacement therapy • With >1 epicardial coronary stenosis of at least 30% of the luminal diameter	Fair
Oestrogen in the Prevention of Reinfarction Trial (ESPRIT)	Cherry et al., 2002[63]	Estradiol valerate 2 mg/day (N=513) Placebo (N=504) 2 years	• United Kingdom • Ages 50–60 years • Admitted to coronary care units or general medical wards in participating hospitals • Met diagnostic criteria for initial myocardial infarction • Discharged from hospital within 31 days of admission	Fair
Greenspan et al.	Greenspan et al., 2005[65]	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=187) Placebo (N=186) 3 years	• United States • Ages 65 or older • Community-dwelling women	Good
Heart and Estrogen/ Progestin Replacement Study (HERS)	Grady et al., 1998;[66] Hulley et al., 1998;[69] Kanaya et al., 2003;[70] Steinauer et al., 2005[71]	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=1,380) Placebo (N=1,383) Mean 4.1 years	• United States • Ages ≤80 years • Intact uterus • Postmenopausal • Established coronary artery disease	Good

Table 3. Characteristics of Randomized Controlled Trials of Use of Menopausal Hormone Therapy

Trial Name (Acronym)	Author, Year	Intervention; Duration	Country; Participants	Quality Rating
Kronos Early Estrogen Prevention Study–Cognitive and Affective Study (KEEPS-Cog)	Gleason et al., 2015[73]	CEE 0.45 mg/day plus MP 200 mg/day 12 days/month (N=220) Transdermal estradiol 50 mg/day plus MP 200 mg/day 12 days/month (N=211) Placebo (N=262) 4 years	• United States • Ages 42–58 years • Intact uterus • Recently postmenopausal • At risk for cardiovascular disease	Fair
Postmenopausal Estrogen and Progestin Interventions Trial (PEPI)	PEPI, 1995[74]	CEE 0.625 mg/day (N=175) CEE 0.625 mg/day plus MPA 10 mg/day 12 days/month (N=174) CEE 0.625 mg/day + MP 200 mg/day for 12 days/month (N=178) Placebo (N=174) 3 years	• United States • Ages 45–64 years • With or without a uterus • Naturally or surgically menopausal	Fair
STOP-IT	Gallagher et al., 2001[75]	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=121) CEE 0.625 mg/day plus MPA 2.5 mg/day plus calcitriol 0.25 mcg twice daily (N=122) Calcitriol 0.25 mcg twice daily (N=123) Placebo (N=123) 3 years	• United States • Ages 65–77 years • Femoral neck density within normal range for age	Fair
Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA)	Ettinger et al., 2004;[76] Johnson et al., 2005;[77] Waetjen et al., 2005;[78] Yaffe et al., 2006[79]	Unopposed transdermal estradiol 0.014 mg/day (N=208) Placebo (N=209) 2 years	• United States • Ages 60–80 years • Intact uterus • At least 5 years past menopause • Bone mineral density normal for age	Good
The Women's Angiographic Vitamin and Estrogen Trial (WAVE)	Waters et al., 2002[80]	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=210) Placebo (N=213) Mean 2.8 years	• United States, Canada • Postmenopausal • Coronary angiogram performed within 4 months of study entry	Fair
Women's Health Initiative (WHI) E Trial	Anderson et al., 2004;[24] Bonds et al., 2006;[106] Brunner et al., 2005;[107] Chlebowski et al., 2010;[108] Cirillo et al., 2005;[88] Curb et al., 2006;[109] Hendrix et al., 2005;[94] Hendrix et al., 2006;[110] Hsia et al., 2006;[111] Manson et al., 2013;[102] Ritenbaugh et al., 2008;[113] Rossouw et al., 2007[35]	CEE 0.625 mg/day (N=5,310) Placebo (N=5,429) Median 7.2 years	• United States • Postmenopausal • Ages 50–79 years • Prior hysterectomy • 3-month washout required for women using hormone therapy at baseline	Fair

Table 3. Characteristics of Randomized Controlled Trials of Use of Menopausal Hormone Therapy

Trial Name (Acronym)	Author, Year	Intervention; Duration	Country; Participants	Quality Rating
WHI E Post-intervvention and Postintervention Extension Phases	Chlebowski et al., 2010;[84] LaCroix et al., 2011;[112] Manson et al., 2013[102]	CEE 0.625 mg/day (N=5,310) Placebo (N=5,429) Mean 6.6 years	9,666 participants from WHI (90%) had any postintervention followup and 7,645 (71%) consented to participate in the extension phase	Fair
WHI E+P Trial	Anderson et al., 2012;[105] Anderson et al., 2003;[81] Canonico et al., 2014;[82] Cauley et al., 2003;[83] Chlebowski et al., 2003;[85] Chlebowski et al., 2004;[87] Cirillo et al., 2005;[88] Cushman et al., 2004;[89] Hays et al., 2003;[91] Hendrix et al., 2003;[93] Hendrix et al., 2005;[94] Hsia et al., 2004;[95] Manson et al., 2003;[96] Manson et al., 2013;[102] Margolis et al., 2004;[97] Prentice et al., 2009;[98] Rossouw et al., 2002;[23] Rossouw et al., 2007;[35] Tang et al., 2011[99] Toh et al., 2010;[100] Wassertheil-Smoller et al., 2003[101]	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=8,506) Placebo (N=8,102) Median 5.6 years	• United States • Postmenopausal • Ages 50–79 years • 3-month washout period for women using hormone therapy at baseline	Fair
WHI E+P Postintervention and Postintervention Extension Phases	Chlebowski et al., 2009;[86] Chlebowski et al., 2010;[84] Gramling et al., 2009;[90] Heiss et al., 2008;[92] Manson et al., 2013[102]	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=8,506) Placebo (N=8,102) Median 8.2 years	15,747 participants from WHI (95%) had any postintervention followup and 12,788 (77%) consented to participate in the extension phase	Fair
Women's Health Initiative Memory Study (WHIMS) E	Espeland et al., 2004;[115] Shumaker et al., 2004[117]	CEE 0.625 mg/day (N=1,464) Placebo (N=1,483) 5.2 years	• United States • WHI participants enrolled in the estrogen-only trial • Age >65 years • Free of probable dementia • Able and willing to undergo annual cognitive assessment	Good

Table 3. Characteristics of Randomized Controlled Trials of Use of Menopausal Hormone Therapy

Trial Name (Acronym)	Author, Year	Intervention; Duration	Country; Participants	Quality Rating
WHIMS E+P	Culhane, 2003;[114] Rapp et al., 2003;[116] Shumaker et al., 2003[118]	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=2,229) Placebo (N=2,303) 5.4 years	• United States • WHI participants enrolled in the E+P trial • Age >65 years • Free of probable dementia • Able and willing to undergo annual cognitive assessment	Good
The Women's Health Initiative Memory Study of Younger Women (WHIMSY)	Espeland et al., 2013[119]	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=696) Placebo (N=630) 7.2 years	• United States • Postmenopausal • Ages 50–79 years • 3-month washout period for women using hormone therapy at baseline	Fair
Women's Health Initiative Study of Cognitive Aging (WHISCA) E	Espeland et al., 2010;[120] Resnick et al., 2009[121]	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=434) Placebo (N=452) 2.7 years	• United States • WHIMS E only trial participants • Free of probable dementia • At 1 of 14 WHIMS centers	Good
WHISCA E+P	Espeland et al., 2010;[120] Resnick et al., 2006[122]	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=690) Placebo (N=726) 3 years	• United States • WHIMS E+P trial participants • Free of probable dementia • At 1 of 14 WHIMS centers	Good
Women's International Study of Long Duration Oestrogen After Menopause (WISDOM)	Vickers et al., 2007[123]	CEE 0.625 mg/day plus MPA 2.5–5.0 mg/day (N=2,196) Placebo (N=2,189) 1 year	• United Kingdom • Postmenopausal • Ages 50–69 years •	Fair

Abbreviations: CEE = conjugated equine estrogen; E = estrogen only; E+P = estrogen plus progestin; mcg = micrograms; mg/dL = milligrams per deciliter; MP = cyclic micronized progesterone; MPA = medroxyprogesterone acetate; N = number of subjects.

Table 4. Baseline Characteristics of Participants in Randomized Controlled Trials of Hormone Therapy to Prevent Chronic Conditions

Characteristic (Hormone Therapy; Placebo)[a]	EMS E+P	EPAT	EPHT	ERA	ESPRIT E	Greenspan et al.	HERS E+P	KEEPS-Cog	PEPI	STOP-IT
N	70;72	111;111	404;373	100;104;105	513;504	187;186	1380; 1383	220;211;262	175;174; 178;174	121;122; 123;123
Age (mean years)	75;74.5	60.9;62.1	58.5;59.0	66.3;65.5;65.6	62.3;62.9	71.1;71.3	67;67	52.8;52.6; 52.5	-	72;71;72; 74
Nonwhite race (%)	4.3;9.7	43.0;38.0	49.6;49.7	19.0;16.0;19.0	3;3	-	12;10	22.3; 22.7;23.3	-	-
Previous or current HT (%)	31.4;23.6	-	9.2;6.4	9.0;8.0;10.0	12;10	-	1.7;1.7	26.4;20.4; 18.3	-	-
Hysterectomy at age <40 years (%)	-	-	-	-	-	-	-	-	-	-
Hysterectomy at ages 40–49 years (%)	-	33.0;44.0[b]	11.4;12.9[b]	56.0;62.0;66.0	-	-	-	-	-	-
Bilateral oophorectomy (%)	-	32.0;19.0	-	25.0;30.0;36.0	-	-	-	-	-	-
Never pregnant (%)	-	-	8.9;8.1	-	-	-	-	-	-	-
First pregnancy age ≥30 years (%)	-	-	-	-	-	-	-	-	-	-
Female relative with breast cancer (%)	-	-	7.2;7.0	-	-	-	-	-	-	-
Current smoker (%)	-	58.0;46.0	16.3;13.9	18.0;16.0;21.0	54;52	-	13;13	5.9;6.6;6.9	-	-
Mean BMI (kg/m^2)	27;26.6	28.7;29.0	27.0;26.9	-	26.8;26.7	27.5;27.7	29;29	26.1;26.1; 26.6	-	-
History of MI (%)	5.7;4.2	-	0.5;0.3	48.0;41.0;55.0	-	-	50;52	-	-	-
History of stroke (%)	-	-	-	-	-	-	-	-	-	-
History of DVT or PE (%)	-	-	-	-	-	-	-	-	-	-
Mean SBP (mm Hg)	-	127.8;128.6	137;137	131.0;136.2;134.4	-	-	135;135	119.1; 117.5;120.1	115;115; 114;116	-
Mean DBP (mm Hg)	-	78.1;77.0	85.7;86	73.4;74.1;74.4	-	-	73;73	75.3;74.1; 75.5	72;72; 73;71	-
Treated for hypertension or BP>140/90 (%)	-	-	13.1;12.1	60.0;73.0;69.0	-	-		-	-	-
Elevated cholesterol requiring medication (%)	-	-	-	34.0;38.0;37.0	-	-		-	-	-
Prior aspirin use or use at baseline (%)	-	-	-	67.0;73.0;70.0	-	-	79;79	-	-	-
History of or treatment for diabetes (%)	7.1;11.1	2.0;4.0	-	25.0;29.0;30.0	15;15	-	19;18	-	-	-
Fracture at age ≥55 years (%)	-	-	-	-	-	-	-	-	-	-

Table 4. Baseline Characteristics of Participants in Randomized Controlled Trials of Hormone Therapy to Prevent Chronic Conditions

Characteristic (Hormone Therapy; Placebo)[a]	ULTRA E	WAVE	WHI E+P	WHI E	WHIMSY	WHIMS E+P	WHIMS E	WHISCA E+P	WHISCA E	WISDOM E+P
N	191;185	210;213	8506;8102	5310;5429	696;630	2229;2303	1464;1483	690;726	434;452	2196;2189
Age (mean years)	66.8;66.7	65.0;69.0	63.2;63.3	63.6;63.6	53.0;52.9	63.2;63.3	63.6;63.6	73.69;73.86	74.01;74.02	63.3;63.3
Nonwhite race (%)	7.2;8.1	35.0;32.0	16.1;16.0	24.5;24.9	20.0;19.2	-	17.3;16.4	8.4;7.0	14.09;13.08	1;1.4
Previous or current HT (%)	-	-	26.1;25.6	47.8;48.9	47.9;53.2	21.8;22.4	45.8;44.7	21.2;22.6	49.54;46.24	55;54.3
Hysterectomy at age <40 years (%)	-	-	-	39.8;39.8	56.6;57.3	-	-	-	-	-
Hysterectomy at ages 40–49 years (%)	-	59.0;58.0[b]	-	43.2;42.2	20.9;16.5	-	-	-	-	-
Bilateral oophorectomy (%)	-	36.0;37.0	-	39.5;42.0	-	-	-	-	-	-
Never pregnant (%)	-	-	10.1;10.3	9.3;8.5	-	-	-	-	-	-
First pregnancy at age ≥30 years (%)	-	-	10.6;9.7	4.9;5.9	-	-	-	-	-	-
Female relative with breast cancer (%)	-	-	16.0;15.3	18.0;17.1	-	-	-	-	-	8;9
Current smoker (%)	7.7;6.2	19.0;19.0	10.5;10.5	10.3;10.6	13.5;16.3	6.7;6.9	7.3;8.0	6.2;5.0	3.72;7.59	12;14
Mean BMI (kg/m^2)	28.3;28.0	31.1;30.3	28.5;28.5	30.1;30.1	-	-	-	28.5;28.1	29.40;29.21	27.9;28.0
History of MI (%)	-	46.0;40.0	1.6;1.9	3.1;3.2	-	-	-	-	-	2;1
History of stroke (%)	-	-	0.7;1.0	1.4;1.7	-	1;1.9	1.8;2.1	1;1	1.15;1.77	1;2
History of DVT or PE (%)	-	-	0.9;0.8	1.6;1.5	-	-	-	-	-	-
Mean SBP (mm Hg)	-	140.0;138.0	127.6;127.8	130.4;130.2	-	-	-	-	-	-
Mean DBP (mm Hg)	-	76.0;75.0	75.6;75.8	76.5;76.5	-	-	-	-	-	-
Treated for hypertension or BP >140/90 (%)	-	77.0;74.0	35.7;36.4	48.0;47.4	21.0;21.0	-	47.3;42.3	44.4;46.0	53.69;51.11	-
Elevated cholesterol requiring medication (%)	-	-	12.5;12.9	14.5;15.9	-	-	-	-	-	-
Prior aspirin use or use at baseline (%)	-	84.0;86.0	19.1;20.1	19.4;19.7	-	28.1;29.6	28.0;30.9	-	-	-
History of or treatment for diabetes (%)	-	42.0;31.0	4.4;4.4	7.7;7.6	-	7;6.5	11.3;10.6	5.4;6.2	10.14;10.84	3;4
Fracture at age ≥55 years (%)	-	-	13.5;13.6	14.0;13.2	-	-	-	-	-	-

[a] Intervention dosages are listed in Table 3 by trial.
[b] Participants of all ages.

Abbreviations: BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; DOPS = Danish Osteoporosis Prevention Trial; DVT = deep vein thrombosis; E = estrogen; E+P = estrogen plus progestin; EMS = Estrogen Memory Study; EPAT = Estrogen in the Prevention of Atherosclerosis; EPHT = Estonian Postmenopausal Hormone Therapy Trial; ERA = Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HERS = Heart and Estrogen/Progestin Replacement Study; HT = hormone therapy; MI = myocardial infarction; P=progestin; PE = pulmonary embolism; PEPI = Postmenopausal Estrogen and Progestin Interventions Trial; SBP = systolic blood pressure; ULTRA = Ultra-Low-Dose Transdermal Estrogen Assessment; WAVE = The Women's Angiographic Vitamin and Estrogen Trial; WHI = Women's Health Initiative; WHIMS = Women's Health Initiative Memory Study; WHISCA = Women's Health Initiative Study of Cognitive Aging; WISDOM = Women's International Study of Long Duration Oestrogen After Menopause.

Table 5. Results of WHI at the End of the Intervention Phase, by Category and Subcategory of Outcome

Outcome[a,b]	Estrogen Only[c] vs. Placebo Hazard Ratio (95% CI)	Estrogen plus Progestin[c] vs. Placebo Hazard Ratio (95% CI)
Cancer		
Breast (invasive)	0.79 (0.61 to 1.02)[102, 112]	1.24 (1.01 to 1.53)[102]
Cervical	Not reported	1.44 (0.47 to 4.42)[81]
Colorectal	1.15 (0.81 to 1.64)[102]	0.62 (0.43 to 0.89)[102]
Endometrial	Not reported	0.83 (0.49 to 1.40)[102]
Lung	1.05 (0.74 to 1.49)[102]	1.05 (0.76 to 1.45)[102]
Ovarian	Not reported	1.41 (0.75 to 2.66)[102]
Cardiovascular events (all)	1.11 (1.01 to 1.22)[102]	1.13 (1.02 to 1.25)[102]
Coronary heart disease	0.94 (0.78 to 1.14)[102]	1.18 (0.95 to 1.45)[102]
Cognitive functioning and dementia		
Mild cognitive impairment	1.34 (0.95 to 1.89)[102]	1.07 (0.74 to 1.55)[102]
Probable dementia	1.49 (0.83 to 2.66)[102, 117]	2.05 (1.21 to 3.48)[118]
Diabetes		
Self-reported new diagnosis requiring treatment with drugs	0.86 (0.76 to 0.98)[102]	0.81 (0.70 to 0.94)[81, 102]
Fractures		
Hip	0.67 (0.46 to 0.96)[102]	0.67 (0.47 to 0.95)[102]
Vertebral	0.64 (0.44 to 0.93)[102]	0.68 (0.48 to 0.96)[102]
Total fractures	0.72 (0.64 to 0.80)[102]	0.76 (0.69 to 0.83)[102]
Gallbladder events	1.67 (1.35 to 2.06)[88]	1.59 (1.28 to 1.97)[88]
Gallbladder disease	1.79 (1.44 to 2.22)[88]	1.61 (1.30 to 2.00)[88]
Cholecystectomy	1.93 (1.52 to 2.44)[88]	1.67 (1.32 to 2.11)[88]
Urinary incontinence (stress, urge, or mixed)		
Overall urinary incontinence	1.53 (1.37 to 1.71)	1.39 (1.27 to 1.52)
Stroke	1.35 (1.07 to 1.70)[102]	1.37 (1.07 to 1.76)[102]
Thromboembolic events		
Deep vein thrombosis	1.48 (1.06 to 2.07)[102]	1.87 (1.37 to 2.54)[102]
Pulmonary embolism	1.35 (0.89 to 2.05)[102]	1.98(1.36 to 2.87)[102]
All-cause mortality	1.04 (0.89 to 1.33)[112]	0.97 (0.81 to 1.16)[92]

[a] Assumes a constant rate of events across the study period, although rates varied depending on outcome (e.g., thromboembolic events occurred early during therapy, cancer cases later).
[b] Hazard ratios not reported for quality of life
[c] Intervention dosages are listed in Table 3 by trial.

Abbreviations: CI = confidence interval; vs. = versus; WHI = Women's Health Initiative.

Table 6. Summary of Evidence: Estrogen-Only Trials

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 1/KQ 2	Menopausal women post-hysterectomy, Estrogen-only therapy	5 RCTs;[24, 60, 62-64, 98, 102, 105, 112] 239 events in 10,739 women contribute to effect estimate (based on 1 RCT[102])	**Invasive breast cancer** (followup 7.2 years): Non-significant lower risk with HT (HR, 0.79; 95% CI, 0.61 to 1.02)	Consistent/ imprecise	Undetected	Fair	Three studies followed participants for a relatively short duration (2–3 years)	Moderate	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women without intact uterus Estrogen-only therapy	1 RCT;[64] 1 event in 1,017 women contribute to effect estimate	**Cervical Cancer** (followup 12.6 years): Relative risk not estimated due to low number of events	NA/ imprecise	Suspected	Fair	One small study followed participants to evaluate a rare cancer outcome over a period of time that included the intervention and an open-label observational period	Insufficient	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen-only therapy	1 RCT;[102, 113] 123 events in 10,739 women contribute to effect estimate	**Colorectal Cancer** (followup: 7.2 years): No significant risk increase/reduction with HT (HR, 1.15; 95% CI, 0.81 to 1.64)	NA/ imprecise	Undetected	Fair	None	Low	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen-only therapy	1 RCT;[102, 108] 123 events in 10,739 women contribute to effect estimate	**Lung Cancer** (followup: 7.2 years): No significant risk increase/reduction with HT (HR, 1.05; 95% CI, 0.74 to 1.49)	NA/ imprecise	Undetected	Fair	None	Low	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women without intact uterus Estrogen-only therapy	1 RCT;[63, 64] 5 events in 1,017 women contribute to effect estimate	**Ovarian Cancer** (followup: 12.6 years): no significant risk increase/reduction with HT (p=0.37); relative risk not reported	NA/imprecise	Suspected	Fair	One small study followed participants to evaluate a rare cancer outcome over a period of time that included the intervention	Insufficient	Generally healthy post-menopausal women 50 years or older

Table 6. Summary of Evidence: Estrogen-Only Trials

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
							and an open-label observational period		
KQ 1/KQ 2	Menopausal women post-hysterectomy Estrogen-only therapy	4 RCTs;[60, 62, 74, 111] 422 events in 11,310 women contribute to effect estimate (based on 3 RCTs[60, 74, 111])	**Coronary heart disease** (followup 6.8 years in meta-analysis): No significant risk reduction/increase with HT (RR, 0.95; 95% CI, 0.79 to 1.14)	Consistent/ precise	Undetected	Fair	None	High	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women post-hysterectomy Estrogen-only therapy	1 RCT;[115, 117, 127] 47 events in 2,947 women contribute to effect estimate	**Probable dementia** (followup 5.2 years): No significant risk increase or reduction with HT (HR, 1.49; 95% CI, 0.83 to 2.66)	NA/ imprecise	Undetected	Fair	None	Low	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women post-hysterectomy Estrogen-only therapy	1 RCT;[102, 106] 976 events in 9,917 women contribute to effect estimate	**Diabetes** (followup 7.1 years): Risk reduction with HT (HR, 0.86; 95% CI, 0.76 to 0.98)	NA/ reasonably precise	Undetected	Fair	Diabetes is self-reported	Moderate	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women post-hysterectomy Estrogen-only therapy	2 RCTs;[62, 81, 102, 112] 1,227 events in 10,739 women contribute to effect estimate (based on 1 RCT[102])	**Fractures** (followup 6.8 years): Significant risk decrease with HT (HR, 0. 70; 95% CI, 0.63 to 0.79)	Consistent/ precise	Undetected	Fair	None	High	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women post-hysterectomy Estrogen-only therapy	2 RCTs;[74, 88] 371 events in 8,376 women contribute to effect estimate (based on 1 RCT[88])	**Gallbladder events** (followup 7.2 years): Significant risk increase with HT (HR, 1.67; 95% CI, 1.35 to 2.06	Consistent/ reasonably precise	Undetected	Fair	Gallbladder disease is self-reported	Moderate	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women post-hysterectomy Estrogen-only therapy	3 RCTs;[60, 62, 112] 298 events in 10,739 women contribute to effect estimate (based on 1 RCT[102])	**Stroke** (followup 7.2 years): Significant increase with HT (HR, 1.35; 95% CI, 1.07 to 1.70)	Consistent/ reasonably precise	Undetected	Fair	Three studies followed participants for a relatively short duration (2–3 years)	Moderate	Generally healthy post-menopausal women 50 years or older

Table 6. Summary of Evidence: Estrogen-Only Trials

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 1/KQ 2	Menopausal women post-hysterectomy Estrogen-only therapy	2 RCTs;[78, 94] 925 events in 3,073 women contribute to effect size (based on 1 RCT[94])	**Urinary incontinence** (followup 1 year): Significant risk increase with HT (RR, 1.53; 95% CI, 1.37 to 1.71)	Consistent/ precise	Undetected	Fair	Urinary incontinence is self-reported	Moderate	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women post-hysterectomy Estrogen-only therapy	2 RCTs;[60, 112] 144 (DVT) and 91 (PE) events in 10,739 women contribute to effect estimates (based on 1 RCT[102])	**Venous thromboembolism** (followup 7.1 years): Nonsignificant increased risk of PE (HR 1.35; 95% CI, 0.89 to 2.05) and significant increased risk of DVT (HR, 1.48: 95% CI, 1.06 to 2.07) in the WHI	Consistent/ reasonably precise	Undetected	Fair	None	Moderate	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women post-hysterectomy Estrogen-only therapy	1 RCT[102]	**Quality of life** (followup 7.1 years): Similar scores on most items of the RAND-36	NA/precise	Undetected	Fair	None	Moderate	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women post-hysterectomy Estrogen-only therapy	3 RCTs;[62, 63, 112] 682 events in 11,961 women contribute to effect estimate	**All-cause mortality** (followup 6.8 years in meta-analysis): No significant risk increase/reduction with HT (RR, 1.01; 95% CI, 0.88 to 1.17)	Consistent/ precise	Undetected	Fair	None	High	Generally healthy post-menopausal women 50 years or older

Abbreviations: CI = confidence interval; DVT = deep vein thrombosis; EPC = evidence-based practice; HR = hazard ratio; HT = hormonal therapy; KQ = Key Question; NA = not applicable; No. = number; p=p-value; PE = pulmonary embolism; RCT = randomized controlled trial; RR = relative risk; vs. = versus; WHI = Women's Health Initiative.

Table 7. Summary of Evidence: Estrogen Plus Progestin Trials

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen plus progestin therapy	5 RCTs;[23, 61, 68, 74, 84, 85, 90, 92, 98, 102, 123] 420 events in 19,371 women contribute to effect estimates (based on 2 RCTs[68, 102])	**Invasive breast cancer** (followup 4.1–5.6 years): Significant risk increase with HT (HR, 1.24; 95% CI, 1.01 to 1.53) in WHI and non-significant increase with HT in HERS I (HR, 1.38; 95% CI, 0.82 to 2.31)	Consistent/ reasonably precise	Undetected	Fair	None	High	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen plus progestin therapy	1 RCT;[81] 13 events in 16,608 women contribute to effect estimate	**Cervical cancer** (followup: 5.6 years): No significant risk increase/reduction with HT (HR, 1.44; 95% CI, 0.47 to 4.42)	NA, single study/imprecise	Undetected	Fair	One study followed participants for a relatively short duration (5.6 years) to evaluate a rare cancer outcome	Low	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with and without intact uterus Estrogen plus progestin therapy	4 RCTs;[23, 59, 68, 87, 92, 98, 102, 123] 152 events in 19,371 women contribute to effect estimates (based on 2 RCTs[68, 102])	**Colorectal Cancer** (followup: 4.1 to 5.6 years): Significant risk reduction with HT (HR, 0.62; 95% CI, 0.43 to 0.89) in the WHI and non-significant risk reduction with HT (HR, 0.69; 95% CI: 0.32 to 1.49) in HERS	Reasonably consistent/ reasonably precise	Undetected	Fair	Studies followed participants for a relatively short duration (up to 5.6 years) to evaluate a cancer outcome	Moderate	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen plus progestin therapy	4 RCTs;[23, 62, 68, 74, 81, 92, 98, 102, 108] 64 events in 19,371 women contribute to effect estimates (based on 2 RCTs[23, 68, 81, 92, 98, 102, 108])	**Endometrial Cancer** (followup: 4.1 to 5.6 years): No significant risk increase/reduction with HT (HR, 0.83; 95% CI, 0.49 to 1.40) in the WHI and (HR, 0.39; 95% CI: 0.08 to 2.02) in HERS	Reasonably consistent/ reasonably precise	Undetected	Fair	Studies followed participants for a relatively short duration (up to 5.6 years) to evaluate a rare cancer outcome	Low	Generally healthy post-menopausal women 50 years or older

Table 7. Summary of Evidence: Estrogen Plus Progestin Trials

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 1/KQ 2	Menopausal women with and without intact uterus Estrogen plus progestin therapy	3 RCTs;[59, 68, 86, 102] 191 events in 19,371 women contribute to effect estimates (based on 2 RCTs[68, 86, 102])	**Lung Cancer** (followup: 4.1 to 5.6 years): No significant risk increase/reduction with HT (HR, 1.05; 95% CI, 0.76 to 1.45) in the WHI and (HR, 1.28; 95% CI, 0.70 to 2.33) in HERS	Reasonably consistent/ reasonably precise	Undetected	Fair	Studies followed participants for a relatively short duration (up to 5.6 years) to evaluate a cancer outcome	Moderate	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen plus progestin therapy	1 RCT;[81, 102] 40 events in 16,608 women contribute to effect estimate	**Ovarian Cancer** (followup: 5.6 years): No significant risk increase/reduction with HT (HR, 1.41; 95% CI, 0.75 to 2.66)	NA/imprecise	Undetected	Fair	Study followed participants for a relatively short duration (5.6 years) to evaluate a rare cancer outcome	Low	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen plus progestin therapy	6 RCTs;[23, 59, 61, 62, 74, 123] 341 events in 18,081 women contribute to effect estimate (based on 3 RCTs[23, 59, 61, 74])	**Coronary heart disease** (followup 5.2 years in meta-analysis): Risk increase with HT (RR, 1.23; 95% CI, 1.00 to 1.52)	Consistent/ precise	Undetected	Fair	None	High	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen plus progestin therapy	1 RCT;[118] 61 events in 4,532 women contribute to effect estimate	**Probable dementia:** (followup 4 years): Significant risk increase with HT (HR, 2.05; 95% CI, 1.21 to 3.48)	NA/ imprecise	Undetected	Fair	None	Moderate	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen plus progestin therapy	2 RCTs;[70, 97, 102] [70, 102]701 events in 15,874 women contribute to effect estimate (based on 1 RCT[102])	**Diabetes** (followup 5.6 years): Significant risk reduction with HT (HR, 0.81; 95% CI, 0.70 to 0.94)	Consistent/ precise	Undetected	Fair	Diabetes is self-reported	Moderate	Generally healthy post-menopausal women 50 years or older

Table 7. Summary of Evidence: Estrogen Plus Progestin Trials

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen plus progestin therapy	5 RCTs;[23, 59, 61, 62, 68, 83, 92, 102] 1,995 events in 20,499 women contribute to effect estimate	**Fractures** (followup from 2 to 5.2 years): Significant risk reduction with HT (RR, 0.80; 95% CI, 0.68 to 0.94)	Consistent/ precise	Undetected	Fair	None	High	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen plus progestin therapy	2 RCTs;[74, 88] 363 events in 14,203 women contribute to effect estimate (based on 1 RCT[88])	**Gallbladder events** (followup 5.6 years): Significant risk increase with HT (HR, 1.59; 95% CI, 1.28 to 1.97)	Consistent/ precise	Undetected	Fair	None	Moderate	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen plus progestin therapy	3 RCTs;[59, 61, 101, 102] 330 events in 17,385 women contribute to effect estimates (based on 2 RCTs[61, 101, 102])	**Stroke** (followup 3.4 to 5.6 years): significant increase with HT in WHI (HR, 1.37; 95% CI, 1.07 to 1.76) Risk of any cerebrovascular event: significant increase with HT in EPHT (HR, 1.06; 95% CI, 0.07 to 17.2)	Consistent/ reasonably precise	Undetected	Fair	Outcome measures heterogeneous; one trial reported on stroke incidence and another reported on composite risk of various cerebrovascular events (e.g., stroke, TIA)	High	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen plus progestin therapy	2 RCTs;[71, 94] 1,397 events in 5,182 women contribute to effect size (based on 1 RCT[94])	**Urinary incontinence** (followup 1 year): Significant risk increase with HT (RR, 1.39; 95% CI, 1.27 to 1.52)	Consistent/ precise	Undetected	Fair	Urinary incontinence is self-reported	Moderate	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen plus progestin therapy	4 RCTs;[59, 61, 62, 89] 182 (DVT) and 124 (PE) events in 16,602 women contribute to effect estimates (based on 1 RCT[102])	**Venous thromboembolism** (followup 5.6 years): Significant Increased risk of PE (HR 1.98; 95% CI, 1.36 to 2.87) and DVT (HR, 1.87; 95% CI, 1.37 to 2.54) with HT in WHI at followup of 5.6 years	Consistent/ reasonably precise	Undetected	Fair	Three studies followed participants for a relatively short duration (2–3 years)	Moderate	Generally healthy post-menopausal women 50 years or older

Table 7. Summary of Evidence: Estrogen Plus Progestin Trials

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 1/KQ 2	Menopausal women post-hysterectomy Estrogen-only therapy	1 RCT[102]	**Quality of life** (followup 5.2 years): Similar scores on most items of the RAND-36	NA/precise	Undetected	Fair	None	Moderate	Generally healthy post-menopausal women 50 years or older
KQ 1/KQ 2	Menopausal women with intact uterus Estrogen plus progestin therapy	3 RCTs;[62, 68, 92] 752 events in 19,580 women contribute to effect estimate	**All-cause mortality** (followup of 5.2 years in meta-analysis): No significant risk increase/reduction with HT (RR, 1.01; 95% CI, 0.88 to 1.17)	Consistent/ reasonably precise	Undetected	Fair	None	Moderate	Generally healthy post-menopausal women 50 years or older

Abbreviations: CI = confidence interval; DVT = deep vein thrombosis; EPC = evidence-based practice; EPHT = Estonian Postmenopausal Hormone Therapy Trial; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; HT = hormone therapy; KQ key question; NA = not applicable; No. = number; p = p-value; PE = pulmonary embolism; RCT = randomized controlled trial; RR = relative risk; TIA = Transient Ischemic Attack; WHI = Women's Health Initiative.

Table 8. Summary of Evidence: Subgroups

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency*/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[102, 104] 600 events in 27,347 women	**Invasive Breast Cancer:** Age: Similar treatment effects in subgroups based on age Timing: Women who initiated estrogen plus progestin closer to menopause had a higher risk of invasive breast cancer than those who initiated later (p for interaction=0.03) Duration: The risk of invasive breast cancer increased for women who initiated estrogen plus progestin with increasing time since randomization (p for trend=0.008). No difference in timing or duration of HRT use for women on estrogen-only therapy	N/A/ reasonably precise N/A/imprecise	Undetected	Fair	None	Low	Generally healthy post-menopausal women 50 years or older
KQ 3	Menopausal women with intact uterus Estrogen plus progestin therapy	No evidence	**Cervical Cancer:** No evidence Timing: No evidence	N/A	Undetected	N/A Fair	N/A	Insufficient	N/A

Table 8. Summary of Evidence: Subgroups

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency*/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[87, 98, 102, 113] 248 events in 27,347 women	**Colorectal Cancer**: For estrogen-only, younger women had significantly lower risk than older women (p for interaction= 0.02). Similar risks for estrogen plus progestin. Similar treatment effects in subgroups based on race or ethnicity or family history of colorectal cancer for both treatment regimens Timing: Similar treatment effects in subgroups based on timing of intervention since menopause for both treatment regimens	N/A/imprecise	Undetected	Fair	Estimates based on 2 studies with few events; lack of power to detect subgroup effects	Insufficient	Generally healthy post-menopausal women 50 years or older
KQ 3	Menopausal women with intact uterus Estrogen plus progestin therapy	1 RCT[102] 57 events in 16,608 women	**Endometrial Cancer:** Similar treatment effects in subgroups based on age in the estrogen plus progestin and placebo groups Timing: No evidence	N/A/imprecise N/A	Undetected	Fair	Estimates based on a single study with few events; lack of power to detect subgroup effects N/A	Insufficient	Generally healthy post-menopausal women 50 years or older N/A
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[102] 271 events in 27,347 women	**Lung Cancer:** Similar treatment effects in subgroups based on age for both treatment regimens Timing: No evidence	N/A/imprecise N/A	Undetected	Fair	Estimates based on 2 studies with few events; lack of power to detect subgroup effects N/A	Insufficient	Generally healthy post-menopausal women 50 years or older N/A

Table 8. Summary of Evidence: Subgroups

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency*/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 3	Menopausal women with intact uterus Estrogen plus progestin therapy	1 RCT[102] 40 events in 16,608 women	**Ovarian Cancer:** No subgroup effects with respect to age for estrogen plus progestin Timing: No evidence	N/A/imprecise N/A	Undetected	Fair	None N/A	Insufficient	Generally healthy post-menopausal women 50 years or older N/A
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[35, 96, 111] 711 event in >27,000 women	**Coronary Heart Disease:** Risk attributable to HT increased numerically with age for estrogen plus progestin; test of interaction was not statistically significant Younger women on estrogen only had lower risks for myocardial infarction than older women. Similar treatment effects in subgroups based on race or ethnicity, hypertension, diabetes, high cholesterol requiring medication, coronary risk factors, years since bilateral oophorectomy, years since hysterectomy, or body mass index for both treatment regimens Timing: Risk attributable to HT increased with time since menopause; test of interaction was not statistically significant (p=0.40)	N/A/ reasonably precise Consistent/ reasonably precise	Undetected	Fair	None For women with hysterect-omy without oophorect-omy, exact timing of menopause is often difficult to determine	Low Moderate Moderate	Generally healthy post-menopausal women 50 years or older

Table 8. Summary of Evidence: Subgroups

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency*/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 3	Menopausal women with intact uterus Estrogen only or estrogen plus progestin therapy	1 RCT[116-118] 108 events in 7,479 women	**Probable Dementia:** Similar treatment effects in subgroups based on race, history of diabetes, stroke, hypertension, or cardiovascular disease for estrogen only Timing: Similar treatment effects in subgroups based on timing of intervention since menopause for estrogen plus progestin	N/A/imprecise	Undetected	Fair	Estimates based on a single study For women with hysterectomy without oophorectomy, exact timing of menopause is often difficult to determine	Low	Generally healthy post-menopausal women 50 years or older
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	1 RCT[97, 102, 106] 1,677 events in 25,791 women	**Diabetes:** Similar treatment effects in subgroups based on age, race/ethnicity, and hypertension for both treatment regimens and similar treatment effects in subgroups based on metabolic syndrome for estrogen only Timing: No evidence	N/A/precise N/A	Undetected	Fair	None N/A	High Insufficient	Generally healthy post-menopausal women 50 years or older N/A
KQ 3	Menopausal women with intact uterus Estrogen only or estrogen plus progestin therapy	1 RCT[81] 1,227 events in 10,739 women Timing: 1 RCT[61] 40 events in 777 women[61]	**Fractures:** No significant difference by age for estrogen only Timing: Similar treatment effects based on timing of intervention since menopause for estrogen plus progestin	N/A	Undetected	N/A	N/A	Insufficient	N/A

Table 8. Summary of Evidence: Subgroups

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency*/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[88] 734 events in 22,579 women	**Gallbladder disease:** Similar treatment effects in subgroups based on age for both treatment regimens Timing: No evidence	N/A/precise N/A	Undetected	Fair	N/A	Moderate Insufficient	Generally healthy post-menopausal women 50 years or older N/A
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[102] 567 events in 27,347 women	**Stroke:** Similar treatment effects in subgroups based on age, race/ethnicity and hypertension for both treatment regimens Timing: Similar treatment effects in subgroups based on timing of intervention since menopause for both treatment regimens	N/A/precise	Undetected	Fair	None	Moderate	Generally healthy post-menopausal women 50 years or older
KQ 3	Menopausal women with intact uterus Estrogen plus progestin therapy	No evidence	**Urinary incontinence:** No evidence Timing: No evidence	N/A	Undetected	N/A Fair	N/A	Insufficient	N/A
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[102] 546 events in 27,347 women	**Venous Thromboembolism:** Similar treatment effects in subgroups based on age for both treatment regimens and similar treatment effects in subgroups based on race/ethnicity and history of cardiovascular disease for estrogen only Timing: Similar treatment effects in subgroups based on timing of intervention since menopause for both treatment regimens	N/A/precise	Undetected	Fair	None For women with hysterect-omy without oophorect-omy, exact timing of menopause is often difficult to determine	Moderate	Generally healthy post-menopausal women 50 years or older

Table 8. Summary of Evidence: Subgroups

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency*/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
KQ 3	Menopausal women with intact uterus Estrogen plus progestin therapy	No evidence	**Quality of life:** No evidence	N/A	Undetected	N/A	N/A	Insufficient	N/A
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[98, 112] 1086 events in 27,347 women	**All-cause mortality:** Risk was significantly lower in younger than older women using estrogen only (p for interaction=0.04); in women on estrogen plus progestin difference did not reach statistical significance. Timing: Similar treatment effects in subgroups based on timing of intervention since menopause for both treatment regimens	N/A/precise	Undetected	Fair	None For women with hysterecto-my without oophorecto-my, exact timing of menopause is often difficult to determine	Moderate High	Generally healthy post-menopausal women 50 years or older

[a] Ratings of consistency pertain to effects of the same treatment regimen (i.e., either estrogen only or combination therapy). In situations where only a single study is available for each regimen, consistency was rated as not applicable (NA).

Abbreviations: EPC = Evidence-based Practice Center; HT = hormone therapy; KQ = Key Question; N/A = not applicable; No. = number; RCT = randomized controlled trial.

Appendix A. Search Strategies

August 1, 2016

#15	Search **("Hormone Replacement Therapy"[Mesh] OR "Estrogen Replacement Therapy"[Mesh] OR "Estrogens"[Mesh] OR "Estradiol Congeners"[Mesh])**	157162
#16	Search **"Perimenopause"[Mesh] OR "Climacteric"[Mesh] OR "Menopause"[Mesh]**	52591
#17	Search **(#15 AND #16)**	18650
#21	Search **(#15 AND #16)** Filters: **Publication date from 2015/06/01**	223
#22	Search **(#15 AND #16)** Filters: **Publication date from 2015/06/01; Humans**	216
#23	Search **(#15 AND #16)** Filters: **Publication date from 2015/06/01; Humans; English**	204
#30	Search **(#21 NOT #23)**	19
#32	Search **(#21 NOT #23)** Filters: **Humans**	12

PubMed (English)= 204 = 189 NEW
PubMed (non-English) = 12

Cochrane
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric)
Reviews =3 =3 NEW
Other reviews = 0 = 0 NEW
Trials =26 = 22 NEW

Embase

'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) =29 = 19 NEW

ClinicalTrials.gov

'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) = 2

WHO ICTRP

'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) = 2 NEW

TOTAL NON-DUPLICATE DATABASE = 237

Drugs@FDA.gov

Will do targeted searches for “harms” as indicated

NON ENGLISH
PubMed (non-English)= 12
Embase = 0 = NEW
Total - 12

IPA
IPA (held as separate file) = 0 New
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric)

Appendix A. Search Strategies

Sept. 28, 2015
PubMed

#1	Search "Hormone Replacement Therapy"[Mesh] OR "Estrogen Replacement Therapy"[Mesh] OR "Estrogens"[Mesh] OR "Estradiol Congeners"[Mesh]	153213
#2	Search "Perimenopause"[Mesh] OR "Climacteric"[Mesh] OR "Menopause"[Mesh]	50740
#3	Search (#1 AND #2)	18187
#4	Search (#1 AND #2) Filters: Humans	17486
#5	Search (#4) AND ("2011/06/01"[Date - Entrez]: "3000"[Date - Entrez]) Filters: Humans	1558
#6	Search (#4) AND ("2011/06/01"[Date - Entrez]: "3000"[Date - Entrez]) Filters: Humans; English	1449
#9	Search (#5 NOT #6) NON ENGLISH	109

PubMed (English) = 1449 = (2 appeared in the original report and have been removed)
PubMed (English) = 1447

Cochrane
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric)
Reviews = 9 = 4 NEW
Other reviews = 5 = 1 NEW
Trials = 62 = 33 NEW

Embase
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) = 459 = 327 NEW

ClinicalTrials.gov
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) = 12

WHO ICTRP
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) = 7 = 4 NEW

TOTAL NON-DUPLICATE DATABASE = 1828

Drugs@FDA.gov
Will do targeted searches for "harms" as indicated

NON ENGLISH
PubMed (non-English) = 109 = NEW
Embase = 16 = 13 NEW
Total - 122

IPA
IPA (held as separate file) =
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) = 6 = 4 NEW

Appendix B. Inclusion and Exclusion Criteria

	Include	Exclude
Population	Generally healthy perimenopausal and postmenopausal women who are eligible for menopausal hormone therapy; women with and without menopausal symptoms will be included if the focus of the analysis is on the prevention of chronic conditions	Animals; men; premenopausal women; postmenopausal women with contraindications for hormone therapy use, such as history of breast cancer, coronary heart disease, previous venous thromboembolic event or stroke, active liver disease, or women who are at high risk of these complications; populations that are not applicable to U.S. primary care
Interventions	Systemic therapy with estrogen-only formulations or estrogen plus progestin for the prevention of chronic conditions; U.S. Food and Drug Administration–approved medications that are available for use in the United States	Localized (nonsystemic) treatments, such as rings or gels, contraceptives, and other hormones or treatments of menopausal symptoms (such as over-the-counter preparations that are not approved by the U.S. Food and Drug Administration)
Comparators	Placebo, no treatment	Active comparator
Outcomes	KQ 1/2: Benefits and harms Cancer (breast, cervical, colorectal, endometrial, nonsmall cell lung, and ovarian) Coronary heart disease Cognitive functioning and dementia Diabetes Gallbladder disease Fractures Stroke Urinary incontinence Venus thromboembolism Quality of life (if related to chronic conditions of interest) Functional capacity All-cause mortality Disease-specific mortality (if related to chronic conditions of interest) KQ 3: Any of the outcomes listed above by subgroups of interest	Any outcomes that are not health outcomes of chronic conditions associated with hormone therapy (e.g., intermediate outcomes, such as bone density and cholesterol level)
Timing: Duration of intervention	≥1 year of treatment	<1 year of treatment
Setting	Primary care or primary care–like settings	Inpatient facilities, nursing homes, and specialist settings (such as endocrinology)
Geography	U.S. adult population or comparable populations (i.e., those categorized as “Very High” on the Human Development Index, as defined by the United Nations Development Programme)	Settings not comparable or applicable to U.S. adult population
Study design	All outcomes: Randomized controlled trials Controlled clinical trials Systematic reviews Large cohort studies (>10,000 women) for outcomes with no evidence from trials or systematic reviews	All other study designs
Publication language	English	Non-English language
Publication type	Published or unpublished original research	Nonsystematic review article, letter, or editorial; results reported elsewhere; no original data
Start date of search	January 2011 onward	Before January 2011

Criteria:

- Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders were distributed equally among groups.
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination).
- Important differential loss to followup or overall high loss to followup.
- Measurements: equal, reliable, and valid (includes masking of outcome assessment).
- Clear definition of interventions.
- Important outcomes considered.
- Analysis: intention-to-treat analysis; for cluster randomized controlled trials, correction for correlation coefficient.

Definition of ratings based on above criteria:

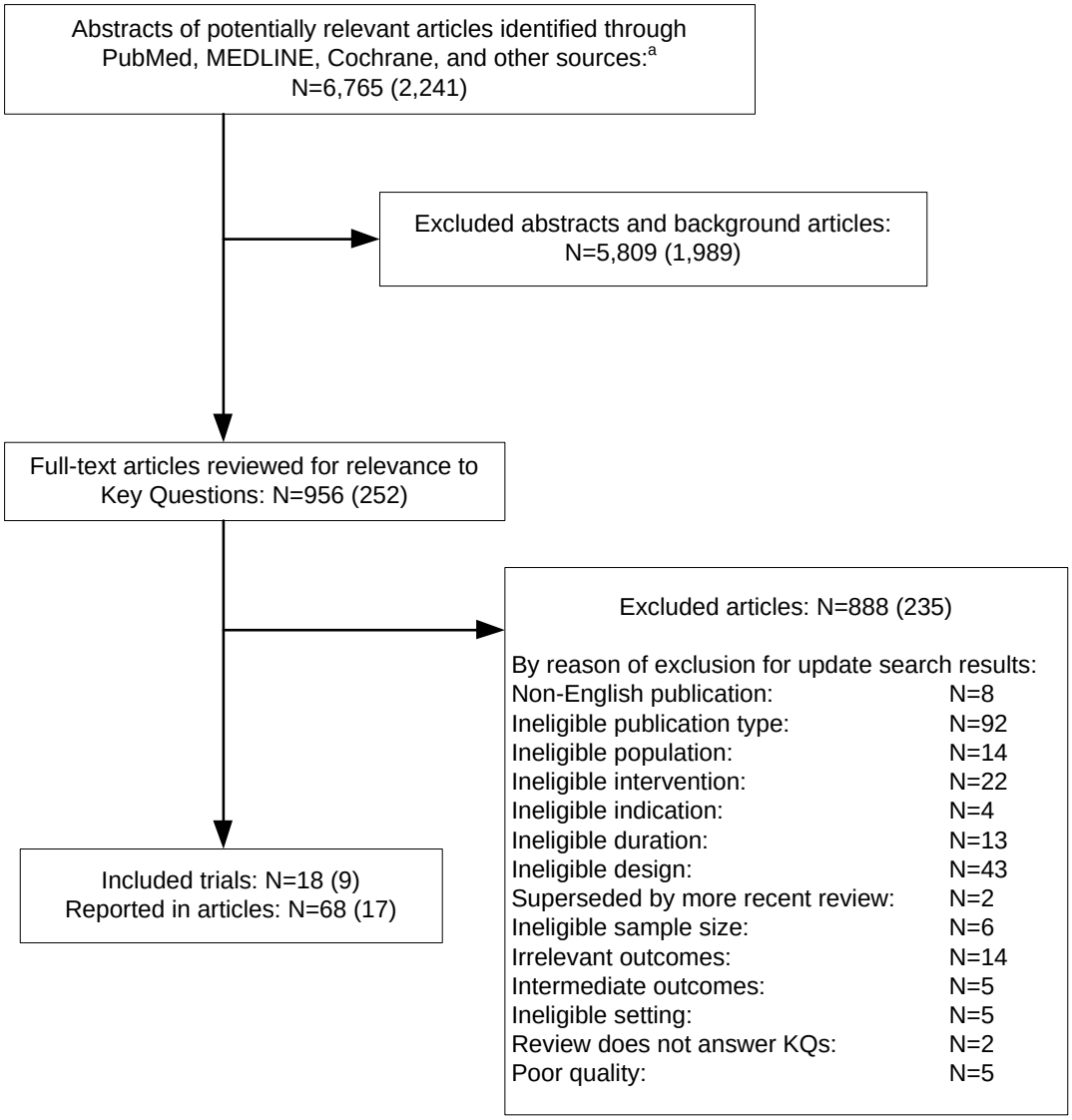
Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Any or all of the following problems occur, without the important limitations noted in the "poor" category below: generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Any of the following major limitations exist: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Source: Harris et al., 2001[43]

Appendix D. Literature Flow Diagram



[a] We conducted searches of PubMed/MEDLINE, the Cochrane Library, EMBASE, International Pharmaceutical Abstracts, ClinicalTrials.gov, Drugs@FDA.gov, the Health Services Research Projects in Process (HSRProj), and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

Abbreviations: KQs = Key Questions; N = number.

Appendix E. Excluded Studies

Code	Exclusion reason
X1	Non-English publication
X2	Ineligible publication type
X3	Ineligible population
X4	Ineligible intervention
X5	Ineligible indication
X6	Ineligible duration
X7	Ineligible design
X8	Superseded by more recent review
X9	Ineligible sample size
X10	Irrelevant outcomes
X11	Intermediate outcomes only
X12	Ineligible setting
X13	Does not answer Key Questions
X14	Excluded for poor quality
X15	Systematic reviews handsearched and excluded

1. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA. 1996 Feb 7;275(5):370-5. PMID: 8569016.Exclusion Code: X10.
2. Hormone therapy has no effect on cognition in younger postmenopausal women. BMJ. 2013;346:f4095. PMID: 23804184.Exclusion Code: X2.
3. Risks and benefits of hormone replacement therapy, revisited. An update on the Women's Health Initiative study, which in 2002 changed the landscape of hormone replacement therapy. Duke Med Health News. 2014 Jan;20(1):5-6.Exclusion Code: X2.
4. Menopausal hormone therapy: is it OK after all? Weighing symptom relief against the risk. Health After 50 Sci Am Consum Health. 2016 Winter;27(14):3-5. PMID: 27062750.Exclusion Code: X2.
5. Postmenopausal hormone replacement therapy: ovarian cancer. Prescrire Int. 2016 Jan;25(167):16. PMID: 26942255.Exclusion Code: X2.
6. Abdelbary AM, El-Dessoukey AA, Massoud AM, et al. Combined Vaginal Pelvic Floor Electrical Stimulation (PFS) and Local Vaginal Estrogen for Treatment of Overactive Bladder (OAB) in Perimenopausal Females. Randomized Controlled Trial (RCT). Urology. 2015 Sep;86(3):482-6. doi: 10.1016/j.urology.2015.06.007. PMID: 26135813.Exclusion Code: X4.
7. Anderson GL, Barrington WE. Narrowing of racial disparities in breast cancer incidence: insights from menopausal hormone therapy study findings. J Natl Cancer Inst. 2016 Apr;108(4)doi: 10.1093/jnci/djv393. PMID: 26613938.Exclusion Code: X2.
8. Antoine C, Ameye L, Paesmans M, et al. Update of the evolution of breast cancer incidence in relation to hormone replacement therapy use in Belgium. Maturitas. 2012;72(4):317-23.Exclusion Code: X7.
9. Antoine C, Ameye L, Paesmans M, et al. Systematic review about breast cancer incidence in relation to hormone replacement therapy use. Climacteric. 2014 Apr;17(2):116-32. doi: 10.3109/13697137.2013.829812 [doi]. PMID: 23909434.Exclusion Code: X7.
10. Antoine C, Ameye L, Paesmans M, et al. Systematic review about breast cancer incidence in relation to hormone replacement therapy use. Maturitas. 2015;81(1):194.Exclusion Code: X7.
11. Archer DF, Pickar JH, MacAllister DC, et al. Transdermal estradiol gel for the treatment of symptomatic postmenopausal women. Menopause. 2012 Jun;19(6):622-9. doi: 10.1097/gme.0b013e31823b8867 [doi]. PMID: 22282101.Exclusion Code: X5.
12. Archer DF, Schmelter T, Schaefers M, et al. A randomized, double-blind, placebo-controlled study of the lowest effective dose of drospirenone with 17beta-estradiol for moderate to severe vasomotor symptoms in postmenopausal women. Menopause. 2014 Mar;21(3):227-35. doi: 10.1097/GME.0b013e31829c1431 [doi]. PMID: 23963307.Exclusion Code: X6.

13. Arem H, Park Y, Felix AS, et al. Reproductive and hormonal factors and mortality among women with colorectal cancer in the NIH-AARP Diet and Health Study. Br J Cancer. 2015;113(3):562-8.Exclusion Code: X4.
14. Bagcchi S. Menopausal hormone therapy reduces liver cancer risk. Lancet Oncol. 2016 Feb;17(2):e50. doi: 10.1016/S1470-2045(16)00003-6. PMID: 26774795.Exclusion Code: X2.
15. Barakat RR, Bundy BN, Spirtos NM, et al. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2006 Feb 1;24(4):587-92. doi: 10.1200/jco.2005.02.8464. PMID: 16446331.Exclusion Code: X3.
16. Barnes EL, Long MD. Colorectal cancer in women: hormone replacement therapy and chemoprevention. Climacteric. 2012 Jun;15(3):250-5. doi: 10.3109/13697137.2012.659450 [doi]. PMID: 22612611.Exclusion Code: X2.
17. Baumgartner AK, Hausler A, Seifert-Klauss V, et al. Breast cancer after hormone replacement therapy--does prognosis differ in perimenopausal and postmenopausal women? Breast. 2011 Oct;20(5):448-54. doi: 10.1016/j.breast.2011.04.010. PMID: 21652211.Exclusion Code: X7.
18. Bayer U, Hausmann M. Estrogen treatment affects brain functioning after menopause. Menopause Int. 2011 Dec;17(4):148-52. doi: 10.1258/mi.2011.011105. PMID: 22120942.Exclusion Code: X2.
19. Benkhadra K, Mohammed K, Al Nofal A, et al. Menopausal Hormone Therapy and Mortality: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2015 Nov;100(11):4021-8. doi: 10.1210/jc.2015-2238 [doi]. PMID: 26544652.Exclusion Code: X12.
20. Benson VS, Kirichek O, Beral V, et al. Menopausal hormone therapy and central nervous system tumor risk: large UK prospective study and meta-analysis. Int J Cancer. 2015 May 15;136(10):2369-77. doi: 10.1002/ijc.29274 [doi]. PMID: 25335165.Exclusion Code: X3.
21. Beral V, Gaitskell K, Hermon C, et al. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet. 2015 May 9;385(9980):1835-42. doi: 10.1016/S0140-6736(14)61687-1. PMID: 25684585.Exclusion Code: X7.
22. Beral V, Reeves G, Bull D, et al. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. J Natl Cancer Inst. 2011 Feb 16;103(4):296-305. doi: 10.1093/jnci/djq527. PMID: 21278356.Exclusion Code: X7.
23. Berent-Spillson A, Briceno E, Pinsky A, et al. Distinct cognitive effects of estrogen and progesterone in menopausal women. Psychoneuroendocrinology. 2015 Sep;59:25-36. doi: 10.1016/j.psyneuen.2015.04.020. PMID: 26010861.Exclusion Code: X6.
24. Besevic J, Gunter MJ, Fortner RT, et al. Reproductive factors and epithelial ovarian cancer survival in the EPIC cohort study. Br J Cancer. 2015 Dec 1;113(11):1622-31. doi: 10.1038/bjc.2015.377. PMID: 26554655.Exclusion Code: X3.
25. Birrer N, Chinchilla C, Del Carmen M, et al. Is Hormone Replacement Therapy Safe in Women With a BRCA Mutation?: A Systematic Review of the Contemporary Literature. American Journal of Clinical Oncology: Cancer Clinical Trials. 2016((Birrer N.) Division of Gynecologic Oncology, Massachusetts General Hospital Cancer Center, Boston, MA).Exclusion Code: X2.
26. Bladbjerg EM, Madsen JS, Kristensen SR, et al. Effect of long-term hormone replacement therapy on tissue factor pathway inhibitor and thrombin activatable fibrinolysis inhibitor in healthy postmenopausal women: a randomized controlled study. J Thromb Haemost. 2003 Jun;1(6):1208-14. PMID: 12871321.Exclusion Code: X10.
27. Boardman H, Hartley L, Eisinga A, et al. Cochrane corner: oral hormone therapy and cardiovascular outcomes in post-menopausal women. Heart. 2016 Jan;102(1):9-11. doi: 10.1136/heartjnl-2015-308287. PMID: 26453279.Exclusion Code: X2.

28. Boardman Henry MP, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2015.Exclusion Code: X7.
29. Bonnelykke K, Raaschou-Nielsen O, Tjonneland A, et al. Postmenopausal hormone therapy and asthma-related hospital admission. J Allergy Clin Immunol. 2015 Mar;135(3):813-6 e5. doi: 10.1016/j.jaci.2014.11.019. PMID: 25579482.Exclusion Code: X2.
30. Boyd NF, Melnichouk O, Martin LJ, et al. Mammographic density, response to hormones, and breast cancer risk. J Clin Oncol. 2011 Aug 1;29(22):2985-92. doi: 10.1200/JCO.2010.33.7964. PMID: 21709206.Exclusion Code: X4.
31. Braganza MZ, de Gonzalez AB, Schonfeld SJ, et al. Benign breast and gynecologic conditions, reproductive and hormonal factors, and risk of thyroid cancer. Cancer Prev Res (Phila). 2014 Apr;7(4):418-25. doi: 10.1158/1940-6207.CAPR-13-0367. PMID: 24449056.Exclusion Code: X7.
32. Brinton LA, Felix AS. Menopausal hormone therapy and risk of endometrial cancer. J Steroid Biochem Mol Biol. 2014 Jul;142:83-9. doi: 10.1016/j.jsbmb.2013.05.001. PMID: 23680641.Exclusion Code: X2.
33. Brown E. Hormone therapy linked to lower non-Hodgkin lymphoma risk. Womens Health (Lond Engl). 2014 May;10(3):235-6. PMID: 25093225.Exclusion Code: X2.
34. Brown S. Hormone replacement therapy and breast cancer: causation and epidemiology. Menopause Int. 2012 Mar;18(1):3-4. PMID: 22493829.Exclusion Code: X2.
35. Brown S. Estradiol associated with lower thrombotic risk than conjugated equine estrogens when used as oral HRT. Menopause Int. 2013 Dec;19(4):145. PMID: 24479171.Exclusion Code: X2.
36. Brown S. Hormone therapy in early menopause does not slow progression of atherosclerosis. Post Reprod Health. 2014 Dec;20(4):130-1. PMID: 25621341.Exclusion Code: X2.
37. Buckler A, Voss J. Menopausal hormone therapy for the primary prevention of chronic conditions. Am Fam Physician. 2013 Mar 15;87(6):437-8. doi: d11000 [pii]. PMID: 23547577.Exclusion Code: X2.
38. Caan B, LaCroix AZ, Joffe H, et al. Effects of estrogen and venlafaxine on menopause-related quality of life in healthy postmenopausal women with hot flashes: a placebo-controlled randomized trial. Menopause. 2015 Jun;22(6):607-15. doi: 10.1097/GME.0000000000000364 [doi]. PMID: 25405571.Exclusion Code: X6.
39. Cahoon EK, Kitahara CM, Ntowe E, et al. Female Estrogen-Related Factors and Incidence of Basal Cell Carcinoma in a Nationwide US Cohort. J Clin Oncol. 2015 Dec 1;33(34):4058-65. doi: 10.1200/JCO.2015.62.0625. PMID: 26527779.Exclusion Code: X7.
40. Caini S, Gibelli B, Palli D, et al. Menstrual and reproductive history and use of exogenous sex hormones and risk of thyroid cancer among women: a meta-analysis of prospective studies. Cancer Causes Control. 2015;26(4):511-8.Exclusion Code: X4.
41. Camargo MC, Goto Y, Zabaleta J, et al. Sex hormones, hormonal interventions, and gastric cancer risk: A meta-analysis. Cancer Epidemiology Biomarkers and Prevention. 2012;21(1):20-38.Exclusion Code: X4.
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44. Canonico M. Hormone therapy and risk of venous thromboembolism among postmenopausal women. Maturitas. 2015 Nov;82(3):304-7. doi: 10.1016/j.maturitas.2015.06.040. PMID: 26276103.Exclusion Code: X2.
45. Casanova G, Bossardi Ramos R, Ziegelmann P, et al. Effects of low-dose versus placebo or conventional-dose postmenopausal hormone therapy on variables related to cardiovascular risk: a systematic review and meta-analyses of randomized clinical trials. J Clin Endocrinol Metab. 2015 Mar;100(3):1028-37. doi: 10.1210/jc.2014-3301 [doi]. PMID: 25514104.Exclusion Code: X11.

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Appendix E. Excluded Studies

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Appendix E. Excluded Studies

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142. Nelson HD. Menopausal hormone therapy and primary prevention. Ann Intern Med. 2013 Jan 15;158(2):141. doi: 10.7326/0003-4819-158-2-201301150-00022. PMID: 23318326.Exclusion Code: X2.

Appendix E. Excluded Studies

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146. Northington GM, de Vries HF, Bogner HR. Self-reported estrogen use and newly incident urinary incontinence among postmenopausal community-dwelling women. Menopause. 2012 Mar;19(3):290-5. doi: 10.1097/gme.0b013e31822bda11 [doi]. PMID: 21997497.Exclusion Code: X9.
147. Notelovitz M, John VA, Good WR. Effectiveness of Alora estradiol matrix transdermal delivery system in improving lumbar bone mineral density in healthy, postmenopausal women. Menopause. 2002 Sep-Oct;9(5):343-53. PMID: 12218723.Exclusion Code: X14.
148. Nyante SJ, Dallal CM, Gierach GL, et al. Risk factors for specific histopathological types of postmenopausal breast cancer in the NIH-AARP Diet and Health Study. Am J Epidemiol. 2013 Aug 1;178(3):359-71. doi: 10.1093/aje/kws471. PMID: 23899816.Exclusion Code: X5.
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150. O'Brien J, Jackson JW, Grodstein F, et al. Postmenopausal hormone therapy is not associated with risk of all-cause dementia and Alzheimer's disease. Epidemiol Rev. 2014;36:83-103. doi: 10.1093/epirev/mxt008. PMID: 24042430.Exclusion Code: X7.
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152. Panay N, Fenton A. Does HRT increase the risk of breast cancer? Don't forget the menopausal woman! Climacteric. 2012 Apr;15(2):103-4. doi: 10.3109/13697137.2012.665224 [doi]. PMID: 22420566.Exclusion Code: X2.
153. Panay N, Hamoda H, Arya R, et al. The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy. Menopause Int. 2013 Jun;19(2):59-68. doi: 10.1177/1754045313489645. PMID: 23761319.Exclusion Code: X2.
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157. Pesatori AC, Carugno M, Consonni D, et al. Hormone use and risk for lung cancer: A pooled analysis from the International Lung Cancer Consortium (ILCCO). Br J Cancer. 2013;109(7):1954-64.Exclusion Code: X7.
158. Pickar JH. Age at menopause, reproductive history and VTE risk. Climacteric. 2013 Dec;16(6):723. PMID: 24383093.Exclusion Code: X2.

Appendix E. Excluded Studies

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160. Pines A. Downside of preventive therapies in menopause. Menopause. 2014 Mar;21(3):207-8. doi: 10.1097/GME.0000000000000135 [doi]. PMID: 24193299.Exclusion Code: X2.
161. Pines A. Primary prevention of stroke in women. Climacteric. 2014;17(3):312-3.Exclusion Code: X2.
162. Pinkerton JV, Abraham L, Bushmakin AG, et al. Evaluation of the efficacy and safety of bazedoxifene/conjugated estrogens for secondary outcomes including vasomotor symptoms in postmenopausal women by years since menopause in the Selective estrogens, Menopause and Response to Therapy (SMART) trials. J Womens Health (Larchmt). 2014 Jan;23(1):18-28. doi: 10.1089/jwh.2013.4392 [doi]. PMID: 24206058.Exclusion Code: X4.
163. Polac I, Borowiecka M, Wilamowska A, et al. Coagulation and fibrynolitic parameters in women and the effects of hormone therapy; comparison of transdermal and oral administration. Gynecol Endocrinol. 2013 Feb;29(2):165-8. doi: 10.3109/09513590.2012.730567 [doi]. PMID: 23116237.Exclusion Code: X5.
164. Racketa J, Pinkerton JV, Pan K, et al. Effects of bazedoxifene/conjugated estrogens on sleep parameters and health-related quality of life in postmenopausal women. Maturitas; 2012. p. S59-S60 Abstract no:137.Exclusion Code: X2.
165. Rahn DD, Carberry C, Sanses TV, et al. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. Obstet Gynecol. 2014 Dec;124(6):1147-56. doi: 10.1097/AOG.0000000000000526. PMID: 25415166.Exclusion Code: X4.
166. Rasgon NL, Geist CL, Kenna HA, et al. Prospective randomized trial to assess effects of continuing hormone therapy on cerebral function in postmenopausal women at risk for dementia. PLoS One. 2014;9(3):e89095. doi: 10.1371/journal.pone.0089095. PMID: 24622517.Exclusion Code: X7.
167. Reid RL, Fortier MP. Menopausal hormone therapy and quality of life: too many pyjamas. J Obstet Gynaecol Can. 2014 Nov;36(11):953-6. PMID: 25574670.Exclusion Code: X2.
168. Roberts H, Hickey M, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia: a Cochrane review summary. Maturitas. 2014 Jan;77(1):4-6. doi: 10.1016/j.maturitas.2013.10.002. PMID: 24182544.Exclusion Code: X2.
169. Rocca WA, Shuster LT, Brown RD. Could estrogen protect younger menopausal women from stroke? Expert Rev Neurother. 2012 Apr;12(4):363-5. doi: 10.1586/ern.12.20 [doi]. PMID: 22449208.Exclusion Code: X2.
170. Rockman CB, Maldonado TS, Jacobowitz GR, et al. Hormone replacement therapy is associated with a decreased prevalence of peripheral arterial disease in postmenopausal women. Ann Vasc Surg. 2012 Apr;26(3):411-8. doi: 10.1016/j.avsg.2011.10.012 PMID: 22285341.Exclusion Code: X7.
171. Rosano G, Vitale C. Cardiovascular benefits of HRT may differ by patient age. Evid Based Med. 2014 Apr;19(2):61. doi: 10.1136/eb-2013-101430. PMID: 24113233.Exclusion Code: X2.
172. Rosano G, Vitale C, Spoletini I, et al. Cardiovascular health in the menopausal woman: impact of the timing of hormone replacement therapy. Climacteric. 2012 Aug;15(4):299-305. doi: 10.3109/13697137.2012.658899 [doi]. PMID: 22424090.Exclusion Code: X2.
173. Rosenberg L, Bethea TN, Viscidi E, et al. Postmenopausal Female Hormone Use and Estrogen Receptor-Positive and -Negative Breast Cancer in African American Women. J Natl Cancer Inst. 2016 Apr;108(4)doi: 10.1093/jnci/djv361. PMID: 26613937.Exclusion Code: X7.
174. Rossouw J. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials. 1998 Feb;19(1):61-109. PMID: 9492970.Exclusion Code: X13.
175. Ruan X. Type, dose of hormones-Breast cancer risk. Eur J Contracept Reprod Health Care; 2014. p. S20.Exclusion Code: X2.

176. Rubinow DR, Girdler SS. Hormones, heart disease, and health: individualized medicine versus throwing the baby out with the bathwater. Depress Anxiety. 2011 Jun;28(6):E1-E15. doi: 10.1002/da.20833 [doi]. PMID: 21648024.Exclusion Code: X2.
177. Sai AJ, Gallagher JC, Fang X. Effect of hormone therapy and calcitriol on serum lipid profile in postmenopausal older women: association with estrogen receptor-alpha genotypes. Menopause. 2011 Oct;18(10):1101-12. doi: 10.1097/gme.0b013e318217d41d. PMID: 21712736.Exclusion Code: X10.
178. Sarri G, Davies M, Lumsden MA. Diagnosis and management of menopause: summary of NICE guidance. BMJ. 2015;351:h5746. PMID: 26563259.Exclusion Code: X2.
179. Scarabin PY. Hormone therapy and venous thromboembolism among postmenopausal women. Front Horm Res. 2014;43:21-32. doi: 10.1159/000360554. PMID: 24943295.Exclusion Code: X2.
180. Schaer TM. Menopausal hormone therapy and primary prevention. Ann Intern Med. 2013 Jan 15;158(2):140-1. doi: 10.7326/0003-4819-158-2-201301150-00021. PMID: 23318325.Exclusion Code: X2.
181. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ. 2012;345:e6409. PMID: 23048011.Exclusion Code: X14.
182. Schonfeld SJ, Ron E, Kitahara CM, et al. Hormonal and reproductive factors and risk of postmenopausal thyroid cancer in the NIH-AARP Diet and Health Study. Cancer Epidemiol. 2011 Dec;35(6):e85-90. doi: 10.1016/j.canep.2011.05.009. PMID: 21852218.Exclusion Code: X7.
183. Scott E, Zhang QG, Wang R, et al. Estrogen neuroprotection and the critical period hypothesis. Front Neuroendocrinol. 2012 Jan;33(1):85-104. doi: 10.1016/j.yfrne.2011.10.001. PMID: 22079780.Exclusion Code: X2.
184. Scott RG. Hormone therapy. Am J Nurs. 2011 Nov;111(11):12. doi: 10.1097/01.NAJ.0000407278.86759.6b. PMID: 22030905.Exclusion Code: X2.
185. Shao H, Breitner JC, Whitmer RA, et al. Hormone therapy and Alzheimer disease dementia: new findings from the Cache County Study. Neurology. 2012 Oct 30;79(18):1846-52. doi: 10.1212/WNL.0b013e318271f823 PMID: 23100399.Exclusion Code: X9.
186. Shapiro S. Risk of breast cancer among users of estrogen plus progestogen and unopposed estrogen: is the likelihood of bias symmetrical? Climacteric. 2015 Jun;18(3):333-5. doi: 10.3109/13697137.2015.1007623 [doi]. PMID: 25651904.Exclusion Code: X2.
187. Shapiro S, Stevenson JC, Mueck AO, et al. Misrepresentation of the risk of ovarian cancer among women using menopausal hormones. Spurious findings in a meta-analysis. Maturitas. 2015 Jun;81(2):323-6. doi: 10.1016/j.maturitas.2015.03.018. PMID: 25891501.Exclusion Code: X2.
188. Shufelt CL, Johnson BD, Berga SL, et al. Timing of hormone therapy, type of menopause, and coronary disease in women: data from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation. Menopause. 2011 Sep;18(9):943-50. doi: 10.1097/gme.0b013e3182113672. PMID: 21532511.Exclusion Code: X7.
189. Shufelt CL, Merz CN, Prentice RL, et al. Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study. Menopause. 2014 Mar;21(3):260-6. doi: 10.1097/GME.0b013e31829a64f9 [doi]. PMID: 24045672.Exclusion Code: X7.
190. Shulman LP. The adverse impact of hormone therapy discontinuation on bone health: initiating a more balanced and comprehensive assessment of the impact and role of postmenopausal hormone therapy. Menopause. 2011 Nov;18(11):1152-3. doi: 10.1097/gme.0b013e31823639d4. PMID: 22033486.Exclusion Code: X2.
191. Sjögren LL, Mørch LS, Løkkegaard E. Hormone replacement therapy and the risk of endometrial cancer: A systematic review. Maturitas. 2016;91((Sjögren L.L., leasjogren@live.dk; Løkkegaard E.) Department of Obstetrics and Gynecology, Nordsjællands Hospital, University of Copenhagen, Denmark):25-35.Exclusion Code: X3.

Appendix E. Excluded Studies

192. Skouby SO, Pan K, Thompson JR, et al. Effects of conjugated estrogens/bazedoxifene on lipid and coagulation variables: a randomized placebo- and active-controlled trial. Menopause. 2015 Jun;22(6):640-9. doi: 10.1097/GME.0000000000000362 [doi]. PMID: 25405570.Exclusion Code: X4.
193. Spas'onova LH, Dmytruk SM, Medvedieva IM, et al. [Characteristics of proatherogenic disorder development in women with different reproductive status]. Lik Sprava. 2013 Jan-Feb(1):59-67. PMID: 23951911.Exclusion Code: X1.
194. Speroff L. The heart and estrogen/progestin replacement study (HERS). Maturitas. 1998 Nov 30;31(1):9-14. PMID: 10091199.Exclusion Code: X2.
195. Stanczyk FZ, Bhavnani BR. Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: is it safe? J Steroid Biochem Mol Biol. 2014 Jul;142:30-8. doi: 10.1016/j.jsbmb.2013.11.011. PMID: 24291402.Exclusion Code: X2.
196. Stanczyk FZ, Winer SA. Effect of hormone therapy on breast epithelial cell proliferation. Menopause. 2013 May;20(5):483-5. doi: 10.1097/GME.0b013e31828ebfb6. PMID: 23615638.Exclusion Code: X2.
197. Stegeman B, Kubinova R, Malyutina S, et al. Exogenous hormone use and all-cause mortality: Results from the HAPIEE study. Eur J Epidemiol. 2013;28(1):S193.Exclusion Code: X4.
198. Stendell-Hollis NR, Thompson PA, Thomson CA, et al. Investigating the association of lactation history and postmenopausal breast cancer risk in the Women's Health Initiative. Nutr Cancer. 2013;65(7):969-81. doi: 10.1080/01635581.2013.815787 [doi]. PMID: 24127779.Exclusion Code: X10.
199. Stevenson JC, Panay N, Pexman-Fieth C. Oral estradiol and dydrogesterone combination therapy in postmenopausal women: review of efficacy and safety. Maturitas. 2013 Sep;76(1):10-21. doi: 10.1016/j.maturitas.2013.05.018. PMID: 23835005.Exclusion Code: X2.
200. Stuenkel CA. Timing of menopausal hormone therapy and myocardial infarction. Menopause. 2015 Jun;22(6):584-6. doi: 10.1097/GME.0000000000000468 [doi]. PMID: 25871003.Exclusion Code: X2.
201. Stute P. [Hormone therapy during peri- and postmenopause]. MMW Fortschr Med. 2014 Apr 30;156(8):37-9. PMID: 24851443.Exclusion Code: X1.
202. Sullivan SD, Lehman A, Thomas F, et al. Effects of self-reported age at nonsurgical menopause on time to first fracture and bone mineral density in the Women's Health Initiative Observational Study. Menopause. 2015 Oct;22(10):1035-44. doi: 10.1097/GME.0000000000000451 [doi]. PMID: 25803670.Exclusion Code: X4.
203. Sumino H, Murakami M. [Investigation of atherosclerosis in postmenopausal women: alteration of atherosclerosis-associated factors and vascular atherosclerosis by oral and transdermal estrogen replacement]. Rinsho Byori. 2013 Mar;61(3):256-62. PMID: 23785796.Exclusion Code: X1.
204. Sweetland S, Beral V, Balkwill A, et al. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. J Thromb Haemost. 2012 Nov;10(11):2277-86. doi: 10.1111/j.1538-7836.2012.04919.x [doi]. PMID: 22963114.Exclusion Code: X7.
205. Tanday S. Hormone therapy increases ovarian cancer risk. Lancet Oncol. 2015 Mar;16(3):e112. doi: 10.1016/S1470-2045(15)70038-0. PMID: 25704437.Exclusion Code: X2.
206. Tang B, Lv J, Li Y, et al. Relationship between female hormonal and menstrual factors and pancreatic cancer: a meta-analysis of observational studies. Medicine (Baltimore). 2015 Feb;94(7):e177. doi: 10.1097/MD.0000000000000177. PMID: 25700305.Exclusion Code: X3.
207. Teras LR, Patel AV, Hildebrand JS, et al. Postmenopausal unopposed estrogen and estrogen plus progestin use and risk of non-Hodgkin lymphoma in the American Cancer Society Cancer Prevention Study-II Cohort. Leuk Lymphoma. 2013 Apr;54(4):720-5. doi: 10.3109/10428194.2012.722216 [doi]. PMID: 22916741.Exclusion Code: X7.
208. Trabert B, Wentzensen N, Yang HP, et al. Ovarian cancer and menopausal hormone therapy in the NIH-AARP diet and health study. Br J Cancer. 2012 Sep 25;107(7):1181-7. doi: 10.1038/bjc.2012.397. PMID: 22929888.Exclusion Code: X7.

209. Tsilidis KK, Allen NE, Key TJ, et al. Menopausal hormone therapy and risk of ovarian cancer in the European prospective investigation into cancer and nutrition. Cancer Causes Control. 2011 Aug;22(8):1075-84. doi: 10.1007/s10552-011-9782-z [doi]. PMID: 21637986.Exclusion Code: X7.
210. Tuomikoski P, Lyytinen H, Korhonen P, et al. Coronary heart disease mortality and hormone therapy before and after the Women's Health Initiative. Obstet Gynecol. 2014 Nov;124(5):947-53. doi: 10.1097/AOG.0000000000000461. PMID: 25437723.Exclusion Code: X7.
211. Tuomikoski P, Mikkola TS. Postmenopausal hormone therapy and coronary heart disease in early postmenopausal women. Ann Med. 2014 Feb;46(1):1-7. doi: 10.3109/07853890.2013.854982 [doi]. PMID: 24266727.Exclusion Code: X2.
212. Utian WH, Woods NF. Impact of hormone therapy on quality of life after menopause. Menopause. 2013 Oct;20(10):1098-105. doi: 10.1097/GME.0b013e318298debe [doi]. PMID: 23799357.Exclusion Code: X2.
213. Valdiviezo C, Lawson S, Ouyang P. An update on menopausal hormone replacement therapy in women and cardiovascular disease. Curr Opin Endocrinol Diabetes Obes. 2013 Apr;20(2):148-55. doi: 10.1097/MED.0b013e32835ed58b [doi]. PMID: 23422240.Exclusion Code: X2.
214. Veerus P, Fischer K, Hakama M, et al. Results from a blind and a non-blind randomised trial run in parallel: experience from the Estonian Postmenopausal Hormone Therapy (EPHT) Trial. BMC Med Res Methodol. 2012;12:44. doi: 10.1186/1471-2288-12-44. PMID: 22475112.Exclusion Code: X10.
215. Veerus P, Fischer K, Hovi SL, et al. Symptom reporting and quality of life in the Estonian Postmenopausal Hormone Therapy Trial. BMC Womens Health. 2008;8:5. doi: 10.1186/1472-6874-8-5. PMID: 18366766.Exclusion Code: X10.
216. Veerus P, Hovi SL, Sevon T, et al. The effect of hormone therapy on women's quality of life in the first year of the Estonian Postmenopausal Hormone Therapy trial. BMC Res Notes. 2012;5:176. doi: 10.1186/1756-0500-5-176. PMID: 22472039.Exclusion Code: X10.
217. Viscoli CM, Brass LM, Kernan WN, et al. A clinical trial of estrogen-replacement therapy after ischemic stroke. N Engl J Med. 2001 Oct 25;345(17):1243-9. doi: 10.1056/NEJMoa010534. PMID: 11680444.Exclusion Code: X3.
218. Vittinghoff E, Shlipak MG, Varosy PD, et al. Risk factors and secondary prevention in women with heart disease: the Heart and Estrogen/progestin Replacement Study. Ann Intern Med. 2003 Jan 21;138(2):81-9. PMID: 12529088.Exclusion Code: X3.
219. Vorobjov S, Hovi SL, Veerus P, et al. Treatment adherence in the Estonian postmenopausal hormone therapy (EPHT) trial [ISRCTN35338757]. Maturitas. 2005 Nov-Dec;52(3-4):286-95. doi: 10.1016/j.maturitas.2005.05.001. PMID: 16055284.Exclusion Code: X10.
220. Waetjen LE, Johnson WO, Xing G, et al. Serum estradiol levels are not associated with urinary incontinence in midlife women transitioning through menopause. Menopause. 2011 Dec;18(12):1283-90. doi: 10.1097/gme.0b013e31821f5d25 [doi]. PMID: 21785372.Exclusion Code: X4.
221. Walker T. Rise in mortality risk seen in hysterectomized women aged 50 to 59 not using estrogen therapy. Formulary. 2013;48(8):254-5.Exclusion Code: X2.
222. Wein AJ. Re: Menopausal hormone therapy for the primary prevention of chronic conditions: a systematic review to update the U.S. Preventive Services Task Force recommendations. J Urol. 2013 Dec;190(6):2168-9. doi: 10.1016/j.juro.2013.08.106. PMID: 24209543.Exclusion Code: X2.
223. Wein AJ. Re: Menopausal hormone therapy for the primary prevention of chronic conditions: a systematic review to update the U.S. Preventive Services Task Force recommendations. J Urol. 2013 Oct;190(4):1329. doi: 10.1016/j.juro.2013.06.108. PMID: 24029335.Exclusion Code: X2.
224. Weinstein MM. Hormone therapy and urinary incontinence. Menopause. 2012 Mar;19(3):255-6. doi: 10.1097/gme.0b013e31824e9bb0. PMID: 22367730.Exclusion Code: X2.

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225. Weiping L, Chenxing L, Enfeng Z. Comment on 'Effect of conjugated estrogen versus conjugated estrogen associated with medroxyprogesterone acetate in postmenopausal women on internal carotid artery pulsatility index: a randomized pilot study'. J Obstet Gynaecol Res. 2012 Mar;38(3):611-2. doi: 10.1111/j.1447-0756.2011.01751.x [doi]. PMID: 22353571.Exclusion Code: X2.

226. Welton AJ, Vickers MR, Kim J, et al. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. BMJ. 2008;337:a1190. doi: 10.1136/bmj.a1190. PMID: 18719013.Exclusion Code: X6.

227. Wild RA, Wu C, Curb JD, et al. Coronary heart disease events in the Women's Health Initiative hormone trials: effect modification by metabolic syndrome: a nested case-control study within the Women's Health Initiative randomized clinical trials. Menopause. 2013 Mar;20(3):254-60. doi: 10.1097/GME.0b013e31826f80e0. PMID: 23435021.Exclusion Code: X2.

228. Wilson LF, Page AN, Dunn NA, et al. Population attributable risk of modifiable risk factors associated with invasive breast cancer in women aged 45-69 years in Queensland, Australia. Maturitas. 2013 Dec;76(4):370-6. doi: 10.1016/j.maturitas.2013.09.002. PMID: 24113278.Exclusion Code: X9.

229. Windler E, Stute P, Ortmann O, et al. Is postmenopausal hormone replacement therapy suitable after a cardio- or cerebrovascular event? Arch Gynecol Obstet. 2015 Jan;291(1):213-7. doi: 10.1007/s00404-014-3485-0 [doi]. PMID: 25322975.Exclusion Code: X2.

230. Xu Y, Lin J, Wang S, et al. Combined estrogen replacement therapy on metabolic control in postmenopausal women with diabetes mellitus. Kaohsiung J Med Sci. 2014 Jul;30(7):350-61. doi: 10.1016/j.kjms.2014.03.002. PMID: 24924841.Exclusion Code: X11.

231. Zhu Y, Yue D, Yuan B, et al. Reproductive factors are associated with oesophageal cancer risk: results from a meta-analysis of observational studies. Eur J Cancer Prev. 2016 Feb 16doi: 10.1097/CEJ.0000000000000234. PMID: 26886236.

232. Ziaei S. The effects of HRT on cognitive function in postmenopausal women Tarbiat Modares University. Tehran, Iran: 2016. Exclusion Code: X12.

233. Ziller M, Herwig J, Ziller V, et al. Effects of a low-dose oral estrogen only treatment on bone mineral density and quantitative ultrasonometry in postmenopausal women. Gynecol Endocrinol. 2012 Dec;28(12):1002-5. doi: 10.3109/09513590.2012.705369 [doi]. PMID: 22835159.Exclusion Code: X3.

Appendix F. Ratings for Domains of Quality Ratings of Randomized Controlled Trials

Trial	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care providers masked?	Patient masked?	Loss to followup ≤20% and differential attrition ≤15%?	Intention-to-treat analysis?	Other biases?	Quality rating
DOPS (Denmark)	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes[a]	Poor
Clarke 2002 (UK)	Unclear	Unclear	Yes	Yes	No	No	No	Yes	No	Poor
EMS (Canada)	Yes	Yes	Mostly, except for prior HT use and amnestic mild cognitive impairment	Yes	Yes	Yes	Yes	Unclear	No	Fair
EPAT (US)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[b]	Fair
EPHT (Estonia)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Fair
ERA (US)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes[c]	Fair
ESPRIT (UK)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Fair
Greenspan 2005 (US)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
Notelovitz 2002 (US)	Unclear	Unclear	Yes	Yes	Yes	Yes	No	No	Yes[d]	Poor
HERS (US)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
KEEPS-Cog (US)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
Pefanco 2007 (US)	Yes	Unclear	Yes	Yes	Unclear	Yes	No	No	No	Poor
PEPI (US)	Yes	Unclear	Unclear	Yes	Unclear	Yes	Unclear	No	Yes[e]	Fair
STOP-IT (US)	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Fair
ULTRA (US)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
WAVE (US, Canada)	Yes	Unclear	Yes	Yes	Yes	Yes	No	Unclear	No	Fair
WHI (US)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
WHIMS (US)	Yes	Yes	Mostly, except for history of stroke, and hypertension	Yes	Yes	Yes	Yes	Yes	No	Good
WHIMSY (US)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
WHISCA (US)	Yes	Yes	Mostly, except for smoking status	Yes	Yes	Yes	Yes	Yes	No	Good
WISDOM (UK, Australia, New Zealand)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Fair

[a] High risk of selection bias and contamination. Invited participants chose whether or not to be part of randomized trial (those who preferred a treatment option where followed in the cohort study). Among those who were randomized to no-HRT and attended 5 -year follow-up, 15% had initiated HRT. Among those randomized to HRT, 18% had changed the type of HRT and 22% had stopped HRT at 5 years.

[b] Although the trial conducted an ITT analysis, it was only for evaluable patients (199/222) from the larger set of randomized patients.

[c] There was a statistically significant difference between placebo and CEE in adherence.

[d] Risk of measurement bias. Some outcome (e.g., breast cancer) were assessed as adverse events; ascertainment of these outcomes is unclear. Although mammograms were performed as part of the study protocol, cases of breast cancer appear to have been self-reported. Some were assessed to be benign; method of determining cancer severity were not described.
[e] Potential risk of contamination and low adherence to assigned study medications. Study authors note that in women assigned to CEE, continuation rate were lowest and potentially due to endometrial hyperplasia. Some women were also initiated on another hormone regimen (other than the one assigned at randomization); this included up to 18% in some study arms.

Abbreviations: BMD = bone mineral density; DOPS = Danish Osteoporosis Prevention Trail; EMS = Estrogen Memory Study; EPAT = Estrogen in the Prevention of Atherosclerosis; EPHT = Estonian Postmenopausal Hormone Therapy Trial; ERA = Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HERS = Heart and Estrogen/Progestin Replacement Study; PEPI = Postmenopausal Estrogen and Progestin Interventions Trial; UK = United Kingdom; ULTRA = Ultra-Low-Dose Transdermal Estrogen Assessment; US = United States; WAVE = The Women's Angiographic Vitamin and Estrogen Trial; WHI = Women's Health Initiative; WHIMS = Women's Health Initiative Memory Study; WHIMSY = The Women's Health Initiative Memory Study of Younger Women; WHISCA = Women's Health Initiative Study of Cognitive Aging; WISDOM = Women's International Study of Long Duration Oestrogen After Menopause.

Appendix G Table 1. Evidence Table of Trials Reporting Incidence of Breast Cancer

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
EPAT Estrogen-only trial Hodis, 2001[60]	111 Estrogen 111 Placebo	**Followup: 2 years** **Breast cancer** 0 vs. 1
EPHT Estrogen plus progestin trial Veerus, 2006[61]	404 Estrogen plus progestin 373 Placebo	**Followup: Mean 3.4 years** **Breast Cancer** 1 vs. 2; HR, 0.55 (95% CI, 0.05 to 6.06)
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[62]	100 Estrogen alone 104 Estrogen plus progestin 105 Placebo	**Followup: Mean 3.2 years** **Breast cancer (not defined)** 1 vs. 0 vs. 0; p=0.35
ESPRIT Estrogen-only trial Cherry (ESPRIT Team), 2002[63]; Cherry, 2014[64]	513 Estrogen[b] 504 Placebo	**Followup: 2 years**[63] **Any breast cancer (measured via ICD codes)** 4 (0.8%) vs. 4 (0.8%); RR, 0.98 (95% CI, 0.25 to 3.91); p=1.00 **Cumulative followup: Mean 12.6 years**[c64] **Any breast cancer (measured via ICD codes)** HR, 0.47 (95% CI, 0.19 to 1.15)
Greenspan, et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[65]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Followup: 3 years** **Breast Cancer** *Analysis did not stratify by treatment regimen* 2 (hormone therapy) vs. 2; p=1.0
HERS Estrogen plus progestin trial Hulley, 2002[68]	1380 Estrogen plus progestin 1383 Placebo Cumulative followup: 1156 Estrogen plus progestin 1383 Placebo	**Followup: 4.1 years** 34 (2.5%) vs. 25 (1.8%); HR, 1.38 (95% CI, 0.82 to 2.31); p=0.22 **Followup: Mean 2.7 years postintervention** HR, 1.08 (95% CI, 0.52 to 2.24); p=0.83 **Cumulative followup: 6.8 years** HR, 1.27 (95% CI, 0.84 to 1.94); p=0.26
PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995[74]	175 Estrogen 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Followup: 3 years** **Breast cancer** 1 (estrogen) vs. 2 (estrogen plus progestin) vs. 4 (estrogen plus micronized progestin) vs. 1 (placebo); p=0.29

Appendix G Table 1. Evidence Table of Trials Reporting Incidence of Breast Cancer

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[75]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Followup: 3 years** **Breast cancer (not defined)** *Analysis did not stratify by treatment regimen* 0 (hormone therapy with or without calcitriol) vs. 4 (calcitriol only and placebo)
WAVE Estrogen-only and estrogen plus progestin trial Waters, 2002[80]	124 Estrogen 86 Estrogen plus progestin 213 Placebo	**Followup: Mean 2.8 years** **Breast Cancer (any)** *Analysis did not stratify by treatment regimen* 3 vs. 1; p=0.37
WHI Estrogen-only trial Anderson, 2004;[24] Anderson, 2012;[105] LaCroix, 2011[112] Prentice 2009[98] Manson, 2013[102] Chlebowski, 2015[104]	5,310 Estrogen 5,429 Placebo Postintervention extension followup: 3,778 Estrogen 3,867 Placebo	**Followup: Median 7.2 years**[102, 112] **Invasive breast cancer** 104 (2.0%) vs. 135 (2.5%); HR, 0.79 (95% CI, 0.61 to 1.02); p=0.07 **Subgroups:** No significant difference by age at randomization[102] Biennial analysis (2, 4, 6, and 8 years since randomization)[104] P for trend=0.29[104] **Risk for invasive breast cancer based on timing of intervention:**[98] No significant association; p for gap time interaction=0.20 **Followup: Median 6.6 years postintervention and postintervention extension**[102] **Invasive breast cancer** HR, 0.80 (95% CI, 0.58 to 1.11); p=0.19 **Cumulative followup: Median 13.0 years**[102] **Invasive breast cancer** HR, 0.79 (95% CI, 0.65 to 0.97); p=0.02
WHI Estrogen plus progestin trial Writing Group for the WHI, 2002;[23]Heiss, 2008;[92] Chlebowski, 2003;[85] Chlebowski, 2010;[84] Gramling, 2009;[90] Prentice 2009[98] Manson, 2013[102] Chlebowski, 2015[104]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention extension followup: 6,545 Estrogen plus progestin 6,243 Placebo	**Followup: Median 5.6 years**[102] **Invasive breast cancer** 206 (2.4%) vs. 155 (1.9%); HR, 1.24 (95% CI, 1.01 to 1.53) **Overall breast cancer mortality**[84] 25 (0.3%) vs. 12 (0.2%); HR, 1.96 (95% CI, 1.00 to 4.04); p=0.049 **Subgroups:** No significant difference by age[102] Time since randomization[104] 2 years since randomization: HR, 0.71 (95% CI, 0.47 to 1.08)

Appendix G Table 1. Evidence Table of Trials Reporting Incidence of Breast Cancer

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
		4 years since randomization: HR, 1.36 (95% CI, 0.95 to 1.94) 6 years since randomization: HR, 1.65 (1.17 to 2.32) P for trend=0.008 **Risk for invasive breast cancer based on timing of intervention:**[98] Initiation of hormone therapy within 5 years of menopause: HR, 2.06 (95% CI, 1.30 to 3.27) Initiation of hormone therapy after 5 years of menopause: HR, 1.30 (95% CI, 0.57 to 2.99) P for gap time interaction=0.03 **Followup: Mean 2.4 years postintervention**[92] **Invasive breast cancer** HR, 1.27 (95% CI, 0.91 to 1.78) **Followup: Median 8.2 years postintervention and postintervention extension**[102] HR, 1.32 (95% CI, 1.08 vs. 1.61); p=0.007 **Cumulative followup: 13.2 years**[102] HR, 1.28 (95% CI, 1.11 to 1.48); p<0.001
WISDOM Estrogen plus progestin trial Vickers, 2007[123]	2,196 Estrogen plus progestin 2,189 Placebo	**Followup: Mean 1 year** **Breast cancer incidence** 5 vs. 7 **Breast cancer mortality** 0 vs. 0

[a] Intervention dosages are listed in Table 3 by trial.
[b] All women enrolled in the initial trial were followed by data linkage to UK mortality and cancer records.
[c] At enrollment, 24% of women reported having a hysterectomy. After the 2-year intervention period, women with an intact uterus were sent a letter each year for the first 5 years after stopping treatment to remind them to seek medical attention if they experienced vaginal bleeding. No attempt was made after the end of the 2-year intervention to obtain medical information from women or their physicians about the use of medications or health events.

Abbreviations: CI = confidence interval; ERA = Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis; EPAT = Estrogen in the Prevention of Atherosclerosis; EPHT = Estonian Postmenopausal Hormone Therapy Trial; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; ICD = International Classification of Diseases; PEPI = Postmenopausal Estrogen and Progestin Interventions Trial; RR = relative risk; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WAVE = Women's Angiographic Vitamin and Estrogen; WHI = Women's Health Initiative; WISDOM = Women's International Study of Long-Duration Oestrogen After Menopause.

Appendix G Table 2. Evidence Table of Trials Reporting Incidence of Cervical Cancer

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
ESPRIT Estrogen-only trial Cherry, 2014[64]	513 Estrogen only[b] 504 Placebo[b]	**Cumulative followup: Mean 12.6 years**[c] 0 vs. 1
WHI Estrogen plus progestin trial Anderson, 2003[81]	8,506 Estrogen plus progestin 8,102 Placebo	**Followup: Median 5.6 years** 8 (0.09%) vs. 5 (0.06%); HR, 1.44 (95% CI, 0.47 to 4.42)

[a] Intervention dosages are listed in Table 3 by trial.
[b] At enrollment, 24% of enrolled women reported having a hysterectomy. After the 2-year intervention period, women with an intact uterus were sent a letter each year for the first 5 years after stopping treatment to remind them to seek medical attention if they experienced vaginal bleeding. No attempt was made after the end of the 2-year intervention to obtain medical information from women or their physicians about the use of medications or health events.
[c] Cancer incidence was determined by data linkage to UK cancer records for a mean 12.6 years after enrollment.

Abbreviations: CI = confidence interval; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HR = hazard ratio; vs. = versus; WHI = Women's Health Initiative.

Appendix G Table 3. Evidence Table of Trials Reporting Incidence of Colorectal Cancer

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
EMS Estrogen plus progestin trial Tierney, 2009[59]	70 Estrogen plus progestin 72 Placebo	**Followup: 2 years** 0 vs. 0
Greenspan, et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[65]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Followup: 3 years** *Analysis did not stratify by treatment regimen* 3 vs. 1; p=0.62
HERS Estrogen plus progestin trial Hulley, 2002[68]	1,380 Estrogen plus progestin 1,383 Placebo Cumulative followup: 1156 Estrogen plus progestin 1383 Placebo	**Followup: Mean 4.1 years** 11 (0.80%) vs. 16 (1.16%); HR, 0.69 (95% CI, 0.32 to 1.49); p=0.43 **Cumulative followup: Mean 6.8 years** HR, 0.81 (95% CI, 0.46 to 1.45); p=0.48
PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995[74]	175 Estrogen only 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Followup: 3 years** *Analysis did not stratify by treatment regimen* 2 colon cancer cases
STOP-IT Estrogen-only and Estrogen plus progestin trial Gallagher, 2001[75]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Followup: 3 years** *Analysis did not stratify by treatment regimen* 1 (hormone therapy with or without calcitriol) vs. 6 (calcitriol only and placebo)
WHI Estrogen-only trial Anderson, 2004;[24] Ritenbaugh, 2008;[113] Prentice, 2009;[98] LaCroix, 2011;[112] Manson, 2013[102]	5,310 Estrogen only 5,429 Placebo Postintervention followup: 4,794 Estrogen only 4,872 Placebo Postintervention extension followup: 4,851 Estrogen only 4,935 Placebo	**Followup: Median 7.2 years** 65 (1.22%) vs. 58 (1.07%); HR, 1.15 (95% CI, 0.81 to 1.64); p=0.44[102] **Invasive colorectal cancer**[113,b] HR, 1.12 (95% CI, 0.77 to 1.63); p=0.55. **Invasive colon cancer**[113,b] HR, 1.26 (95% CI, 0.84 to1.88); p=0.26. **Invasive rectal cancer**[113,b] HR, 0.53 (95% CI, 0.18 to 1.56); p=0.25. **Subgroups:**[113, b] No significant difference by race or ethnic group, bilateral oophorectomy status, family history of colorectal cancer, treated diabetes status Age at randomization[102] Among women 50–59 years at randomization: HR, 0.71 (95% CI, 0.30 to 1.67) Among women 60–69 years at randomization: HR, 0.88 (95% CI, 0.53 to 1.47) Among women 70–79 years at randomization: HR, 2.24 (95% CI, 1.16 to 4.30) p for trend = 0.02

Appendix G Table 3. Evidence Table of Trials Reporting Incidence of Colorectal Cancer

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
		Risk for colorectal cancer based on timing of intervention:[98] No significant association; p for gap time interaction=0.34 **Followup: Median 6.6 years postintervention and postintervention extension**[102] HR, 1.10 (95% CI, 0.68 to 1.78); p=0.69 **Cumulative followup: Median 13.0 years**[102] HR, 1.13 (95% CI, 0.85 to 1.51); p=0.39 **Subgroups:**[102] No significant difference by age at randomization
WHI Estrogen plus progestin trial Writing Group for the Women's Health Initiative Investigators, 2002;[23] Chlebowski, 2004;[87] Heiss, 2008;[92] Prentice, 2009;[98] Manson, 2013[102]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,060 Estrogen plus progestin 7,687 Placebo Postintervention extension followup:[e] 6,545 Estrogen plus progestin 6,243 Placebo	**Followup: Median 5.6 years** 50 (0.59%) vs. 75 (0.93%); HR, 0.62 (95% CI, 0.43 to 0.89); p=0.009[102] **Invasive colorectal cancer**[87,d] HR, 0.56 (95% CI, 0.38 to 0.81); p=0.003 **Invasive colon cancer**[87,d] HR, 0.54 (95% CI, 0.36 to 0.82); p=0.004 **Invasive rectal cancer**[87,d] HR, 0.66 (95% CI, 0.26 to 1.64); p=0.37 **Subgroups:** No significant difference by age at randomization,[102] race or ethnic group, family history of colorectal cancer,[87, 98, d] **Risk for colorectal cancer based on timing of intervention:**[98] No significant association; p for gap time interaction=0.42 **Followup: Median 8.2 years postintervention and postintervention extension**[102] HR, 0.97 (95% CI, 0.70 to 1.33); p=0.83 **Cumulative followup: Median 13.2 years**[102] HR, 0.80 (95% CI, 0.63 to 1.01); p=0.06 **Subgroups:**[102] No significant difference by age at randomization
WISDOM Estrogen plus progestin trial Vickers 2007[123]	2,196 Estrogen plus progestin[f] 2,189 Placebo[f]	**Followup: Median 11.9 months** 2 vs. 2

[a] Intervention dosages are listed in Table 3 by trial.
[b] The mean followup for some of these analyses (Ritenbaugh, 2008 and Prentice, 2009) was 7.1 years, suggesting that the results are based on an earlier adjudication of intervention phase data than the most recent intervention data from Manson, 2013.[102]

[c] Women were ineligible if they were deceased or provided no contact through the postintervention phase. By the end of the postintervention phase, 7,878/8,506 (93% of women randomized to estrogen plus progestin) and 7,530/8,102 (93% of women randomized to placebo) were eligible for the postintervention extension phase.
[d] The analysis was based on 122 centrally adjudicated colorectal cancers, which were diagnosed before 7/8/2002, the date participants were instructed to discontinue their study medication.
[e] The mean followup for this analysis was 5.5 years, suggesting that the results are based on an earlier adjudication of intervention phase data than the most recent intervention data from Manson, 2013.[102]
[f] The estrogen plus progestin arm includes 1,862 women with an intact uterus and 334 women with a prior hysterectomy who had agreed to be randomized to estrogen plus progestin, estrogen only, or placebo (the women randomized to estrogen only included women who agreed to placebo (n=341) and women who did not agree to placebo (n=485), so there is a selection bias that precludes us from including any results for the estrogen-only women.

Abbreviations: CI = confidence interval; EMS = Estrogen Memory Study; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; PEPI = Postmenopausal Estrogen/Progestin Interventions Trail; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WHI = Women's Health Initiative; WISDOM = Women's International Study of Long-Duration Oestrogen After Menopause.

Appendix G Table 4. Evidence Table of Trials Reporting Incidence of Endometrial Cancer

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
EPAT Estrogen-only trial Hodis, 2001[60]	133 (60%) of enrolled women had an intact uterus 111 Estrogen only 111 Placebo	**Followup: 2 years**[b] 0 (0.0%) vs. 0 (0.0%)
ERA Estrogen only and estrogen plus progestin trial Herrington, 2000[62]	120 (39%) of enrolled women had an intact uterus, including 44 (44%) women in the estrogen-only arm, 40 (38%) women in the estrogen plus progestin arm, and 36 (34%) women in the placebo arm 100 Estrogen only 104 Estrogen plus progestin 105 Placebo	**Followup: 3.2 years** 0 (0.0%) vs. 0 (0.0%) vs. 0 (0.0%)
ESPRIT Estrogen-only trial Cherry, 2002;[63] Cherry, 2014[64]	At enrollment, 24% of women had an intact uterus, including 373 (73%) of women in the active treatment arm[d] 513 Estrogen only 504 Placebo	**Followup: 2 years**[63] 0 (0.0%) vs. 0 (0.0%) **Cumulative followup: Mean 12.6 years**[64] HR, 0.52 (95% CI, 0.05 to 5.80)
Greenspan, et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[65]	243 (65%) of enrolled women had an intact uterus, including 121 (65%) in the hormone therapy arm and 122 (66%) in the placebo arm. Women with an intact uterus received estrogen plus progestin; women with a hysterectomy received estrogen only. 187 Hormone therapy 186 Placebo	**Followup: 3 years** 1 vs. 0; p=1.0[d]

Appendix G Table 4. Evidence Table of Trials Reporting Incidence of Endometrial Cancer

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
HERS Estrogen plus progestin trial Hulley, 2002[68]	All enrolled women had an intact uterus 1,380 Estrogen plus progestin 1,383 Placebo Cumulative followup: 1156 Estrogen plus progestin 1383 Placebo	**Followup: Mean 4.1 years** 2 (0.14%) vs. 5 (0.36%); HR, 0.39 (95% CI, 0.08 to 2.02); p=0.26 **Cumulative followup: Mean 6.8 years** HR, 0.25 (95% CI, 0.05 to 1.18); p=0.08
PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995[74]	Approximately 68% of women had an intact uterus; women with an intact uterus had to have a normal endometrial biopsy at baseline 175 Estrogen only 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Followup: 3 years** 1 (estrogen only) vs. 0 (estrogen plus progestin) vs. 0 (estrogen plus micronized progestin) vs. 0 (placebo)
STOP-IT Estrogen only and estrogen plus progestin Gallagher, 2001[75]	199 (41%) of enrolled women had an intact uterus; women with a prior hysterectomy who were randomized to receive estrogen plus progestin, with or without calcitriol, received estrogen only 121 Estrogen plus progestin 122 Estrogen plus progestin plus calcitriol 123 Calcitriol only 123 Placebo	**Followup: 3 years** *Analysis did not stratify by treatment regimen* 0 (hormone therapy with or without calcitriol) vs. 1 (calcitriol only or placebo)
ULTRA Estrogen-only trial Johnson, 2005[77]	All enrolled women had an intact uterus 208 Estrogen only 209 Placebo	**Followup: 2 years** 0 (0.0%) vs. 0 (0.0%); difference, 0.0 (95% CI, -4.2 to 3.1); p=1.000[e]

Appendix G Table 4. Evidence Table of Trials Reporting Incidence of Endometrial Cancer

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
WHI Estrogen plus progestin trial Writing Group for the Women's Health Initiative Investigators, 2002;[23] Anderson, 2003;[81] Heiss, 2008;[92] Prentice, 2009;[98] Chlebowski, 2010;[108] Manson, 2013[102, 103]	Women with an intact uterus 8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,060 Estrogen plus progestin 7,687 Placebo Postintervention extension followup:[f] 6,545 Estrogen plus progestin 6,243 Placebo	**Followup: Median 5.6 years**[102] 27 (0.32%) vs. 30 (0.37%); HR, 0.83 (95% CI, 0.49 to 1.40); p=0.49 **Subgroups:**[102] No significant difference by age at randomization **Followup: Median 8.2 years postintervention and postintervention extension**[102] HR, 0.58 (95% CI, 0.40 to 0.86); p=0.007 **Cumulative followup: Median 13.2 years**[102] HR, 0.67 (95% CI, 0.49 to 0.91); p=0.01 **Subgroups:**[102] No significant difference by age at randomization

[a] Intervention dosages are listed in Table 3 by trial.
[b] Adverse event reporting was only among women who received uterine biopsies (30 women in the estrogen-only arm and 5 women in the placebo arm).
[c] Women with an intact uterus were sent an annual letter for 5 years reminding them to seek medical attention if they experienced vaginal bleeding.
[d] The mean followup was 5.5 years, suggesting that the results are based on an earlier adjudication of intervention phase data than the most recent intervention data from Manson, 2013.[102]
[d] Because women with an intact uterus received estrogen plus progestin if they were randomized to the hormone therapy arm, this woman had received estrogen plus progestin.
[e] Analysis focused on women with endometrial biopsy results, including 188 women in the estrogen-only arm and 177 women in the placebo arm.
[f] Women were ineligible if they were deceased or provided no contact through the postintervention phase. By the end of the postintervention phase, 7,878/8,506 (93% of women randomized to estrogen plus progestin) and 7,530/8,102 (93% of women randomized to placebo) were eligible for the postintervention extension phase.

Abbreviations: CI = confidence interval; EPAT = Estrogen in the Prevention of Atherosclerosis Trial; ERA = Estrogen Replacement and Atherosclerosis; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; PEPI = Postmenopausal Estrogen/Progestin Interventions Trial; STOP IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; ULTRA = Ultra-Low-Dose Transdermal Estrogen Replacement Assessment; vs. = versus; WHI = Women's Health Initiative.

Appendix G Table 5. Evidence Table of Trials Reporting Incidence of Lung Cancer

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
EMS Estrogen plus progestin trial Tierney, 2009[59]	70 Estrogen plus progestin 72 Placebo	**Followup: 2 years** 1 vs. 0
HERS Estrogen plus progestin trial Hulley, 2002[68]	1,380 Estrogen plus progestin 1,383 Placebo Cumulative followup: 1156 Estrogen plus progestin 1383 Placebo	**Followup: Mean 4.1 years** 24 (1.74%) vs. 19 (1.37%); HR, 1.28 (95% CI, 0.70 to 2.33); p=0.43 **Cumulative followup: Mean 6.8 years** Unadjusted ITT: HR, 1.39 (95% CI, 0.84 to 2.28); p=0.20 Adjusted ITT: HR, 1.43 (95% CI, 0.87 to 2.37) Adjusted As-Treated: HR, 1.73 (95% CI, 0.93 to 3.21)
PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995[74]	175 Estrogen only 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Followup: 3 years** *Analysis did not stratify by treatment regimen* 2 lung cancer cases
WHI Estrogen-only trial Chlebowski, 2010;[108] Manson, 2013[102]	5,310 Estrogen only 5.429 Placebo Postintervention followup: 4,794 Estrogen only 4,872 Placebo Postintervention extension followup: 4,851 Estrogen only 4,935 Placebo	**Followup: Median 7.2 years**[102] 62 (1.17 %) vs. 61 (1.12%); HR, 1.05 (95% CI, 0.74 to 1.49); p=0.79 **Subgroups:**[102] No significant difference by age at randomization **Followup: Mean 7.9 years**[108,b] **Lung cancer** HR, 1.17 (95% CI, 0.81 to 1.69); p=0.39 **Non-small cell lung cancer** HR, 1.10 (95% CI, 0.74 to 1.64); p=0.62 **Small cell lung cancer** HR, 1.57 (95% CI, 0.56 to 4.41); p=0.39 **Followup: Median 6.6 years postintervention and postintervention extension**[102] HR, 0.90 (95% CI, 0.61 to 1.34); p=0.61 **Cumulative followup: Median 13.0 years**[102] HR, 0.98 (95% CI, 0.75 to 1.27); p=0.87 **Subgroups:**[102] No significant difference by age at randomization

Appendix G Table 5. Evidence Table of Trials Reporting Incidence of Lung Cancer

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
WHI Estrogen plus progestin trial Chlebowski, 2009;[86] Manson, 2013[102]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,060 Estrogen plus progestin 7,687 Placebo Postintervention extension followup:[c] 6,545 Estrogen plus progestin 6,243 Placebo	**Followup: Median 5.6 years**[102] 78 (0.92%) vs. 70 (0.86%); HR, 1.05 (95% CI, 0.76 to 1.45); p=0.78 **Subgroups:**[102] No significant difference by age at randomization **Followup: Mean 7.9 years**[86, b] **Lung cancer** HR, 1.23 (95% CI, 0.92 to 1.63); p=0.16 **Non-small cell** HR, 1.28 (95% CI, 0.94 to 1.73); p=0.12 **Small cell lung cancer** HR, 0.96 (95% CI, 0.44 to 2.07); p=0.91 **Followup: Median 8.2 years postintervention and postintervention extension**[102] HR, 1.13 (95% CI, 0.86 to 1.47); p=0.38 **Cumulative followup: Median 13.2 years**[102] HR, 1.10 (95% CI, 0.89 to 1.35); p=0.38 **Subgroups:**[102] No significant difference by age at randomization

[a] Intervention dosages are listed in Table 3 by trial.
[b] Authors state ascertainment of lung cancer cases is through 3/31/2005, which is the end of the postintervention phase according to Manson[102]; this would mean these results are for trial and posttrial phases combined together.
[c] Women were ineligible if they were deceased or provided no contact through the postintervention phase. By the end of the postintervention phase, 7,878/8,506 (93% of women randomized to estrogen plus progestin) and 7,530/8,102 (93% of women randomized to placebo) were eligible for the postintervention extension phase.

Abbreviations: CI = confidence interval; EMS = Estrogen Memory Study; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; ITT = intention to treat; PEPI = Postmenopausal Estrogen/Progestin Interventions; vs. = versus; WHI = Women's Health Initiative.

Appendix G Table 6. Evidence Table of Trials Reporting Incidence of Ovarian Cancer

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
ESPRIT Estrogen-only trial Cherry, 2014[64]	513 Estrogen only[b] 504 Placebo[b]	**Followup: Mean 12.6 years** 4 (0.78%) vs. 1 (0.20%); Fisher's exact test p=0.37
WHI Estrogen plus progestin trial Anderson, 2003;[81] Manson, 2013[102]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,060 Estrogen plus progestin 7,687 Placebo Postintervention extension followup:[c] 6,545 Estrogen plus progestin 6,243 Placebo	**Followup: Median 5.6 years**[102] 24 (0.28%) vs.16 (0.20%); HR, 1.41 (95% CI, 0.75 to 2.66); p=0.28 **Subgroups:**[102] No significant difference by age at randomization **Followup: Median 8.2 years postintervention and postintervention extension**[102] HR, 1.12 (95% CI, 0.65 to 1.90); p=0.69 **Cumulative followup: Median 13.2 years**[102] HR, 1.24 (95% CI, 0.83 to 1.87); p=0.30 **Subgroups:**[102] Among women 50–59 years at randomization: HR, 0.55 (95% CI, 0.24 to 1.25) Among women 60–69 years at randomization: HR, 1.25 (95% CI, 0.72 to 2.18) Among women 70–79 years at randomization: HR, 3.82 (95% CI, 1.27 to 11.52) p for trend=0.005

[a] Intervention dosages are listed in Table 3 by trial.
[b] Women were ineligible if they were deceased or provided no contact through the postintervention phase. By the end of the postintervention phase, 7,878/8,506 (93% of women randomized to estrogen plus progestin) and 7,530/8,102 (93% of women randomized to placebo) were eligible for the postintervention extension phase.
[c] At enrollment, 24% of women reported having a hysterectomy. After the 2-year intervention period, women with an intact uterus were sent a letter each year for the first 5 years after stopping treatment to remind them to seek medical attention if they experienced vaginal bleeding. No attempt was made after the end of 2-year intervention to obtain medical information from women or their physicians about the use of medications or health events.

Abbreviations: CI = confidence interval; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HR = hazard ratio; vs. = versus; WHI = Women's Health Initiative.

Appendix G Table 7. Evidence Table of Trials Reporting Incidence of Coronary Heart Disease

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
EMS Estrogen plus progestin trial Tierney, 2009[59]	70 Estrogen plus progestin 72 Placebo	**Followup: Mean 2 years** **Any cardiovascular event** 11 (15.7%) vs. 8 (11.1%); no statistically significant differences between groups
EPAT Estrogen-only trial Hodis,2001[60]	111 Estrogen 111 Placebo	**Followup: Mean 2 years** **Cardiovascular events** 3 (2.7%) vs. 4 (3.6%); p>0.2
EPHT Estrogen plus progestin trial Veerus, 2006[61]	404 Estrogen plus progestin 373 Placebo	**Followup: Mean 3.4 years** **CHD** 66 (16.3%) vs. 62 (16.6%); HR 1.03 (95% CI, 0.73 to 1.46)
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[62]	Women with angiographically verified coronary disease 100 Estrogen 104 Estrogen plus progestin 105 Placebo	**Followup: Mean 3.2 years** **Cardiovascular events** 29 (29.0%) vs. 28 (26.9%) vs. 34 (32.4%); p=0.69
Greenspan, et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[65]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Followup: Mean 3 years** **Myocardial infarction** *Analysis did not stratify by treatment regimen* 1 (0.5%) vs. 3 (1.6%); p=0.37
PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995[74]	175 Estrogen only 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Followup: Mean 3 years** **CHD** 1 (estrogen: 0.6%) vs. 1 (estrogen plus progestin: 0.3%) vs. 3 (estrogen plus micronized progestin: 1.7%) vs. 0 (placebo); p=0.29
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[75]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Followup: Mean 3 years** **Cardiovascular events** *Analysis did not stratify by treatment regimen* 8 (hormone therapy with or without calcitriol: 3.3%) vs. 7 (calcitriol only or placebo: 2.8%)
WAVE Estrogen-only and estrogen plus progestin trial Waters, 2002[80]	Women with a coronary stenosis of 15%–75% 124 Estrogen (with or without vitamins C and E) 86 Estrogen plus progestin (with or without vitamins C and E) 213 Placebo (with or without vitamins C and E)	**Followup: Mean 2.8 years** **Nonfatal myocardial infarction or cardiovascular death** *Analysis did not stratify by treatment regimen* 18 (8.6%) vs. 12 (5.6%)

Appendix G Table 7. Evidence Table of Trials Reporting Incidence of Coronary Heart Disease

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
WHI Estrogen-only trial Anderson, 2004;[24] Manson, 2003;[96] Rossouw, 2007;[35] Hsia, 2006;[111] Prentice 2009;[98] LaCroix, 2011;[112] Manson, 2013[102]	5,310 Estrogen 5,429 Placebo Postintervention followup: 3,778 Estrogen 3,867 Placebo	**Followup: Mean 7.1 years** **Overall CHD (nonfatal myocardial infarction, death due to CHD)** [111] 201 (3.8%) vs. 217 (4.0%); HR, 0.95 (95% CI, 0.79 to 1.16) **Subgroups:**[111,102] No significant difference by race or ethnic group, age, years since bilateral oophorectomy, hypertension, diabetes, high cholesterol requiring medication, coronary risk factors, CVD at baseline, or CHD at baseline Younger women had a lower risk for myocardial infarction than older women relative to placebo (p=0.02) [102] **Risk for CHD based on timing of intervention:** No significant association; p for gap time interaction=0.40[98] No significant association; p for trend=0.16[102] **Followup: Mean 3.9 years postintervention**[112] **Overall CHD (nonfatal myocardial infarction, death due to CHD)** HR, 0.97 (95% CI, 0.75 to 1.25)
WHI Estrogen plus progestin trial Writing Group for the WHI, 2002;[23] Manson, 2003;[96] Rossouw, 2007;[35] Heiss, 2008;[92] Prentice 2009;[98] Manson, 2013[102]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,052 Estrogen plus progestin 7,678 Placebo	**Followup: Mean 5.2 years**[102] **Overall CHD (nonfatal myocardial infarction, death due to CHD)** 196 (2.0%) vs. 159 (2.0%); HR, 1.18 (95% CI, 0.95 to 1.45) **Nonfatal myocardial infarction** 151 (1.8%) vs. 114 (1.4%); HR, 1.28 (95% CI, 1.00 to 1.63) **CHD death** 39 (0.5%) vs. 34 (0.4%); HR, 1.10 (95% CI, 0.70 to 1.75) **Subgroups:**[96, 102] No significant difference by race or ethnic group, age, hypertension, diabetes, CVD at baseline, or CHD at baseline **Risk based on timing of intervention:** **Overall CHD** No significant association; p for gap time interaction=0.42[98] No significant association; p for trend=0.08[102] **Nonfatal myocardial infarction**[102] <10 years after menopause: HR, 0.91 10–<20 years after menopause: HR, 1.16 ≥20 years after menopause: HR, 1.99 p for trend=0.01 **Followup: Mean 2.4 years postintervention**[92] **Overall CHD** HR, 1.04 (95% CI, 0.89 to 1.21)

Appendix G Table 7. Evidence Table of Trials Reporting Incidence of Coronary Heart Disease

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
WISDOM Estrogen plus progestin trial Vickers, 2007[123]	826 Estrogen 2,196 Estrogen plus progestin 2,189 Placebo	**Followup: Mean 1 year** **Cardiovascular events** 2 (0.2%) vs. 7 (0.3%) vs. 0 (0.0%); p=0.016

[a] Intervention dosages are listed in Table 3 by trial.

Abbreviations: CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; DOPS = Danish Osteoporosis Prevention Study; EMS = Estrogen Memory Study; EPAT = Estrogen in the Prevention of Atherosclerosis Trial; EPHT = Estonian Postmenopausal Hormone Therapy Trial; ERA = Estrogen Replacement and Atherosclerosis; HR = hazard ratio; PEPI = Postmenopausal Estrogen/Progestin Interventions Trial; RR = relative risk; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WHI = Women's Health Initiative; WISDOM = Women's International Study of Long Duration Oestrogen After Menopause.

Appendix G Table 8. Evidence Table of Trials Reporting Incidence of Cognitive Function and Dementia

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)				
		PD Incidence	MCI Incidence	Other Dementia Diagnosis Outcomes	3MSE Scores (0-100, Higher Better)	Other Measures
EMS Estrogen plus progestin trial Tierney, 2009[59]	Women with normal to just below normal scores on cognitive battery tests, but free of dementia: 70 Estrogen plus progestin 72 Placebo	NR	NR	NR	NR	**Followup: 1 year** **CVLT short-delay verbal recall** p=0.15 **Followup: 2 years** **CVLT short-delay verbal recall** p=0.11
HERS Estrogen plus progestin trial Grady, 2002[72]	662 Estrogen plus progestin 666 Placebo	NR	NR	NR	**Followup: 4.2 years** 93.1 (SD, 6.4) vs. 93.4 (SD, 6.4); difference, -0.4 (95% CI, -1.1 to 0.4); p=0.36	**Followup: 4.2 years** **Verbal fluency** (0-∞, higher better) 15.9 (SD, 4.8) vs. 16.6 (SD, 4.8); difference, -0.7 (95% CI, -1.3 to -0.1); p=0.02 No other differences between groups for Boston Naming, Word List Memory, Word List Recall, or Trials B
KEEPS-Cog Estrogen plus progestin trial Gleason, 2015[73]	431 Estrogen plus progestin 262 Placebo	NR	NR	NR	**Followup: 4 years** **Oral estrogen** Beta estimate, 1.02 x 10^{-2} (CI, -4.45 x 10^{-3} to 2.48 x 10^{-2}); p=0.178 **Transdermal estrogen** Beta estimate, -9.40 x 10^{-4} (CI, -1.57 x 10^{-2} to 1.38 x 10^{-2}); p=0.840	NR

Appendix G Table 8. Evidence Table of Trials Reporting Incidence of Cognitive Function and Dementia

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)				
		PD Incidence	MCI Incidence	Other Dementia Diagnosis Outcomes	3MSE Scores (0-100, Higher Better)	Other Measures
ULTRA Estrogen-only trial Yaffe, 2006[79]	417 Enrolled 208 Estrogen 209 Placebo	NR	NR	NR	**Followup: 2 years** Baseline 3MSE ≤90: 5.90 vs. 7.10; difference, -1.21 (95% CI, -5.05 to 2.64); p=0.53 Baseline 3MSE >90: 0.57 vs. 0.87; difference, -0.30 (95% CI, -0.74 to 0.14); p=0.18	**Followup: 2 years** No differences between groups on Logical Memory, Brief Visuospatial Memory Test, Word List, Trails B, Modified Boston Naming Test, Verbal Fluency
WHIMS Estrogen-only trial Shumaker, 2004,[117] Espeland, 2004[115]	Women without probable dementia Dementia outcomes, WHI:[117] 1,464 Estrogen 1,483 Placebo General cognitive function, enrolled in WHIMS >6 months after initiation of assigned WHI therapy and with >1 post-randomization 3MSE score:[115] 1,387 Estrogen 1,421 Placebo Subgroup analysis: 1,464 Estrogen 1,483 Placebo	**Followup: 5.2 years**[117] 28 (1.9%) vs. 19 (1.3%); cumulative HR, 1.49 (95% CI, 0.83 to 2.66); p=0.18 **Subgroups:**[117] No difference in the hazard rate for probable dementia by race or history of cardiovascular disease, diabetes, hypertension, or stroke	**Followup: 5.2 years**[117] 76 (5.2%) vs. 58 (3.9%); cumulative HR, 1.34 (95% CI, 0.95 to 1.89); p=NS	**Followup: 5.2 years**[117] PD or MCI: 93 (6.4%) vs. 69 (4.7%); cumulative HR, 1.38 (95% CI, 1.01 to 1.89); p=0.04	**Followup: Mean 5.4 years**[115] Mean difference in change from baseline, -0.26 (95% CI, -0.52 to 0.00); p=0.04	NR

Appendix G Table 8. Evidence Table of Trials Reporting Incidence of Cognitive Function and Dementia

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)				
		PD Incidence	MCI Incidence	Other Dementia Diagnosis Outcomes	3MSE Scores (0-100, Higher Better)	Other Measures
WHIMS Estrogen plus progestin trial Shumaker, 2003;[118], Shumaker, 2004;[117], Rapp, 2003[116]; Espeland, 2004[115]	Women without probable dementia Dementia and cognitive impairment outcomes:[118] 2,229 Estrogen plus progestin 2,303 Placebo Cognitive function outcomes:[115] 2,131 Estrogen plus progestin 2,213 Placebo	**Followup: ~4 years**[118] 40 (1.8%) vs. 21 (0.9%); cumulative HR, 2.05 (95% CI, 1.21 to 3.48); p=0.01 **Subgroups:**[118] No difference in the hazard rate for probable dementia by race or history of cardiovascular disease, diabetes, hypertension, or stroke	**Followup: ~4 years**[118] 56 (2.5%) vs. 55 (2.4%); cumulative HR, 1.07 (95% CI, 0.74 to 1.55); p=0.72	**Followup: ~4 years**[118] PD or MCI: 85 (3.8%) vs. 66 (2.9%); cumulative HR, 1.37 (95% CI, 0.99 to1.89)	**Followup: 5.4 years**[115] Mean difference in change from baseline, -0.18 (95% CI, -0.37 to 0.00); p=0.055 **Subgroups:**[116] No difference in the rate of change by race, length of use, or history of cardiovascular disease, diabetes, or hypertension **Timing:**[116] No difference in the rate of change by time to initiation of therapy after last menstrual period	NR
WHIMSY Estrogen-only and estrogen plus progestin trial Espeland, 2013[119]	696 Hormone therapy 630 Placebo	NR	NR	NR	NR	**Followup: 7.2 years postintervention** **Verbal fluency** 18.90 (estrogen: SE 0.33) vs. 19.91 (placebo: SE 0.34) No other differences between groups for Telephone Interview for Cognitive Status–modified, East Boston Memory Test, Verbal Memory, Attention, Executive Function, Working Memory, Composite

Appendix G Table 8. Evidence Table of Trials Reporting Incidence of Cognitive Function and Dementia

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)				
		PD Incidence	MCI Incidence	Other Dementia Diagnosis Outcomes	3MSE Scores (0-100, Higher Better)	Other Measures
WHIMSY Estrogen-only and estrogen plus progestin trial Espeland, 2013[119]	696 Hormone therapy 630 Placebo	NR	NR	NR	NR	**Followup: 7.2 years** **Verbal fluency** 21.04 (estrogen plus progestin: SE 0.25) vs. 20.65 (placebo: SE 0.27) No other differences between groups for Telephone Interview for Cognitive Status–modified, East Boston Memory Test, Verbal Memory, Attention, Executive Function, Working Memory, Composite
WHISCA Estrogen-only trial Resnick, 2009[121]; Espeland, 2010[120]	Dementia outcomes, WHISCA:[121] 434 Estrogen 452 Placebo Cognitive measures, WHISCA extension:[120] 601 Hormone therapy 612 Placebo	**Followup: 2.7 years** (during WHISCA, after being enrolled in WHI for 3 years)[121] 4 (0.9%) vs. 2 (0.4%); calculated RR, 2.08 (95% CI, 0.38 to 11.31); p=0.40	**Followup: 2.7 years** (during WHISCA, after being enrolled in WHI for 3 years)[121] 18 (4.1%) vs. 15 (3.3%); calculated RR, 1.25 (95% CI, 0.64 to 2.45); p=0.52	NR	**Followup: 3.6 years** (during WHISCA, after being enrolled in WHI for 3 years)[120] Mean decrement in global cognitive function, -0.092 (SE, 0.039); p=0.02 **Followup: Mean 2.4 years posttrial** (after being enrolled in WHI for 3 years and WHISCA for .36 years)[120] Mean decrement in global cognitive function, -0.081 (SE 0.047); p=0.09	**Followup: Mean 3.6 years** (during trial)[120] **Verbal knowledge** -0.100 (SE, 0.051); p=0.05 **Verbal fluency** -0.118 (SE, 0.054); p=0.03 **Figural memory** -0.132 (SE, 0.048); p=0.006 **Spatial ability** -0.137 (SE, 0.057); p=0.02 Verbal memory and attention and working memory not significant at p=0.05 **Followup: 2.4 years postintervention**[120] **Spatial ability** -0.179 (SE, 0.063); p=0.004

Appendix G Table 8. Evidence Table of Trials Reporting Incidence of Cognitive Function and Dementia

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)				
		PD Incidence	MCI Incidence	Other Dementia Diagnosis Outcomes	3MSE Scores (0-100, Higher Better)	Other Measures
						Verbal knowledge, verbal fluency, verbal memory, figural memory, attention and working memory differences not significant at p=0.05
WHISCA Estrogen plus progestin trial Resnick, 2006;[122] Espeland, 2010[120]	Probable dementia or cognitive impairment, WHIMS:[122] 690 Estrogen plus progestin 726 Placebo Cognitive measures, WHISCA extension:[120] 601 Hormone therapy 612 Placebo	**Followup: 1.4 years** (during WHISCA, after being enrolled in WHI for 3 years)[122] 5 (0.7%) vs. 6 (0.8%); calculated RR, 0.88 (95% CI, 0.27 to 2.86); p=0.83	**Followup: 1.4 years** (during WHISCA, after being enrolled in WHI for 3 years)[122] 6 (0.9%) vs. 13 (1.8%); calculated RR, 0.49 (95% CI, 0.19 to 1.27); p=0.14	NR	**Followup: Mean 2 years** (during WHISCA, after being enrolled in WHI for 3 years)[120] Mean decrement in global cognitive function, -0.080 (SE, 0.034); p=0.02 **Followup: Mean 4 years post-trial** (after being enrolled in WHI for 3 years and in WHISCA for 2 years)[120] Mean decrement in global cognitive function, -0.059 (SE, 0.032); p=0.06	**Followup: Mean 3 years** (pre-WHISCA, 2 years during WHISCA trial)[120] Spatial ability, verbal knowledge, verbal fluency, verbal memory, figural memory, attention and working memory not statistically significant at p=0.05 **Followup: Mean 4 years post-trial**[120] Spatial ability, verbal knowledge, verbal fluency, verbal memory, figural memory, attention and working memory not statistically significant at p=0.05

[a] Intervention dosages are listed in Table 3 by trial.

Abbreviations: 3MSE = Modified Mini-Mental State Examination; CI = confidence interval; EMS = Estrogen Memory Study; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; MCI = mild cognitive impairment; NR = not reported; NS = not significant; PD = probable dementia; RR = relative risk; SD = standard deviation; SE = standard error; ULTRA = Ultra-Low-Dose Transdermal Estrogen Replacement Assessment; WHI = Women's Health Initiative; WHIMS = Women's Health Initiative Memory Study; WHIMSY = Women's Health Initiative Memory Study of Younger Women; WHISCA = Women's Health Initiative Study of Cognitive Aging; vs. = versus.

Appendix G Table 9. Evidence Table of Trials Reporting Incidence of Diabetes

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
Greenspan, et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[65]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Followup: 3 years** *Analysis did not stratify by regimen* 2 (1.1%) vs. 6 (3.2%); p=0.17
HERS Estrogen plus progestin trial Kanaya, 2003[70]	Women without self-reported diabetes at baseline 999 Estrogen plus progestin 1,030 Placebo	**Followup: Mean 4.1 years** **Overall** 62 (6.2%) vs. 98 (9.5%); NNT, 30 (95% CI, 18 to 103); p=0.006 **Of those with normal glucose at baseline** 38/904 (4.2%) vs. 52/907 (5.7%); p=0.13 **Of those with impaired fasting glucose at baseline** 24/95 (25.3%) vs. 46/123 (37.4%); p=0.06 **Risk for incident diabetes** HR, 0.65 (95% CI, 0.48 to 0.89)
WHI Estrogen-only trial Bonds, 2006;[106] Manson, 2013[102]	Women not receiving treatment for diabetes at baseline 4,900 Estrogen 5,017 Placebo	**Followup: Mean 7.1/median 7.2 years** **Overall**[102] 449 (9.2%) vs. 527 (10.5%); HR, 0.86; 95% CI, 0.76 to 0.98); p=0.02 **Of those who adhered to ≥80% of medication**[106] HR, 0.73 (95% CI, 0.60 to 0.88) **Subgroups:**[106] No significant difference by race/ethnicity, age at screening, hypertension, or metabolic syndrome at baseline **Followup: Median 6.6 years postintervention**[102] HR, 1.07; 95% CI, 0.92 to 1.25
WHI Estrogen plus progestin trial Margolis, 2004;[97] Manson, 2013[102]	Women not receiving treatment for diabetes at baseline 8,132 Estrogen plus progestin 7,742 Placebo	**Followup: Mean 5.6 years**[97] 328 (4.0%) vs. 373 (4.8%); HR, 0.81 (95% CI, 0.70 to 0.94); p=0.005 **Subgroups:**[97] No significant difference by race/ethnicity, age at screening, or hypertension at baseline **Followup: Median 8.2 years postintervention**[102] HR, 1.19, 95% CI, 1.05 to 1.34

[a] Intervention dosages are listed in Table 3 by trial.

Abbreviations: CI = confidence interval; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; NNT = number needed to treat; RR = relative risk; vs. = versus; WHI = Women's Health Initiative.

Appendix G Table 10. Evidence Table of Trials Reporting Incidence of Fractures

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
EMS Estrogen plus progestin trial Tierney 2009[59]	70 Estrogen plus progestin 72 Placebo	**Followup: 2 years** **Hip fractures** 0 (0.0%) vs. 1 (1.4%)
EPHT Estrogen plus progestin trial Veerus, 2006[61]	404 Estrogen plus progestin 373 Placebo	**Followup: 5 years** **Bone fractures[b]** 15 (3.7%) vs. 25 (6.7%) HR, 0.52 (95% CI, 0.27 to 0.98)
ERA Estrogen-only and estrogen plus progestin trial Herrington 2000[62]	100 Estrogen 104 Estrogen plus progestin 105 Placebo	**Followup: 3.2 years** **Fractures (all sites)** 6 (6.0%) vs. 7 (6.7%) vs. 15 (14.3%) Estrogen: Calculated RR, 0.42 (95% CI, 0.17 to 1.04); p=0.06 Estrogen plus progestin: Calculated RR, 0.47 (95% CI, 0.24 to 1.11); p=0.09
HERS Estrogen plus progestin trial Hulley, 2002[68]	1,380 Estrogen plus progestin 1,383 Placebo	**Followup: Mean 4.1 years** **Hip** 15 vs. 13; HR, 1.16 (95% CI, 0.55 to 2.44); p=0.69 **Wrist** 29 vs. 29; HR, 1.01 (95% CI, 0.60 to 1.68); p=0.98 **Vertebral** 14 vs. 19; HR, 0.74 (95% CI, 0.37 to 1.48); p=0.40 **Other** 91 vs. 101; HR, 0.91 (95% CI, 0.69 to 1.21); p=0.52 **Any** 140 vs. 148; HR, 0.96 (95% CI, 0.76 to 1.20); p=0.70
STOP-IT Estrogen plus progestin trial Gallagher 2001[75]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Followup: 3 years** **Vertebral fractures** *Analysis did not stratify by regimen* 2 (hormone therapy with or without calcitriol) vs. 1 (calcitriol only or placebo)
WHI Estrogen-only trial LaCroix, 2011;[112] Anderson, 2004;[81] Manson, 2013[102]	5,310 Estrogen 5,429 Placebo Postintervention followup: 3,778 Estrogen 3,867 Placebo	**Followup time: Median 7.2 years**[81, 102] **Vertebral** 44 (0.8%) vs. 70 (1.3%); HR, 0.64 (95% CI, 0.44 to 0.93) **Hip** 48 (0.9%) vs. 74 (1.4%); HR, 0.67 (95% CI, 0.46 to 0.96) **Total** 544 (10.2%) vs. 767 (14.1%); HR, 0.72 (95% CI, 0.64 to 0.80) **Subgroups:** No significant difference by age **Followup: Mean 5.9 years**[112] **Hip fractures** HR, 0.67 (95% CI, 0.46 to 0.96)

Appendix G Table 10. Evidence Table of Trials Reporting Incidence of Fractures

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
		Followup: Mean 10.7 years postintervention[112] **Hip fractures** HR, 1.27 (95% CI, 0.88 to 1.82) **Cumulative followup: Median 13.0 years**[112] **Hip fractures** HR, 0.92 (95% CI, 0.71 to 1.18) **Subgroups:** No significant difference by age
WHI Estrogen plus progestin trial Heiss, 2008;[92], Cauley, 2003;[83] Rossouw, 2002[23]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,052 Estrogen plus progestin 7,678 Placebo	**Followup: Mean 5.6 years**[92, 102] **Hip fractures** 53 vs. 75; HR, 0.67 (95% CI, 0.47 to 0.96) **Vertebral fractures** 56 vs. 78; HR, 0.68 (95% CI, 0.48 to 0.96) **Other osteoporotic fractures** 650 vs. 800; HR, 0.75 (95% CI, 0.68 to 0.83) **Total (hip, vertebral, or other osteoporotic fractures)** 741 vs. 903; HR, 0.76 (95% CI, 0.69 to 0.83) **Followup: Mean 2.4 years postintervention**[92] **Hip fractures** HR, 0.92 (95% CI, 0.64 to 1.34) **Vertebral fractures** HR, 0.96 (95% CI, 0.64 to 1.44) **Other osteoporotic fractures** HR, 0.87 (95% CI, 0.74 to 1.03) **Total (hip, vertebral, or other osteoporotic fractures)** HR, 0.91 (95% CI, 0.78 to 1.06)

[a] Intervention dosages are listed in Table 3 by trial.
[b] Bone fractures defined as diagnoses Sx2 (x=1-9) according to ICD-10 (fracture of neck, fractures of ribs, sternum and thoracic spine, fracture of lumbar spine and pelvis, fracture of shoulder and upper arm, fracture of forearm, fracture at wrist and hand level, fracture of femur, fracture of lower leg, including ankle).

Abbreviations: CI = confidence interval; EMS = Estrogen Memory Study; EPHT – Estonian Postmenopausal Hormones Therapy Trial; ERA = Estrogen Replacement and Atherosclerosis Trial; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; RR = relative risk; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WHI = Women's Health Initiative.

Appendix G Table 12. Evidence Table of Trials Reporting Incidence of Stroke

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
Greenspan, et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[65]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Follow-up: 3 years** **Gallstones** *Analysis did not stratify by regimen* 1 (0.5%) vs. 1 (0.5%)
PEPI Estrogen-only and estrogen plus progestin trial PEPI, 1995[74]	175 Estrogen only 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Followup: 3 years** **Gallbladder disease** 2 (estrogen: 1.1%) vs. 9 (estrogen plus progestin: 2.6%) vs. 4 (estrogen plus micronized progestin 2.2%) vs. 2 (placebo: 1.1%)
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[75]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Followup: 3 years** **Gallstones or cholecystitis** *Analysis did not stratify by regimen* 8 (hormone therapy with or without calcitriol: 3.3%) vs. 3 (calcitriol only or placebo: 1.2%)
WHI Estrogen-only trial Cirillo, 2005;[88] LaCroix, 2011;[112] Manson, 2013[102]	Women without cholecystectomy or gallbladder disease at baseline 4,141 Estrogen 4,235 Placebo	**Followup: Mean 7.1 years**[88] **Gallbladder event incidence** 228 (5.5%) vs. 143 (3.4%); HR, 1.67 (95% CI, 1.35 to 2.06); p<0.001 **Cholecystectomy** 192 (4.6%) vs. 104 (2.5%); HR, 1.93 (95% CI, 1.52 to 2.44); p<0.001 **Global gallbladder disease** 223 (5.4%) vs. 130 (3.1%); HR, 1.79 (95% CI, 1.44 to 2.22); p<0.001 **Cholecystitis** 186 (4.5%) vs. 107 (2.5%); HR, 1.80 (95% CI, 1.42 to 2.28); p<0.001 **Subgroups:**[88] No significant difference by age **Followup: Median 6.6 years postintervention**[102] **Gallbladder disease** HR, 0.98 (95% CI, 0.68 to 1.41); p=0.92
WHI Estrogen plus progestin trial Cirillo, 2005;[88] Manson, 2013[102]	Women without cholecystectomy or gallbladder disease at baseline 7,308 Estrogen plus progestin 6,895 Placebo	**Followup: Mean 5.6 years**[88] **Gallbladder event incidence** 228 (3.1%) vs. 135 (2.0%); HR, 1.59 (95% CI, 1.28 to 1.97); p<0.001 **Cholecystectomy** 190 (2.6%) vs. 107 (1.6%); HR, 1.67 (95% CI, 1.32 to 2.11); p<0.001 **Global gallbladder disease** 223 (3.1%) vs. 130 (1.9%); HR, 1.61 (95% CI, 1.30 to 2.00); p<0.001 **Cholecystitis** 192 (2.6%) vs. 117 (1.7%); HR, 1.54 (95% CI, 1.22 to 1.94); p<0.001

Appendix G Table 12. Evidence Table of Trials Reporting Incidence of Stroke

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
		Subgroups:[88] No significant difference by age **Followup: Median 8.2 years postintervention**[102] **Gallbladder disease** HR, 1.24 (95% CI, 1.01 to 1.52); p=0.04

[a] Intervention dosages are listed in Table 3 by trial.

Abbreviations: CI = confidence interval; HR = hazard ratio; PEPI = Postmenopausal Estrogen/Progestin Interventions; RR = relative risk; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WHI = Women's Health Initiative.

Appendix G Table 12. Evidence Table of Trials Reporting Incidence of Stroke

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
EMS Estrogen plus progestin trial Tierney, 2000[59]	70 Estrogen plus progestin 72 Placebo	**Followup: 2 years** **Intracerebral hemorrhage** 1 (1.4%) (fatal) vs. 0; p=NS **Transient ischemic attack** 1 (1.4%) vs. 1 (1.4%); p=NS
EPAT Estrogen-only trial Hodis,2001[60]	111 Estrogen[b] 111 Placebo[b]	**Followup: 2 years** **Cerebrovascular accidents** 0 vs. 1
EPHT Estrogen plus progestin trial Veerus, 2006[61]	404 Estrogen plus progestin 373 Placebo	**Follow-up: Mean 3.4 years** **Any cerebrovascular disease**[c] 23 (5.7%) vs. 9 (2.4%); HR 2.46 (1.14 to 5.34) **Stroke** 1 (0.2%) vs 1 (0.3%); HR 1.06 (0.07 to 17.2)
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[62]	Women with angiographically verified coronary disease 100 Estrogen 104 Estrogen plus progestin 105 Placebo	**Followup: Mean 3.2 years** **Stroke or transient ischemic attack** 5 vs. 6 vs. 6; p=1.0
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[75]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Followup: Mean 3 years** **Cerebrovascular accidents** *Analysis did not stratify by regimen* 10 (hormone therapy with or without calcitriol) vs. 7 (calcitriol only or placebo)
WAVE Estrogen-only and estrogen plus progestin trial Waters, 2002[80]	Women with a coronary stenosis of 15%–75% 124 Estrogen (with or without vitamins C and E) 86 Estrogen plus progestin (with or without vitamins C and E) 213 Placebo (with or without vitamins C and E)	**Followup: Mean 2.8 years** **Stroke** *Analysis did not stratify by regimen* 9 (4.3%) vs. 4 (1.9%); p=0.17
WHI Estrogen-only trial Hendrix, 2006;[110] LaCroix, 2011;[112] Manson, 2013;[102] Prentice, 2009[98]	5,310 Estrogen 5,429 Placebo Postintervention followup: 3,778 Estrogen 3,867 Placebo	**Followup: Median 7.2 years**[102] **All stroke** 169 (3.2%) vs. 129 (2.4%); HR, 1.35 (95% CI, 1.07 to 1.70); p=0.01 **Subgroups:**[110] No significant difference by race or ethnicity, age, prior CVD, diabetes, hypertension

Appendix G Table 12. Evidence Table of Trials Reporting Incidence of Stroke

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
		Risk for stroke based on timing of intervention:[98] No significant association; p for gap time interaction=0.96 **Followup: Mean 3.9 years postintervention**[112] **All stroke** HR, 0.89 (95% CI, 0.64 to 1.24) **Cumulative followup: Median 13.0 years**[102, 112] **All stroke** HR, 1.15 (95% CI, 0.97 to 1.37)
WHI Estrogen plus progestin trial Wassertheil-Smoller, 2003[101] Heiss, 2008;[92] Cushman, 2004;[89]Manson, 2013[102]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,052 Estrogen plus progestin 7,678 Placebo	**Followup: Mean 5.6 years** **All stroke**[102] 159 (1.9%) vs. 109 (1.3%); HR, 1.37 (95% CI, 1.07 to 1.76) **Ischemic stroke**[101] 125 vs. 81; HR, 1.44 (95% CI, 1.09 to 1.90) **Hemorrhagic stroke**[101] 18 vs. 20; HR, 0.82 (95% CI, 0.43 to 1.56) **Subgroups:** No significant difference by race or ethnicity, age, diabetes, or hypertension **Risk for stroke based on timing of intervention:**[98] No significant association; p for gap time interaction=1.00 **Followup: Mean 2.4 years postintervention**[102] **All Stroke** HR, 1.04 (95% CI, 0.89 to 1.23) **Cumulative followup: Median 13.2 years**[102] **All stroke** HR, 1.16 (95% CI, 1.00 to 1.35)

[a] Intervention dosages are listed in Table 3 by trial.
[b] Unopposed micronized 17V-estradiol (1mg/d).
[c] Defined as diagnoses of one of the following (ICD-10 or 160-169 codes): subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, stroke, occlusion and stenosis of precerebral arteries, occlusion and stenosis of cerebral arteries, other cerebrovascular diseases, cerebrovascular disorders, sequelae of cerebrovascular disease.

Abbreviations: CI = confidence interval; CVD = cardiovascular disease; EMS = Estrogen Memory Study; EPAT = Estrogen in the Prevention of Atherosclerosis; EPHT = Estonian Postmenopausal Hormone Therapy Trial; ERA = Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis; HR = hazard ratio; RR = relative risk; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WAVE = The Women's Angiographic Vitamin and Estrogen Trial; WHI = Women's Health Initiative.

Appendix G Table 13. Evidence Table of Trials Reporting Incidence of Urinary Incontinence

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
HERS Estrogen plus progestin trial Steinauer, 2005[71]	Women reporting no episodes of incontinence in the past week at baseline 597 Estrogen plus progestin 611 Placebo	**Followup: 4.2 years** **Weekly urinary incontinence** 382 vs. 302, OR,1.6 (95% CI, 1.3 to 1.9); p<0.001 **Stress urinary incontinence** OR, 1.7 (95% CI, 1.5 to 2.1); p<0.001 **Urge urinary incontinence** OR, 1.5 (95% CI, 1.2 to 1.8); p<0.001
ULTRA Estrogen-only trial Waetjen, 2005[78]	Women who were continent at baseline 122 Estrogen (calculated) 117 Placebo (calculated)	**Followup: 2 years** 39.0% vs. 36.8%; OR, 1.2 (95% CI, 0.7 to 2.2); p=0.74
WHI Estrogen-only trial Hendrix, 2005[94]	Women with urinary incontinence data at baseline and 1 year 1,526 Estrogen (all continent at baseline, 96 continent at 1 year) 1,547 Placebo (all continent at baseline, 136 continent at 1 year)	**Followup: 1 year** **Incident urinary incontinence** 557 (36.5%) vs. 368 (23.8%); RR, 1.53 (95% CI, 1.37 to 1.71) **Stress urinary incontinence** 266 (17.4%) vs. 131 (8.5%); RR, 2.15 (95% CI, 1.77 to 2.62); p<0.001 **Urge urinary incontinence** 210 (13.8%) vs. 184 (11.9%); RR, 1.32 (95% CI, 1.10 to 1.58); p=0.003 **Mixed urinary incontinence** 76 (5.0%) vs. 50 (3.2%); RR, 1.79 (95% CI, 1.26 to 2.53); p=0.001 **Followup: 3 years** 27/96 (28.1%) vs. 26/136 (19.1%) of continent women at baseline and 1 year reported incident urinary incontinence at 3 years; RR, 1.47 (95% CI, 0.92 to 2.36)
WHI Estrogen plus progestin trial Hendrix, 2005[94]	Women with urinary incontinence data at baseline and 1 year 2,675 Estrogen plus progestin (all continent at baseline, 153 continent at 1 year) 2,507 Placebo (all continent at baseline, 185 continent at 1 year)	**Followup: 1 year** **Incident urinary incontinence** 834 (31.2%) vs. 563 (22.5%); RR, 1.39 (95% CI, 1.27 to 1.52) **Stress urinary incontinence** 429 (16.0%) vs. 218 (8.7%); RR, 1.87 (95% CI, 1.61 to 2.18); p<0.001 **Urge urinary incontinence** 304 (11.4%) vs. 272 (10.8%); RR, 1.15 (95% CI, 0.99 to 1.34); p = 0.06 **Mixed urinary incontinence** 99 (3.7%) vs. 69 (2.8%); RR, 1.49 (95% CI, 1.10 to 2.01); p = 0.01 **Followup: 3 years** 39/153 (25.5%) vs. 26/185 (14.1%) of continent women at baseline and 1 year reported incident urinary incontinence at 3 years; RR, 1.81 (95% CI, 1.16 to 2.84)

[a] Intervention dosages are listed in Table 3 by trial.

Abbreviations: CI = confidence interval; HERS = Heart and Estrogen/Progestin Replacement Study; OR = odds ratio; RR = relative risk; ULTRA = Ultra Low-Dose Transdermal Estrogen Replacement Assessment; vs. = versus; WHI = Women's Health Initiative.

Appendix G Table 14. Evidence Table of Trials Reporting Incidence of Venous Thromboembolism

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
EMS Estrogen plus progestin trial Tierney, 2000[59]	70 Estrogen plus progestin 72 Placebo	**Followup: 2 years** **Deep vein thrombosis** 1 vs. 0; p=NS
EPAT Estrogen-only trial Hodis, 2001[60]	111 Estrogen 111 Placebo	**Followup: 2 years** **Deep vein thrombosis or pulmonary embolism** 0 (0.0%) vs. (0.0%)
EPHT Estrogen plus progestin trial Veerus, 2006[61]	404 Estrogen plus progestin 373 Placebo	**Followup: Mean 3.4 years** **Venous thromboembolism** 0 (0.0%) vs. 0 (0.0%)
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[62]	100 Estrogen 104 Estrogen plus progestin 105 Placebo	**Followup: 3.2 years** 1 vs. 0 vs. 0; p=0.35
Greenspan, et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[65]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Followup: 3 years** **Deep vein thrombosis** *Analysis did not stratify by regimen* 2 vs. 1 ; p=1.0
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[75]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Followup: 3 years** **Deep vein thrombosis** *Analysis did not stratify by regimen* 4 (hormone therapy with or without calcitriol) vs. 1 (calcitriol only or placebo)
WAVE Estrogen-only and estrogen plus progestin trial Waters, 2002[80]	Women with a coronary stenosis of 15%–75% 124 Estrogen (with or without vitamins C and E) 86 Estrogen plus progestin (with or without vitamins C and E) 213 Placebo (with or without vitamins C and E)	**Followup: 2.8 years** **Deep vein thrombosis or pulmonary embolism** *Analysis did not stratify by treatment regimen* 4 vs. 4; p=0.93
WHI Estrogen-only trial LaCroix, 2011;[112] Curb, 2006[109] Prentice, 2009;[98] Manson, 2013[102]	5,310 Estrogen 5,429 Placebo Postintervention followup: 3,778 Estrogen 3,867 Placebo	**Followup: Mean 7.1 years**[102, 112] **Deep vein thrombosis** 85 (1.6%) vs. 59 (1.0%); HR, 1.48 (95% CI, 1.06 to 2.07); p=0.02 **Pulmonary embolism** 52 (0.98%) vs. 39 (0.72%); HR, 1.35 (95% CI, 0.89 to 2.05); p=0.15 **Subgroups:**[109] No significant difference by race or ethnicity, age, or history of CVD **Risk for venous thromboembolism based on timing of intervention:**[98] No significant association; p for gap time interaction=0.65

Appendix G Table 14. Evidence Table of Trials Reporting Incidence of Venous Thromboembolism

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
		Followup: Mean 3.9 years postintervention[112] **Deep vein thrombosis** HR, 0.63 (95% CI, 0.41 to 0.98); p=0.003 **Pulmonary embolism** HR, 0.98 (95% CI, 0.62 to 1.55); p=0.29 **Cumulative followup: Median 13.0 years**[102] **Deep vein thrombosis** HR 1.05 (95% CI, 0.82 to 1.33) **Pulmonary embolism** HR, 1.15 (95% CI, 0.87 to 1.51)
WHI Estrogen plus progestin trial Heiss, 2008;[92] Cushman, 2004;[89] Manson, 2013;[102] Prentice, 2009[98]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,052 Estrogen plus progestin 7,678 Placebo	**Followup: Median 5.6 years** **Venous thrombosis**[89] 167 vs. 76; HR, 2.06 (95% CI, 1.57 to 2.70) **Deep vein thrombosis**[102] 122 (1.4%) vs. 61 (0.8%); HR, 1.87 (95% CI, 1.37 to 2.54); p<0.001 **Pulmonary embolism**[102] 87 (1.0%) vs. 41(0.5%); HR, 1.98 (95% CI, 1.36 to 2.87); p<0.001 **Subgroups:**[102] No significant difference by age **Risk for venous thromboembolism based on timing of intervention:**[98] No significant association; p for gap time interaction=0.45 **Followup: Mean 2.4 years postintervention**[92] **Deep vein thrombosis** HR, 1.07 (95% CI, 0.66 to 1.75) **Pulmonary embolism** HR 1.07 (95% CI, 0.62 to 1.86) **Cumulative Followup: Median 13.0 years**[89, 92, 102] **Deep vein thrombosis** HR, 1.05 (95% CI, 0.82 to 1.33) **Pulmonary embolism** HR 1.15 (95% CI, 0.87 to 1.51)

[a] Intervention dosages are listed in Table 3 by trial.

Abbreviations: CI = confidence interval; CVD = cardiovascular disease; EMS = Estrogen Memory Study; EPAT = Estrogen in the Prevention of Atherosclerosis; EPHT = Estonian Postmenopausal Hormone Therapy Trial; ERA = Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis; HR = hazard ratio; NS = not sufficient; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WAVE = The Women's Angiographic Vitamin and Estrogen Trial; WHI = Women's Health Initiative.

Appendix G Table 15. Evidence Table of Trials Reporting Incidence of Quality of Life

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
WHI Estrogen-only trial Manson, 2013[102]	5,310 Estrogen 5,429 Placebo	**Followup: Mean 7.1 years**[102] RAND 36: Similar scores on all items except for emotional role (81.0 vs. 82.2, p=0.04) and social functioning (85.8 vs. 86.9, p=0.01) for which women on placebo had statistically significantly better scores than women on estrogen-only therapy
WHI Estrogen plus progestin trial Manson, 2013;[102] Hays, 2003[91]	8,506 Estrogen plus progestin 8,102 Placebo	**Followup: Mean 5.6 years**[102] RAND 36: Similar scores on all items except for physical functioning (82.6 vs. 81.8, p<0.001), physical role (77.4 vs. 76.2, p=0.02), bodily pain (77.6 vs. 75.6, p<0.001), and general health (76.6 vs. 76.1, p=0.02) for which women on hormone therapy had statistically significantly better scores than women on placebo

[a] Intervention dosages are listed in Table 3 by trial.

Abbreviation: WHI = Women's Health Initiative.

Appendix G Table 16. Evidence Table of Trials Reporting Incidence of All-Cause Mortality

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[62]	100 Estrogen 104 Estrogen plus progestin 105 Placebo	**Followup: Mean 3.2 years** 8 (8.0%) vs. 3 (2.9%) vs. 6 (5.7%); p=0.28
ESPRIT Estrogen-only trial Cherry, 2002;[63] Cherry, 2014[64]	513 Estrogen 504 Placebo	**Followup: 2 years**[63] 32 (6.2%) vs. 39 (7.7%); Rate ratio, 0.79 (95% CI, 0.50 to 1.27); p=0.34 **Cumulative followup: Mean 14.1 years**[64] HR, 1.07 (95% CI, 0.88-1.29)
HERS Estrogen plus progestin trial Hulley, 2002[68]	1,380 Estrogen plus progestin 1,383 Placebo Cumulative followup: 1,156 Estrogen plus progestin 1,383 Placebo	**Followup: Mean 4.1 years** 130 (9.4%) vs. 123 (8.9%); HR, 1.06 (95% CI, 0.83 to 1.36); p=0.62 **Cumulative followup: Mean 6.8 years** HR, 1.10 (95% CI, 0.92 to 1.31); p=0.29
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[75]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Followup: 3 years** *Analysis did not stratify by regimen* 3 (hormone therapy with or without calcitriol: 1.2%) vs. 2 (calcitriol only or placebo: 0.8%)
WAVE Estrogen-only and estrogen plus progestin trial Waters, 2002[80]	124 Estrogen (with or without vitamins C and E) 86 Estrogen plus progestin (with or without vitamins C and E) 213 Placebo (with or without vitamins C and E)	**Followup: Mean 2.8 years** *Analysis did not stratify by treatment regimen* 14 (6.7%) vs. 8 (3.8%)
WHI Estrogen-only trial LaCroix, 2011;[112] Manson, 2013;[102] Prentice, 2009[98]	5,310 Estrogen 5,429 Placebo	**Followup: Mean 7.1 years**[112] 300 (5.6%) vs. 297 (5.5%); HR, 1.04 (95% CI, 0.89 to 1.22) **Subgroups:**[112] Among women 50–59 years at randomization: HR, 0.73 (95% CI, 0.53 to 1.00) Among women 60–69 years at randomization: HR, 1.04 (95% CI, 0.88 to 1.24) Among women 70–79 years at randomization: HR, 1.12 (95% CI, 0.94 to 1.33) p for trend=0.04 **Risk for death based on timing of intervention:**[98] **Among women without prior HT use** No significant association; p for gap time interaction=0.14 **Followup: Mean 3.9 years postintervention**[112] HR, 1.00 (95% CI, 0.84 to 1.18) **Cumulative followup: Mean 10.7 years**[112] HR, 1.02 (95% CI, 0.91 to 1.15)

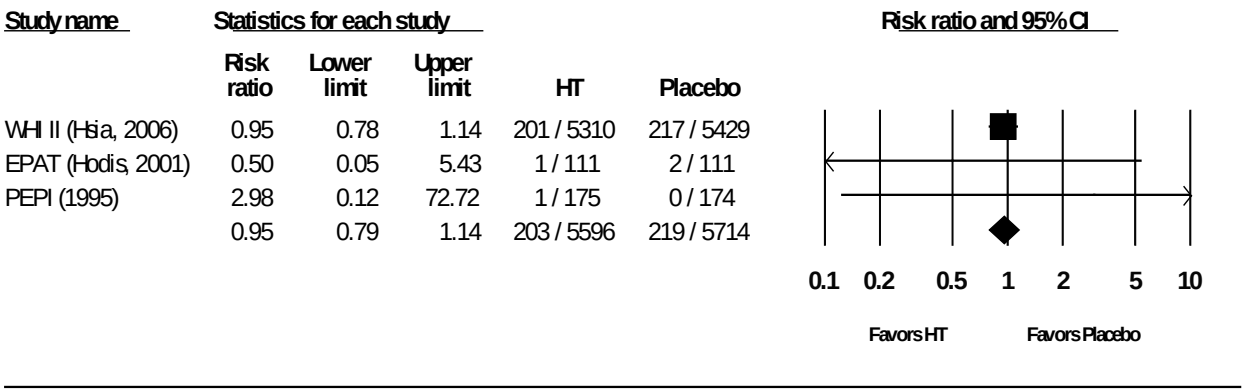
Appendix G Table 16. Evidence Table of Trials Reporting Incidence of All-Cause Mortality

Study Author, Year	Population	Results (Treatment[a] vs. Placebo)
WHI Estrogen plus progestin trial Heiss, 2008;[92] Manson, 2013;[102] Prentice, 2009[98]	8,506 Estrogen plus progestin 8,102 Placebo	**Followup: Mean 5.6 (weighted mean 5.2) years**[92] 250 (2.9%) vs. 239 (2.9%); HR, 0.97 (95% CI, 0.81 to 1.16) **Risk for death based on timing of intervention:**[98] No significant association; p for gap time interaction=0.36 **Followup: Mean 2.4 years postintervention**[92] HR, 1.15 (95% CI, 0.95 to 1.39) **Of those who adhered to ≥80% of medication**[92] HR, 1.53 (95% CI, 1.04 to 2.24) **Followup: Median 8.2 years postintervention**[102] HR, 1.01 (95% CI, 0.91 to 1.11); p=0.90

[a] Intervention dosages are listed in Table 3 by trial.

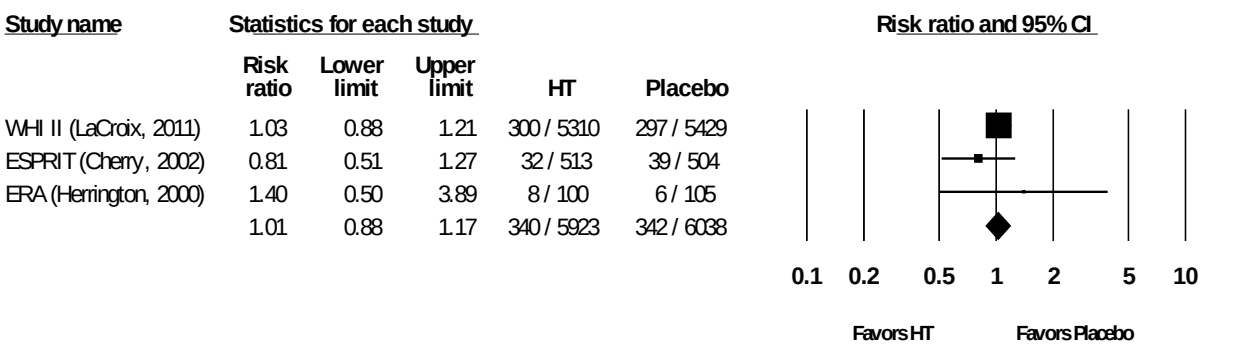
Abbreviations: CI = confidence interval; ERA = Estrogen Replacement and Atherosclerosis Trial; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; HT = hormone therapy; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WAVE = Women's Angiographic Vitamin and Estrogen Trial; WHI = Women's Health Initiative.

Appendix H Figure 1. Forest Plot of Meta-analyses: Estrogen Only, Coronary Heart Disease



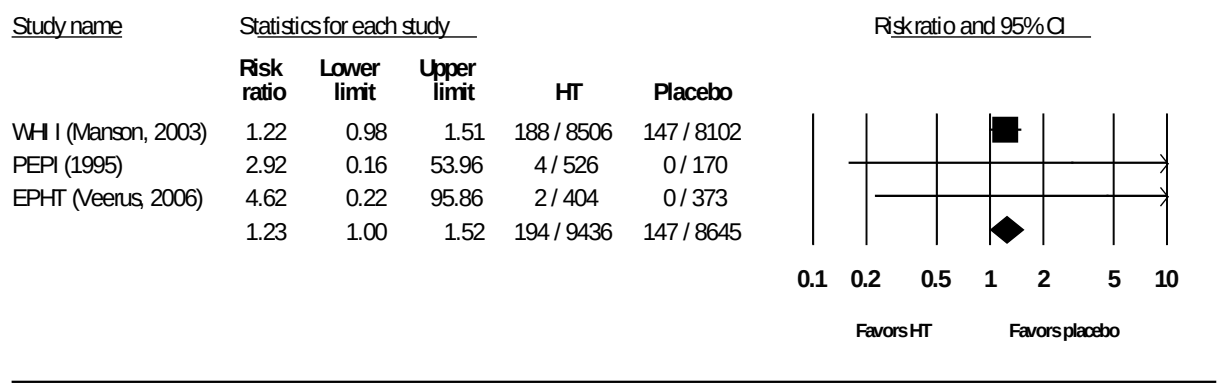
Abbreviations: CI = confidence interval; EPAT = Estrogen in the Prevention of Atherosclerosis Trial; HT = hormone therapy; PEPI = Postmenopausal Estrogen/Progestin Interventions; WHI = Women's Health Initiative.

Appendix H Figure 2. Forest Plot of Meta-analyses: Estrogen Only, All-Cause Mortality



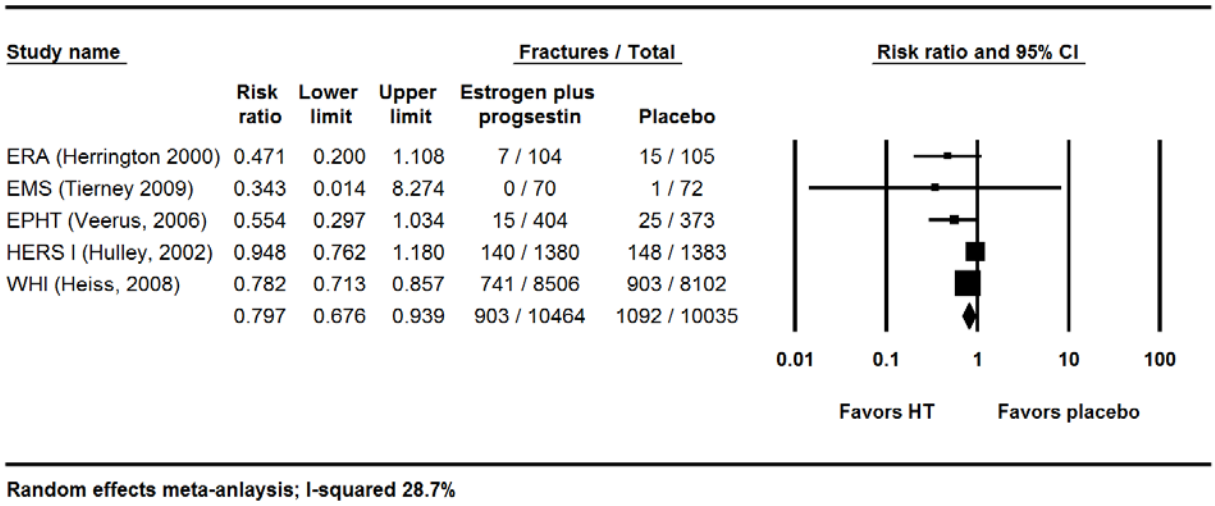
Abbreviations: CI = confidence interval; ERA = Estrogen Replacement and Atherosclerosis Study; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HT = hormone therapy; WHI = Women's Health Initiative.

Appendix H Figure 3. Forest Plot of Meta-analyses: Estrogen Plus Progestin, Coronary Heart Disease



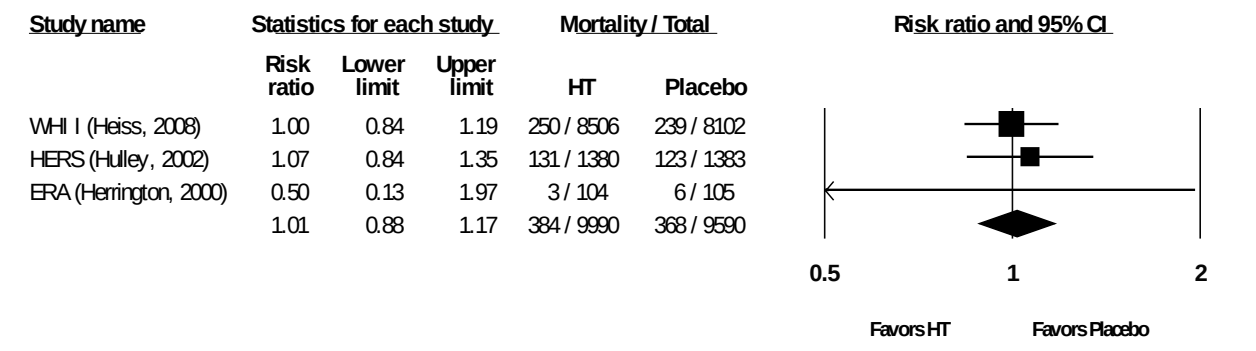
Abbreviations: CI = confidence interval; EMS = Estrogen Memory Study; EPHT = Estonian Postmenopausal Hormone Therapy Trial; HT = hormone therapy; PEPI = Postmenopausal Estrogen/Progestin Interventions; WHI = Women's Health Initiative.

Appendix H Figure 4. Forest Plot of Meta-analyses: Estrogen Plus Progestin, Fractures



Abbreviations: CI = confidence interval; EMS = Estrogen Memory Study; EPHT = Estonian Postmenopausal Hormone Therapy Trial; ERA = Estrogen Replacement and Atherosclerosis Study; HERS = Heart and Estrogen Replacement Study; HT = hormone therapy; WHI = Women's Health Initiative.

Appendix H Figure 5. Forest Plot of Meta-analyses: Estrogen Plus Progestin, All-Cause Mortality



Abbreviations: CI = confidence interval; ERA = Estrogen Replacement and Atherosclerosis Study; HERS = Heart and Estrogen Replacement Study; HT = hormone therapy; WHI = Women's Health Initiative.