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

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Structured Abstract

Background: Hormone therapy plays an important role in the clinical management of menopausal symptoms. Because of an increased risk of harms, 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 risk of 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 October 12, 2021). We conducted searches for unpublished literature by searching ClinicalTrials.gov, HSRProj, the World Health Organization's International Clinical Trials Registry Platform, and NIH RePORTER.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. We conducted surveillance of the literature through June 1, 2022.

Study Selection: We dually reviewed the literature and included randomized, placebo-controlled trials and large controlled cohort studies 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: Twenty fair- or good-quality trials and three large controlled cohort studies met eligibility criteria. The Women's Health Initiative was the largest study and most applicable to the target population.

Results of our review indicate differences in the risk-benefit profile between treatment formulations. Women using estrogen only had statistically significantly lower risk (per 10,000 women over 6.8 to 7.2 years) of diabetes (134 fewer cases) and fractures (388 fewer cases) than women taking placebo. However, risk (per 10,000 women over 5.4 to 7.1 years) was statistically significantly increased for gallbladder disease (377 more cases), stroke (79 more cases), and venous thromboembolism (77 more cases).

Women using estrogen plus progestin therapy experienced statistically significantly lower risk (per 10,000 women over 5.0 to 5.6 years) for colorectal cancer (34 fewer cases), diabetes (78 fewer cases), and fractures (230 fewer cases) than women taking placebo. Risk (per 10,000 women over 4 to 5.6 years) of invasive breast cancer (51 more cases), probable dementia (88 more cases), gallbladder disease (260 more cases), stroke (52 more cases), and venous thromboembolism (120 more cases) was statistically significantly increased compared with women taking placebo. The risk of urinary incontinence (562 more cases per 10,000 women) was increased during a followup of 1 year.

Meta-analyses rendered no statistically significant differences in all-cause mortality between women receiving hormone therapy and those receiving placebo (over 2 to 7.2 years for estrogen-only therapy and over 3.2 to 5.6 years for estrogen plus progestin therapy).

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 to manage menopausal symptoms and to women of non-White ethnic backgrounds might be limited.

Conclusions: Women undergoing hormone therapy for the primary prevention of chronic conditions experience some beneficial effects but also an increased risk of harms.

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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 2017 recommendation on the use of hormone therapy for postmenopausal persons[a] to prevent chronic health conditions such as cardiovascular disease, types of cancer, and osteoporotic fractures.[1] In 2017, the USPSTF recommended against the use of estrogen plus progestogens for the prevention of chronic conditions in postmenopausal persons (grade D recommendation) and against the use of estrogen for the prevention of chronic conditions in postmenopausal persons who have had a hysterectomy (grade D recommendation).[1] These recommendations do not apply to persons with primary ovarian insufficiency or who have had surgical menopause.

The purposes of this report are to update evidence about the benefits and harms of systemic hormone therapy for preventing chronic conditions in postmenopausal persons and to examine whether outcomes vary among persons in different subgroups. While hormone therapy plays an important role in treatment of menopausal symptoms, such as vasomotor hot flashes, indications other than primary prevention of chronic health conditions are outside the scope of this review.

Condition Definition

Menopause is the cessation of the menstrual cycle and the end of 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 and late perimenopause are characterized by variable to progressive menstrual irregularity, respectively. 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. Menopause transition is the period of time with menstrual irregularity prior to the final menstrual period. Although current use of hormone therapy targets the earlier stages of menopause for the treatment of menopause-associated symptoms,[4] in the past, hormone therapy was prescribed across the stages of menopause for chronic conditions.

"Chronic conditions" are broadly defined as conditions that last 1 or more years and require ongoing medical attention, limit activities of daily living, or both. The following are classified as major chronic diseases by the Centers for Disease Control and Prevention because they are leading drivers of death, disability, and healthcare costs: heart disease, cancer, chronic lung disease, stroke, Alzheimer's disease, diabetes, and chronic kidney disease.[5] These conditions all

[a] We refer to postmenopausal persons in overview sections of the report to be as inclusive as possible. However, most studies were limited to generally healthy perimenopausal and postmenopausal women who have traditionally been targeted for hormone therapy, and we use the term "women" when discussing individual and pooled study results.

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 some of these conditions based on evidence from observational studies,[6, 7]

Prior to 2002, 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[8, 9] (as well as increased incidence of biomarkers associated with chronic conditions, such as elevated lipid levels[10]) and 2) several observational studies and meta-analyses suggesting that hormone therapy including estrogen was beneficial for the prevention of chronic diseases such as coronary heart disease, osteoporosis, dementia, and all-cause mortality.[6, 11-13] Before the publication of randomized, controlled trials (RCTs) of hormone therapy in postmenopausal persons, guidelines advocated for the use of hormone therapy for prevention of chronic diseases, and it was commonly prescribed for primary prevention of these conditions and others such as osteoporosis in persons without menopausal symptoms.[14] After the publication of RCTs, the indication for hormone treatment shifted toward menopausal symptom management in the earlier stages of menopause.

Prevalence and Burden

Natural menopause occurs at a median age of 51.3 years.[15] Premature menopause (defined as menopause that occurs before the age of 40 years) may be induced by surgery (bilateral oophorectomy), chemotherapy, or radiation; in the absence of one of these causes, menopause before age 40 years is referred to as primary ovarian insufficiency.[16] In some persons, menopause is associated with its own morbidity. Approximately 85 percent of persons 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.[15, 17] Vasomotor symptoms in particular are reported by 80 percent of menopausal persons and persist for a median of 7.4 years.[18]

The prevalence and incidence of most chronic diseases increase with age, and the average U.S. person who reaches menopause is expected to live another 30 years.[19] However, the excess risk for chronic conditions 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[17] and 2) chronic conditions are multifactorial. In a recent scientific statement, the American Heart Association identified the menopausal transition as a time of accelerating cardiovascular risk,[20] associated with increases in lipid levels (cholesterol, low-density lipoprotein, and apolipoprotein B) independent of aging alone[21, 22] and adverse vascular changes (carotid atherosclerosis and arterial stiffness) not explained by aging or traditional cardiovascular risk factors.[23, 24] The American Heart Association concluded that future risk assessment guidelines should include menopause among cardiovascular risk factors in women.[20] Meta-analyses pooling data across 32 observational studies show persons with early-onset menopause (<45 years of age) have significantly increased risk of overall and fatal coronary heart disease compared with persons with menopause ≥ 45 years,[25] though data are conflicting regarding older

ages of natural menopause and associated cardiovascular risk. Data suggest that timing of surgical menopause relative to natural menopause affects cardiovascular risk; in a 2007 review, there was limited association between surgical menopause and cardiovascular disease risk when bilateral oophorectomy occurred around the time of natural menopause, although coronary heart disease risk was significantly higher if surgery was performed at a younger age (<40–45 years).[26]

Interventions

Hormone Therapy

Currently, hormone therapy is approved by the U.S. Food and Drug Administration[27] only for treatment of menopausal symptoms and prevention, and treatment of osteoporosis, with the recommendation to use hormone therapy at the lowest dose that relieves symptoms and for the shortest time needed.[28] Hormone therapy includes the use of various forms, doses, and regimens of estrogen with or without progestogen (progestin or progesterone).[27] Persons who have not had a previous hysterectomy should use a combination therapy of estrogen plus progestogen (sometimes denoted combined hormone therapy, but hereafter in this report specified as estrogen plus progestogen) to prevent endometrial proliferation and endometrial cancer, whereas persons with a previous hysterectomy should use only estrogen (estrogen-only hormone therapy). Products approved for use in the United States are listed in **Table 1**.

Hormone therapy can be taken orally, vaginally, or intranasally or as an implant, skin patch, cream, gel, or spray. Formulations of oral estrogen may include estradiol (derived from the Mexican yam), estradiol valerate (a prodrug for estradiol), ethinyl estradiol, estropipate, estradiol acetate, esterified estrogens, synthetic conjugated estrogen (prepared from plant sources), or conjugated equine estrogen (derived from horse mare urine).[29] Observational studies suggest that oral estrogen may carry a higher risk of venous thromboembolism compared with transdermal estrogen,[30] and a large case-control study did not observe an elevated risk of venous thromboembolism in individuals using transdermal estrogen across several different regimens.[31]

The progestogens include synthetic derivatives of progesterone or progestins (e.g., norethindrone acetate, levonorgstrel, drosperinone, norgestimate, and medroxyprogesterone acetate) and natural progesterones derived from plants (e.g., orally administered micronized progesterone) and identical to the steroid produced by the corpus luteum. Progestins and micronized progesterone differ in that micronized progesterone appears metabolically neutral with lower risk of adverse effects on blood lipids, breast tenderness, and headaches, although data are limited.[29, 32] For estrogen plus progestogen therapy, progestogen can be taken either every day (continuous combined therapy) or cyclically with estrogens taken daily and progestogen taken for part of the month (sequentially combined hormone therapy).

A systematic review supported by the Agency for Healthcare Research and Quality (AHRQ) synthesized evidence from 283 RCTs, 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.[33] The authors concluded that estrogens are the most effective treatment for vasomotor symptom

relief and confer the greatest improvement in quality-of-life measures with high strength of evidence for both outcomes compared with nonhormonal treatments, which had lower effect sizes and strength of evidence. The authors concluded that compared with placebo, nonhormonal treatments show similar effects as estrogens for other common symptoms, such as psychological symptoms, urogenital symptoms, and sleep disturbance.[33] The review also highlighted potential long-term harms of long-term hormone therapy, including increased risk of venous thromboembolism, stroke, breast cancer, and other conditions.

Current Clinical Practice

The number of persons using menopausal hormone therapy has declined significantly in recent years.[34] 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.[35] Results from the Women's Health Initiative (WHI),[36, 37] a large U.S.-based RCT of hormone therapy versus placebo, were first released in 2002; findings indicated that hormone therapy use was 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. The reduction in hormone therapy has been sustained: in 2010, the prevalence of hormone therapy use in the National Health and Nutrition Examination Survey was estimated at 4.7 percent overall, and the Study of Women's Health Across the Nation estimated initiation of menopausal hormone therapy of 2.8 percent in 2013 compared with 8.6 percent before the WHI.[38, 39] A growing proportion of hormone therapy users have turned to compounded bioidentical hormone therapy as an alternative to Food and Drug Administration (FDA)-approved hormone therapies,[40] considering them safer or "more natural" than medications studied in trials. However, professional societies have recommended against the use of compounded bioidentical hormone therapy because of the lack of regulatory oversight and lack of scientific evidence for efficacy or safety.[41]

Despite an overall decline in hormone therapy use, some current recommendations by professional societies consider the use of hormone therapy for prevention in some cases and advocate hormone therapy use to treat menopausal symptoms. For example, some guidelines recommend considering hormone therapy for persons at increased risk of osteoporosis and fracture.[42-44] Some organizations also cite data suggesting that the overall net benefit of hormone therapy use may be increased for persons who initiate treatment during the menopause transition or early postmenopause rather than late postmenopause and can be considered in patients with vasomotor symptoms.[42, 44] This approach is often referred to as the "timing hypothesis" (i.e., a critical window for favorable outcomes of hormone therapy treatment).[45] The hypothesis proposes that hormone therapy given at or soon after menopause reduces the risk of cardiovascular disease, but the potential beneficial effects are attenuated or not experienced when hormone therapy is initiated several years after menopause.[46]

The timing hypothesis arose initially from data from the Framingham study, which indicated that natural menopause increases the risk of cardiovascular disease. Studies in female monkeys[47] and large observational studies in women[6, 48, 49] showed 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,[50] reduced risk of dementia, and better cognition.[51] 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, although most differences did not reach statistical significance.[52] Two RCTs assessing the intermediate cardiovascular outcome of carotid artery intima-media thickness showed mixed results regarding the timing hypothesis.[46, 53]

Summary of Guidelines From Other Groups

Several organizations have issued clinical practice guidelines related to using hormone therapy in postmenopausal persons 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. The American College of Obstetricians and Gynecologists guidelines,[42] the American Association of Clinical Endocrinologists guidelines,[43] and the North American Menopause Society[44] note that hormone therapy is FDA approved for persons at increased risk of osteoporosis and fracture. The American College of Obstetricians and Gynecologists guidelines also mention the uncertainty about whether the potential cardiovascular benefits may differ based on early versus late initiation of hormone therapy.[42, 44] The North American Menopause Society guidelines[44] focus primarily on considerations for persons with symptoms; they note that the balance of potential health benefits and risks should be weighed individually for each person.

Chapter 2. Methods

Key Questions and Analytic Framework

The investigators, USPSTF members, and AHRQ Medical Officers developed the scope, key questions (KQs), and analytic framework (**Figure 1**) that guided our literature search and review. Specifically, the KQs were:

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 when used for the primary prevention of chronic conditions differ by subgroup (race or ethnicity; women with premature menopause; women with surgical menopause; age during use; duration of use; type, dose, and mode of delivery; and comorbid condition) or by timing of intervention (initiation during perimenopause vs. postmenopause)?

We also looked to 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?

Data Sources and Searches

For this update, we searched MEDLINE® (via PubMed), the Cochrane Library, and Embase for English-language articles published from January 1, 2016, through January 28, 2021. We conducted a bridge search on October 12, 2021, and surveillance through June 1, 2022. We used Medical Subject Headings as search terms when available and keywords when appropriate. **Appendix A** describes the search strategies in detail.

We conducted targeted searches for unpublished literature by searching ClinicalTrials.gov, HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and Drugs@FDA.gov. 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. Additionally, to ensure that our update was cumulative of all relevant evidence, we reviewed included citations from recent systematic reviews[54-60] and included all relevant citations that met our criteria for fair or good quality. (We also manually reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.)

Since January 2021, we conducted active surveillance of the literature through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that

may affect the conclusions or understanding of the evidence and the related USPSTF recommendation.

Study Selection

We selected hormone therapy studies using inclusion and exclusion criteria that we developed for each KQ based on population, intervention, comparator, outcome, timing, and setting and other elements such as study designs. The basic criteria are described below, and **Appendix B** provides more details. For this update, we excluded populations who used hormone therapy for secondary prevention of chronic conditions.

In addition to the searches for the updated literature, we incorporated all except one included citation from the previous reports, which covered the publication period of January 2002 through August 2016.[61, 62] We excluded the Oestrogen in the Prevention of Reinfarction Trial because it assessed secondary prevention.[63]

Populations

We included studies of generally healthy perimenopausal and postmenopausal women who were eligible for 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 the harms of hormone therapy.

Interventions

We included studies that examined the use of systemic therapy with estrogen-only formulations or combination preparations of estrogen plus progestogens for the primary prevention of chronic conditions. We limited our evaluation to medications that have been approved by the FDA 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 (i.e., patch, pill, or injection), 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 progestogens).

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 incidence outcomes for the following: several types of cancer (breast, cervical, endometrial, ovarian, colorectal, non-Hodgkin's lymphoma, and lung), coronary heart disease,

stroke (ischemic and hemorrhagic), and thromboembolism (deep vein thrombosis and pulmonary embolism). We also included trials that assessed cognitive functioning and dementia, diabetes, fractures, gallbladder disease (cholecystitis and cholelithiasis), chronic obstructive pulmonary disease (COPD), peripheral arterial disease, quality of life, and urinary incontinence (stress, urge, and overall). Finally, we included studies that measured disease-specific and all-cause mortality.

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

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).

Settings

For all KQs, we included trials conducted in all primary care or primary care–like settings but not 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.[64]

Study Designs

In our searches, we included the following study designs: RCTs, controlled trials, and systematic reviews. We also included large, controlled cohort studies (>10,000 women) for outcomes for which we had little or 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 risk 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 for most outcomes, we used observational studies only to address outcomes for which we had no or very little evidence from RCTs. Systematic reviews were used only to identify studies (from their reference lists) that we might otherwise have missed.

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 or with a third reviewer if necessary.

Subgroups

Our subgroups of interest included race/ethnicity; women with premature menopause (defined as women who experienced menopause before the age of 40); women with surgical menopause

(defined as women who underwent bilateral oophorectomy before natural menopause); age during use; duration of use; type, dose, and mode of delivery; and comorbid conditions.

Data Abstraction and Quality Rating

One reviewer abstracted pertinent information from each included study, including study characteristics (i.e., population, intervention, comparator) and data for eligible outcomes, into a structured form. A second investigator checked all data abstractions for completeness and accuracy. We resolved differences by consensus or adjudication by a third senior investigator. We contacted study authors to clarify data when needed.

Using predefined criteria developed by the USPSTF, two investigators independently assessed the quality of each study as good, fair, or poor.[65] The USPSTF criteria are listed in **Appendix C**. 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, high overall or differential attrition, and use of unreliable or invalid measurement instruments or unequal application among groups (including not masking outcome assessment). For RCTs, 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.[66] To do this, we qualitatively assessed the populations, similarities and differences in treatments used, and similarities in outcomes and timing of outcomes assessed.

Our analysis prioritized outcomes that were prespecified by study authors. 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. Based on a communication with the WHI Researcher Help Desk (https://www.whi.org/helpdesk; July 2021), we relied on a publication by Manson et al.[67] for results of patient-reported outcomes (i.e., diabetes, urinary incontinence, gallbladder disease).

When at least three similar trials were available, we conducted quantitative synthesis of studies with random-effects models (restricted maximum likelihood method). 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 chance) to assess statistical heterogeneity in effects between studies.[68, 69] An I^2 from 0 to 40 percent might not be important, 30 to 60 percent may represent moderate heterogeneity, 50 to 90 percent may represent

substantial heterogeneity, and 75 percent or greater represents considerable heterogeneity.[70] The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence (SOE) 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.[71] We conducted all the quantitative analyses using Stata 16.1 (StataCorpLLC, College Station, TX).

We rated the SOE for each major outcome for each KQ using the domains set out in the AHRQ guidance:[72] study limitations,[73] consistency,[74] precision,[75] directness,[76] and reporting bias.[77] 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).[78]

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

A draft research plan for this topic was posted on the USPSTF website for public comment from February 18, 2021, to March 17, 2021. In response, we added language to clarify the term "chronic conditions" based on a definition of the Centers for Disease Control and Prevention. The final version of the research plan was posted on the USPSTF website on May 27, 2021.

A draft report was reviewed by four content experts, five representatives of Federal partners, USPSTF members, and AHRQ Medical Officers and was revised based on comments received. In response to these comments, we provided additional information regarding overall mortality in the abstract, clarified the definition of subgroups, and emphasized in the Introduction that this report does not address hormone therapy for the treatment of menopausal symptoms.

The draft evidence report was posted on the USPSTF website for public comment from April 19, 2022, to May 16, 2022. In response to public comments, we added three publications which met inclusion criteria but were not part of this evidence report. Two studies of WHI data were of moderate risk of bias and did not detect any statistically significant differences in the risk of peripheral arterial disease in women taking estrogen-only[79] or a combination of estrogen and

progesterone.[80] One study on atrial fibrillation linked data from the WHI with data from the Centers for Medicare and Medicaid Services.[81] We rated this study as high risk of bias because of potential assessment bias and did not include it in the evidence synthesis of the report. Overall, these three studies did not change any conclusions of the evidence report.

USPSTF and AHRQ Involvement

Members of the USPSTF helped to develop the scope of the work, including the analytic framework and KQs, and to review the evidence synthesis. AHRQ staff provided project oversight, conducted reviews of the draft report, and helped facilitate an external review of the evidence synthesis.

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 hormone therapy that our searches might have missed. Furthermore, because we had sufficient evidence from randomized trials for most outcomes, we used observational studies only to address outcomes for which we had no or very little evidence from RCTs.

Following those sections, we present a summary of the available trial evidence regarding benefits and harms (KQ 1 and KQ 2) and differences in effects among 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 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

For this update, we identified 2,208 citations. Of these, we excluded 1,920 abstracts and reviewed 288 full-text articles; we also reviewed 68 full-text articles included in the previous review. We retained 20 new articles reporting on three new trials, two previously included trials, and three new observational studies; we retained 30 additional articles that met inclusion criteria for observational studies. Combined with articles we carried forward from the previous review, we included 85 articles representing 20 unique fair- or good-quality trials and three large controlled cohort studies (**Figure 2**). **Appendix D** lists articles excluded at full-text review, and **Appendix E** provides quality ratings for included studies and studies excluded for poor quality.[81-86]

Description of Trials

The 20 RCTs provided data on 39,145 perimenopausal and postmenopausal women comparing the effects of estrogen, either alone or in combination with progestin, versus placebo for the prevention of chronic conditions (**Table 3**).

Of the 20 included trials, 17 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 4.3 years. The mean age of women participating in trials ranged from 53 (Kronos Early Estrogen Prevention Study–Cognitive and Affective [KEEPS-Cog]) to 75 years (Estrogen Memory Study [EMS]). The majority of women were White; the proportions of non-White women ranged from 1 (Women's International Study of Long Duration Oestrogen After Menopause [WISDOM]) to 43 percent (Estrogen in the Prevention of

Atherosclerosis [EPAT]). The proportions of women with previous or current hormone therapy use ranged from 2 to 74 percent. Between 3 and 58 percent of women in the trials were current smokers.

Most studies assessed conjugated estrogens with or without progestogen. The majority of FDA-approved hormone therapy formulations have not been assessed in clinical trials. **Table 4** presents approved hormone therapy formulations and the number of included trials using these formulations. Of the 20 included studies, the WHI trials[67] 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 0.625 mg/day of oral conjugated equine estrogen with or without 2.5 mg/day of medroxyprogesterone with placebo. The WHI trials also had the longest durations of followup among included trials (median intervention of 7.2 years for the estrogen-only trial and 5.6 years for the estrogen plus progestin trial; long-term followup of up to 20.4 years).

Table 5 presents baseline characteristics of participants in the included trials.

Summary of Evidence

The WHI reported most of the results and was most applicable to the target population of interest to the USPSTF. This summary section provides an overview of results. More detailed findings by chronic condition and regimen follow this summary.

Figures 3 and **4** depict the absolute risk reductions or increases for various benefit or harm outcomes of interest for women who received hormone therapy for 5 to 7 years compared with those who received 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 3 and **4** also present the relative risk (RR) and the SOE for each outcome. We calculated RRs based primarily on a publication summarizing results of the WHI trials.[67] Therefore, effect estimates might differ slightly from hazard ratios (HRs) reported in WHI publications. We chose RR because it is more intuitive to interpret than HR.

Outcomes associated with a statistically significant benefit of treatment included a reduction of fractures, diabetes, and colorectal cancer. Outcomes associated with statistically significant harm included probable dementia, gallbladder disease, stroke, urinary incontinence, and venous thromboembolism; these are described below. Some of the statistically nonsignificant 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?

Compared with the 2017 review, we added 20 new publications[79, 80, 87-104] of three new trials, two previously included trials, and three new observational studies. We excluded one RCT,[63] which was conducted in persons who took hormone therapy for the secondary prevention of cardiovascular events. The majority of the new publications reported long-term results of WHI. Three ancillary studies of previously reported RCTs assessed cognitive functioning. Despite this change in the body of evidence, the overall conclusions about the benefits of hormone therapy for the primary prevention of chronic conditions remain unchanged from the prior report.

Overall, trials reported several statistically significant benefits of treatment. For women using estrogen only, risk of fractures (388 fewer cases per 10,000 women over 7.2 years [95% CI, 489 to 277 fewer]) and diabetes (134 fewer cases per 10,000 women over 7.1 years [95% CI, 237 to 18]) were statistically significantly reduced compared with women taking placebo (**Figure 3**). The risk of breast cancer was numerically reduced but did not reach statistical significance (HR, 0.79 [95% CI, 0.61 to 1.02]).

Women using estrogen plus progestin therapy experienced statistically significantly reduced risk of colorectal cancer (34 fewer cases per 10,000 women over 5.6 years [95% CI, 9 to 51]), fractures (230 fewer cases per 10,000 women over 5.0 years [95% CI, 372 to 66 fewer]), and diabetes (78 fewer cases per 10,000 women over 5.6 years [95% CI, 133 to 15 fewer]) compared with women in the placebo groups (**Figure 4**).

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. The risk reduction became statistically significant during cumulative (trial and postintervention phase) followup (median 13 years: HR, 0.79 [95% CI, 0.65 to 0.97];[67] median 20.7 years: HR, 0.78 [95% CI, 0.65 to 0.93][87]). Likewise, after 13.2 years of cumulative followup, the risk for endometrial cancer became statistically significantly lower in women who were on estrogen plus progestin therapy (HR, 0.65 [95% CI, 0.48 to 0.89]). 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?

The 20 new publications also provided evidence on potential harms of hormone therapy.[79, 80, 87-104] Despite the new evidence, the overall conclusions about harms of hormone therapy remained unchanged from the prior report.

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 receiving estrogen-only therapy had statistically significantly increased risk of gallbladder disease (377 more cases per 10,000 women over 7.1 years [95% CI, 234 to 540]),

stroke (79 more cases per 10,000 women over 7.2 years [95% CI, 15 to 159]), urinary incontinence (885 more cases per 10,000 women over 1 year [95% CI, 659 to 1,135]), and venous thromboembolism (77 more cases per 10,000 women over 7.2 years [95% CI, 19 to 153]; **Figure 3**).

For women receiving estrogen plus progestin therapy, risk of invasive breast cancer (51 more cases per 10,000 women over 5.6 years [95% CI, 6 to 106]), probable dementia (88 more cases per 10,000 women over 4 years [95% CI, 15 to 212]), gallbladder disease (260 more cases per 10,000 women over 5.6 years [95% CI, 169 to 364]), stroke (52 more cases per 10,000 women over 5.6 years [95% CI, 12 to 104]), urinary incontinence (562 more cases per 10,000 women over 1 year [95% CI, 412 to 726]), and venous thromboembolism (120 more cases per 10,000 women over 5.6 years [95% CI, 68 to 185]) were statistically significantly increased compared with women taking placebo (**Figure 4**). We did not find any evidence on other harms or on the effect of harms on functional capacity.

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

Compared with the 2017 review, 12 new publications reported on subgroups or the timing of the intervention.[79, 80, 87-93, 95, 97, 102] Overall conclusions about differences in benefits and harms of hormone therapy for subgroups did not change in the updated report.

Subgroups specified for this KQ included the following: race/ethnicity; women with premature menopause; women with surgical menopause; age; duration of use; type, dose, and mode of delivery of hormone therapy; and presence of comorbid conditions. Trials did not report results for most of these subgroups. Subgroup analyses of trial results based on these characteristics were restricted to age, race/ethnicity, oophorectomy status, and a limited number of coexisting conditions or risk factors.

Some subgroup analyses indicated that age may modify the effects of hormone therapy. Analyses that compared younger (ages 50 to 59 years) with older (ages 70 to 79 years) women using estrogen-only therapy yielded a statistically significant trend for increasing risk by age of myocardial infarction (HR, 0.55 [95% CI, 0.31 to 1.00] vs. HR, 1.24 [95% CI, 0.88 to 1.75]; p=0.02 for trend),[67] colorectal cancer (HR, 0.71 [95% CI, 0.30 to 1.67] vs. HR, 2.24 [95% CI, 1.16 to 4.30]; p=0.02 for trend),[67] and all-cause mortality (HR, 0.71 [95% CI, 0.46 to 1.09] vs. HR, 1.22 [95% CI, 0.95 to 1.56]; p=0.04 for trend).[67] Post hoc subgroup analyses regarding the effects of time since menopause were inconclusive.

Some of these subgroup differences, however, are based on relatively few events and need to be interpreted cautiously. In addition, many of the subgroup analyses were post hoc analyses. In its study protocol, WHI specified age, race/ethnicity, obesity, hysterectomy, and cardiovascular disease at baseline as subgroups of interest.

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. We specifically comment on the various types of cancer (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 is presented last. We also address differences of effects by subgroups and by the timing of the intervention, when such data were available. **Appendix F** presents results of individual trials for each outcome in more detail. Although data from the four trials that did not stratify results by treatment regimen were not analyzed in our main analyses, they are included in Tables 1, 3, 4, 10, 13, 14, 15, 16, 17, 19, and 21 in **Appendix F**.[93, 105-107] In **Appendix G**, we present HRs for outcomes with results from three or more time points, and in **Appendix H**, we present meta-analyses. We present eligible observational studies in **Appendix I**. In **Appendix J**, we present literature addressing the contextual question on differences in hormone therapy use by subgroups. We did not find any evidence addressing the contextual question on average duration of hormone therapy use in women who initiate its use for the treatment of menopausal symptoms.

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 6**. In the sections that follow, 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). Furthermore, the same trial (e.g., WHI) may have reported a different sample size for different outcomes because of differences in missing baseline or followup data across the many various outcomes reported.

Estrogen Only: Cancer

Breast Cancer

Benefits and Harms of Hormone Therapy

Four RCTs (WHI [N=10,739],[37, 67, 87-91, 95, 101, 108-111] Estrogen in the Prevention of Atherosclerosis [EPAT] [N=222],[112] Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis [ERA] [N=205],[113] and Postmenopausal Estrogen and Progestin Interventions Trial [PEPI] [N=349][32]) comparing estrogen only with placebo reported on breast cancer incidence (**Appendix F Table 1**). We did not pool trial results, primarily because of heterogeneity in study duration and definitions of breast cancer incidence.

Only the WHI followed women for more than 3 years and reported on risk of invasive breast cancer (vs. any breast cancer). In the WHI, the decrease in invasive breast cancer risk among women assigned to estrogen alone 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]) was not statistically significant.[67, 108] The risk reduction became statistically significant during cumulative (trial and postintervention phase) followup (median 13 years: HR, 0.79 [95% CI, 0.65 to 0.97];[67] median

20.7 years: HR, 0.78 [95% CI, 0.65 to 0.93][87]). **Appendix G Figure 1** presents HRs for invasive breast cancer at different followup periods of the WHI. The three other trials reported on any breast cancer incidence over 2 to 3 years, and results were inconclusive.[32, 112, 113] Only four cases of breast cancer were reported across the trials (2 cases each in the estrogen-only and placebo groups).

Only the WHI reported on breast cancer mortality. During the 7.2-year intervention period, breast cancer mortality between the estrogen-only and the placebo group did not differ statistically significantly (HR, 0.45 [95% CI, 0.14 to 1.46]).[88] During cumulative followup at 17.7 years (HR, 0.55 [95% CI, 0.33 to 0.92])[88] and 20.7 years (HR, 0.60 [95% CI, 0.37 to 0.97]),[87] however, women who received only estrogen during the intervention phase had statistically significantly lower risk of breast cancer mortality than women who were in the placebo group. **Appendix G Figure 2** presents HRs for breast cancer mortality at different followup periods of the WHI.

Differences in Treatment Effects Based on Subgroups

In the WHI, no difference in risk for invasive breast cancer or breast cancer mortality by subgroups based on age,[67, 87, 88, 91] race,[87, 95] or oophorectomy status[89] could be detected.

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) vs. later (≥5 years).[110] During the 20.7-year cumulative followup, the risk remained similar.[87]

Cervical Cancer

We found no studies reporting cervical cancer incidence outcomes among women who received estrogen-only hormone therapy.

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 F Table 3**).[37, 67, 108, 110, 114]

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]).[67] Similarly, in the postintervention phase (median 6.6 years) and cumulative followup (median 13.0 years), there were no significant differences in colorectal cancer incidence among women receiving estrogen-only hormone therapy vs. placebo (HR, 1.10 [95% CI, 0.68 to 1.78] and HR, 1.13 [95% CI, 0.85 to 1.51], respectively).[67]

We identified one prospective cohort study with data on 85,734 postmenopausal women who have ever or never used hormone therapy (**Appendix F Table 3**).[103] During 16 years of followup, there were fewer cases of colorectal cancer among those who had ever taken estrogen-only therapy compared with those who had never used hormone therapy. Risk of colorectal cancer among ever and current users of estrogen-only therapy in this study was statistically significantly lower compared with never users (HR, 0.85 [95% CI, 0.76 to 0.94] and HR, 0.77 [95% CI, 0.66 to 0.89], respectively).

One publication of the WHI estrogen-only trial examined colorectal cancer mortality at the completion of the intervention phase (7.2 years' followup), the postintervention phase (10.8 years' followup), and cumulative followup at 17.7 years.[88] Colon cancer mortality did not differ statistically between treatment groups at any of the followup times (HR, 0.98 [95% CI, 0.50 to 1.95], HR, 1.36 [95% CI, 0.79 to 2.34], and HR, 1.21 [95% CI, 0.79 to 1.84] at each respective followup time).[88]

Differences in Treatment Effects Based on Subgroups

In the WHI intervention phase, there was a statistically significant trend toward higher risk of developing colorectal cancer in older women compared with younger women, relative to women taking placebo (p=0.02). Among women ages 50 to 59 years and 60 to 69 years at randomization, there were no statistically significant differences in the risk of colorectal cancer between women taking estrogen-only hormone therapy and placebo (HR, 0.71 [95% CI, 0.30 to 1.67] vs. HR, 0.88 [95% CI, 0.53 to 1.47], respectively). The risk of colorectal cancer among women ages 70 to 79 years was significantly higher for those taking estrogen-only therapy than for those taking 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[67] or 18.0 years.[91]

The WHI did not detect any statistically significant subgroup effects regarding race/ethnicity, diabetes status, previous use of menopausal hormone therapy, or bilateral oophorectomy status after a mean of 7.1 years.[114] Additionally, there were no differences by race[95] at cumulative followup of 13.0 years, nor oophorectomy status at cumulative followup of 18.0 years.[89, 91]

For the outcome of colon cancer mortality, there were no differences by age after the intervention and postintervention phases.[88] However, after cumulative followup of 17.7 years, higher colon cancer mortality was observed in older women (ages 70 to 79: HR, 2.13 [95% CI, 1.10 to 4.12]) compared with younger women (ages 50 to 59: HR, 0.65 [95% CI, 0.21 to 2.00]; ages 60 to 69: HR, 0.81 [95% CI, 0.41 to 1.60]) (p=0.03).[88]

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 to years since menopause (i.e., <10 years, 10 to <20 years, and ≥20 years since menopause) in the WHI.[67] 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.[110]

Endometrial Cancer

Benefits and Harms of Hormone Therapy

Four trials (ERA [N=205],[113] EPAT [N=222],[112] PEPI [N=349],[32] and Ultra-Low-Dose Transdermal Estrogen Assessment [ULTRA] [N=417][115]) provided data on endometrial cancer incidence among women who received estrogen-only hormone therapy or placebo. We present results in **Appendix F 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

A large, retrospective Danish cohort study assessed the risk of endometrial cancer with hormone therapy during an average followup time of 9.8 years reported no statistically significant differences in risk of endometrial cancer among women based on age, hypertension, or diabetes.[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.

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 F Table 5**).[67, 116]

Only 1.2 percent of women who received estrogen-only hormone therapy and 1.1 percent 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 [95% CI, 0.74 to 1.49]).[67] During the postintervention followup period (mean duration 6.8 years) and cumulative followup (median 13.0 years), the risk between treatment groups remained similar.[67] **Appendix G Figure 3** presents HRs for incident lung cancer at different followup periods of the WHI.

The WHI also reported lung cancer mortality after followup of 7.9 years. There was no difference in lung cancer mortality between estrogen-only and placebo groups (HR, 1.17 [95% CI, 0.81 to 1.69]).[116]

Differences in Treatment Effects Based on Subgroups

The WHI reported no statistically significant differences in risk of lung cancer incidence among

women based on age at randomization[67] or in lung cancer mortality among women based on age, race, or ethnicity.[116]

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.

Non-Hodgkin's Lymphoma

Benefits and Harms of Hormone Therapy

One trial (WHI [N=10,685]) evaluated the incidence of non-Hodgkin's lymphoma among women who received either estrogen-only hormone therapy or placebo (**Appendix F Table 6**).[96] The incidence of non-Hodgkin's lymphoma did not differ significantly between groups during the 7.2-year intervention phase (HR, 0.89 [95% CI, 0.56 to 1.42]).[96] Risk remained similar during a median cumulative followup of 12.9 years (HR, 1.02 [95% CI, 0.74 to 1.39]). Eighty women who received estrogen and 80 women who received placebo developed non-Hodgkin's lymphoma during this cumulative followup period.[96]

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.

Ovarian Cancer

Benefits and Harms of Hormone Therapy

No eligible RCTs reported on incidence of ovarian cancer (**Appendix F Table 7**). However, we identified one prospective cohort study with data on 7,166 postmenopausal Black women who have taken estrogen-only therapy or have never used hormone therapy.[104] During 18 years of followup, there were fewer cases of ovarian cancer among those who had ever taken estrogen-only therapy compared with those who had never used hormone therapy (0.7% vs. 1.3%), although the difference in risk was not statistically significant (HR, 1.66 [95% CI, 0.90 to 3.07]).

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.

Total Cancer Mortality

Benefits and Harms of Hormone Therapy

Only the WHI reported total cancer mortality (N=10,739, **Appendix F Table 8**).[67, 88] Death by any cancer was similar between the estrogen-only and placebo groups during the 7.2-year intervention phase (0.33% annualized vs. 0.34% annualized; HR, 0.96 [95% CI, 0.75 to 1.22]), as well as at various postintervention and cumulative followup. **Appendix G Figure 4** presents available HRs for total cancer mortality for different followup periods of the WHI trial.

Differences in Treatment Effects Based on Subgroups

The WHI reported no statistically significant differences in risk of lung cancer incidence among women based on age or oophorectomy status.[67, 88, 89]

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

COPD

Benefits and Harms of Hormone Therapy

No eligible studies reported on COPD incidence. The WHI [N=10,739][88]) was the only trial that provided information about the prevention of COPD mortality with estrogen only (**Appendix F Table 9**). COPD mortality was measured at multiple time points and identified via data linkage to the U.S. National Death Index (NDI). Women assigned to estrogen alone had a similar risk of COPD mortality compared with placebo during the 7.2-year (median) intervention phase (HR, 0.76 [95% CI, 0.26 to 2.20]). The risk remained similar during a 10.8-year (median) postintervention followup (HR, 1.09 [95% CI, 0.79 to 1.51]) and 17.7-year (median) cumulative followup (HR, 1.07 [95% CI, 0.78 to 1.45]). **Appendix G Figure 5** presents HRs for COPD mortality at different followup periods of the WHI.

Differences in Treatment Effects Based on Subgroups

In the WHI, no difference in risk of COPD mortality by subgroups based on age at randomization (in age bands 50 to 59 years, 60 to 69 years, or 70 to 79 years) could be detected during the 7.2-year (median) intervention phase.[88] However, women ages 50 to 59 years at randomization who had been assigned to estrogen only experienced a statistically significant reduction in risk compared with placebo at the 10.8-year (median) postintervention followup (4 vs. 16 events; HR, 0.24 [95% CI, 0.08 to 0.73]). This risk reduction among women ages 50 to 59 years persisted at the 17.7-year (median) cumulative followup (6 vs. 17 events; HR, 0.35 [95% CI, 0.14 to 0.88]). These findings, however, need to be viewed cautiously because only 20 and

23 women, respectively, in the 50- to 59-year-old age group had died of COPD at these two followup periods.

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.

Coronary Heart Disease

Benefits and Harms of Hormone Therapy

Four trials (EPAT [N=222],[112] PEPI [N=349],[32] WHI [N=10,739],[117] and ERA [N=205][113]) provided data on the risk of coronary heart disease in women who used estrogen only (**Appendix F Table 10**).

Of these, three trials (EPAT,[112] PEPI,[32] and WHI[117]) were similar enough to be combined in a meta-analysis (**Appendix H Figure 1**). We did not include the ERA study in the meta-analysis because only women with an elevated cardiovascular risk were eligible for enrollment.[113] 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 duration ranged from 2 to 7.2 years. The WHI and EPAT trials defined coronary heart disease as nonfatal myocardial infarction or coronary death;[112, 117] the definition used in the PEPI trial was unclear.[32] A meta-analysis of these three trials, which was limited by the domination of the WHI (i.e., contributed 99% of events), rendered no statistically significant difference in coronary events between women taking estrogen therapy and those taking placebo (RR, 0.95 [95% CI, 0.79 to 1.14]). In the meta-analysis, 3.6 percent of women receiving estrogen-only therapy and 4.0 percent of those receiving placebo experienced coronary heart disease during a mean followup of 4.1 years. A sensitivity analysis including the ERA trial rendered similar results.

A postintervention followup study of the WHI reported that 3.9 years after stopping the randomized treatment, the risk for coronary heart disease was still similar between women who received hormone therapy during the trial and those who were randomized to placebo (HR, 0.97 [95% CI, 0.75 to 1.25]).[108] Risk remained similar between treatment groups at 13 and 19.4 years of cumulative followup (HR, 0.94 [95% CI, 0.82 to 1.09] and HR, 0.97 [95% CI, 0.86 to 1.09], respectively).[67, 101] **Appendix G Figure 6** presents available HRs for coronary heart disease for different followup periods of the WHI trial.

Only the WHI reported mortality due to coronary heart disease. Death from coronary heart disease was similar between the estrogen-only and placebo groups during the 7.2-year intervention phase (66 vs. 67 events), at 10.8 years postintervention (174 vs. 210 events), and after 17.7 years of cumulative followup (240 vs. 277 events).[88] **Appendix G Figure 7** presents available HRs for coronary heart disease mortality for different followup periods of the WHI trial.

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 race/ethnicity, age, diabetes, hypertension, high cholesterol requiring medication, coronary risk factors, and years since bilateral oophorectomy.[52, 67, 117] Although risk for coronary heart disease in women taking estrogen-only therapy increased numerically with age, this trend did not reach statistical significance.[67] 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 ages 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=0.08). Analyses that focused just on myocardial infarction yielded a statistically significant trend for increasing risk by age (comparing ages 50 to 59, 60 to 69, and 70 to 79 years), with more favorable effects among younger women (p=0.02).[67] These findings, however, need to be viewed cautiously because only 48 women in the 50- to 59-year-old age group experienced a myocardial infarction.[67] No differences in coronary heart disease mortality between treatments were detected by subgroups based on age or by oophorectomy status within any age group.[88, 89]

Differences in Treatment Effects Based on Timing of the Intervention

In the WHI, time since menopause did not have a statistically significant effect on the risk of coronary heart disease.[67] 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).[110]

Peripheral Arterial Disease

Benefits and Harms of Hormone Therapy

The WHI [N=10,739][79] was the only trial that provided information about peripheral arterial disease with estrogen only (**Appendix F Table 11**). Peripheral arterial disease was defined as incident carotid artery disease, abdominal aortic aneurysm, or lower extremity arterial disease. In participants who did not have coronary heart disease or peripheral arterial disease at baseline, women assigned to estrogen alone had a similar risk of developing peripheral arterial disease compared with placebo during the 7.1-year (median) intervention phase (HR, 1.35 [95% CI, 0.97 to 1.88]).

Differences in Treatment Effects Based on Subgroups

In the WHI, no difference in risk of incident peripheral arterial disease by subgroups based on age, ethnicity, diabetes, or body mass index could be detected during the 7.1-year (median) intervention phase.[79]

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.

Cognitive Functioning and Dementia

Benefits and Harms of Hormone Therapy

Dementia and mild cognitive impairment incidence. The WHI trials evaluated the incidence of dementia or mild cognitive impairment (**Appendix F Table 12**). The Women's Health Initiative Memory Study (WHIMS) trial (N=2,947), a subset of the WHI trial, was limited to women ages 65 to 79 years 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. Women's Health Initiative Study of Cognitive Aging (WHISCA), an ancillary study (N=434 in the estrogen arm, N=452 in the placebo arm) of the WHIMS trial, began 3 years after the start of the WHI and WHIMS trials; was limited to 14 of 39 trial centers; and was designed to evaluate changes in more detailed, domain-specific cognitive functioning over time.[118] Participants in WHISCA were followed for approximately 2.7 years during the WHISCA trial. Neither WHIMS nor WHISCA found an elevated risk of probable dementia among women taking hormone therapy; likewise, both studies found no difference in mild cognitive impairment between women taking hormone therapy vs. placebo.[119, 120] When using a composite outcome measure of probable dementia or mild cognitive impairment, the WHIMS study found a statistically significantly higher risk among women taking estrogen-only therapy compared with women taking placebo (6.4% vs. 4.7%; cumulative HR, 1.38 [95% CI, 1.01 to 1.89]).[119]

The WHI estrogen-only trial (n=10,739) evaluated Alzheimer's disease or other dementia mortality following the intervention phase (median 7.2 years), postintervention phase (median 10.8 years), and cumulative followup of 17.7 years (median).[88] There was no difference in dementia-related mortality at the end of the intervention phase (5 vs. 6 deaths). However, participants randomized to estrogen were less likely to have dementia-related mortality compared with the placebo group at postintervention followup at 10.8 years (122 vs. 169; HR, 0.73 [95% CI, 0.58 to 0.92]) and cumulative followup (127 vs. 175; HR, 0.74 [95% CI, 0.59 to 0.94]).[88] **Appendix G Figure 8** presents available HRs for dementia-related mortality for different followup periods of the WHI estrogen-only trial.

Global cognitive function. Four trials (WHIMS [N=4,344],[121] WHISCA [N=1,213],[122] Women's Health Initiative Memory Study of Younger Women [WHIMSY] [N=1,326],[123] and ULTRA [N=417][124]) measured global cognitive functioning using the Modified Mini-Mental State (3MSE) examination or the Telephone Interview for Cognitive Status-modified (TICS-m); heterogeneity in timing precluded meta-analysis (**Appendix F Table 13**). The WHIMS and WHISCA trials are described above. The WHIMSY trial, an extension of the WHI trial, was limited to 1,326 enrolled active participants in treatment or placebo arms in the WHI trials who were ages 50 to 55 years at enrollment and agreed to be contacted for recruitment (N by treatment regimen not reported); women in this extension were followed for 7.2 years after the end of the trials.[123] The ULTRA trial randomized women to estrogen only or placebo transdermal patches, with all participants receiving 400 mg of calcium twice daily and 400 IU of vitamin D once daily.[124] The ULTRA trial followed participants for 2 years. The WHI trials found larger cognitive deficits among the intervention group (change in 3MSE score at 3.6 years during the WHISCA trial, -0.092; p=0.02;[122] change in 3MSE score at 5.4 years at the end of the WHIMS trial, -0.26 [95% CI, -0.52 to 0.00]; p=0.04[121]). In a long-term extension of the

WHISCA trial, with outcomes measured at 2.4 years after stopping therapy, these differences were not sustained.[122] The ULTRA and WHIMSY studies found no differences.[123, 124]

Other cognitive measures. Four trials (WHISCA [N=1,213],[120, 122] WHIMSY [N=1,326],[123], Early vs. Late Intervention Trial with Estradiol, Cognitive Endpoints [ELITE-Cog] [N=643],[92] and ULTRA [N=417][124]) evaluated other measures of cognitive functioning (e.g., spatial ability, verbal knowledge, verbal fluency, verbal memory, figural memory, attention, and working memory); heterogeneity in outcome measures precluded meta-analysis (**Appendix F Table 13**). The WHISCA, WHIMSY, and ULTRA trials are described above. ELITE-Cog examined differences in cognitive changes for women enrolled in the ELITE trial, which was designed to test the timing hypothesis.[92] All four trials found no differences between women receiving estrogen only or placebo for the majority of outcomes.

Differences in Treatment Effects Based on Subgroups

The WHIMS study reported no difference in risk for probable dementia by race/ethnicity or history of diabetes, stroke, hypertension, or cardiovascular disease.[119] There were no differences in other measures of cognitive function (i.e., change in verbal memory, executive function, or global cognition) by women experiencing surgical vs. natural menopause in the ELITE-Cog study.[92] The WHI study reported no difference in risk for dementia-related mortality by age.[88]

Differences in Treatment Effects Based on Timing of the Intervention

In the ELITE-Cog study, there were no differences in treatment effects on other cognitive measures (i.e., change in verbal memory, executive function, or global cognition) based on timing of the intervention.[92]

Diabetes

Benefits and Harms of Hormone Therapy

The WHI (N=9,917)[67, 125] was the only trial that reported on the incidence of diabetes among women not receiving treatment for diabetes at baseline (**Appendix F Table 14**). 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.[125]

During a median of 7.2 years of followup, 1.34 percent (annualized) of women receiving estrogen therapy and 1.55 percent (annualized) of those receiving placebo reported a new diabetes diagnosis. The difference in risks between these groups reached statistical significance (HR, 0.86 [95% CI, 0.76 to 0.98]).[67] The overall reduction in diabetes risk was no longer observed 6.6 years postintervention (HR, 1.07 [95% CI, 0.92 to 1.25]) or after 13.0 years of cumulative followup (HR, 0.94 [95% CI, 0.85 to 1.04]).[67] **Appendix G Figure 9** presents hazard ratios for incident diabetes at different followup periods of WHI.

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 estrogen-only trial.[125]

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

Two trials (the WHI [N=10,739][67] and ERA [N=205][113]) provided information on preventing fractures with estrogen-only therapy among 10,944 women (**Appendix F Table 15**). The WHI found a reduced risk of total fractures in the estrogen-only arm compared with placebo during the 7.2-year intervention phase (1.53% annualized vs. 2.14% annualized; HR, 0.72 [95% CI, 0.64 to 0.80])[67] and after 4.3 years of postintervention followup (3.11% annualized vs. 3.69% annualized; HR, 0.85 [95% CI, 0.73 to 0.98]).[97] The ERA trial randomized women to the same treatment regimen as the WHI and followed them for 3.2 years. The study found fewer fractures at all sites in the estrogen-only arm (6.0% vs. 14.3%), but the difference was not statistically significant (calculated RR, 0.42 [95% CI, 0.17 to 1.04]).[113] **Appendix G Figure 10** presents effect estimates for total fractures at different followup periods of the WHI and the ERA.

Differences in Treatment Effects Based Subgroups

Tests for interaction did not detect any statistically significant subgroup effects with respect to age[67, 89, 91, 97, 108, 126] among women in the WHI estrogen-only trial.

Differences in Treatment Effects Based on Timing of the Intervention

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

Gallbladder Disease

Benefits and Harms of Hormone Therapy

Two trials (PEPI [N=349][32] and WHI [N=8,376][67, 127]) 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 F Table 16**). Treatment duration was 3.0 years among women in PEPI and an average of 7.1 years among those in the WHI. The definition of gallbladder disease used in PEPI is unclear; for WHI, global gallbladder disease was a self-reported endpoint that included all acute or chronic gallbladder inflammation and all

gallbladder or biliary tract stone disease.[32, 67, 127] Gallbladder procedures, including biliary tract procedures such as cholecystectomy, were also reported for women in the WHI.[127]

The larger of the two trials, WHI, reported global gallbladder disease after 7.1 years of treatment for 1.64 percent (annualized) of women receiving estrogen therapy and 1.06 percent (annualized) of those taking placebo.[67] The difference in global gallbladder disease between these groups was statistically significant (HR, 1.55 [95% CI, 1.34 to 1.79]).[67] However, the risk of gallbladder disease was no longer significant 6.6 years postintervention (HR, 0.98 [95% CI, 0.68 to 1.41]).[67]

The PEPI trial had few cases of gallbladder disease and reported inconclusive results.[32]

Differences in Treatment Effects Based on Subgroups

The risk of gallbladder events attributable to estrogen therapy among women in the WHI increased with age but did not reach statistical significance.[127] 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],[67, 88, 101, 108] EPAT [N=222],[112] and ERA [N=205][113]) reported on risk of stroke (**Appendix F Table 17**). We did not pool trial results because of heterogeneity in study duration and outcome measures.

During the WHI 7.2-year intervention phase, women receiving estrogen only had a statistically significantly higher risk of stroke compared with those receiving placebo (3.2% vs. 2.4%; HR, 1.35 [95% CI, 1.07 to 1.70]).[67] During the postintervention period (3.9 years after stopping therapy), the risk between the two treatment groups was similar.[108] Cumulatively across the intervention and postintervention periods (19.4 years of followup), stroke risk was not significantly different between the estrogen-only and placebo groups (7.5% vs. 7.2%; HR, 1.06 [95% CI, 0.92 to 1.22]).[101] **Appendix G Figure 11** presents available HRs for stroke for different followup periods of the WHI trial.

The two smaller trials (EPAT[112] and ERA)[113] also reported on stroke risk among women randomized to estrogen or placebo; however, few events occurred overall and results were inconclusive. In the EPAT trial, one participant (randomized to placebo) had a cerebrovascular accident at 2 years.[112] 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).[113]

Only the WHI reported stroke mortality. Death from stroke was similar between the estrogen-only and placebo groups during the 7.2-year intervention phase (23 vs. 24 events, respectively).[88]

Stroke mortality remained similar between the two groups during the postintervention period (10.8 years after stopping therapy) and during cumulative followup (17.7 years of followup).[88]

Differences in Treatment Effects Based on Subgroups

In the WHI estrogen-only trial, no differences in stroke risk between treatments were detected by subgroups, including those based on race/ethnicity, age, prior cardiovascular disease, diabetes, hypertension, or oophorectomy status within any age group.[128] No differences by age were detected in risk for death from stroke.[88]

Differences in Treatment Effects Based on Timing of the Intervention

The risk of stroke in the WHI was similar among women who initiated estrogen soon after menopause (<5 years) vs. later (≥5 years).[110]

Urinary Incontinence

Benefits and Harms of Hormone Therapy

Two trials (WHI [N=5,644 continent][67] and ULTRA [N=239 continent][129]) provided results on incident urinary incontinence (self-reported). The WHI followed continent women through 1 year of intervention and then evaluated incontinence at study closeout (i.e., median followup of 6.6 years postintervention). The ULTRA study followed participants for 2 years.[124] Both studies defined urinary incontinence as at least one episode weekly.[67, 129] The WHI also evaluated various subtypes of urinary incontinence.[130] Detailed results can be found in **Appendix F Table 18**.

The WHI found a higher risk of urinary incontinence in the estrogen-only treatment arm at 1 year (22.6% annualized vs. 14.0% annualized; HR, 1.61 [95% CI, 1.46 to 1.79]) and 6.6 years after stopping treatment (28.6% vs. 23.1%; HR, 1.24 [95% CI, 1.13 to 1.35]).[67] Results from the smaller ULTRA trial at 2 years did not find a statistically significant difference between groups (39.0% vs. 36.8%; odds ratio [OR], 1.2 [95% CI, 0.7 to 2.2]).[129] **Appendix G Figure 12** presents effect estimates for incident weekly urinary incontinence at different followup periods of the WHI and the ULTRA.

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

Three trials (WHI [N=10,739],[67, 101, 108] EPAT [N=222],[112] and ERA [N=205][113]) reported on risk of thromboembolism (**Appendix F Table 19**). We did not pool trials because of heterogeneity in study duration and outcome measures.

In the WHI, women randomized to estrogen alone had a marginally significant increased risk of venous thromboembolism compared with women receiving placebo during the 7.2-year intervention phase (2.1% vs. 1.6%; HR, 1.32 [95% CI, 1.00 to 1.76]).[101] Women receiving estrogen alone had an increased risk of deep vein thrombosis compared with placebo that was statistically significant (1.6% vs. 1.0%; HR, 1.48 [95% CI, 1.06 to 2.07]);[67] the risk of pulmonary embolism was also higher in the estrogen group than in the placebo group, but results were not significant (0.98% vs. 0.72%; HR, 1.35 [95% CI, 0.89 to 2.05]).[67] After 3.9 years postintervention, women in the estrogen-only group had lower risk of deep vein thrombosis compared with those in the placebo group (HR, 0.63 [95% CI, 0.41 to 0.98]); there was no difference between groups for risk of pulmonary embolism in the postintervention period.[108] Risks of deep vein thrombosis and of pulmonary embolism were similar in the estrogen-only and placebo groups after 13 years of cumulative followup.[67] After 19.4 years of cumulative followup, risk of venous thromboembolism overall was similar between the two groups.[101] **Appendix G Figures 13** and **14** present available HRs for deep vein thrombosis and pulmonary embolism, respectively, for different followup periods of the WHI trial.

The EPAT and ERA trials had shorter followup than the WHI (2.0 and 3.2 years, respectively). No venous thromboembolic events were reported in either group in the EPAT trial; in the ERA trial, events were reported for five women receiving estrogen-only therapy and one woman receiving placebo.[112, 113]

Differences in Treatment Effects Based on Subgroups

The WHI reported no differences between treatments by subgroups based on race/ethnicity, age, history of cardiovascular disease, or within any age group during the intervention period.[67, 91, 131] During cumulative followup, risk remained similar by age but not by race.[67, 95] After 13 years, Black women had a lower risk of venous thromboembolism than White women (HR, 0.63 [95% CI, 0.38 to 1.06] vs. HR, 1.11 [95% CI, 0.88 to 1.39], respectively, p=0.049).[95]

Differences in Treatment Effects Based on Timing of the Intervention

The risk of venous thromboembolism or pulmonary embolism specifically in the WHI estrogen-only trial was similar among women who initiated estrogen soon after menopause vs. later.[67, 110]

Health-Related Quality of Life

Benefits and Harms of Hormone Therapy

The WHI (N=10,739)[67] was the only trial that reported on health-related quality of life (**Appendix F Table 20**). It used the Short Form Health Survey (SF-36) form, which assesses physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. At post-intervention (mean 7.2 years), women in both groups had similar scores on all items except for emotional role and social functioning, for which women taking placebo had statistically significantly better scores than women taking 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 (ELITE-Cog [N=643],[92] ERA [N=205],[113] and WHI [N=10,739][67, 88, 101, 108]) provided information about the risk of death from any cause among 11,587 women receiving estrogen therapy (**Appendix F Table 21**). The treatment duration of these trials ranged from 2 to 7.2 years.[108, 113] A meta-analysis of these trials, which was limited by the domination of WHI (i.e., contributed 97% of events), rendered no statistically significant difference in all-cause mortality between women receiving estrogen therapy and those receiving placebo (**Appendix H Figure 2**; RR, 1.04 [95% CI, 0.89 to 1.21]) during a mean followup of 7.1 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 5.7 and 5.5 percent of women in the active and placebo groups, respectively.[88] The difference in risk between the two groups remained similar at various postintervention and cumulative followup. **Appendix G Figure 15** presents HRs for all-cause mortality at different followup periods of the WHI.

Differences in Treatment Effects Based on Subgroups

In the WHI, authors observed a significant trend toward lower risk of death in younger women receiving estrogen therapy compared with older women at postintervention (mean 7.2 years followup) relative to women receiving placebo (p=0.04 for trend).[88] The HR was 0.71 (95% CI, 0.46 to 1.09) among women ages 50 to 59 years compared with 1.02 (95% CI, 0.80 to 1.30) among women ages 60 to 69 years and 1.22 (95% CI, 0.95 to 1.56) among women ages 70 to 79 years. We found no evidence of differences in treatment effects by age for longer

postintervention or cumulative followup except by age among women with oophorectomy after 18 years of cumulative followup (p=0.034).[67, 88, 89, 101] Further, we found no evidence of differences in treatment effects during cumulative followup by race, by oophorectomy status in the overall sample or prior hormone therapy use, by age at oophorectomy among younger or older women, or by age among women without oophorectomy.[89, 95]

Differences in Treatment Effects Based on Timing of the Intervention

The effect of estrogen-only therapy on all-cause mortality did not differ significantly between women who initiated hormone therapy sooner after menopause and those who initiated hormone therapy later.[67, 110]

Estrogen Plus Progestin: Cancer

Breast Cancer

Benefits and Harms of Hormone Therapy

Six trials (WHI [N=16,608],[36, 67, 87, 88, 91, 101, 110, 111, 132-135] Heart and Estrogen/Progestin Replacement Study [HERS] [N=2,763],[136] PEPI [N=700],[32] EPHT [N=777],[137] ERA [N=209],[113] and WISDOM [N=4,385])[138] comparing estrogen plus progestin with placebo reported on breast cancer incidence (**Appendix F 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 (vs. any breast cancer).

During the 5.6-year intervention phase of the WHI, women assigned to estrogen plus progestin had a significantly increased risk of invasive breast cancer compared with women taking placebo (2.4% vs. 1.9%; HR, 1.24 [95% CI, 1.01 to 1.53]).[67] The risk of invasive breast cancer in women who took estrogen plus progestin remained significantly increased compared with women who took placebo during a median postintervention followup of 8.2 years (HR, 1.32 [95% CI, 1.08 to 1.61])[67] and during 19.4 years of cumulative (trial and postintervention phase) followup (HR, 1.28 [95% CI, 1.13 to 1.45).[101] **Appendix G Figure 16** presents HRs for invasive breast cancer at different followup periods of the WHI.

In the HERS trial, more women randomized to estrogen plus progestin developed breast cancer during the 4.1-year intervention phase than 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]).[136] Four other trials also reported any breast cancer incidence but for shorter intervention periods.[32, 113, 137, 139] In three small trials, few cases occurred overall, and risk of breast cancer incidence was similar between groups randomized to estrogen plus progestin and placebo over approximately 3 years (no cases overall in ERA and 3 vs. 3 cases, respectively, across PEPI and EPHT); few cases of breast cancer were reported overall.[32, 113, 137] The fourth trial, WISDOM, 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 estrogen plus progestin and placebo groups at 1 year (5 vs. 7 cases, respectively).[138]

Only the WHI reported on breast cancer mortality. During the 5.6-year intervention period, breast cancer mortality between the estrogen plus progestin and the placebo groups did not reach statistical significance (HR, 1.08 [95% CI, 0.29 to 4.03]).[88] During cumulative followup to 20.3 years (median), the risk of breast cancer mortality was numerically higher for women in the estrogen plus progestin than in the placebo group, but the difference did not reach statistical significance (HR, 1.35 [95% CI, 0.94 to 1.95]).[87] **Appendix G Figure 17** presents HRs for breast cancer mortality at different followup periods of the WHI.

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[67] or race.[87, 90] Breast cancer mortality did not differ by age.[88]

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 plus progestin soon after menopause (<5 years) vs. later (≥5 years) for most followup periods.[67, 87] An exception was the 11-year cumulative followup, which showed a higher risk for women who initiated within 5 years of menopause. (p=0.03 for interaction).[110]

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 F Table 2**).[126] 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.[126] 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],[36, 67, 88, 91, 110, 132, 140] EMS [N=142],[141] HERS [N=2,763],[136] and

WISDOM [N=4,385][138]) reported on the incidence of colorectal cancer (**Appendix F 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.[67] Over the entire median followup period of 13.2 years, the risk of colorectal cancer remained lower in the hormone therapy arm (HR, 0.80 [95% CI, 0.63 to 1.01]) but lost statistical significance.[67] 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 of 4.1 years, which persisted after cumulative followup of a mean of 6.8 years (HR, 0.82 [95% CI, 0.46 to 1.47]).[136] However, this decrease was not statistically significant at any time point. **Appendix G Figure 18** presents HRs of colorectal cancer at different time points in the WHI and HERS trials.

The EMS and WISDOM trials reported no statistically significant differences in risk of colorectal cancer. Event rates in these studies, however, were low (no events in EMS and 4 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.

We identified one prospective cohort study with data on 85,734 postmenopausal women who had ever or never used hormone therapy (**Appendix F Table 3**).[103] During 16 years of followup, there were fewer cases of colorectal cancer among those who had ever taken estrogen plus progestin therapy compared with those who had never used hormone therapy. Risk of colorectal cancer among ever and current users of estrogen plus progestin therapy in this study was statistically significantly lower compared with never users (HR, 0.76 [95% CI, 0.68 to 0.86] and HR, 0.72 [95% CI, 0.62 to 0.84], respectively).

Only the WHI examined colorectal cancer mortality after a median of 5.6 years, 12.5 years, and 17.7 years.[88] There were no statistically significant differences for women receiving hormone therapy compared with placebo at each respective followup time (HR, 0.87 [95% CI, 0.38 to 1.98]; HR, 1.06 [95% CI, 0.68 to 1.64)]; and HR, 1.01 [95% CI, 0.69 to 1.49]).

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,[67, 91] race/ethnicity, and family history of colorectal cancer.[110, 140] Likewise, there were no statistically significant difference in incidence of colorectal cancer by age after cumulative followup of 13.2 years[67] and 18.0 years.[91] For the outcome of colon cancer mortality, there were no statistically significant differences by age between women who received estrogen plus progestin hormone therapy and women who received placebo after the intervention period or cumulative followup of 12.5 years and 17.7 years, respectively.[88]

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 the number of years since menopause (i.e., <10 years, 10 to <20 years, and ≥20 years) in the WHI intervention phase.[67] 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.[110]

Endometrial Cancer

Benefits and Harms of Hormone Therapy

Two trials (WHI [N=16,608][67, 91, 94] and HERS[136] [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. In addition, we included one retrospective cohort study[102] with data on more than 900,000 women (**Appendix F 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]).[67] Likewise, during the HERS trial phase (mean followup 4.1 years), no statistically significant differences in risk could be detected (0.14% vs. 0.36%; HR, 0.39 [95% CI, 0.08 to 2.02]).[136] Overall, however, only 64 women experienced endometrial cancer in these studies.

A large, retrospective Danish cohort study based on more than 900,000 women between ages 50 and 79 years without hysterectomy assessed the risk of endometrial cancer with hormone therapy during an average followup time of 9.8 years.[102] The analysis was based on 4,475 cases of endometrial cancer. Compared with women who never used hormone therapy, women with current use of estrogen plus progestin had a statistically significantly higher risk for endometrial cancer (RR, 1.71 [95% CI, 1.58 to 1.86]). A stratification by treatment regimen, however, revealed that a continuous combined estrogen and progestin regimen (which was also used in the WHI) had no increased risk (RR, 1.02 [95% CI, 0.87 to 1.20]); by comparison, a cyclic combined regimen increased the risk to a statistically significant level (RR, 2.06 [95% CI, 1.88 to 1.20]), as did a long cyclic combined regimen (RR, 2.89 [95% CI, 2.27 to 3.67]). No difference in risks could be detected between oral and transdermal use.

During 8.2 years of the WHI postintervention period, statistically significantly fewer women who were randomized to hormone therapy during the trial phase developed endometrial cancer (HR, 0.59 [95% CI, 0.40 to 0.88]) compared with women who had received placebo.[94] Likewise, when assessing 13.2 years of cumulative followup (i.e., intervention plus postintervention period), the risk for endometrial cancer was lower in women who were on hormone therapy (HR, 0.65 [95% CI, 0.48 to 0.89]).[94] **Appendix G Figure 19** presents the HRs for endometrial cancer over different followup periods.

Two additional trials (ERA [N=209][113] and PEPI [N=700][32]) reported no 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 risk or to combine in meta-analysis with the WHI and HERS.

Differences in Treatment Effects Based on Subgroups

The WHI reported no significant differences by age at randomization, race, diabetes, or hypertension in the incidence of endometrial cancer between women who received estrogen plus progestin hormone therapy and those who received placebo.[67, 94] The large Danish retrospective cohort study described above also reported no statistically significant differences in the incidence of endometrial cancer among women based on age, hypertension, or diabetes.[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.[94, 110]

Lung Cancer

Benefits and Harms of Hormone Therapy

Two trials (WHI [N=16,608][67, 142] and HERS [N=2,763][136]) 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 F 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]).[67] 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]).[136] The risk between groups remained similar during the postintervention followup and cumulative followup in both trials.[67, 136] **Appendix G Figure 20** presents hazard ratios for incident lung cancer at different followup periods of the WHI and HERS.

The WHI trial reported mortality from lung cancer (median followup 14 years) of 0.13 percent of women receiving estrogen plus progestin compared with 0.12 percent of women receiving placebo (HR, 1.09 [95% CI, 0.87 to 1.38]).[98]

A small trial (EMS [N=142][141]) reported only a single lung cancer case among women receiving estrogen plus progestin and no 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.[141]

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.[67]

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.

Non-Hodgkin's Lymphoma

Benefits and Harms of Hormone Therapy

One trial (WHI [N=16,544]) evaluated the incidence of non-Hodgkin's lymphoma among women who received either estrogen plus progestin hormone therapy or placebo (**Appendix F Table 6**).[96] The incidence of non-Hodgkin's lymphoma did not differ significantly between groups at a median followup of 5.6 years during the intervention phase (HR, 0.81 [95% CI, 0.51 to 1.29]).[96] Risk remained similar during a median cumulative followup of 13.5 years (HR, 0.98 [95% CI, 0.76 to 1.28]); 113 women who received estrogen plus progestin hormone therapy and 110 women who received placebo developed non-Hodgkin's lymphoma during this cumulative followup period.[96]

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.

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 F Table 7**).[67, 126] 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.[67] Risk remained similar during the postintervention followup (during the 8.2 years after stopping therapy; HR, 1.12 [95% CI, 0.65 to 1.90]).[67]

Further, we identified one prospective cohort study with data on 6,525 postmenopausal Black women who have taken estrogen plus progestin therapy or have never used hormone therapy.[104]

During 18 years of followup, there were fewer cases of ovarian cancer among those who had ever taken estrogen plus progestin therapy compared with those who had never used hormone therapy (0.8% vs. 1.3%), although the difference in risk was not statistically significant (HR, 1.37 [95% CI, 0.73 to 2.55]).

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.[67]

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.

Total Cancer Mortality

Benefits and Harms of Hormone Therapy

Only the WHI reported total cancer mortality (N=16,608, **Appendix F Table 8**).[67, 88] Death from any cancer was similar between the estrogen plus progestin and placebo groups during the 5.6-year intervention phase (0.27% annualized vs. 0.24% annualized; HR, 1.10 [95% CI, 0.86 to 1.42]), as well as at various postintervention and cumulative followups.[67, 88] **Appendix G Figure 21** presents available HRs for total cancer mortality for different followup periods of the WHI trial.

Differences in Treatment Effects Based on Subgroups

We found no evidence on differences in treatment effects by subgroups based on age for total cancer mortality.

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

COPD

Benefits and Harms of Hormone Therapy

No eligible studies reported on COPD incidence. The WHI (N=16,608)[88] was the only trial that provided information about the prevention of COPD mortality with estrogen plus progestin (**Appendix F Table 9**). COPD mortality was measured at multiple time points and identified via data linkage to the NDI. The WHI found a reduced risk of COPD mortality among women who took estrogen plus progestin compared with those who received placebo during the 5.6-year (median) intervention phase (1 vs. 8 events; HR, 0.12 [95% CI, 0.01 to 0.93]). This finding needs

to be viewed cautiously because only nine women had died of COPD by this time point. However, the reduction in risk was no longer observed during a 12.5-year (median) postintervention followup (HR, 1.13 [95% CI, 0.85 to 1.49]) or 17.7-year (median) cumulative followup (HR, 1.03 [95% CI, 0.79 to 1.36]). **Appendix G Figure 22** presents HRs for COPD mortality at different followup periods of the WHI.

Differences in Treatment Effects Based on Subgroups

In the WHI, no differences in risk of COPD mortality by subgroups based on age at randomization were detected at any phase of followup.[88]

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.

Coronary Heart Disease

Benefits and Harms of Hormone Therapy

Overall, six trials (EMS [N=142],[141] EPHT [N=777)],[137] PEPI [N=700],[32] WHI [N=16,608],[36] WISDOM [N=4,385],[138] and ERA [N=209][113]) provided information about preventing coronary heart disease with estrogen plus progestin (**Appendix F Table 10**).

Of these, three trials (EPHT,[137] PEPI,[32] and WHI[67]) were similar enough to be combined in a meta-analysis (Appendix H Figure 3). We did not include the ERA study, which enrolled only women with an elevated cardiovascular risk;[113] the EMS trial[141] 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.[138] Trials included in the meta-analysis provided data on 18,085 women with treatment durations of 2 to 5.6 years. Results of the meta-analysis showed a numerically higher (but not statistically significant) risk of coronary heart disease in women treated with hormone therapy than in those treated with placebo (2.8% vs. 2.6%; RR, 1.12 [95% CI, 0.94 to 1.33]) during a mean followup of 4 years.

Postintervention followup of women in the WHI showed that 2.4 years after stopping therapy, the risk of coronary heart disease was similar between women who took estrogen plus progestin during the trial and those who received placebo (HR, 1.04 [95% CI, 0.89 to 1.21]).[132] Risk remained similar between treatment groups at 13 and 19.4 years of cumulative followup (HR, 1.09 [95% CI, 0.96 to 1.24] and HR, 1.05 [95% CI, 0.95 to 1.17], respectively).[67, 101] **Appendix G Figure 23** presents available HRs for coronary heart disease for different followup periods of the WHI trial.

The WISDOM trial was prematurely closed because of findings of the WHI. However, after 1 year of followup (6,498 women-years), women taking estrogen plus progestin had a statistically significantly higher risk of cardiovascular events (0.3% vs. 0.0%; p=0.016) than women taking placebo.[138]

Only the WHI reported mortality due to coronary heart disease. Death from coronary heart disease was similar between the estrogen plus progestin and placebo groups during the 5.6-year intervention phase (40 vs. 40 events), at 12.5 years postintervention (270 vs. 245 events), and after 17.7 years of cumulative followup (310 vs. 285 events).[88] **Appendix G Figure 24** presents available HRs for coronary heart disease mortality for different followup periods of the WHI trial.

Differences in Treatment Effects Based on Subgroups

WHI subgroup analyses indicated no significant differences in subgroups based on age.[67] No differences in coronary heart disease mortality between treatments were detected by subgroups based on age.[88]

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.[67] When the analyses focused just on myocardial infarction, women who initiated estrogen plus progestin therapy closer to menopause did not have the elevated risk of myocardial infarction compared with women 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.[67]

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.[110] This analysis, therefore, addressed the effect of timing better than analyses that focused 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 (p=0.42).[110]

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 Study) and ELITE (Early vs. Late Intervention Trial with Estradiol) trials used change in carotid artery intima-media thickness as the primary outcome.[46, 53] 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 ages 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 μg/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.[53]

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 (<6 years since menopause) but not among late postmenopausal women (>10 years since menopause). The clinical significance of this difference, however, is unclear.

Peripheral Arterial Disease

Benefits and Harms of Hormone Therapy

The WHI [N=16,608][80] was the only trial that provided information about peripheral arterial disease among women taking estrogen plus progestin (**Appendix F Table11**). Peripheral arterial disease was defined as incident carotid artery disease, abdominal aortic aneurysm, or lower extremity arterial disease. In participants who did not have coronary heart disease or peripheral arterial disease at baseline, women assigned to estrogen alone had a similar risk of developing peripheral arterial disease compared with placebo during the 5.6-year (median) intervention phase (HR, 0.89 [95% CI, 0.60 to 1.32]).

Differences in Treatment Effects Based on Subgroups

In the WHI, no difference in risk of incident peripheral arterial disease by subgroups based on age, diabetes, or body mass index could be detected during the 5.6-year (median) intervention phase.[80]

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.

Cognitive Functioning and Dementia

Benefits and Harms of Hormone Therapy

Dementia and mild cognitive impairment incidence. Two WHI trials (WHIMS [N=4,532][143] and WHISCA, a subset of WHIMS [N=1,416][144]) evaluated the risk of the two outcomes on probable dementia and mild cognitive impairment among women taking estrogen plus progestin (**Appendix F Table 12**). Women using estrogen plus progestin had a higher risk of probable dementia than those taking placebo (1.8% vs. 0.9%; HR, 2.05 [95% CI, 1.21 to 3.48]); the difference in risk of mild cognitive impairment was not statistically significant.[143] The WHISCA trial did not find an elevated risk of probable dementia or mild cognitive impairment among women receiving estrogen plus progestin compared with placebo after 4.4 years of intervention (1.4 years in WHISCA after being enrolled in the WHI for 3 years).[119, 144]

The WHI estrogen plus progestin trial (n=16,608) evaluated Alzheimer's disease or other dementia mortality.[88] There were no cases of dementia-related mortality at the end of the 5.6-year intervention phase in either group, and no significant differences in dementia-related

mortality 12.5 years after stopping therapy (HR, 0.94 [95% CI, 0.78 to 1.13]) or after 17.7 years of cumulative followup (HR, 0.93 [95% CI, 0.77 to 1.11]).[88]

Global cognitive function. Three studies (HERS, KEEPS, and WHI) comprising six trials (HERS [N=1,328],[145] KEEPS-Cog [N=693],[146] Kronos Early Estrogen Prevention Study-MRI [KEEPS-MRI] [N=101],[100] WHIMS [N=4,532],[121, 147] WHISCA [N=1,213],[122] and WHIMSY [N=1,326][123]) measured global cognitive functioning using a short form of the 3MSE or the TICS-m (**Appendix F Table 12**). 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 difference in 3MSE scores between groups through 4 years of followup (-0.4, p=0.36).[145] Similarly, there were no significant difference in change in 3MSE scores in the WHIMS estrogen plus progestin trial during 5.4 years of followup (-0.18, p=0.055). In WHISCA, the WHIMS ancillary study, differences in 3MSE scores during the 2-year intervention period among participants for the estrogen and progestin arm (-0.09, p=0.02) were not sustained at the postintervention followup (-0.081, p=0.09).[122] The WHIMSY trial, a subset of the WHI limited to women ages 50 to 55 years at enrollment, found no difference in mean TICS-m scores with adjustment for age and visit year between women assigned to estrogen plus progestin and women assigned placebo 7.2 years after stopping therapy.[123] Neither KEEPS-Cog, an ancillary study that recruited patients from all sites of the KEEPS trial, nor KEEPS-MRI, an ancillary study that recruited patients from one site of the KEEPS trial, found differences between women randomized to either estrogen plus progestin therapy and women randomized to placebo in change in 3MSE score over a 4-year period of observation for either oral or transdermal estrogen.[100, 146]

Other cognitive measures. Four trials (EMS [N=142],[141] HERS [N=1,328],[145] WHISCA [N=1,213],[122] and WHIMSY [N=1,326][93, 123]) evaluated other measures of cognitive functioning; heterogeneity in outcome measures precluded meta-analysis (**Appendix F Table 13**). The HERS, WHISCA, and WHIMSY trials are described above. 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 other cognitive functioning measures evaluated.

Differences in Treatment Effects Based on Subgroups

WHIMS found no difference in possible dementia by history of diabetes, stroke, hypertension, cardiovascular disease, or race/ethnicity.[119] It also found no difference in the rate of change in 3MSE scores by race/ethnicity, body mass index, history of cardiovascular disease, hypertension, diabetes, or length of use.[147] There was no difference in dementia-related mortality by age at randomization in the WHI estrogen plus progestin trial at the postintervention followup (12.5 years) or cumulative followup (17.7 years).[88]

Differences in Treatment Effects Based on Timing of the Intervention

WHIMS found no difference in the rate of change in 3MSE scores by time to initiation of hormone therapy after the last menstrual period.[147]

Diabetes

Benefits and Harms of Hormone Therapy

Two trials (HERS [N=2,029][148] and WHI [N=15,874][67, 149]) provided information about the prevention of diabetes with estrogen plus progestin among 17,903 women without diabetes or not receiving treatment for diabetes at baseline (**Appendix F Table 14**). Incident diabetes was defined in HERS as having a fasting glucose level of 6.9 mmol/L or greater (≥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 taking an antidiabetic medication), or initiation of hypoglycemic medication; this analysis was conducted post hoc and should be considered cautiously.[148] 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.[149]

Estrogen plus progestin therapy reduced incident diabetes among women in HERS (mean followup, 4.1 years; HR, 0.65 [95% CI, 0.48 to 0.89]) and the WHI (mean followup, 5.6 years; HR, 0.81 [95% CI, 0.70 to 0.94]) through the end of the intervention phase.[148, 149] In the WHI, the larger trial of the two, new diabetes diagnoses were reported during followup by 0.72 percent (annualized) of women randomized to active treatment and 0.88 percent (annualized) of those taking placebo.[67, 149] However, women receiving active treatment actually experienced an increased risk of diabetes compared with those taking placebo 8.2 years postintervention (HR, 1.19 [95% CI, 1.05 to 1.34]).[67] No between-group difference in risk was observed after 13.2 years of cumulative followup (HR, 1.02 [95% CI, 0.93 to 1.12]).[67] **Appendix G Figure 25** presents HRs for incident diabetes at different followup periods of HERS and the WHI.

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, or hypertension at baseline for women in the WHI.[149]

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],[141] EPHT [N=777],[137] ERA [N=209],[113] HERS [N=2,763],[136] and WHI [N=16,608][36, 67, 132, 150]) provided information on preventing fractures with estrogen plus progestin among 20,499 women (**Appendix F Table 15**). These trials spanned reporting periods from 2 through 5.6 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).

A random-effects meta-analysis of these five trials measuring total fractures during or at the end of the intervention period (N=20,499) yielded a statistically significantly reduction of fractures in women taking estrogen plus progestin (RR, 0.79 [95% CI, 0.66 to 0.94]) (**Appendix H Figure 4**). In the meta-analysis, 8.7 percent of women taking estrogen plus progestin and 10.9 percent of women taking placebo experienced fractures. **Appendix G Figure 26** presents HRs for total fractures at different followup periods of the five trials.

Differences in Treatment Effects Based on Subgroups

Tests for interaction did not detect any statistically significant subgroup effects with respect to age in the WHI.[67, 97]

Differences in Treatment Effects Based on Timing of the Intervention

In the WHI and EPHT, no statistically significant differences in incidence of total fractures emerged between women who received estrogen plus progestin hormone therapy and those who received placebo according to years since menopause (i.e., ≤3 years or <10 years, 10 to <20 years, and ≥20 years).[97, 137]

Gallbladder Disease

Benefits and Harms of Hormone Therapy

Two trials (PEPI [N=700][32] and WHI [N=14,203][67, 127]) provided information about the prevention of gallbladder disease with estrogen plus progestin among 14,903 women with gallbladders and without gallbladder disease (**Appendix F Table 16**). Treatment duration was 3.0 years for women in PEPI and 5.6 years, on average, for women in the WHI. The definition of gallbladder disease used in PEPI is unclear; for the WHI, global gallbladder disease was a self-reported endpoint that included all acute or chronic gallbladder inflammation and all gallbladder or biliary tract stone disease.[32, 67, 127] Gallbladder procedures were also reported in the WHI, which included biliary tract procedures such as cholecystectomy.[127]

The WHI, which is the larger of the two trials, reported global gallbladder disease during followup for 1.31 percent (annualized) of women randomized to active treatment and 0.84 percent (annualized) of those taking placebo; this difference was statistically significant (HR, 1.57 [95% CI, 1.36 to 1.80]).[67] During postintervention followup (median 8.2 years), the risk of gallbladder disease continued to favor placebo over estrogen plus progestin therapy (HR, 1.24 [95% CI, 1.01 to 1.52]).[67]

The PEPI trial had few cases of gallbladder disease and reported inconclusive results.[32]

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.[127]

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

Four trials reported on risk of stroke (WHI [N=16,608],[37, 67, 88, 101, 108, 110, 151] EMS [N=142],[141] EPHT [N=777],[137] and ERA [N=209][113]) (**Appendix F Table 17**). We did not pool trial results because of heterogeneity in study duration and outcome measures.

During the WHI 5.6-year intervention phase, 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]).[67] During postintervention followup (2.4 years after stopping therapy), stroke risk was similar between these two groups (HR, 1.04 [95% CI, 0.86 to 1.26]).[67] Cumulatively, after 19.4 years of total followup, stroke risk was statistically higher in the estrogen plus progestin group compared with the placebo group (HR, 1.13 [95% CI, 1.00 to 1.27]).[101]

The three other trials comparing estrogen plus progestin and placebo reported on the incidence of various cerebrovascular events as harms of treatment.[113, 137, 141] In EPHT, although risk of stroke was similar between the treatment and placebo groups (0.2% vs. 0.3%; HR, 1.06 [95% CI, 0.07 to 17.2]) after 3.4 years of intervention, risk of any cerebrovascular event (composite stroke, transient ischemic attack, and 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]).[137] In EMS, few events occurred over 2 years (3 events total), and the results were inconclusive.[141] In the ERA trial, the risk of stroke or transient ischemic attack was similar in both groups (6 events each).[113] **Appendix G Figure 27** presents available HRs for stroke for different followup periods.

Only the WHI reported stroke mortality. Death from stroke was similar between the estrogen plus progestin and placebo groups during the 5.6-year intervention phase (0.3% vs. 0.2%; HR, 1.58 [95% CI, 0.85 to 2.94]).[88] Stroke mortality remained similar between the two groups during the postintervention period (12.5 years after stopping therapy: HR, 1.08 [95% CI, 0.86 to 1.35]) and during cumulative followup (17.7 years of followup: HR, 1.12 [95% CI, 0.91 to 1.38]).[88]

Differences in Treatment Effects Based on Subgroups

No difference between treatments was seen in stroke risk in the WHI by subgroups based on race/ethnicity, age, diabetes, or hypertension.[151] No differences by age were detected in risk for death from stroke.[88]

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).[110]

Urinary Incontinence

Benefits and Harms of Hormone Therapy

Two trials (WHI [N=10,073][67] and HERS [N=1,208][152]) provided results on incident urinary incontinence (self-reported) in women who had been continent at baseline. The WHI followed continent women through year 1 and then evaluated incontinence at study closeout (i.e., median followup of 8.2 years after stopping therapy) 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. These studies defined urinary incontinence as at least one episode weekly.[67, 152] Both the WHI[130] and HERS[152] also evaluated various subtypes of urinary incontinence. Detailed results can be found in **Appendix F Table 18**.

Both studies showed a consistently higher risk of urinary incontinence at all time points for the estrogen plus progestin group compared with placebo. In the WHI, 16.6 percent (annualized) of women taking hormone therapy reported incident incontinence after 1 year of treatment compared with 11.1 percent (annualized) of women taking placebo (HR, 1.49 [95% CI, 1.36 to 1.63]).[67] After 8.2 years of stopping therapy, the risk remained statistically significantly elevated (HR, 1.16 [95% CI, 1.08 to 1.25]).[67] In the HERS trial, women taking estrogen plus progestin had a higher risk of incontinence compared with women taking placebo at the 4.2-year followup (OR, 1.60 [95% CI, 1.30 to 1.90]).[152] **Appendix G Figure 28** presents effect estimates for incident weekly urinary incontinence at different followup periods of the WHI and the HERS.

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

Five trials (WHI [N=16,608],[67, 101, 110, 132, 153] ERA [N=209],[113] EMS [N=142],[141] EPHT [N=777],[137] and HERS [N=2,763][136]) reported on risk of thromboembolism (**Appendix F Table 19**). We did not pool trials because of heterogeneity in study duration and outcome measures.

In the WHI 5.6-year intervention period, women randomized to estrogen plus progestin had an increased risk of venous thrombosis (1.96% vs. 0.94%; HR, 2.06 [95% CI, 1.57 to 2.70]), deep vein thrombosis (1.4% vs. 0.8%; HR, 1.87 [95% CI, 1.37 to 2.54]), and pulmonary embolism (1.0% vs. 0.5%; HR, 1.98 [95% CI, 1.36 to 2.87]) compared with women in the placebo group.[67, 153] In the HERS 4.1 intervention period, women randomized to estrogen plus progestin had a significantly increased risk of total thromboembolic events (2.5% vs. 0.9%; HR, 2.66 [95% CI, 1.41 to 5.04]) and deep vein thrombosis (1.8% vs. 0.7%; HR, 2.82 [95% CI, 1.32 to 6.04]), but

not of pulmonary embolism (0.8% vs. 0.3%; HR, 2.78 [95% CI, 0.89 to 8.74]).[136] The WHI groups did not differ for risk of deep vein thrombosis or pulmonary embolism during the 2.4-year postintervention period after women stopped therapy.[132] However, increased risk for deep vein thrombosis and pulmonary embolism remained for women in the estrogen plus progestin group after 13.2 years of cumulative followup (HR, 1.24 [95% CI, 1.01 to 1.53] and HR, 1.26 [95% CI, 1.00 to 1.59], respectively). In the HERS trial, higher risk for overall venous thromboembolism remained after 6.8 years of cumulative followup (4.2% vs. 1.7%; HR, 2.06 [95% CI, 1.26 to 3.36]) but was no longer statistically significant in the WHI trial after 19.4 years of cumulative followup (4.9% vs. 4.3%; HR, 1.14 [95% CI, 0.99 to 1.31]).[67, 101] **Appendix G Figures 29** and **30** present available HRs for deep vein thrombosis and pulmonary embolism, respectively, for different followup periods of the WHI and HERS trials.

In the three smaller trials (N=142 to 777), groups did not differ in risk of venous thromboembolic events among participants randomized to estrogen plus progestin or placebo over 2 to 3.4 years (3 events vs. 1 event across all three trials).[113, 137, 141]

Differences in Treatment Effects Based on Subgroups

In the WHI, risk of pulmonary embolism or deep vein thrombosis did not differ between treatments by subgroups based on age.[67, 91]

Differences in Treatment Effects Based on Timing of the Intervention

Risk of venous thromboembolism or pulmonary embolism in the WHI was similar for women who began hormone therapy within 5 or 10 years after menopause and for those who started later.[67, 110]

Health-Related Quality of Life

Benefits and Harms of Hormone Therapy

The WHI (N=16,608)[67] was the only trial that reported on health-related quality of life (**Appendix F Table 20**). It used the SF-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 taking hormone therapy had statistically significantly better scores than women taking 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],[113] HERS [N=2,763],[136] and WHI [N=16,608][132]) 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 F Table 21**). The treatment duration for these trials ranged from 3.2 to 5.6 years.[113, 132, 136] A meta-analysis of these trials yielded no statistically significant difference in all-cause mortality between women taking hormone therapy or placebo (**Appendix H Figure 5**; RR, 1.01 [95% CI, 0.88 to 1.16]).

The WHI, the largest of the three trials, reported an HR of 0.97 (95% CI, 0.81 to 1.16) for its 5.6-year intervention period; 2.9 percent of women in both treatment groups died.[132] The risk of death among women who had received estrogen plus progestin and those who had received placebo remained similar at various postintervention and cumulative followup (**Appendix G Figure 31**).[67, 88, 101, 132]

Differences in Treatment Effects Based on Subgroups

We found no evidence on differences in treatment effects by subgroups based on age for all-cause mortality.

Differences in Treatment Effects Based on Timing of the Intervention

The effect of estrogen plus progestin on all-cause mortality did not differ significantly between women who initiated hormone therapy within 5 or 10 years after menopause and those who started it later.[67, 110]

Chapter 4. Discussion

This chapter begins with a summary of review findings for each KQ regarding the use of hormone therapy for primary prevention of chronic disease. Following those sections, we present limitations of the evidence and the review and end with conclusions.

Summary of Review Findings

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

Twenty trials and three observational studies (reported in 85 publications) comparing the effects of estrogen only or estrogen plus progestogen with placebo for preventing chronic conditions in persons experiencing menopause met our eligibility criteria. **Tables 7** and **8** summarize findings, SOE, and applicability for various outcomes for both KQs 1 and 2. From the previous review, the SOE grade for probable dementia was changed to low in light of the low number of outcomes (<100) and lack of additional evidence identified in the update compared to other outcomes. The SOE grade for all-cause mortality was changed to high because a calculation of an absolute risk difference indicated a precise estimate.

The WHI was the only trial designed and powered to evaluate the effectiveness of hormone therapy for the 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 posttrial phases, it had up to 20.4 years of followup to assess how risk of 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, risk of diabetes (134 fewer cases per 10,000 women over 7.1 years) and risk of fractures (388 fewer cases per 10,000 women over 7.2 years) were statistically significantly reduced compared with women taking placebo. The risk for invasive breast cancer was numerically reduced in women using estrogen only, but the difference compared with placebo did not reach statistical significance (HR, 0.79 [95% CI, 0.61 to 1.02]). Women using estrogen plus progestin therapy experienced statistically significantly reduced risk of colorectal cancer (34 fewer cases per 10,000 women over 5.6 years), diabetes (78 fewer cases per 10,000 women over 5.6 years), and fractures (230 fewer cases per 10,000 women over 2 to 5.6 years) compared with women in the placebo groups. Benefits of hormone therapy for colorectal cancer attenuated with extended followup and were no longer statistically significant.

Our review also documented several important harms of hormone therapy (KQ 2). Women taking estrogen-only therapy had a statistically significant increased risk of gallbladder disease (377 more cases per 10,000 women over 7.1 years), stroke (79 more cases per 10,000 women over 7.2 years), urinary incontinence (885 more cases per 10,000 women over 1.0 year), and venous thromboembolism (77 more cases per 10,000 women over 7.2 years) compared with women in the placebo groups.

Likewise, for women taking estrogen plus progestin therapy, risks of invasive breast cancer (51 more cases per 10,000 women over 5.6 years), probable dementia (88 more cases per 10,000 women over 4 years), gallbladder disease (260 more cases per 10,000 women over 5.6 years), stroke (52 more cases per 10,000 women over 5.6 years), urinary incontinence (562 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. A Danish retrospective cohort study also reported an increased risk for endometrial cancer (RR, 1.71 [1.58 to 1.86] over 9.8 years).

Based on high- or moderate-strength evidence, the risks for coronary heart disease and all-cause mortality were similar between estrogen-only hormone therapy and placebo. Likewise, high- or moderate-strength evidence indicates similar risks for lung cancer and all-cause mortality between estrogen plus progestin hormone therapy and placebo.

The WHI used a global index based on beneficial and harmful events to assess the trade-off between advantages and disadvantages of hormone therapy. Overall, estrogen plus progestin led to 20 additional adverse events per 10,000 person-years at the end of the intervention phase (HR, 1.12 [95% CI, 1.02 to 1.24]).[67] After 18 years of cumulative followup, no statistically significant differences between groups were still apparent.[91]

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]). Long-term followup also did not show any statistically significant differences between groups.[91]

Information About Subgroups (KQ 3)

Subgroups (KQ 3) of interest for this report include the following characteristics: race/ethnicity; persons with premature menopause; persons with surgical menopause; age; duration of use; type, dose, and mode of delivery of hormone therapy; timing of the intervention; and presence of coexisting conditions.

Trials did not report results for most of these subgroups. Subgroup analyses of trial results based on these characteristics were restricted to race/ethnicity, age, oophorectomy status, and a limited number of comorbid conditions 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 myocardial infarction, colorectal cancer, and all-cause mortality. Analyses that compared women ages 50 to 59, 60 to 69, and 70 to 79 years using estrogen-only therapy yielded a statistically significant trend for increasing risk by age for myocardial infarction ($p=0.02$ for trend), colorectal cancer ($p=0.02$ for trend), and all-cause mortality ($p=0.04$ for trend). The significant interaction of colorectal cancer and all-cause mortality with age was no longer present with extended followup of 13 to 18 years.

These findings, however, have to be interpreted cautiously. For example, 489 women died in the WHI estrogen-only trial, which could lead to chance findings when assessing differences in subgroups. In addition, many of the subgroup analyses were post hoc analyses. In its study

protocol, the WHI specified only age, race/ethnicity, obesity, hysterectomy, and cardiovascular disease at baseline as subgroups of interest.

Recent subgroup analyses of the WHI regarding the effect of timing on risk of coronary events provide consistent findings. Time since menopause did not have a statistically significant effect on the risk of coronary heart disease in women using estrogen-only therapy. Women who initiated 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 risk. It remains unclear whether a shorter time interval than 10 years might have been a more appropriate measure to assess the effect of timing. An additional subgroup analysis took hormone therapy use before enrollment into the WHI into consideration (e.g., about 40% of women in the estrogen-only trial used hormone therapy before enrollment) and also found no difference in coronary risk between early and late initiation of hormone therapy. 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.

Two recent trials, KEEPS and ELITE,[46, 53] 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 of hormone therapy on carotid artery intima-media thickness.

A 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, which is a substantial limitation of this review).[29] If this information was not available, the authors used the mean age of participants at baseline as a surrogate. Results provided some support of the timing hypothesis. All-cause mortality was lower in the subgroup of studies in which treatment was started within 10 years of menopause compared with studies in which 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 sometimes viewed as supporting the timing hypothesis is the Danish Osteoporosis Prevention Study.[154] We did not consider this study because of poor quality due to lack of blinding of outcomes assessors. The study 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 effect of dose and mode 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 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.[29] For this report, the PEPI trial was the only eligible study that used different types (regular synthetic and micronized progestins) and regimens of progestins (continuous and sequential progestin regimens) within the same study.[32] 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 in outcomes that are of interest for this report. All the other studies included in this review used continuous progestin regimens. While observational studies suggest transdermal estrogen has a lower risk of venous thromboembolism compared with oral estrogen, there were no eligible trials of transdermal estrogen identified.

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 and estrogen plus progestin therapy are different. As a consequence, we were not able to include four trials that did not report results stratified by treatment regimen in our analyses.[93, 105-107]

The WHI provided the best and most applicable information for many of our outcomes of interest. 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., gallbladder disease, urinary incontinence), when available. Based on a communication with the WHI Researcher Help Desk (https://www.whi.org/helpdesk; July 2021), we relied on a publication by Manson et al.[67] for results of patient-reported outcomes (i.e., diabetes, urinary incontinence, gallbladder disease). 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, 40 women developed ovarian cancer. Likewise, event rates for cervical and endometrial cancer were low, rendering wide CIs that encompassed clinically meaningful differences in risk. The confidence in conclusions about benefits and risks of hormone therapy regarding these outcomes is low.

A recent analysis of individual patient data from 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 (RR, 1.37 [95% CI, 1.29 to 1.46]).[155] The risk was similar between estrogen-only and estrogen plus progestin therapies. Even 10 years after stopping long-duration hormone therapy, the risk of serious and endometrioid ovarian tumors was still elevated (RR, 1.25 [95% CI, 1.07 to 1.46]).

Some outcomes that relied on self-reporting (e.g., diabetes and urinary incontinence) might be affected by potential biases or limited by disparate adherence rates (e.g., cognitive function)

(WHIMS: 61.4% vs. 32.3% for placebo vs. estrogen plus progestin, respectively). 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 inclusion criteria 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 effect 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 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 with <80% compliance with study pills) were generally similar to intention-to-treat results[67] 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 taking estrogen-only therapy and 1.52 (95% CI, 1.15 to 2.00) for women taking estrogen plus progestin (compared with HR, 0.79 [95% CI, 0.61 to 1.02] and HR, 1.26 [95% CI, 1.02 to 1.55], respectively, in the intention-to-treat analyses).[67]

The applicability of our findings may be limited by three main aspects. First, the average age of women in the included studies ranged from 50 to 79 years, which is older than the average age of women experiencing menopause (51 years). For example, in the WHI, the average age of women was 64 years; approximately 30 percent of women in the WHI were ages 50 to 59 years at the time of enrollment, and 12.5 percent were ages 50 to 54, an age range when most women are likely to consider hormone therapy for the treatment of menopausal symptoms. Second, the majority of women (around 80%) were White. Subgroup analyses did not reveal differences in beneficial or harmful effects among racial/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 (0.625 mg/day of oral conjugated equine estrogen, with or without 2.5 mg/day of medroxyprogesterone). The PEPI trial was the only study that directly compared different formulations of estrogen and progestin combinations. To date, however, the evidence regarding the effect of different formulations, doses, and modes of delivery of hormone therapy on benefits and risks is insufficient to draw firm conclusions.

Continuing research on long-term outcomes, such as cancer, mortality, or debilitating diseases that have not been assessed by the available studies, 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 risk of invasive breast cancer, were still 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 effect 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 from all trials to conduct individual patient data meta-analyses could probably overcome this issue and provide more definitive answers.

Conclusions

Hormone therapy plays an important role in the clinical management of menopausal symptoms, but it has a complex pattern of risks and benefits in the primary prevention of chronic conditions. Depending on the treatment regimen, the risk-benefit profile of hormone therapy for the prevention of chronic conditions differs for women ages 50 to 79 years. Women undergoing hormone therapy experience some beneficial effects (e.g., reduced risk of fractures or diabetes) but also an increased risk of harms (e.g., higher risk of stroke, thromboembolic events, gallbladder disease, and possibly urinary incontinence), particularly among women older than age 60 years. Some evidence suggests that age at the initiation of hormone therapy can modify the risk-benefit profile (with more favorable results in younger women), particularly for overall mortality and cardiovascular events. To date, however, the available evidence regarding benefits and harms of early initiation of hormone therapy is inconclusive.

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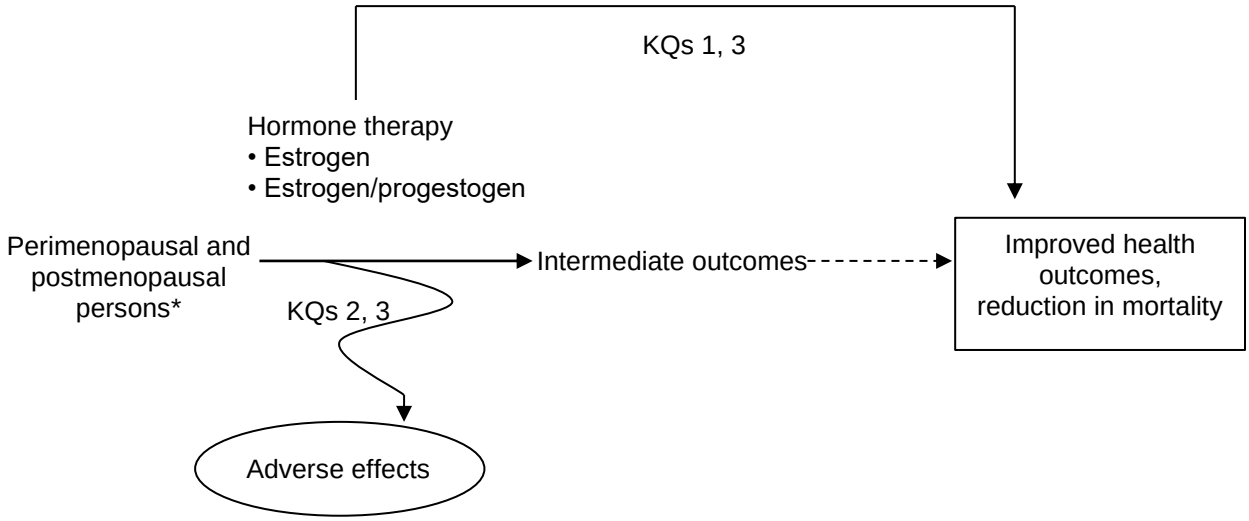
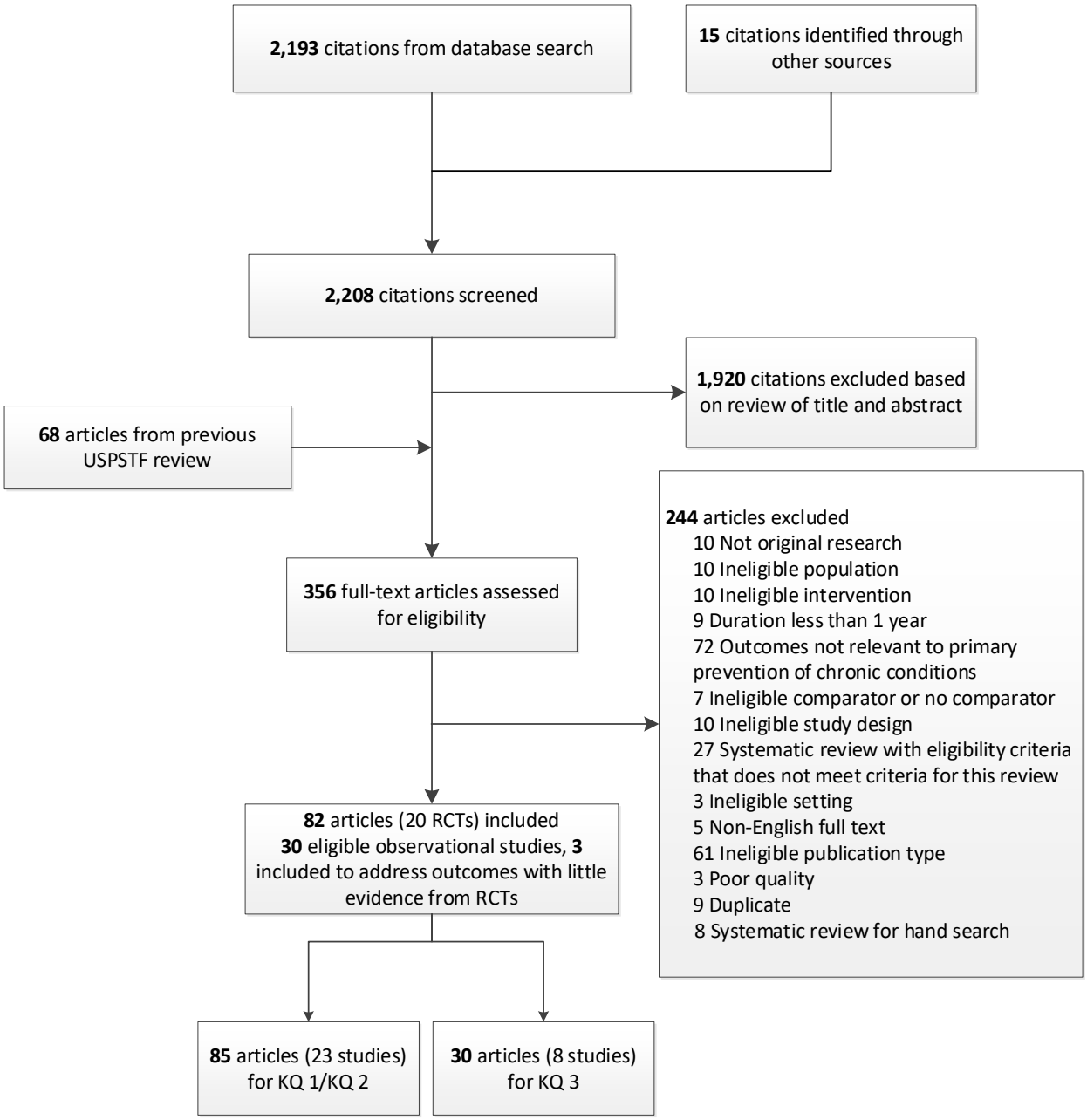
Figure 1. Analytic Framework



* Definitions of perimenopausal and postmenopausal women are based on STRAW+ 10 criteria.

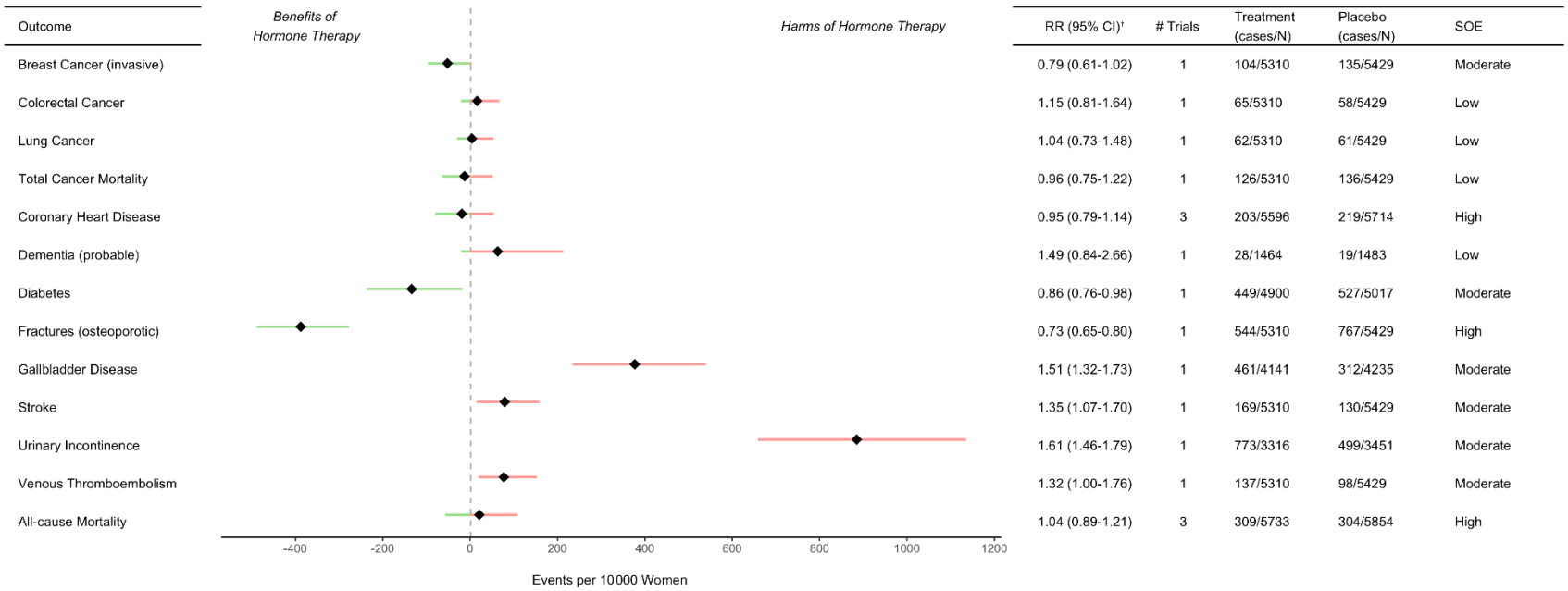
Abbreviation: KQ=key question.

Figure 2. Literature Flow Diagram



Abbreviations: KQ=key question; RCT=randomized, controlled trial; USPSTF=U.S. Preventive Services Task Force.

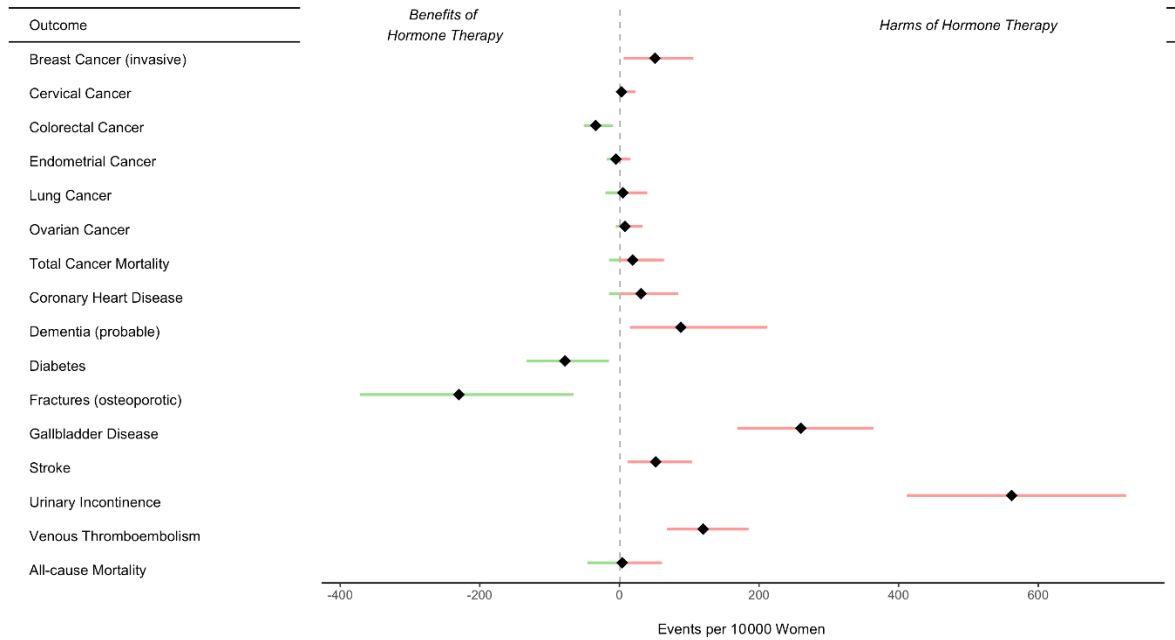
Figure 3. Absolute Risk Reductions or Increases During the Intervention Period for Women Treated With Estrogen Only*



* Findings 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); followup periods for all outcomes are 7.1 years except all-cause mortality, 2 to 7.2 years; fractures, 7.2 years; dementia, 5.2 years; and urinary incontinence, 1 year.
† We calculated relative 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 HRs of trials that are presented in the text.

Abbreviations: CI=confidence interval; HR=hazard ratio; N=number; RR=relative risk; SOE=strength of evidence.

Figure 4. Absolute Risk Reductions or Increases During the Intervention Period for Women Treated With Estrogen Plus Progestin*



Outcome	RR (95% CI)†	# Trials	Treatment (cases/N)	Placebo (cases/N)	SOE
Breast Cancer (invasive)	1.27 (1.03-1.56)	1	206/8506	155/8102	High
Cervical Cancer	1.52 (0.50-4.66)	1	8/8506	5/8102	Low
Colorectal Cancer	0.62 (0.43-0.89)	1	50/8506	75/8102	Moderate
Endometrial Cancer	0.83 (0.49-1.40)	1	27/8506	30/8102	Low
Lung Cancer	1.06 (0.77-1.46)	1	78/8506	70/8102	Moderate
Ovarian Cancer	1.41 (0.75-2.66)	1	24/8506	16/8102	Low
Total Cancer Mortality	1.14 (0.89-1.47)	1	133/8506	111/8102	Low
Coronary Heart Disease	1.12 (0.94-1.33)	3	266/9506	221/8649	High
Dementia (probable)	1.97 (1.16-3.33)	1	40/2229	21/2303	Low
Diabetes	0.81 (0.70-0.94)	1	328/8132	373/7742	Moderate
Fractures (osteoporotic)	0.79 (0.66-0.94)	5	906/10464	1098/10035	High
Gallbladder Disease	1.56 (1.36-1.79)	1	528/7308	319/6895	Moderate
Stroke	1.37 (1.07-1.76)	1	159/8506	109/8102	Moderate
Urinary Incontinence	1.49 (1.36-1.63)	1	1021/5981	641/5597	Moderate
Venous Thromboembolism	2.06 (1.57-2.70)	1	209/8506	102/8102	Moderate
All-cause Mortality	1.01 (0.88-1.16)	3	383/9990	368/9590	High

*Findings 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); followup periods for all outcomes are 5.6 years except fractures, 2 to 5.6 years; coronary heart disease, 2 to 5.6 years; dementia, 4 years; and urinary incontinence, 1 year.
† We calculated relative 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 HRs of trials that are presented in the text.

Abbreviations: CI=confidence interval; HR=hazard ratio; N=number; RR=relative risk; SOE=strength of evidence.

Table 1. List of Included Interventions, Extracted From FDA List of Approved Hormone Therapy*

Category of Hormone Therapy and Generic Name	Brand Name	Product Type	Dosage†
Estrogen-Only or Progestogen-Only Formulations			
Conjugated estrogens¶	Premarin	Pill, IM, IV	0.3 mg/day cyclically,§ single 25-mg injection
Estradiol‡	Estrace	Pill	0.5–2 mg/day
Estradiol‡	Alora	Patch	0.025–0.1 mg/day twice weekly
Estradiol‡	Climara	Patch	0.025–0.1 mg/day once weekly
Estradiol‡	Menostar	Patch	0.014 mg/day once weekly
Estradiol‡	Minivelle	Patch	0.025–0.1 mg/day twice weekly
Estradiol‡	Vivelle	Patch	0.0375–0.1 mg/day twice weekly
Estradiol‡	Vivelle-Dot	Patch	0.025–0.1 mg twice weekly
Estradiol‡	Divigel	Topical	0.25-1.25 g/day
Estradiol‡	Elestrin	Topical	0.87 g/day
Estradiol‡	Estrogel	Topical	1.25 g/day
Estradiol‡	Evamist	Topical	1.53–4.59 mg/day
Estradiol valerate	Delestrogen	IM	10/20/40 mg/mL/month
Esterified estrogen‡	Menest	Pill	0.3–1.25 mg/day cyclically§
Micronized progesterone	Prometrium	Pill	0.625 mg/day
Medroxyprogesterone acetate	Provera	Pill	100–200 mg/day
Combination Estrogen Plus Progestogen Formulations			
Estradiol‡ + drospirenone**	Angeliq	Pill	Drospirenone 0.25–0.5 mg/day with estradiol 0.5–1.0 mg/day
Estradiol‡ + norethindrone acetate#	Activella	Pill	Estradiol 0.5–1.0 mg/day with norethindrone 0.1 mg/day
Estradiol‡ + norgestimate**	Prefest	Pill	Repeat estradiol 1 mg/day for 3 days followed by estradiol 1 mg/day with norgestimate 0.09 mg/day for 3 days
Estradiol‡ + levonorgestrel**	Climara Pro	Patch	Estradiol 0.045 mg with levonorgestrel 0.015 mg worn for 24 hours once weekly
Estradiol + micronized progesterone	Bijuvia	Pill	Estradiol 1 mg/micronized progesterone 100 mg daily
Estradiol‡ + norethindrone acetate**	Combipatch	Patch	Estradiol 0.05 mg with norethindrone 0.14–0.25 mg worn for 24 hours once weekly
Estradiol valerate + dienogest	Natazia	Pill	Estrogen valerate 1 mg–3 mg/day; dienogest 1–2 mg/day
Conjugated estrogene + medroxyprogesterone acetate**	Prempro	Pill	Conjugated estrogen 0.625 mg/day with medroxyprogesterone acetate 5 mg/day
Ethinyl estradiol‡ + norethindrone acetate#	Femhrt	Pill	Ethinyl estradiol 0.0025 mg/day with norethindrone acetate 0.500 mg/day

* Source: U.S. Food and Drug Administration. Menopause: Medicines to Help You. https://www.fda.gov/consumers/free-publications-women/menopause-medicines-help-you. Accessed August 30, 2021.
† Dosages are based on the package inserts for the brand name formulations.
‡ Estradiol can be from natural sources or prepared synthetically.
§ Cyclically means "within a cycle" (e.g., repeat 3 weeks of treatment and 1 week off).
l Natural estrogenic substance prepared from purified crystalline estrone.
¶ Conjugated estrogens, such as conjugated equine estrogens, are derived wholly or partially from the urine of pregnant mares or synthetic estrone and equilin.
# Synthetic conjugated estrogens are prepared using plant sources, such as yams and soy, and use only synthetic resources.
** Synthetic progestin.

Abbreviations: FDA=Food and Drug Administration; IM=intramuscular injection; IV=intravenous injection.

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

Organization, Year	Recommendations
American Academy of Family Physicians (AAFP), 2018[156]	Recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women (Grade: D recommendation). AAFP recommends against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy (Grade: D recommendation).
American College of Obstetricians and Gynecologists, 2013–2014[157]	Recommends against the use of menopausal HT for primary and secondary prevention of coronary heart disease because of insufficient evidence for benefit. The guidelines also note the following considerations: • 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 HT is used close to the onset of menopause, but the relationship of duration of therapy to cardiovascular outcomes awaits further study with cardiovascular health outcomes rather than surrogate CVD outcomes. • HT (i.e., estrogen or combined estrogen/progestogen) positively affects bone health; it is approved for use in women with an increased risk of osteoporosis[158] and fracture. Reaffirmed 2020.
American Heart Association, 2011, 2014[159, 160]	Recommends against the use of HT and selective estrogen-receptor modulators for primary and secondary prevention of CVD in women (Class III, Level of Evidence A). HT (CEE with or without medroxyprogesterone) should not be used for primary or secondary prevention of stroke in postmenopausal women (Class III; Level of Evidence A).
American Association of Clinical Endocrinologists, 2017[161, 162]	Reaffirmation of 2011 statement • Menopausal HT is not recommended for primary or secondary prevention of CVD (Grade D; Best Evidence Level [BEL] 1). • HT should be used for the prevention and treatment of osteoporosis within the context of the overall benefit vs. risk analysis of each patient. Data from multiple RCTs substantiate the efficacy of estrogens in preserving bone mass and, less consistently, preventing fractures, but nonhormonal therapeutic options for bone health exist (Grade A; BEL 1). • HT for the prevention or treatment (or both) of dementia is not recommended (Grade D; BEL 1).
American College of Physicians, 2015, 2017[163, 164]	Recommends the U.S. Preventive Services Task Force website and the North American Menopause Society[165] guidelines. Recommends against using menopausal estrogen therapy or menopausal estrogen plus progestin therapy or raloxifene for the treatment of osteoporosis in women. (Grade: strong recommendation; moderate-quality evidence)
The North American Menopause Society, 2014, 2017[44]	HT should not be prescribed for chronic disease prevention. (Level I) Benefits are most likely to outweigh risks for symptomatic women who initiate HT when age 60 years or younger or who are within 10 years of menopause onset. (Level I) Decisions about duration of HT require individualization, including consideration of personal preferences, balancing potential ongoing benefits and risks, and decisions to continue HT for preventive and/or QOL purposes. (Level III)
Society of Obstetricians and Gynaecologists of Canada, 2014[166]	Healthcare providers should not initiate HT for the sole purpose of preventing CVD (coronary artery disease and stroke) in older postmenopausal women because there are no data to support this indication for HT. (I-A) If prescribing HT to older postmenopausal women, healthcare providers should address cardiovascular risk factors; low- or ultralow-dose estrogen therapy is preferred. (I-B)

Abbreviations: AAFP=American Academy of Family Physicians; BEL=Best Evidence Level; CEE=conjugated equine estrogen; CVD=cardiovascular disease; HT=hormone therapy; QOL=quality of life; RCT=randomized, controlled trial.

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

Trial Name (Acronym)	Author, Year	Country; Participants	Intervention; Duration	Quality Rating
Early vs. Late Intervention Trial with Estradiol, Cognitive Endpoints (ELITE-Cog)	Henderson et al, 2016[92]	• United States • Ages 41–84 years • Within 6 years of natural or surgical menopause (early postmenopause group) or at least 10 years beyond natural or surgical menopause (late menopause group) • Serum estradiol level <25 pg/mL	17β-estradiol 1 mg/day (N=323) Placebo (N=320) Women with a uterus: cyclic micronized progesterone (45 mg) as a 4% vaginal gel Mean 4.8 years	Fair
Estrogen Memory Study (EMS)	Tierney et al, 2009[141]	• Canada • Ages 61–87 years • Last menstrual cycle >12 months before screening • Fluent in English and could read normal print and hear normal speech	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	Fair
Estrogen in the Prevention of Atherosclerosis (EPAT)	Hodis et al, 2001[112]	• United States • Postmenopausal women • Ages 46–80 years • Low-density lipoprotein cholesterol level ≥130 mg/dL	Micronized 17β-estradiol 1 mg/day (N=111) Placebo (N=111) 2 years	Fair
Estonian Postmenopausal Hormone Therapy Trial (EPHT)	Veerus et al, 2006[137]	• Estonia • Ages 50–64 years • An elapsed ≥12 months since last period at the randomization stage	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=404) Placebo (N=373) Mean 3.4 years	Fair
Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis (ERA)	Herrington et al, 2000[113]	• United States • Ages 41–79 years • Postmenopausal women not currently receiving estrogen replacement therapy • With >1 epicardial coronary stenosis of ≥30% of the luminal diameter	CEE 0.625 mg/day (N=100) CEE 0.625 mg/day plus MPA 2.5 mg/day (N=104) Placebo (N=105) 3.2 years	Fair
Greenspan et al	Greenspan et al, 2005[107]	• United States • Ages 65–90 years • Community-dwelling women	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=121) CEE 0.625 mg/day (N=66) Placebo (N=186) 3 years	Good
Heart and Estrogen/ Progestin Replacement Study (HERS)	Grady et al, 1998;[167] Hulley et al, 1998;[168] Kanaya et al, 2003;[148] Steinauer et al, 2005[136, 152]	• United States • Age ≤80 years (mean, 66.7) • Intact uterus • Postmenopausal • Established coronary artery disease	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=1,380) Placebo (N=1,383) Mean 4.1 years CEE 0.625 mg/day plus MPA 2.5 mg/day (N=1,156) Placebo (N=1,165) Mean 6.8 years	Good

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

Trial Name (Acronym)	Author, Year	Country; Participants	Intervention; Duration	Quality Rating
Kronos Early Estrogen Prevention Study–Cognitive and Affective Study (KEEPS-Cog)	Gleason et al, 2015[146]	• United States • Ages 42–58 years • Intact uterus • Recently postmenopausal • At risk for cardiovascular disease	CEE 0.45 mg/day plus MP 200 mg/day for 12 days/month (N=220) Transdermal estradiol 50 µg/day plus MP 200 mg/day for 12 days/month (N=211) Placebo (N=262) 4 years	Fair
Kronos Early Estrogen Prevention Study-MRI (KEEPS-MRI)	Kantarci et al, 2016[100]	• United States • Ages 42–59 years • In good cardiovascular health • 5–36 months past menopause • No MRI contraindications for safety and neurological disorders	CEE 0.45 mg/day plus MP 200 mg/day for 12 days/month (N=31) Transdermal 17β-estradiol 50 µg/day plus MP 200 mg/day for 12 days/month (N=31) Placebo (N=39) 4 years	Fair
Postmenopausal Estrogen and Progestin Interventions Trial (PEPI)	PEPI, 1995[32]	• United States • Ages 45–64 years • With or without a uterus • Naturally or surgically menopausal	CEE 0.625 mg/day (N=175) CEE 0.625 mg/day plus MPA 10 mg/day for 12 days/month (N=174) CEE 0.625 mg/day plus MP 200 mg/day for 12 days/month (N=178) Placebo (N=174) 3 years	Fair
STOP-IT	Gallagher et al, 2001[106]	• United States • Ages 65–77 years • Femoral neck density within normal range for age	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 µg twice daily (N=122) Calcitriol 0.25 µg twice daily (N=123) Placebo (N=123) 3 years	Fair
Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA)	Ettinger et al, 2004;[169] Johnson et al, 2005;[115] Waetjen et al, 2005;[129] Yaffe et al, 2006[124]	• United States • Ages 60–80 years • Intact uterus • ≥5 years past menopause • Bone mineral density normal for age	Unopposed transdermal estradiol 0.014 mg/day (N=208) Placebo (N=209) 2 years	Good
Women's Angiographic Vitamin and Estrogen Trial (WAVE)	Waters et al, 2002[105]	• United States, Canada • Postmenopausal • Mean age of 65 years • Coronary angiogram performed within 4 months of study entry	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=86) CEE 0.625 mg/day (N=124) Placebo (N=213) Mean 2.8 years	Fair
Women's Health Initiative (WHI) E Trial	Anderson et al, 2004;[37] Bonds et al, 2006;[125] Brunner et al, 2005;[170] Chlebowski et al, 2010;[116] Cirillo et al, 2005;[127] Curb et al, 2006;[131] Hendrix et al, 2005;[130] Hendrix et al, 2006;[128] Hsia et al, 2006;[117] Manson et al, 2013;[67] Ritenbaugh et al, 2008;[114] Rossouw et al, 2007[52]	• United States • Postmenopausal • Ages 50–79 years • Prior hysterectomy • 3-month washout period required for women using hormone therapy at baseline	CEE 0.625 mg/day (N=5,310) Placebo (N=5,429) Median 7.2 years	Fair

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

Trial Name (Acronym)	Author, Year	Country; Participants	Intervention; Duration	Quality Rating
WHI E Postintervention and Postintervention Extension Phases	Chlebowski et al, 2010;[134] LaCroix et al, 2011;[108] Manson et al, 2013;[67] Manson, 2017;[88] Prentice, 2020;[91] Prentice, 2020[101]	• 9,666 participants from WHI (90%) had any postintervention followup and 7,645 (71%) consented to participate in the extension phase	Postintervention followup CEE 0.625 mg/day (N=4,794) Placebo (N=4,872) Mean 6.6 years Postintervention extension followup CEE 0.625 mg/day (N=3,778) Placebo (N=3,867)	Fair
WHI E+P Trial	Anderson et al, 2012;[109] Anderson et al, 2003;[126] Canonico et al, 2014;[171] Cauley et al, 2003;[150] Chlebowski et al, 2003;[133] Chlebowski et al, 2004;[140] Cirillo et al, 2005;[127] Cushman et al, 2004;[153] Hays et al, 2003;[172] Hendrix et al, 2003;[173] Hendrix et al, 2005;[130] Hsia et al, 2004;[80] Manson et al, 2003;[174] Manson et al, 2013;[67] Margolis et al, 2004;[149] Prentice et al, 2009;[110] Rossouw et al, 2002;[36] Rossouw et al, 2007;[52] Tang et al, 2011;[175] Toh et al, 2010;[176] Wassertheil-Smoller et al, 2003[151]	• United States • Postmenopausal • Ages 50–79 years • 3-month washout period for women using hormone therapy at baseline	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=8,506) Placebo (N=8,102) Median 5.6 years	Fair
WHI E+P Postintervention and Postintervention Extension Phases	Chlebowski et al, 2009;[142] Chlebowski et al, 2010;[134] Gramling et al, 2009;[135] Heiss et al, 2008;[132] Manson et al, 2013;[67] Manson, 2017;[88] Prentice, 2020;[91] Prentice, 2020[101]	• 15,747 participants from WHI (95%) had any postintervention followup and 12,788 (77%) consented to participate in the extension phase	Postintervention followup CEE 0.625 mg/day plus MPA 2.5 mg/day (N=8,060) Placebo (N=7,687) Median 8.2 years Postintervention extension followup CEE 0.625 mg/day plus MPA 2.5 mg/day (N=6,545) Placebo (N=6,243)	Fair
Women's Health Initiative Memory Study (WHIMS) E	Espeland et al, 2004;[121] Shumaker et al, 2004[119]	• United States • WHI participants enrolled in the estrogen-only trial • Ages 65–79 years • Free of probable dementia • Able and willing to undergo annual cognitive assessment	CEE 0.625 mg/day (N=1,464) Placebo (N=1,483) 5.2 years	Good
WHIMS E+P	Culhane, 2003;[177] Rapp et al, 2003;[147] Shumaker et al, 2003[143]	• 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	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=2,229) Placebo (N=2,303) 5.4 years	Good

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

Trial Name (Acronym)	Author, Year	Country; Participants	Intervention; Duration	Quality Rating
Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO)	Espeland et al, 2017[93]	• United States • Postmenopausal • Ages 65–79 years • 3-month washout period for women using hormone therapy at baseline • Received clinic-based cognitive testing as part of WHIMS	CEE 0.625 mg/day plus MPA 2.5 mg/day or CEE 0.625 mg/day only* (N=1,402) Placebo (N=1,478) 6.4 years overall group 7.1 years for those with prior hysterectomy 5.4 years for those without prior hysterectomy	Fair
Women's Health Initiative Memory Study of Younger Women (WHIMSY)	Espeland et al, 2013[93, 123]	• United States • Postmenopausal • Ages 50–55 years • 3-month washout period for women using hormone therapy at baseline	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=696) Placebo (N=630) 7.2 years	Fair
Women's Health Initiative Study of Cognitive Aging (WHISCA) E	Espeland et al, 2010;[122] Resnick et al, 2009[120]	• United States • WHIMS E-only trial participants • Free of probable dementia • At 1 of 14 WHIMS centers • Began 3 years after enrollment in WHI	CEE 0.625 mg/day (N=434) Placebo (N=452) 3.6 years	Good
WHISCA E Post intervention Phase	Espeland et al, 2010;[122]	• United States • WHIMS E-only trial participants • Free of probable dementia • At 1 of 14 WHIMS centers • Began 3 years after enrollment in WHI	CEE 0.625 mg/day (N=434) Placebo (N=452) 2.4 years	Good
WHISCA E+P	Espeland et al, 2010;[122] Resnick et al, 2006[144]	• United States • WHIMS E+P trial participants • Free of probable dementia • At 1 of 14 WHIMS centers • Began 3 years after enrollment in WHI	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=690) Placebo (N=726) 2 years	Good
WHISCA E+P Post intervention Phase	Espeland et al, 2010;[122]	• United States • WHIMS E+P trial participants • Free of probable dementia • At 1 of 14 WHIMS centers • Began 3 years after enrollment in WHI	CEE 0.625 mg/day plus MPA 2.5 mg/day (N=690) Placebo (N=726) 4 years	Good

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

Trial Name (Acronym)	Author, Year	Country; Participants	Intervention; Duration	Quality Rating
Women's International Study of Long Duration Oestrogen After Menopause (WISDOM)	Vickers et al, 2007[138]	• United Kingdom, Australia, New Zealand • Postmenopausal • Ages 50–69 years	CEE 0.625 mg/day plus MPA 2.5–5.0 mg/day (N=2,196) CEE 0.625 mg/day (N=826) Placebo (N=2,189) 1 year	Fair

* Analysis did not stratify by treatment regimen.

Abbreviations: AAFP=American Academy of Family Physicians; CEE=conjugated equine estrogen; HT=hormone therapy; MP=micronized progesterone; MPA=medroxyprogesterone acetate; MRI=magnetic resonance imaging; N=number; WHI=Women's Health Initiative.

Table 4. Number of Trials Using FDA-Approved Hormone Therapy Formulations

Substance	Number of Trials and References
Estrogen-only formulation	
Conjugated estrogens	8 trials: Greenspan et al, 2005;[107] Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis (ERA);[113] Postmenopausal Estrogen and Progestin Interventions Trial (PEPI);[32] Women's Angiographic Vitamin and Estrogen Trial (WAVE);[105] Women's Health Initiative (WHI) E Trial;[37, 52, 67, 79, 88, 91, 101, 108, 114, 116, 117, 125, 127, 128, 130, 131, 134, 170] Women's Health Initiative Memory Study (WHIMS) E;[119, 121] Women's Health Initiative Study of Cognitive Aging (WHISCA) E;[120, 122] Women's International Study of Long Duration Oestrogen After Menopause (WISDOM)[138]
Conjugated estrogen/bazedoxifene	No trials
Estradiol	3 trials: Early vs. Late Intervention Trial with Estradiol, Cognitive Endpoints (ELITE-Cog);[92] Estrogen in the Prevention of Atherosclerosis (EPAT);[112] Ultra-Low-Dose Transdermal Estrogen[115, 124, 129, 169]
Estradiol acetate	No trials
Estradiaol valerate	No trials
Esterified estrogen	No trials
Estropipate	No trials
Synthetic conjugated estrogens	No trials
Estrogen plus progestogen formulations	
Conjugated estrogens + medroxyprogesterone acetate	14 trials: Estonian Postmenopausal Hormone Therapy Trial (EPHT);[137] Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis (ERA);[113] Greenspan et al, 2005;[107] Heart and Estrogen/Progestin Replacement Study (HERS);[148, 152, 167, 168] Postmenopausal Estrogen and Progestin Interventions Trial (PEPI);[32] STOP-IT;[106] Women's Angiographic Vitamin and Estrogen Trial (WAVE);[105] WHI E+P Trial;[36, 52, 67, 80, 88, 91, 101, 109, 110, 126, 127, 130, 132-135, 140, 142, 149-151, 153, 171-176] WHIMS E+P;[143, 147, 177] Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO);[93] Women's Health Initiative Memory Study of Younger Women (WHIMSY);[93, 123] WHISCA E+P;[120, 122] Women's International Study of Long Duration Oestrogen After Menopause (WISDOM)[138]
Estradiol + drospirenone	No trials
Estradiol + levonorgestrel	No trials
Estradiol + norethindrone acetate	1 trial: Estrogen Memory Study[141]
Estradiol + norgestimate	No trials
Estradiol + micronized progesterone	3 trials: Kronos Early Estrogen Prevention Study–Cognitive and Affective Study (KEEPS-Cog);[146] KEEPS-MRI;[100] Postmenopausal Estrogen and Progestin Interventions Trial (PEPI)[32]
Ethinyl estradiol + norethindrone acetate	No trials

Abbreviation: FDA=Food and Drug Administration.

Table 5. Baseline Characteristics of Participants in Randomized, Controlled Trials of Hormone Therapy to Prevent Chronic Conditions

Part A

Characteristic (Hormone Therapy; Placebo)*	ELITE-Cog	EMS E+P	EPAT	EPHT	ERA	Greenspan et al	HERS E+P	KEEPS-Cog	KEEPS-MRI	PEPI	STOP-IT
N	323; 320	70; 72	111; 111	404; 373	100; 104; 105	187; 186	1,380; 1,383	220; 211; 262	31; 31; 39	175; 174; 178; 174	121; 122; 123; 123
Age (mean years)	60.9; 60.5	75; 74.5	60.9; 62.1	58.5; 59.0	66.3; 65.5; 65.6	71.1; 71.3	67; 67	52.8; 52.6; 52.5	53; 53; 53	-	72; 71; 72; 74
Non-White race (%)	27.1; 32.9	4.3; 9.7	43.0; 38.0	-	19.0; 16.0; 19.0	-	12; 10	22.3; 22.7; 23.3	-	-	-
Previous or current HT (%)	73.6; 70.7	31.4; 23.6	-	9.2; 6.4	9.0; 8.0; 10.0	-	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†	11.4; 12.9†	56.0; 62.0; 66.0	-	-	-	-	-	-
Bilateral oophorectomy (%)	9.9; 11.3	-	32.0; 19.0	-	25.0; 30.0; 36.0	-	-	-	-	-	-
Never pregnant (%)	-	-	-	8.9; 8.1	-	-	-	-	-	-	-
First pregnancy at age ≥30 years (%)	-	-	-	-	-	-	-	-	-	-	-
Female relative with breast cancer (%)	-	-	-	7.2; 7.0	-	-	12; 11	-	-	-	-
Current smoker (%)	3.9; 2.8	-	58.0; 46.0	16.3; 13.9	18.0; 16.0; 21.0	-	13; 13	5.9; 6.6; 6.9	7; 10; 9	-	-
Mean BMI (kg/m^2)	27.5; 26.9	27; 26.6	28.7; 29.0	27.0; 26.9	-	27.5; 27.7	29; 29	26.1; 26.1; 26.6	28; 26; 27	-	-
History of MI (%)	-	5.7; 4.2	-	0.5; 0.3	48.0; 41.0; 55.0	-	50; 52	-	-	-	-

Table 5. Baseline Characteristics of Participants in Randomized, Controlled Trials of Hormone Therapy to Prevent Chronic Conditions

Characteristic (Hormone Therapy; Placebo)*	ELITE-Cog	EMS E+P	EPAT	EPHT	ERA	Greenspan et al	HERS E+P	KEEPS-Cog	KEEPS-MRI	PEPI	STOP-IT
History of stroke (%)	-	-	-	-	-	-	-	-	-	-	-
History of DVT or PE (%)	-	-	-	-	-	-	-	-	-	-	-
Mean SBP (mm Hg)	117.8; 117.3	-	127.8; 128.6	137; 137	131.0; 136.2; 134.4	-	135; 135	119.1; 117.5; 120.1	122; 120; 122	115; 115; 114; 116	-
Mean DBP (mm Hg)	74.9; 74.9	-	78.1; 77.0	85.7; 86	73.4; 74.1; 74.4	-	73; 73	75.3; 74.1; 75.5	77; 73; 76	72; 72; 73; 71	-
Treated for hypertension or BP >140/90 mm Hg (%)	-	-	-	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	-	19; 18	-	-	-	-
Fracture at age ≥55 years (%)	-	-	-	-	-	-	-	-	-	-	-

Table 5. Baseline Characteristics of Participants in Randomized, Controlled Trials of Hormone Therapy to Prevent Chronic Conditions

Part B

Characteristic (Hormone Therapy; Placebo)*	ULTRA E	WAVE	WHI E	WHI E+P	WHIMSY	WHIMS E	WHIMS E+P	WHIMS-ECHO	WHISCA E	WHISCA E+P	WISDOM E+P
N	208; 209	124; 86; 213	5,310; 5,429	8,506; 8,102	696; 630	1,464; 1,483	2,229; 2,303	1,402; 1,478	434; 452	690; 726	2,196; 2,189
Age (mean years)	66.8; 66.7	65.0; 69.0	63.6; 63.6	63.2; 63.3	53.0; 52.9	63.6; 63.6	63.2; 63.3	70.3; 70.3	74.01; 74.02	73.69; 73.86	63.3; 63.3
Non-White race (%)	7.2; 8.1	35.0; 32.0	24.5; 24.9	16.1; 16.0	20.0; 19.2	17.3; 16.4	-	11.6; 10.8	14.09; 13.08	8.4; 7.0	1; 1.4
Previous or current HT (%)	-	-	47.8; 48.9	26.1; 25.6	47.9; 53.2	45.8; 44.7	21.8; 22.4	46.9; 43.4	49.54; 46.24	21.2; 22.6	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[†]	43.2; 42.2	-	20.9; 16.5	-	-	37.0; 35.9	-	-	-
Bilateral oophorectomy (%)	-	36.0; 37.0	39.5; 42.0	-	-	-	-	-	-	-	-
Never pregnant (%)	-	-	9.3; 8.5	10.1; 10.3	-	-	-	-	-	-	-
First pregnancy at age ≥30 years (%)	-	-	4.9; 5.9	10.6; 9.7	-	-	-	-	-	-	-
Female relative with breast cancer (%)	-	-	18.0; 17.1	16.0; 15.3	-	-	-	-	-	-	8; 9
Current smoker (%)	7.7; 6.2	19.0; 19.0	10.3; 10.6	10.5; 10.5	13.5; 16.3	7.3; 8.0	6.7; 6.9	4.2; 5.6	3.72; 7.59	6.2; 5.0	12; 14
Mean BMI (kg/m^2)	28.3; 28.0	31.1; 30.3	30.1; 30.1	28.5; 28.5	-	-	-	25-29; 25-29	29.40; 29.21	28.5; 28.1	27.9; 28.0
History of MI (%)	-	46.0; 40.0	3.1; 3.2	1.6; 1.9	-	-	-	16.9; 15.4	-	-	2; 1

Table 5. Baseline Characteristics of Participants in Randomized, Controlled Trials of Hormone Therapy to Prevent Chronic Conditions

Characteristic (Hormone Therapy; Placebo)*	ULTRA E	WAVE	WHI E	WHI E+P	WHIMSY	WHIMS E	WHIMS E+P	WHIMS-ECHO	WHISCA E	WHISCA E+P	WISDOM E+P
History of stroke (%)	-	-	1.4; 1.7	0.7; 1.0	-	1.8; 2.1	1.0; 1.9	16.9; 15.4	1.15; 1.77	1; 1	1; 2
History of DVT or PE (%)	-	-	1.6; 1.5	0.9; 0.8	-	-	-	16.9; 15.4	-	-	-
Mean SBP (mm Hg)	-	140.0; 138.0	130.4; 130.2	127.6; 127.8	-	-	-	-	-	-	-
Mean DBP (mm Hg)	-	76.0; 75.0	76.5; 76.5	75.6; 75.8	-	-	-	-	-	-	-
Treated for hypertension or BP >140/90 mm Hg (%)	-	77.0; 74.0	48.0; 47.4	35.7; 36.4	21.0; 21.0	47.3; 42.3	-	35.6; 33.2	53.69; 51.11	44.4; 46.0	-
Elevated cholesterol requiring medication (%)	-	-	14.5; 15.9	12.5; 12.9	-	-	-	-	-	-	-
Prior aspirin use or use at baseline (%)	-	84.0; 86.0	19.4; 19.7	19.1; 20.1	-	28.0; 30.9	28.1; 29.6	-	-	-	-
History of or treatment for diabetes (%)	-	42.0; 31.0	7.7; 7.6	4.4; 4.4	-	11.3; 10.6	7.0; 6.5	5.8; 6.4	10.14; 10.84	5.4; 6.2	3; 4
Fracture at age ≥55 years (%)	-	-	14.0; 13.2	13.5; 13.6	-	-	-	-	-	-	-

* Intervention dosages are listed in Table 3 by trial.
† Participants of all ages.

Abbreviations: BMI=body mass index; BP=blood pressure; DBP=diastolic blood pressure; DVT=deep vein thrombosis; E=estrogen; E+P=estrogen plus progestin; ELITE-Cog=Early vs. Late Intervention Trial with Estradiol, Cognitive Endpoints; 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; HERS=Heart and Estrogen/Progestin Replacement Study; HT=hormone therapy; KEEPS=Kronos Early Estrogen Prevention Study; KEEPS-MRI=Kronos Early Estrogen Prevention Study-MRI; 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=Women's Angiographic Vitamin and Estrogen Trial; WHI=Women's Health Initiative; WHIMS=Women's Health Initiative Memory

Table 5. Baseline Characteristics of Participants in Randomized, Controlled Trials of Hormone Therapy to Prevent Chronic Conditions

Study; WHIMS-ECHO=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 6. Results of WHI at the End of the Intervention Phase, by Category and Subcategory of Outcome

Outcome*†	Estrogen Only‡ vs. Placebo§ Hazard Ratio (95% CI)	Estrogen Plus Progestin‡ vs. Placebo‖ Hazard Ratio (95% CI)
Cancer		
Breast (invasive)	0.79 (0.61 to 1.02)[67, 108]	1.24 (1.01 to 1.53)[67]
Cervical	Not reported	1.44 (0.47 to 4.42)[126]
Colorectal	1.15 (0.81 to 1.64)[67]	0.62 (0.43 to 0.89)[67]
Endometrial	Not reported	0.83 (0.49 to 1.40)[67]
Lung	1.05 (0.74 to 1.49)[67]	1.05 (0.76 to 1.45)[67]
Non-Hodgkin's lymphoma	0.89 (0.56 to 1.42)[96]	0.81 (0.51 to 1.29)[96]
Ovarian	Not reported	1.41 (0.75 to 2.66)[67]
Cardiovascular disease		
Cardiovascular events (all)	1.11 (1.01 to 1.22)[67]	1.13 (1.02 to 1.25)[67]
Coronary heart disease	0.95 (0.79 to 1.16)[117]	1.18 (0.95 to 1.45)[67]
Cognitive functioning and dementia¶		
Mild cognitive impairment	1.34 (0.95 to 1.89)[119]	1.07 (0.74 to 1.55)[143]
Probable dementia	1.49 (0.83 to 2.66)[119]	2.05 (1.21 to 3.48)[143]
Diabetes		
Self-reported new diagnosis requiring treatment with drugs	0.86 (0.76 to 0.98)[67]	0.81 (0.70 to 0.94)[67, 126]
Fractures		
Total fractures	0.72 (0.64 to 0.80)[67]	0.76 (0.69 to 0.83)[67]
Gallbladder events	1.67 (1.35 to 2.06)[127]	1.59 (1.28 to 1.97)[127]
Gallbladder disease	1.55 (1.34 to 1.79)[67]	1.57 (1.36 to 1.80)[67]
Cholecystectomy	1.93 (1.52 to 2.44)[127]	1.67 (1.32 to 2.11)[127]
Peripheral arterial disease		
Overall peripheral arterial disease	1.35 (0.97 to 1.88)[79]	0.89 (0.60 to 1.32)[80]
Urinary incontinence (stress, urge, or mixed)		
Overall urinary incontinence	1.61 (1.46 to 1.79)[67]	1.49 (1.36 to 1.63)[67]
Stroke	1.35 (1.07 to 1.70)[67]	1.37 (1.07 to 1.76)[67]
Thromboembolic events		
Deep vein thrombosis	1.48 (1.06 to 2.07)[67]	1.87 (1.37 to 2.54)[67]
Pulmonary embolism	1.35 (0.89 to 2.05)[67]	1.98 (1.36 to 2.87)[67]
Mortality		
All-cause mortality	1.04 (0.89 to 1.22)[67, 178]	0.97 (0.81 to 1.16)[88, 132]
Total cancer mortality	0.96 (0.75 to 1.22)[88]	1.10 (0.86 to 1.42)[88]

* 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).

† HRs not reported for quality of life.

‡ Intervention dosages are listed in Table 3 by trial.

§ Followup periods for all estrogen-only outcomes are 7.1 years except for fractures, 7.2 years; dementia, 5.2 years; and urinary incontinence, 1 year.

‖ Followup periods for all estrogen plus progestin outcomes are 5.6 years except for dementia, 4 years; and urinary incontinence, 1 year.

¶ Results from the WHIMS trial, a subset of the WHI trial, limited to women ages 65 to 79 years at baseline, free of probable dementia, and recruited from 39 of 40 WHI trial centers. Participants in WHIMS Estrogen only were followed for approximately 5.2 years and in WHIMS Estrogen and Progestin for approximately 4 years.

Abbreviations: CI=confidence interval; HR=hazard ratio; WHI=Women's Health Initiative; WHIMS=Women's Health Initiative Memory Study.

Table 7. Summary of Evidence: Estrogen-Only Trials

No. of Studies/Study Designs; No. of Participants	Summary of Findings by Outcome	Consistency and Precision	Limitations	Strength of Evidence*	Applicability
4 RCTs;[32, 37, 67, 87, 88, 108-110, 112, 113] during the intervention phase, 239 events in 10,739 women contributed to effect estimate (based on 1 RCT[67]) During cumulative followup, number of events that contributed to effect estimate NR (based on 1 RCT[88])	**Invasive breast cancer** Intervention followup of 7.2 years Nonsignificant lower risk with HT (HR, 0.79 [95% CI, 0.61 to 1.02]) During cumulative followup of 20.7 years, statistically significantly lower risk with HT (HR, 0.78 [95% CI, 0.65 to 0.93])	Consistent; imprecise	Fair quality; 3 studies followed participants for a relatively short duration (2–3 years)	Moderate for benefit	Generally healthy postmenopausal women age ≥50 years
1 RCT;[88] during cumulative followup, 63 events in 10,739 women contributed to effect estimate (based on 1 RCT)[88] During cumulative followup, 63 events in 10,739 women contributed to effect estimate	**Breast cancer mortality** Intervention followup of 7.2 years, similar risk (HR, 0.45 [95% CI, 0.14 to 1.46]) Significantly lower risk with HT during cumulative followup of 17.7 years (HR, 0.55 [95% CI, 0.33 to 0.92]) and 20.7 years (HR, 0.60 [95% CI, 0.37 to 0.97])	NA; imprecise	Fair quality; evidence is limited to a single study	Low for benefit	Generally healthy postmenopausal women age ≥50 years
1 RCT;[67, 91, 114] during intervention period, 123 events in 10,739 women contributed to effect estimate During cumulative followup, 123 events in 9,786 women contributed to effect estimate	**Colorectal cancer** Intervention followup of 7.2 years, no significant risk increase/reduction with HT (HR, 1.15 [95% CI, 0.81 to 1.64]) During cumulative followup (13.0 years), similarly, no significant risk increase/reduction with HT (HR, 1.13 [95% CI, 0.85 to 1.51])	NA; imprecise	Fair quality; none	Low for similar risks	Generally healthy postmenopausal women age ≥50 years

Table 7. Summary of Evidence: Estrogen-Only Trials

No. of Studies/Study Designs; No. of Participants	Summary of Findings by Outcome	Consistency and Precision	Limitations	Strength of Evidence*	Applicability
1 RCT;[88] during intervention period, 33 events in 10,739 women contributed to effect estimate During cumulative followup, 87 events in 10,739 women contributed to effect estimate	**Colorectal cancer mortality** No significant risk increase or reduction at followup of 7.2 years (HR, 0.98 [95% CI, 0.50 to 1.95]) or cumulative followup of 17.7 years (HR, 1.21 [95% CI, 0.79 to 1.84])	NA; imprecise	Fair quality; estimates based on a single study	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
1 RCT;[67, 116] during the intervention phase, 123 events in 10,739 women contributed to effect estimate During cumulative followup, 223 events in 9,786 women contributed to effect estimate	**Lung cancer** Intervention followup of 7.2 years, no significant risk increase/reduction with HT (HR, 1.05 [95% CI, 0.74 to 1.49]) During cumulative followup (13.0 years), no significant risk increase/reduction with HT (HR, 0.98 [95% CI, 0.75 to 1.27])	NA; imprecise	Fair quality; none	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
1 RCT;[116] during intervention period, 67 events in 10,379 women contributed to effect estimate	**Lung cancer mortality** Intervention followup of 7.9 years, no significant risk increase with HT (HR, 1.07 [95% CI, 0.66 to 1.72])	NA; imprecise	Fair quality; estimates based on a single study; short duration followup for a mortality outcome	Insufficient	Generally healthy postmenopausal women age ≥50 years
1 RCT;[96] 160 events in 10,685 women contributed to effect estimate	**Non-Hodgkin's lymphoma** Cumulative followup of 12.9 years, no significant risk increase/reduction with HT (HR, 1.02 [95% CI, 0.74 to 1.39])	NA; imprecise	Fair quality; none	Low for similar risks	Generally healthy postmenopausal women age ≥50 years

Table 7. Summary of Evidence: Estrogen-Only Trials

No. of Studies/Study Designs; No. of Participants	Summary of Findings by Outcome	Consistency and Precision	Limitations	Strength of Evidence*	Applicability
1 RCT;[88] during cumulative followup, 863 events in 10,739 women contributed to effect estimate During cumulative followup, 863 events in 10,739 women contributed to effect estimate	**Total cancer mortality** Intervention followup of 7.2 years, no significant risk reduction/increase with HT (HR, 0.96 [95% CI, 0.75 to 1.22]) Cumulative followup of 17.7 years, no significant risk reduction/increase with HT (HR, 0.99 [95% CI, 0.86 to 1.13])	NA; imprecise	Fair quality; evidence is limited to a single study	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
4 RCTs;[32, 112, 113, 117] 422 events in 11,310 women contributed to meta-analysis (based on 3 RCTs[32, 112, 117]) During cumulative followup, 1,071 events in 7,645 women contributed to effect estimate (based on 1 RCT[101])	**Coronary heart disease** Intervention followup of 2 to 7.2 years in meta-analysis, no significant risk reduction/increase with HT (RR, 0.95 [95% CI, 0.79 to 1.14]) Cumulative followup of 19.4 years, no significant risk reduction/increase with HT (HR, 0.97 [95% CI, 0.86 to 1.09])	Consistent; precise	Fair quality; none	High for similar risks	Generally healthy postmenopausal women age ≥50 years
1 RCT;[88] 517 events in 10,739 women contributed to effect estimate During cumulative followup, 517 events in 7,645 women contributed to effect estimate	**Coronary heart disease mortality** Intervention followup of 7.2 years, no significant risk reduction/increase with HT (HR, 1.02 [95% CI, 0.72 to 1.43]) Cumulative followup of 17.7 years, no significant risk reduction/increase with HT (HR, 0.89 [95% CI, 0.75 to 1.05])	NA; precise	Fair quality; evidence is limited to a single study	Low for similar risks	Generally healthy postmenopausal women age ≥50 years

Table 7. Summary of Evidence: Estrogen-Only Trials

No. of Studies/Study Designs; No. of Participants	Summary of Findings by Outcome	Consistency and Precision	Limitations	Strength of Evidence*	Applicability
1 RCT; [79] 144 events in 10,739 women contributed to effect estimate	**Peripheral arterial disease** Intervention followup of 7.1 years, no significant risk reduction/increase with HT (HR, 1.35 [95% CI, 0.97 to 1.88])	NA; imprecise	Fair quality; evidence is limited to a single study	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
1 RCT;[119, 121] During the intervention phase, 47 events in 2,947 women contributed to effect estimate	**Probable dementia** Intervention followup of 5.2 years, no significant risk increase/reduction with HT (HR, 1.49 [95% CI, 0.83 to 2.66])	NA; imprecise	Fair quality; none	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
1 RCT[88] During intervention period, 11 events in 10,739 women contributed to effect estimate During cumulative followup, 302 events in 10,739 women contributed to effect estimate	**Alzheimer's disease or other dementia mortality** Intervention followup of 7.2 years, no significant risk increase/reduction with HT (HR, 0.90 [95% CI, 0.27 to 2.95]) Cumulative followup of 17.7 years, significantly lower risk with HT (HR, 0.74 [95% CI, 0.59 to 0.94])	NA; imprecise for intervention phase, precise for cumulative phase	Fair quality; few events and short-term followup for mortality outcome (intervention phase only)	Low for benefit	Generally healthy postmenopausal women age ≥50 years
1 RCT;[67, 125] During the intervention phase, 976 events in 9,917 women contributed to effect estimate During cumulative followup, 1,605 events in 9,917 women contributed to effect estimate	**Diabetes** Intervention followup of 7.1 years, risk reduction with HT (HR, 0.86 [95% CI, 0.76 to 0.98]) Cumulative followup of 13.0 years, no significant risk increase/reduction with HT (HR, 0.94 [95% CI, 0.85 to 1.04])	NA; precise	Fair quality; diabetes is self-reported	Moderate for benefit	Generally healthy postmenopausal women age ≥50 years

Table 7. Summary of Evidence: Estrogen-Only Trials

No. of Studies/Study Designs; No. of Participants	Summary of Findings by Outcome	Consistency and Precision	Limitations	Strength of Evidence*	Applicability
2 RCTs;[67, 97, 108, 113, 126] During the intervention phase, 1,311 events in 10,739 women contributed to effect estimate (based on 1 RCT[67]) During postintervention followup, 699 events in 5,053 women contributed to effect estimate (based on 1 RCT[97])	**Fractures** Intervention followup of 7.2 years, significant risk reduction with HT (HR, 0.72 [95% CI, 0.64 to 0.80]) Postintervention followup of 4.3 years, significant risk reduction with HT (HR, 0.85 [95% CI, 0.73 to 0.98])	Consistent; precise	Fair quality; none	High for benefit	Generally healthy postmenopausal women age ≥50 years
2 RCTs;[32, 67] 773 events in 8,376 women contributed to effect estimate (based on 1 RCT[67])	**Gallbladder disease** Intervention followup of 7.1 years, significant risk increase with HT (HR, 1.55 [95% CI, 1.34 to 1.79])	Consistent; precise	Fair quality; gallbladder disease is self-reported	Moderate for harm	Generally healthy postmenopausal women age ≥50 years
3 RCTs;[108, 112, 113] 298 events in 10,739 women contributed to effect estimate (based on 1 RCT[67]) During cumulative followup 791 events in 10,739 women contributed to effect estimate (based on 1 RCT[101])	**Stroke** Intervention followup of 7.2 years, significant increase with HT (HR, 1.35 [95% CI, 1.07 to 1.70]) Cumulative followup of 19.4 years, no significant risk reduction/increase with HT (HR, 1.06 [95% CI, 0.92 to 1.22])	Consistent; precise	Fair quality; 3 studies followed participants for a relatively short duration (2–3 years)	Moderate for harm	Generally healthy postmenopausal women age ≥50 years
1 RCT;[88] 258 events in 10,739 women contributed to effect estimate During cumulative followup, 258 events in 10,739 women contributed to effect estimate	**Stroke mortality**[88] Intervention followup of 7.2 years, no significant risk reduction/increase with HT (HR, 1.00 [95% CI, 0.57 to 1.78]) Cumulative followup of 17.7 years, no significant risk reduction/increase with HT (HR, 0.98 [95% CI, 0.77 to 1.26])	NA; imprecise	Fair quality; evidence is limited to a single study	Low for similar risks	Generally healthy postmenopausal women age ≥50 years

Table 7. Summary of Evidence: Estrogen-Only Trials

No. of Studies/Study Designs; No. of Participants	Summary of Findings by Outcome	Consistency and Precision	Limitations	Strength of Evidence*	Applicability
2 RCTs;[67, 129] 1,272 events in 6,767 women contributed to effect size (based on 1 RCT[67]) During postintervention followup, 1,456 events in 5,644 women contributed to effect estimate (based on 1 RCT[67])	**Urinary incontinence** Intervention followup of 1 year, significant risk increase with HT (HR, 1.61 [95% CI, 1.46 to 1.79]) Postintervention followup of 6.6 years, significant risk increase with HT (HR, 1.24 [95% CI, 1.13 to 1.35])	Consistent; precise	Fair quality; urinary incontinence is self-reported	Moderate for harm	Generally healthy postmenopausal women age ≥50 years
2 RCTs;[108, 112] 144 (DVT) and 91 (PE) events in 10,739 women contributed to effect estimates (based on 1 RCT[67]) During cumulative followup, 471 events in 9,939 women contributed to effect estimates (based on 1 RCT[67])	**Venous thromboembolism** Intervention followup of 7.1 years, significant increased risk of DVT with HT (HR, 1.48 [95% CI, 1.06 to 2.07]) and no significant risk reduction/increase with HT in PE (HR, 1.35 [95% CI, 0.89 to 2.05]) Cumulative followup of 13.0 years, no significant risk reduction/increase with HT in DVT (HR, 1.05 [95% CI, 0.82 to 1.33]) or PE (HR, 1.15 [95% CI, 0.87 to 1.51])	Consistent; imprecise	Fair quality; none	Moderate for harm	Generally healthy postmenopausal women age ≥50 years
1 RCT[67]; observed in 10,739 women	**Quality of life** Intervention followup of 7.1 years, similar scores on most items of the SF-36	Inconsistent regarding subscales; precise	Fair quality; none	Moderate for similar risks	Generally healthy postmenopausal women age ≥50 years
3 RCTs;[92, 108, 113] 613 events in 11,587 women contributed to meta-analysis	**All-cause mortality** Intervention followup of 2 to 7.2 years in meta-analysis, no significant risk increase/reduction with HT (RR, 1.04 [95% CI, 0.89 to 1.21])	Consistent; precise	Fair quality; none	High for similar risks	Generally healthy postmenopausal women age ≥50 years

Table 7. Summary of Evidence: Estrogen-Only Trials

No. of Studies/Study Designs; No. of Participants	Summary of Findings by Outcome	Consistency and Precision	Limitations	Strength of Evidence*	Applicability
1 RCT;[101] 613 events in 10,739 women contributed to effect estimate	**All-cause mortality** Cumulative followup of 19.4 years, no significant risk reduction/increase with HT (HR, 0.97 [95% CI, 0.91 to 1.03])	NA; precise	Fair quality; evidence is limited to a single study	High for similar risks	Generally healthy postmenopausal women age ≥50 years

* Strength of evidence ratings refer to the intervention phase except for mortality, for which they refer to cumulative followup.

Abbreviations: CI=confidence interval; DVT=deep vein thrombosis; HR=hazard ratio; HT=hormonal therapy; KQ=key question; NA=not applicable; No.=number; NR=not reported; PE=pulmonary embolism; RCT=randomized, controlled trial; RR=relative risk; SF-36=36-Item Short-Form Survey.

Table 8. Summary of Evidence: Estrogen Plus Progestin Trials

No. of studies/study designs; No. of participants	Summary of Findings by Outcome	Consistency and Precision	Limitations	Strength of Evidence*	Applicability
6 RCTs;[32, 36, 67, 87, 88, 110, 132-138, 143] [113] during the intervention phase 420 events in 25,442 women contributed to effect estimates (based on 2 RCTs[67, 136]) During cumulative followup, 1,006 events in 16,608 women contributed to effect estimate (based on 1 RCT[101])	**Invasive breast cancer** Intervention followup of 4.1–5.6 years, significant risk increase with HT (HR, 1.24 [95% CI, 1.01 to 1.53]) in WHI and nonsignificant increase with HT in HERS I (HR, 1.38 [95% CI, 0.82 to 2.31]) During cumulative followup, the risk remained significantly increased at 19.4 years (HR, 1.28 [95% CI, 1.13 to 1.45])	Consistent; precise	Fair; none	High for harm	Generally healthy postmenopausal women age ≥50 years
1 RCT;[87] during intervention period, 9 events in 16,608 women contributed to effect estimate During cumulative followup, 124 events in 16,608 women contributed to effect estimate	**Breast cancer mortality** Intervention followup of 5.6 years, similar risk (HR, 1.08 [95% CI, 0.29 to 4.03]), no significant risk increase/reduction with HT during cumulative followup at 20.3 years (HR, 1.35 [95% CI, 0.94 to 1.95])	NA; imprecise	Fair; none	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
1 RCT;[126] 13 events in 16,608 women contributed to effect estimate	**Cervical cancer** Intervention followup of 5.6 years, no significant risk increase/reduction with HT (HR, 1.44 [95% CI, 0.47 to 4.42])	NA; imprecise	Fair; 1 study followed participants for a relatively short duration (5.6 years) to evaluate a rare cancer outcome	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
4 RCTs;[36, 67, 91, 110, 132, 136, 138, 140, 141] during the intervention period, 152 events in 19,371 women contributed to effect estimates (based on 2 RCTs[67, 136]) During cumulative followup, number of events that contributed to effect estimate NR; based on 2 RCTs[67, 136]	**Colorectal cancer** Intervention followup of 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 nonsignificant risk reduction with HT (HR, 0.69 [95% CI, 0.32 to 1.49]) in HERS During cumulative followup, nonsignificant risk increase in WHI (13.0 years followup, HR, 1.13 [95% CI, 0.85 to 1.51]) and nonsignificant decreased risk in HERS (6.8 years followup, HR, 0.82 [95% CI, 0.46 to 1.47])	Consistent; precise	Fair; long-term evidence is limited to the WHI	Moderate for benefit	Generally healthy postmenopausal women age ≥50 years

Table 8. Summary of Evidence: Estrogen Plus Progestin Trials

No. of studies/study designs; No. of participants	Summary of Findings by Outcome	Consistency and Precision	Limitations	Strength of Evidence*	Applicability
1 RCT;[88] during intervention period, 22 events in 16,608 women contributed to effect estimate During cumulative followup, 103 events in 16,608 women contributed to effect estimate	**Colorectal cancer mortality** Intervention followup 5.6 years, no significant differences (HR, 0.87 [95% CI, 0.38 to 1.98]) or cumulative followup 17.7 years (HR, 1.01 [95% CI, 0.69 to 1.49])	NA; imprecise	Fair; estimates based on a single study	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
4 RCTs;[32, 36, 67, 110, 113, 116, 126, 132, 136] 64 events in 19,371 women contributed to effect estimates (based on 2 RCTs[36, 67, 110, 116, 126, 132, 136]) 1 retrospective cohort study[179] with 4,379 events in more than 900,000 women	**Endometrial cancer** Intervention followup of 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 Statistically significant risk reduction with HT after 13.2 years of followup in the WHI (HR, 0.65 [95% CI, 0.48 to 0.89])	Consistent; imprecise	Fair; long-term evidence is limited to the WHI and a retrospective cohort study; because endometrial cancer is rare, overall few events in RCTs (n = 161 after 13.2 years followup)	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
3 RCTs;[67, 136, 141, 142, 98] during intervention period, 191 events in 19,371 women contributed to effect estimates (based on 2 RCTs[67, 136, 142]) During cumulative followup, 433 events in 15,327 women contributed to effect estimates (based on 2 RCTs[67, 136])	**Lung cancer** Intervention followup of 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 During cumulative followup, no significant risk increase with HT in WHI (13.2 years followup, HR, 1.10 [95% CI, 0.89 to 1.35]) and HERS (6.8 years followup, HR, 1.43 [95% CI, 0.87 to 2.37])	Consistent; precise	Fair; long-term evidence is limited to the WHI	Moderate for similar risks	Generally healthy postmenopausal women age ≥50 years
1 RCT;[180] for cumulative followup, 285 events in 16,608 women contributed to effect estimate	**Lung cancer mortality** Followup of 14.0 years, no significant risk increase with HT in WHI (HR, 1.09 [95% CI, 0.87 to 1.38])	NA; imprecise	Fair; estimates based on a single study	Low for similar risks	Generally healthy postmenopausal women age ≥50 years

Table 8. Summary of Evidence: Estrogen Plus Progestin Trials

No. of studies/study designs; No. of participants	Summary of Findings by Outcome	Consistency and Precision	Limitations	Strength of Evidence*	Applicability
1 RCT;[96] 223 events in 16,544 women contributed to effect estimate	**Non-Hodgkin's lymphoma** Cumulative followup of 13.5 years, no significant risk increase/reduction with HT (HR, 0.98 [95% CI, 0.76 to 1.28])	NA; imprecise	Fair; none	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
1 RCT;[67, 126] 40 events in 16,608 women contributed to effect estimate	**Ovarian cancer** Intervention followup of 5.6 years, no significant risk increase/reduction with HT (HR, 1.41 [95% CI, 0.75 to 2.66])	NA; imprecise	Fair; study followed participants for a relatively short duration (5.6 years) to evaluate a rare cancer outcome	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
1 RCT;[88] during intervention followup, 244 events in 16,608 women contributed to effect estimate During cumulative followup, 1,344 events in 16,608 women contributed to effect estimate	**Total cancer mortality** Intervention followup of 5.6 years, no significant risk reduction/increase with HT (HR, 1.10 [95% CI, 0.86 to 1.42]) Cumulative followup of 17.7 years, no significant risk reduction/increase with HT (HR, 1.06 [95% CI, 0.95 to 1.18])	NA; precise	Fair; evidence is limited to a single study	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
6 RCTs;[32, 67, 113, 137, 138, 141] during intervention period, 487 events in 18,085 women contributed to meta-analysis (based on 3 RCTs[32, 67, 98, 137]) During cumulative followup, 1,362 events in 15,730 women contributed to effect estimate (based on 1 RCT[101])	**Coronary heart disease** Intervention followup of 2 to 5.6 years in meta-analysis, no significant risk reduction/increase with HT (RR, 1.12 [95% CI, 0.94 to 1.33]) Cumulative followup of 19.4 years, no significant risk reduction/increase with HT (HR, 1.05 [95% CI, 0.95 to 1.17])	Consistent; precise	Fair; none	High for similar risks	Generally healthy postmenopausal women age ≥50 years
1 RCT;[88] during intervention period, 80 events in 16,608 women contributed to effect estimate During cumulative followup, 595 events in 16,608 women contributed to effect estimate	**Coronary heart disease mortality** Intervention followup of 5.6 years, no significant risk reduction/increase with HT (HR, 0.94 [95% CI, 0.60 to 1.45]) Cumulative followup of 17.7 years, no significant risk reduction/increase with HT (HR, 1.05 [95% CI, 0.89 to 1.23])	NA; precise	Fair; evidence is limited to a single study	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
1 RCT, [80] 98 events in 16,608 women contributed to effect estimate	**Peripheral arterial disease** Intervention followup of 5.6 years, no significant risk reduction/increase with HT (HR, 0.89 [95% CI, 0.60 to 1.32])	NA; imprecise	Fair quality; evidence is limited to a single study	Low for similar risks	Generally healthy postmenopausal women age ≥50 years

Table 8. Summary of Evidence: Estrogen Plus Progestin Trials

No. of studies/study designs; No. of participants	Summary of Findings by Outcome	Consistency and Precision	Limitations	Strength of Evidence*	Applicability
1 RCT;[143] 61 events in 4,532 women contributed to effect estimate	**Probable dementia** Intervention followup of 4 years, significant risk increase with HT (HR, 2.05 [95% CI, 1.21 to 3.48])	NA; imprecise	Fair; none	Low for harm	Generally healthy postmenopausal women age ≥50 years
1 RCT;[88] during intervention period, 0 events in 16,608 women contributed to effect estimate During cumulative followup, 456 events in 16,608 women contributed to effect estimate	**Alzheimer's disease or other dementia mortality** No events during intervention followup of 5.6 years Cumulative followup of 17.7 years, no significant risk increase/reduction with HT (HR, 0.93 [95% CI, 0.77 to 1.11])	NA; imprecise	Fair; evidence based on a single study	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
2 RCTs;[67, 148, 149] during intervention followup, 861 events in 17,903 women contributed to effect estimates During cumulative followup, 1,786 events in 15,874 women contributed to effect estimate (based on 1 RCT[67])	**Diabetes** Intervention followup of 4.1 to 5.6 years, significant risk reduction with HT in WHI (HR, 0.81 [95% CI, 0.70 to 0.94]) and HERS (HR, 0.65 [95% CI, 0.48 to 0.89]) Cumulative followup of 13.2 years, no significant risk increase/reduction with HT in WHI (HR, 1.02 [95% CI, 0.93 to 1.12])	Consistent; precise	Fair; diabetes is self-reported	Moderate for benefit	Generally healthy postmenopausal women age ≥50 years
5 RCTs;[36, 67, 113, 132, 136, 137, 141, 150] during intervention period, 2,004 events in 20,499 women contributed to meta-analysis During postintervention followup, 1,184 events in 10,134 women contributed to effect estimate (based on 1 RCT[97])	**Fractures** Intervention followup of 2 to 5.6 years, significant risk reduction with HT (RR, 0.79 [95% CI, 0.66 to 0.94]) Postintervention followup of 4.2 years, no significant risk increase/reduction with HT (HR, 0.97 [95% CI, 0.87 to 1.09])	Consistent; precise	Fair; none	High for benefit	Generally healthy postmenopausal women age ≥50 years
2 RCTs;[32, 67] 847 events in 14,203 women contributed to effect estimate (based on 1 RCT[67])	**Gallbladder disease** Intervention followup of 5.6 years, significant risk increase with HT (HR, 1.57 [95% CI, 1.36 to 1.80])	Consistent; precise	Fair; gallbladder disease is self-reported	Moderate for harm	Generally healthy postmenopausal women age ≥50 years

Table 8. Summary of Evidence: Estrogen Plus Progestin Trials

No. of studies/study designs; No. of participants	Summary of Findings by Outcome	Consistency and Precision	Limitations	Strength of Evidence*	Applicability
3 RCTs;[67, 137, 141] during intervention period, 270 events in 17,385 women contributed to effect estimates (based on 2 RCTs[67, 137]) During cumulative followup, 1,071 events in 16,608 women contributed to effect estimate (based on 1 RCT[101])	**Stroke** Intervention followup, significant increase with HT after 5.6 years in WHI (HR, 1.37 [95% CI, 1.07 to 1.76]) and no significant risk reduction/increase with HT after 3.4 years in EPHT (HR, 1.06 [95% CI, 0.07 to 17.2]) Cumulative followup of 19.4 years, increased risk with HT (HR, 1.13 [95% CI, 1.00 to 1.27])	Consistent; precise	Fair; outcome measures heterogeneous (stroke incidence vs. composite risk of various cerebrovascular events)	Moderate for harm	Generally healthy postmenopausal women age ≥50 years
1 RCT;[88] during intervention period, 43 events in 16,608 women contributed to the effect estimate During cumulative followup, 349 events in 16,608 women contributed to effect estimate (based on 1 RCT[101])	**Stroke mortality** Intervention followup of 5.6 years, no significant risk reduction/increase with HT (HR, 1.58 [95% CI, 0.85 to 2.94]) Cumulative followup of 17.7 years, no significant risk reduction/increase with HT (HR, 1.12 [95% CI, 0.91 to 1.38])	NA; imprecise	Fair; evidence is limited to a single study	Low for similar risks	Generally healthy postmenopausal women age ≥50 years
2 RCTs;[67, 152] during the intervention period, 2,346 events in 12,786 women contributed to effect estimates During postintervention followup, 2,211 events in 10,073 women contributed to the effect estimate (based on 1 RCT[67])	**Urinary incontinence** Intervention followup of 1 to 4.2 years, significant risk increase with HT in WHI (HR, 1.49 [95% CI, 1.36 to 1.63]) and HERS (OR, 1.60 [95% CI, 1.30 to 1.90]) Postintervention followup of 8.2 years, significant risk increase with HT in WHI (HR, 1.16 [95% CI, 1.08 to 1.25])	Consistent; precise	Fair; urinary incontinence is self-reported	Moderate for harm	Generally healthy postmenopausal women age ≥50 years
5 RCTs;[113, 136, 137, 141, 153] during intervention period, 216 DVT events and 143 PE events in 19,371 women contributed to effect estimates (based on 2 RCTs[67]) During cumulative followup, 674 events in 15,730 women contributed to effect estimate (based on 1 RCT[67])	**Venous thromboembolism** Intervention followup of 4.1–5.6 years, significant increased risk with HT in DVT in WHI (HR, 1.87 [95% CI, 1.37 to 2.54]) and in HERS (HR, 2.82 [95% CI, 1.32 to 6.04]); significant increased risk with HT in PE in WHI (HR, 1.98 [95% CI, 1.36 to 2.87]) but not in HERS (HR, 2.78 [95% CI, 0.89 to 8.74]) Cumulative followup of 13.2 years, significant increase with HT in DVT (HR, 1.24 [95% CI, 1.01 to 1.53]) or PE (HR, 1.26 [95% CI, 1.00 to 1.59]) in WHI	Consistent; precise	Fair; 3 studies followed participants for a relatively short duration (2–3 years)	Moderate for harm	Generally healthy postmenopausal women age ≥50 years
1 RCT;[67] observed in 16,608 women	**Quality of life** Intervention followup of 5.6 years, similar scores on most items of the SF-36	Inconsistent regarding subscales; precise	Fair; none	Moderate for similar risks	Generally healthy postmenopausal women age ≥50 years

Table 8. Summary of Evidence: Estrogen Plus Progestin Trials

No. of studies/study designs; No. of participants	Summary of Findings by Outcome	Consistency and Precision	Limitations	Strength of Evidence*	Applicability
3 RCTs;[113, 132, 136] 751 events in 19,580 women contributed to meta-analysis	**All-cause mortality** Intervention followup of 3.2 to 5.6 years in meta-analysis, no significant risk increase/reduction with HT (RR, 1.01 [95% CI, 0.88 to 1.16])	Consistent; precise	Fair; none	High for similar risks	Generally healthy postmenopausal women age ≥50 years
1 RCT;[101] 5,440 events in 16,608 women contributed to effect estimate	**All-cause mortality** Cumulative followup of 19.4 years, no significant risk reduction/increase with HT (HR, 1.02 [95% CI, 0.97 to 1.08])	NA; precise	Fair; evidence is limited to a single study	High for similar risks	Generally healthy postmenopausal women age ≥50 years

*Strength of evidence ratings refer to the intervention phase except for mortality, for which they refer to cumulative followup.

Abbreviations: CI=confidence interval; DVT=deep vein thrombosis; 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; NR=not reported; OR=odds ratio; PE=pulmonary embolism; RCT=randomized, controlled trial; RR=relative risk; SF-36=36-Item Short Form Survey; WHI=Women's Health Initiative.

Appendix A. Search Strategies

28 January 2021
PubMed:

Search	Query	Results
#1	"Hormone Replacement Therapy"[Mesh] OR "Hormone Replacement Therapy"[tiab] OR "Hormone Replacement Therapies"[tiab] OR "Estrogen Replacement Therapy"[Mesh] OR "estrogen replacement"[tiab] OR "estrogen replacements"[tiab] OR "estrogen therapy"[tiab] OR "estrogen therapies"[tiab] OR "progestin replacement"[tiab] OR "estrogen progestin combination therapy"[tiab] OR Alora[tiab] OR Cenestin[tiab] OR Climara[tiab] OR Delestrogen[tiab] OR Esclim[tiab] OR Estrace[tiab] OR Estraderm[tiab] OR Menostar[tiab] OR Minivelle[tiab] OR "Ortho-Est"[tiab] OR Prometrium[tiab] OR Provera[tiab] OR Vivelle[tiab] OR "Vivelle-Dot"[tiab] OR Femtrace[tiab] OR Menest[tiab] OR Ogen[tiab] OR Premarin[tiab] OR Enjuvia[tiab] OR Angeliq[tiab] OR Activella[tiab] OR Prefest[tiab] OR Climara Pro[tiab] OR Combipatch[tiab] OR Prempro[tiab] OR Femhrt[tiab] OR "Estradiol"[Mesh] OR Estradiol[tiab] OR Oestradiol[tiab] OR Progynova[tiab] OR Vivelle[tiab] OR Aerodiol[tiab] OR Estrace[tiab] OR "Estraderm TTS"[tiab] OR "Progynon-Depot"[tiab] OR "Progynon Depot"[tiab] OR Delestrogen[tiab] OR Ovocyclin[tiab] OR Estropipate[tiab] OR "Micronized progesterone"[tiab] OR "Medroxyprogesterone Acetate"[Mesh] OR "Medroxyprogesterone acetate"[tiab] OR "Medroxyprogesterone 17-Acetate"[tiab] OR "Medroxyprogesterone 17 Acetate"[tiab] OR Depo-Provera[tiab] OR Depo Provera[tiab] OR DepoProvera[tiab] OR Farlutal[tiab] OR Gestapuran[tiab] OR Curretab[tiab] OR Perlutex[tiab] OR Provera[tiab] OR Veramix[tiab] OR Cycrin[tiab] OR "Estrogens, Esterified (USP)"[Mesh] OR "Esterified Estrogen"[tiab] OR "Esterified Estrogens"[tiab] OR "Estrogens, Conjugated (USP)"[Mesh] OR "Conjugated Estrogen"[tiab] OR "Conjugated Estrogens"[tiab] OR "Conjugated Estrogenic"[tiab] OR "Conjugated Equine Estrogens"[tiab] OR "Conjugated Equine Estrogen"[tiab] OR Dagynil[tiab] OR Oestrofeminal[tiab] OR "Oestro-Feminal"[tiab] OR "Oestro Feminal"[tiab] OR "Estro-Feminal"[tiab] OR "Estro Feminal"[tiab] OR Premarin[tiab] OR Climopax[tiab] OR Climarest[tiab] OR Presomen[tiab] OR Progens[tiab] OR Progen[tiab] OR Transannon[tiab] OR Femavit[tiab] OR Carentil[tiab] OR Prelestrin[tiab] OR "Estradiol Congeners"[Mesh:NoExp] OR "Synthetic Estrogen"[tiab] OR "Synthetic Estrogens"[tiab]	162,654
#2	"Climacteric"[Mesh:NoExp] OR climacteric[tiab] OR "Menopause"[Mesh] OR menopause[tiab] OR menopausal[tiab] OR perimenopause[tiab] OR perimenopausal[tiab] OR "Hot Flashes"[Mesh] OR "hot flashes"[tiab] OR "Postmenopause"[Mesh] OR "Post-Menopausal"[tiab] OR Postmenopausal[tiab] OR "Post-Menopause"[tiab] OR Postmenopause[tiab] OR "Osteoporosis, Postmenopausal"[Mesh] OR "Hysterectomy"[Mesh] OR Hysterectomy[tiab]	160,379
#3	#1 AND #2	31,390
#4	#3 AND ("2016/01/01"[Date – Publication] : "3000"[Date – Publication])	3,522
#5	#4 AND English[lang]	3,420
#6	#5 NOT (animals[mh] NOT humans[mh])	3,116
#7	#6 AND ("Clinical Trial" [Publication Type:NoExp] OR "controlled clinical trial"[pt] OR "randomized controlled trial"[pt] OR "Randomized Controlled Trials as Topic"[mh] OR "Random Allocation"[mh] OR "randomized"[tiab] OR "99nglish9999t"[tiab] OR "randomization"[tiab] OR "99nglish9999tion"[tiab] OR "randomly"[tiab] OR placebo*[tiab] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR "Clinical Trials as Topic"[mh] OR trial[ti] OR "Clinical Trial, Phase III"[pt] OR "Clinical Trials, Phase III as Topic"[mh] OR "Clinical Trial, Phase IV"[pt] OR "Clinical Trials, Phase IV as Topic"[mh] OR systematic[sb] OR "systematic review"[tiab] OR "meta-analysis"[pt] OR "meta-analysis as topic"[mh] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta-synthesis"[tiab] OR "meta-syntheses"[tiab] OR "Cohort Studies"[Mesh:NoExp] OR "cohort study"[tiab] OR "cohort analysis"[tiab] OR "cohort analyses"[tiab]) NOT (Editorial[pt] OR Letter[pt] OR Case Reports[pt] OR "a case report"[ti] OR ": case report"[ti] OR Comment[pt])	1,012

Appendix A. Search Strategies

Embase:

Search	Query	Results
#1	'hormone substitution'/exp OR 'Hormone Replacement Therapy':ti,ab OR 'Hormone Replacement Therapies':ti,ab OR 'estrogen replacement':ti,ab OR 'estrogen replacements':ti,ab OR 'estrogen therapy':ti,ab OR 'estrogen therapies':ti,ab OR 'progestin replacement':ti,ab OR 'estrogen progestin combination therapy':ti,ab OR Alora:ti,ab OR Cenestin:ti,ab OR Climara:ti,ab OR Delestrogen:ti,ab OR Esclim:ti,ab OR Estrace:ti,ab OR Estraderm:ti,ab OR Menostar:ti,ab OR Minivelle:ti,ab OR 'Ortho-Est':ti,ab OR Prometrium:ti,ab OR Provera:ti,ab OR Vivelle:ti,ab OR 'Vivelle-Dot':ti,ab OR Femtrace:ti,ab OR Menest:ti,ab OR Ogen:ti,ab OR Premarin:ti,ab OR Enjuvia:ti,ab OR Angeliq:ti,ab OR Activella:ti,ab OR Prefest:ti,ab OR Climara Pro:ti,ab OR Combipatch:ti,ab OR Prempro:ti,ab OR Femhrt:ti,ab OR 'estradiol'/exp OR Estradiol:ti,ab OR Oestradiol:ti,ab OR Progynova:ti,ab OR Vivelle:ti,ab OR Aerodiol:ti,ab OR Estrace:ti,ab OR 'Estraderm TTS':ti,ab OR 'Progynon-Depot':ti,ab OR 'Progynon Depot':ti,ab OR Delestrogen:ti,ab OR Ovocyclin:ti,ab OR Estropipate:ti,ab OR 'Micronized progesterone':ti,ab OR 'medroxyprogesterone acetate'/exp OR 'Medroxyprogesterone acetate':ti,ab OR 'Medroxyprogesterone 17-Acetate':ti,ab OR 'Medroxyprogesterone 17 Acetate':ti,ab OR Depo-Provera:ti,ab OR Depo Provera:ti,ab OR DepoProvera:ti,ab OR Farlutal:ti,ab OR Gestapuran:ti,ab OR Curretab:ti,ab OR Perlutex:ti,ab OR Provera:ti,ab OR Veramix:ti,ab OR Cycrin:ti,ab OR 'conjugated estrogen'/exp OR 'Esterified Estrogen':ti,ab OR 'Esterified Estrogens':ti,ab OR 'Conjugated Estrogen':ti,ab OR 'Conjugated Estrogens':ti,ab OR 'Conjugated Estrogenic':ti,ab OR 'Conjugated Equine Estrogens':ti,ab OR 'Conjugated Equine Estrogen':ti,ab OR Dagynil:ti,ab OR Oestrofeminal:ti,ab OR 'Oestro-Feminal':ti,ab OR 'Oestro Feminal':ti,ab OR 'Estro-Feminal':ti,ab OR 'Estro Feminal':ti,ab OR Premarin:ti,ab OR Climopax:ti,ab OR Climarest:ti,ab OR Presomen:ti,ab OR Progens:ti,ab OR Progen:ti,ab OR Transannon:ti,ab OR Femavit:ti,ab OR Carentil:ti,ab OR Prelestrin:ti,ab OR 'estradiol derivative'/exp OR 'Synthetic Estrogen':ti,ab OR 'Synthetic Estrogens':ti,ab	174,757
#2	'menopause and climacterium'/exp OR climacteric:ti,ab OR menopause:ti,ab OR menopausal:ti,ab OR perimenopause:ti,ab OR perimenopausal:ti,ab OR 'hot flush'/exp OR "hot flashes":ti,ab OR "Post-Menopausal":ti,ab OR Postmenopausal:ti,ab OR "Post-Menopause":ti,ab OR Postmenopause:ti,ab OR 'menopause related disorder'/exp OR 'hysterectomy'/exp OR Hysterectomy:ti,ab	266,960
#3	#1 AND #2	27,670
#4	AND ([100nglish100 review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [humans]/lim AND [100nglish]/lim AND [2016-2021]/py	754

Appendix A. Search Strategies

Cochrane Library:

Search	Query	Results
#1	(“Hormone Replacement Therapy” OR “Hormone Replacement Therapies” OR “estrogen replacement” OR “estrogen replacements” OR “estrogen therapy” OR “estrogen therapies” OR “progestin replacement” OR “estrogen progestin combination therapy” OR Alora OR Cenestin OR Climara OR Delestrogen OR Esclim OR Estrace OR Estraderm OR Menostar OR Minivelle OR “Ortho-Est” OR Prometrium OR Provera OR Vivelle OR “Vivelle-Dot” OR Femtrace OR Menest OR Ogen OR Premarin OR Enjuvia OR Angeliq OR Activella OR Prefest OR Climara Pro OR Combipatch OR Prempro OR Femhrt OR Estradiol OR Oestradiol OR Progynova OR Vivelle OR Aerodiol OR Estrace OR “Estraderm TTS” OR “Progynon-Depot” OR “Progynon Depot” OR Delestrogen OR Ovocyclin OR Estropipate OR “Micronized progesterone” OR “Medroxyprogesterone acetate” OR “Medroxyprogesterone 17-Acetate” OR “Medroxyprogesterone 17 Acetate” OR Depo-Provera OR Depo Provera OR DepoProvera OR Farlutal OR Gestapuran OR Curretab OR Perlutex OR Provera OR Veramix OR Cycrin OR “Esterifield Estrogen” OR “Esterifield Estrogens” OR “Conjugated Estrogen” OR “Conjugated Estrogens” OR “Conjugated Estrogenic” OR “Conjugated Equine Estrogens” OR “Conjugated Equine Estrogen” OR Dagynil OR Oestrofeminal OR “Oestro-Feminal” OR “Oestro Feminal” OR “Estro-Feminal” OR “Estro Feminal” OR Premarin OR Climopax OR Climarest OR Presomen OR Progens OR Progen OR Transannon OR Femavit OR Carentil OR Prelestrin OR “Synthetic Estrogen” OR “Synthetic Estrogens”):ti,ab,kw	16,824
#2	(climacteric OR menopause OR menopausal OR perimenopause OR perimenopausal OR “hot flashes” OR “Post-Menopausal” OR Postmenopausal OR “Post-Menopause” OR Postmenopause OR Hysterectomy):ti,ab,kw	33,180
#3	#1 AND #2	7,592
#4	#3 AND (“2016/01/01”[Date – Publication] : “3000”[Date – Publication])	1,105

Appendix B. Inclusion and Exclusion Criteria

	Include	Exclude
Population	• Generally healthy perimenopausal and postmenopausal women eligible for menopausal HT • Women with and without menopausal symptoms will be included if the focus of the analysis is on the primary prevention of chronic conditions	• Animals; men; premenopausal women; postmenopausal women with contraindications for HT use such as history of breast cancer, coronary heart disease, a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications; populations not applicable to U.S. primary care • Postmenopausal women who use HT for secondary prevention of chronic conditions
Interventions	Systemic therapy with estrogen-only formulations or combinations with progestogens (progesterone or progestin) for prevention of chronic conditions. Medications are FDA-approved and available for use in the United States (see Table 1)	Localized (nonsystemic) treatments such as rings, creams, or gels; contraceptives; other hormones; treatments of menopausal symptoms such as over-the-counter preparations or compounded bioidentical therapies that are not FDA-approved
Control interventions	Placebo, no treatment	Active comparator
Outcomes	• Overall mortality • Disease-specific mortality (if related to chronic conditions* of interest) • Coronary heart disease • Stroke • Thromboembolism • Cancer (breast, colorectal, endometrial, ovarian, and non-small cell lung) • Cholecystitis • Fractures • Cognition • Quality of life (if related to chronic conditions of interest) • Functional capacity • Urinary incontinence • Diabetes	Any outcomes that are not health outcomes of chronic conditions associated with HT; intermediate outcomes, such as bone density and cholesterol level
Duration of intervention	≥1 year of treatment	Less than 1 year of treatment
Publication language	English	Non-English language
Study design	All outcomes: • RCTs • Controlled clinical trials • Systematic reviews For outcomes or subgroups with no evidence from trials or systematic reviews: • Large cohort studies (more than 10,000 women)	All other study designs
Publication type	Published or unpublished original research	Nonsystematic review article, letter, editorial, results reported elsewhere, no original data
Geography	U.S. adult population or comparable populations (categorized as "Very High" using the Human Development Index, as defined by the United Nations Development Programme)	Not comparable or applicable to U.S. adult population
Setting	Primary care or primary-care–like settings	Inpatient facilities, nursing homes, hormone specialist offices

* The Centers for Disease Control and Prevention defines chronic diseases as conditions that last 1 or more years and require ongoing medical attention, limit activities of daily living, or both. The following are classified as chronic diseases: heart disease, cancer, chronic lung disease, stroke, Alzheimer's disease, diabetes, and chronic kidney disease. Source: Centers for Disease Control and Prevention. About Chronic Diseases. https://www.cdc.gov/chronicdisease/about/index.htm. Accessed May 7, 2021.

Abbreviations: FDA=Food and Drug Administration; HT=hormone therapy; RCT=randomized, controlled trial.

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[65]

Appendix D. Excluded Studies

Exclusion Legend:
X1: Not original research
X2: Ineligible population
X3: Ineligible intervention
X4: Intervention duration less than 1 year
X5: Outcomes not relevant to prevention of chronic conditions
X6: Ineligible comparator or no comparator
X7: Ineligible study design
X8: Systematic review with eligibility criteria that does not meet criteria for this review
X9: Ineligible setting
X10: Non-English full text
X11: Ineligible publication type
X12: Poor quality
X13: Duplicate
X14: Systematic review for hand search

1. A 17β-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: a randomized controlled trial: correction. *Obstet Gynecol*. 2018 Sep;132(3):786. doi: 10.1097/aog.0000000000002859. PMID: 30134411. Exclusion Code: X1.
2. Hormone therapy during peri- and postmenopause. *Deutsche medizinische Wochenschrift (1946)*. 2018;143(22):1636-47. doi: 10.1055/a-0441-4540. PMID: CN-01932256. Exclusion Code: X10.
3. 2017 - Pooled RCTs: in postmenopausal women, hormone therapy for 6 to 7 years did not affect mortality at 18 years. *ACP J Club*. 2018;168(2):1-. PMID: CN-02113784. Exclusion Code: X11.
4. Hormone therapy effective in preventing depressive symptoms in menopause transition. *Brown University psychopharmacology update*. 2018;29(5):1-2. doi: 10.1002/pu.30318. PMID: CN-02198431. Exclusion Code: X1.
5. A 17β-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: a randomized controlled trial. *Obstet Gynecol Surv*. 2018;73(11):630-2. doi: 10.1097/01.ogx.0000549834.30469.f2. PMID: CN-01925338. Exclusion Code: X1.
6. Erratum: a 17Î²-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: a randomized controlled trial: correction (Obstetrics and Gynecology (2018) 132 1 (161-170)). *Obstet Gynecol*. 2018;132(3):786-. doi: 10.1097/AOG.0000000000002859. PMID: CN-02002256. Exclusion Code: X11.
7. The bioavailability of TX-001hr (estradiol and micronized progesterone capsules): effect of food and varying dosing profiles. *Endocr Rev*. 2018; Conference: 100th Annual Meeting of the Endocrine Society, ENDO 2018. United States. 39(2 Supplement 1). PMID: CN-01920886. Exclusion Code: X11.
8. Prior menopausal hormone treatments and association of peripheral markers of neurovascular unit integrity and beta-amyloid in the brains of menopausal women. *FASEB J*. 2018; Conference: Experimental Biology 2018, EB. United States. 32(1 Supplement 1)PMID: CN-01920438. Exclusion Code: X5.
9. Estradiol/progesterone (Bijuva) for menopausal vasomotor symptoms. *Med Lett Drugs Ther*. 2019 Jul 1;61(1575):99-101. PMID: 31381541. Exclusion Code: X1.
10. Menopausal hormone therapy and risks of first hospitalized heart failure and its subtypes during the intervention and extended postintervention follow-up of the Women's Health Initiative randomized trials. *J Card Fail*. 2019.

doi: 10.1016/j.cardfail.2019.09.006. PMID: CN-02011210. Exclusion Code: X13.

11. Estrogen-based hormone replacement [HRT] therapy is substantially more effective than tamoxifen in reducing breast cancer mortality and breast cancer case fatality ratio: emergence of a new paradigm. *Cancer Res*. 2019;79(4)doi: 10.1158/1538-7445.SABCS18-P6-13-06. PMID: CN-02081180. Exclusion Code: X6.
12. The effect of estroprogestagen therapy on lipid status in menopause depending on the drug administration route. *Vojnosanit Pregl*. 2020;77(4):418-25. doi: 10.2298/VSP170318080C. PMID: CN-02164698. Exclusion Code: X5.
13. Abdi F, Mobedi H, Bayat F, et al. The Effects of transdermal estrogen delivery on bone mineral density in postmenopausal women: a meta-analysis. *Iran J Pharm Res*. 2017 Winter;16(1):380-9. PMID: 28496491. Exclusion Code: X8.
14. Abdi F, Mobedi H, Mosaffa N, et al. Hormone therapy for relieving postmenopausal vasomotor symptoms: a systematic review. *Arch Iran Med*. 2016 Feb;19(2):141-6. PMID: 26838086. Exclusion Code: X5.
15. Ahmed I, Bano F. Hormone replacement therapy (HRT) after hysterectomy? *BJOG*. 2019;126:183-. doi: 10.1111/1471-0528.13_15703. PMID: CN-01960522. Exclusion Code: X11.
16. Alyono J, Qin F, Hedlin H, et al. Effects of menopausal hormone therapy on hearing loss. *Otolaryngology - Head and Neck Surgery (United States)*. 2017;157(1):P243. doi: 10.1177/0194599817717250. Exclusion Code: X11.
17. Anonymous. Erratum: a 17beta-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: a randomized controlled trial: correction (Obstetrics and Gynecology (2018) 132 1 (161-170)). *Obstet Gynecol*. 2018;132(3):786RCT. PMID: CN-02072353. Exclusion Code: X11.
18. Archer D, Pickar J, Graham S, et al. Effects of single-capsule 17β-estradiol/progesterone (TX-001HR) on weight and blood pressure in menopausal women of the replenish trial. *Menopause*. 2018;25(12):1496-7. doi: 10.1097/GME.0000000000001251. Exclusion Code: X11.
19. Archer D, Pickar J, Graham S, et al. Effects of single-capsule 17beta-estradiol/progesterone (TX-001HR) on weight and blood pressure in menopausal women of the replenish trial. *Menopause. Conference: 29th Annual Meeting of the North American Menopause Society. United States*. 2018;25(12):1496-7. PMID: CN-01911188. Exclusion Code: X11.
20. Archer DF, Bernick BA, Mirkin S. A combined, bioidentical, oral, 17Î²-estradiol and progesterone capsule for the treatment of moderate to severe vasomotor symptoms due to menopause. *Expert Rev Clin Pharmacol*. 2019;12(8):729-39. doi: 10.1080/17512433.2019.1637731. PMID: CN-01989692. Exclusion Code: X13.
21. Archer DF, Bernick BA, Mirkin S. A combined, bioidentical, oral, 17beta-estradiol and progesterone capsule for the treatment of moderate to severe vasomotor symptoms due to menopause. *Expert Rev Clin Pharmacol*. 2019;12(8):729-39. doi: 10.1080/17512433.2019.1637731. PMID: CN-01968598. Exclusion Code: X5.
22. Archer DF, Graham S, Gasper G, et al. Replenish trial: combination capsule of estradiol/progesterone (TX-001HR) for treating hot flushes. *Obstet Gynecol*. 2017;129:133S-4S. Exclusion Code: X11.
23. Archer DF, Lobo RA, Kagan R, et al. Replenish trial: endometrial safety with a 173-estradiol and progesterone combination (TX-001HR) in postmenopausal women with vasomotor symptoms. *Endocr Rev*. 2017;38(3). Exclusion Code: X11.

24. Archer DF, Pickar JH, Graham R, et al. Incidence of abnormal mammograms with oral, combined 17β-estradiol and progesterone capsules. *Endocr Rev*. 2018;39(2). Exclusion Code: X11.
25. Armstrong NM, Espeland MA, Chen JC, et al. Associations of hearing loss and menopausal hormone therapy with change in global cognition and incident cognitive impairment among postmenopausal women. *J Gerontol A Biol Sci Med Sci*. 2020 Feb 14;75(3):537-44. doi: 10.1093/gerona/glz173. PMID: 31326978. Exclusion Code: X7.
26. Asi N, Mohammed K, Haydour Q, et al. Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis. *Syst Rev*. 2016 Jul 26;5(1):121. doi: 10.1186/s13643-016-0294-5. PMID: 27456847. Exclusion Code: X8.
27. Barnes JN, Harvey RE, Eisenmann NA, et al. Cerebrovascular reactivity after cessation of menopausal hormone treatment. *Climacteric*. 2019 Apr;22(2):182-9. doi: 10.1080/13697137.2018.1538340. PMID: 30661405. Exclusion Code: X5.
28. Bezwada P, Shaikh A, Misra D. The effect of transdermal estrogen patch use on cardiovascular outcomes: a systematic review. *J Womens Health (Larchmt)*. 2017 Dec;26(12):1319-25. doi: 10.1089/jwh.2016.6151. PMID: 28622476. Exclusion Code: X8.
29. Black DR, Minkin MJ, Graham S, et al. Effects of combined 17β-estradiol and progesterone on weight and blood pressure in postmenopausal women of the REPLENISH trial. *Menopause*. 2020 Sep 14;28(1):32-9. doi: 10.1097/gme.0000000000001659. PMID: 32932401. Exclusion Code: X5.
30. Black DR, Minkin MJ, Graham S, et al. Effects of combined 17β-estradiol and progesterone on weight and blood pressure in postmenopausal women of the REPLENISH trial. *Menopause*. 2021;28(1):32-9. doi: 10.1097/GME.0000000000001659. Exclusion Code: X13.
31. Blondon M, Timmons AK, Baraff AJ, et al. Comparative venous thromboembolic safety of oral and transdermal postmenopausal hormone therapies among women Veterans. *Menopause*. 2021 Jul 26;28(10):1125-9. doi: 10.1097/gme.0000000000001823. PMID: 34313612. Exclusion Code: X6.
32. Brusselaers N, Tamimi RM, Konings P, et al. Different menopausal hormone regimens and risk of breast cancer. *Ann Oncol*. 2018 Aug 1;29(8):1771-6. doi: 10.1093/annonc/mdy212. PMID: 29917061. Exclusion Code: X4.
33. Bumbu A, Bianca P, Tit DM, et al. The effects of soy isoflavones and hormonal replacing therapy on the incidence and evolution of postmenopausal female urinary incontinence. *Farmacia*. 2016;64(3):419-22. Exclusion Code: X12.
34. Chang WC, Wang JH, Ding DC. Conjugated equine estrogen used in postmenopausal women associated with a higher risk of stroke than estradiol. *Sci Rep*. 2021 May 24;11(1):10801. doi: 10.1038/s41598-021-90357-6. PMID: 34031535. Exclusion Code: X6.
35. Chaves JDP, Figueredo TFM, Warnavin SVSC, et al. Sex hormone replacement therapy in periodontology—A systematic review. *Oral Dis*. 2020;26(2):270-84. doi: 10.1111/odi.13059. Exclusion Code: X8.
36. Chen PJ, Chung CH, Chien WC, et al. Hormone therapy is not associated with the risk of sudden sensorineural hearing loss in postmenopausal women: a 10-year nationwide population-based study. *Menopause*. 2019 Aug;26(8):892-8. doi: 10.1097/gme.0000000000001323. PMID: 30969183. Exclusion Code: X2.
37. Chen YY, Su TH, Lau HH. Estrogen for the prevention of recurrent urinary tract infections in postmenopausal women: a meta-analysis of randomized controlled trials. *Int Urogynecol J*. 2021 Jan;32(1):17-25. doi: 10.1007/s00192-

020-04397-z. PMID: 32564121. Exclusion Code: X8.

38. Cherry N, Gilmour K, Hannaford P, et al. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet*. 2002 Dec 21-28;360(9350):2001-8. PMID: 12504395. Exclusion Code: X5.
39. Cherry N, McNamee R, Heagerty A, et al. Long-term safety of unopposed estrogen used by women surviving myocardial infarction: 14-year follow-up of the ESPRIT randomised controlled trial. *BJOG*. 2014 May;121(6):700-5; discussion 5. doi: 10.1111/1471-0528.12598. PMID: 24533510. Exclusion Code: X5.
40. Chi CI. Multicenter randomized controlled trial of low-dose hormone replacement therapy for low bone density in early postmenopause females. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-IOR-16008202*. 2016PMID: CN-01853904. Exclusion Code: X5.
41. Chi CI. Prevention and treatment of estrogen therapy on the perimenopausal diseases of multi-center study in China. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-IPR-16008754*. 2016PMID: CN-01808068. Exclusion Code: X9.
42. ChiCtr. Menopausal hormone therapy in patients with CSVD, a double–blind, double-dummy randomized controlled trial. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2100043205*. 2021PMID: CN-02282985. Exclusion Code: X1.
43. Chlebowski RT, Anderson GL, Aragaki AK, et al. Long-term influence of estrogen plus progestin and estrogen alone use on breast cancer incidence: The women's health initiative randomized trials. *Cancer Res*. 2020;80(4)doi: 10.1158/1538-7445.SABCS19-GS5-00. Exclusion Code: X11.
44. Chlebowski RT, Cirillo DJ, Eaton CB, et al. Estrogen alone and joint symptoms in the Women's Health Initiative randomized trial. *Menopause*. 2018 Nov;25(11):1313-20. doi: 10.1097/gme.0000000000001235. PMID: 30358728. Exclusion Code: X5.
45. Choudhary Y, Walji N. Peri-menopausal estrogen could prevent breast cancer; AGAINST. *BJOG*. 2021 Jul;128(8):1385. doi: 10.1111/1471-0528.16687. PMID: 33822439. Exclusion Code: X1.
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145. Nct. Efficacy Study of Progesterone Tablet in Post-menopausal Women. *https://clinicaltrials.gov/show/NCT02841137*. 2016PMID: CN-01506977. Exclusion Code: X11.
146. Nct. Effects of Hormone Replacement Therapy on Arthralgia in Postmenopausal Women. *https://clinicaltrials.gov/show/NCT02838576*. 2016PMID: CN-01506928. Exclusion Code: X11.
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148. Nct. Estrogen Diastolic Heart Failure. *https://clinicaltrials.gov/show/NCT02693002*. 2016PMID: CN-01556092. Exclusion Code: X4.
149. Nct. The Anabolic Effects of Estrogen on Skeletal Muscles. *https://clinicaltrials.gov/show/NCT03020953*. 2017PMID: CN-01561266. Exclusion Code: X4.
150. Nct. Estrogen and the Urogenital Microbiome in GSM. *https://clinicaltrials.gov/show/NCT03336437*. 2017PMID: CN-01577655. Exclusion Code: X3.
151. Nct. Study of Progesterone in Treatment of Vasomotor Symptoms. *https://clinicaltrials.gov/show/NCT03202186*. 2017PMID: CN-01495306. Exclusion Code: X4.
152. Nct. The Benefits and Risks of Different Menopausal Hormone Replacement Therapy Regimes in the Treatment of Menopause Syndrome. *https://clinicaltrials.gov/show/NCT03436303*. 2018PMID: CN-01523065. Exclusion Code: X6.
153. Nct. The Kronos Early Estrogen Prevention Study (KEEPS). *https://clinicaltrials.gov/show/NCT03718494*. 2018PMID: CN-01664416. Exclusion Code: X11.
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157. Nct. Discontinuation of Postmenopausal Hormone Therapy: impact on the Cardiovascular System and Quality of Life. *https://clinicaltrials.gov/show/NCT04050592*. 2019PMID: CN-01966288. Exclusion Code: X11.
158. Nct. Oophorectomy, Estrogen Therapy and Cardiovascular Disease Risk in Young Women. *https://clinicaltrials.gov/show/NCT03815929*. 2019PMID: CN-01796048. Exclusion Code: X2.
159. Nct. Pilot Study of Effects of Duavee® on Imaging and Blood Biomarkers In Women With Menopausal Symptoms. *https://clinicaltrials.gov/show/NCT04379024*. 2020PMID: CN-02103799. Exclusion Code: X11.
160. Nct. Effects of Hormone Replacement Therapy on Cardiovascular Risk and Body Composition Parameters. *https://clinicaltrials.gov/show/NCT04453332*. 2020PMID: CN-02134048. Exclusion Code: X4.
161. Nct. Impact of Estradiol on Endothelial Function in Peri-Menopausal Women. *https://clinicaltrials.gov/show/NCT04255160*. 2020PMID: CN-02080073. Exclusion Code: X4.
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Appendix E Table 1. Quality Ratings of Randomized, Controlled Trials

Trial	Randomi-zation 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*	Poor
Clarke 2002 (U.K.)	Unclear	Unclear	Yes	Yes	No	No	No	Yes	No	Poor
ELITE-Cog (U.S.)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
EMS (Canada)	Yes	Yes	Mostly, except for prior HT use and amnestic mild cognitive impairment	Yes	Yes	Yes	Yes	Unclear	No	Fair
EPAT (U.S.)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes†	Fair
EPHT (Estonia)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Fair
ERA (U.S.)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes‡	Fair
Greenspan 2005 (U.S.)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
Notelovitz 2002 (U.S.)	Unclear	Unclear	Yes	Yes	Yes	Yes	No	No	Yes§	Poor
HERS (U.S.)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
KEEPS-Cog (U.S.)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
KEEPS-MRI (U.S.) – global cognition score	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	Poor
KEEPS-MRI (U.S.) – global cognitive function	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
Pefanco 2007 (U.S.)	Yes	Unclear	Yes	Yes	Unclear	Yes	No	No	No	Poor
PEPI (U.S.)	Yes	Unclear	Unclear	Yes	Unclear	Yes	Unclear	No	Yes‖	Fair
STOP-IT (U.S.)	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Fair
Bumbu 2016 (Romania)	Unclear	Unclear	Unclear	Unclear	Unclear	No	Yes	Unclear	Unclear	Poor
ULTRA (U.S.)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
WAVE (U.S., Canada)	Yes	Unclear	Yes	Yes	Yes	Yes	No	Unclear	No	Fair
WHI (U.S.)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
WHI (U.S.) – breast cancer	Yes	Yes	Yes	Unclear	Yes	No	Yes	Yes	No	Fair
WHI (U.S.) – breast cancer, CHD, stroke, hip fracture, non-Hodgkin's lymphoma	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	No	Fair
WHI (U.S.) – fractures	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Fair
WHI (U.S.) – lung cancer	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	No	Fair
WHI (U.S.) – stroke, VTE, mortality, breast cancer, CHD	Yes	Yes	Yes	Unclear	Unclear	Unclear	No	Yes	No	Fair

Appendix E Table 1. Quality Ratings of Randomized, Controlled Trials

Trial	Randomi-zation 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
WHI (U.S.) – mortality	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Good
WHI (U.S.) – endometrial cancer	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
WHIMS (U.S.)	Yes	Yes	Mostly, except for history of stroke and hypertension	Yes	Yes	Yes	Yes	Yes	No	Good
WHIMS-ECHO (U.S.)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Fair
WHIMSY (U.S.)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
WHISCA (U.S.)	Yes	Yes	Mostly, except for smoking status	Yes	Yes	Yes	Yes	Yes	No	Good
WISDOM (U.K., Australia, New Zealand)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Fair

* High risk of selection bias and contamination. Invited participants chose whether to be part of randomized trial (those who preferred a treatment option were followed in the cohort study). Among those who were randomized to no HT and attended the 5-year followup, 15% had initiated HT. Among those randomized to HT, 18% had changed the type of HT and 22% had stopped HT at 5 years.

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

‡ There was a statistically significant difference between placebo and CEE in adherence.

§ Risk of measurement bias. Some outcomes (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; methods of determining cancer severity were not described.

‖ Potential risk of contamination and low adherence to assigned study medications. Study authors noted that in women assigned to CEE, continuation rate was 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: CEE=conjugated equine estrogen; CHD=coronary heart disease; DOPS=Danish Osteoporosis Prevention Trial; ELITE=Early versus Late Intervention Trial with Estradiol; 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; HERS=Heart and Estrogen/Progestin Replacement Study; HRT=hormone replacement therapy; HT=hormone therapy; ITT=intention to treat; KEEPS=Kronos Early Estrogen Prevention Study; KEEPS-MRI=Kronos Early Estrogen Prevention Study-MRI; PEPI=Postmenopausal Estrogen and Progestin Interventions Trial; STOP-IT=Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; ULTRA=Ultra-Low-Dose Transdermal Estrogen Assessment; VTE=venous thromboembolism; WAVE=Women's Angiographic Vitamin and Estrogen Trial; WHI=Women's Health Initiative; WHIMS=Women's Health Initiative Memory Study; WHIMS-ECHO=Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes; WHIMSY=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 E Table 2. Quality Ratings of Observational Studies

	Bias due to confounding				Bias in selection of participants into the study			Bias in classification of interventions	
Reference	Potential for confounding?	Appropriate analysis method to control for all the important confounding domains?	Confounding domains measured reliably?	Risk of bias	Selection based on participants characteristics observed after the start of the intervention?	Most participants followed from the start of the intervention?	Risk of bias	Intervention groups clearly defined?	Risk of bias
Morch, 2016[102]	Probably yes	Probably yes	Probably yes	Moderate	No	Yes	Low	Yes	Low
Bethea, 2017[104]	Probably yes	Probably yes	Probably yes	Moderate	No	Probably yes	Low	Probably yes	Moderate
Park, 2016[103]	Probably yes	Probably yes	Probably yes	Moderate	No	Probably no	Moderate	Probably yes	Moderate
Perez, 2012[81]	No	No	No information	Low	No	Probably no	Moderate	Yes	Low

Bias due to deviations from intended interventions				Bias due to missing data				
Deviations from intended interventions?	Deviations unbalanced between groups?	Co-interventions balanced across intervention groups?	Risk of bias	Outcome data available for nearly all participants?	Participants excluded due to missing data?	Proportions of participants and reasons for missing data similar across interventions?	Results robust?	Risk of bias
No	Probably no	Probably yes	Low	Yes	Probably no	Probably yes	Yes	Low
No	No	Probably yes	Low	Yes	Probably no	Probably yes	Probably yes	Low
No	No	Probably yes	Low	Yes	Yes	Probably yes	Yes	Low
No information	No information	No information	No information	Probably yes	Probably no	Probably yes	Probably yes	Low

Bias in measurement of outcomes				Bias in selection of the reported result			
Could the outcome measure have been influenced by knowledge of the intervention received?	Were outcome assessors aware of the intervention received by study participants?	Were the methods of outcome assessment comparable across intervention groups?	Risk of Bias	Results likely to be selected from multiple measurements?	Results likely to be selected from different subgroups?	Risk of bias	Overall risk of bias
No	No	Yes	Low	Probably no	Probably no	Low	Moderate risk of bias
No	No	Yes	Low	Probably no	Probably no	Low	Moderate risk of bias
No	No	Yes	Low	Probably no	Probably no	Low	Moderate risk of bias
Probably no	No	Probably no	Low	Probably no	Probably no	Low	Serious risk of bias

Appendix F Table 1. Outcomes From Trials Reporting Incidence of Breast Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
EPAT Estrogen-only trial Hodis, 2001[112]	111 Estrogen 111 Placebo	**Intervention followup: Mean 2 years** **Breast cancer (not defined)** 0 (0%) vs. 1 (1%)
EPHT Estrogen plus progestin trial Veerus, 2006[137]	404 Estrogen plus progestin 373 Placebo	**Intervention followup: Mean 3.4 years** **Breast cancer (not defined)** 1 (0.2%) vs. 2 (0.5%); HR, 0.55 (95% CI, 0.05 to 6.06)
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[113]	100 Estrogen alone 104 Estrogen plus progestin 105 Placebo	**Intervention followup: Mean 3.2 years** **Breast cancer (not defined)** 1 vs. 0 vs. 0; p=0.35
Greenspan, et al Estrogen-only and estrogen plus progestin trial Greenspan, 2005[107]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Intervention followup: Mean 3 years** **Breast cancer (not defined)** *Analysis did not stratify by treatment regimen* 2 (hormone therapy) vs. 2; p=1.0
HERS Estrogen plus progestin trial Hulley, 2002[136]	1380 Estrogen plus progestin 1383 Placebo Cumulative followup: 1156 Estrogen plus progestin 1383 Placebo	**Intervention followup: Mean 4.1 years** **Breast cancer (not defined)** 34 (2.5%) vs. 25 (1.8%); HR, 1.38 (95% CI, 0.82 to 2.31); p=0.22 **Postintervention followup: Mean 2.7 years** **Breast cancer (not defined)** HR, 1.08 (95% CI, 0.52 to 2.24); p=0.83 **Cumulative followup: Mean 6.8 years** **Breast cancer (not defined)** 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[32]	175 Estrogen 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Intervention followup: Mean 3 years** **Breast cancer (not defined)** 1 (estrogen) vs. 2 (estrogen plus progestin) vs. 4 (estrogen plus micronized progestin) vs. 1 (placebo); p=0.29
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[106]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Intervention followup: Mean 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)

Appendix F Table 1. Outcomes From Trials Reporting Incidence of Breast Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WAVE Estrogen-only and estrogen plus progestin trial Waters, 2002[105]	124 Estrogen 86 Estrogen plus progestin 213 Placebo	**Intervention 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;[37] Anderson, 2012;[109] LaCroix, 2011;[108] Prentice, 2009;[110] Manson, 2013;[67] Chlebowski, 2015;[111] Manson, 2019;[89] Chlebowski, 2016;[90] Chlebowski, 2020;[87] Chlebowski, 2017;[95] Prentice, 2019;[101] Prentice, 2020;[91] Manson, 2017[88]	5,310 Estrogen 5,429 Placebo Postintervention extension followup: 3,778 Estrogen 3,867 Placebo Cumulative followup (intervention plus postintervention extension phases): 4,911 Estrogen 5,028 Placebo	**Intervention followup: Median 7.2 years** **Invasive breast cancer**[67, 108] 104 (0.28%) vs. 135 (0.35%); HR, 0.79 (95% CI, 0.61 to 1.02); p=0.07 *Subgroups*: No significant differences by race,[95] age at randomization,[67, 111] and oophorectomy status[89] *Risk based on timing of intervention:* No significant differences by timing of intervention[67, 110] **Breast cancer mortality**[88] 4 (0.010% annualized) vs. 9 (0.023%); HR, 0.45 (95% CI, 0.14 to 1.46); p=0.17 *Subgroups:* No significant difference by age at randomization **Postintervention followup: Median 6.6 years**[67] **Invasive breast cancer** HR, 0.80 (95% CI, 0.58 to 1.11); p=0.19 **Postintervention followup: Median 10.8 years**[88] **Invasive breast cancer** 18 (0.037% annualized) vs. 32 (0.065% annualized); HR, 0.57 (95% CI, 0.32 to 1.02); p=0.06 *Subgroups:* No significant difference by age at randomization **Cumulative followup: Median 13.0 years** **Invasive breast cancer** 168 (0.28% annualized) vs. 216 (0.35% annualized); HR, 0.79 (95% CI, 0.65 to 0.97); p=0.02[67] *Subgroups:* No significant differences by age[67] or race[90, 95] **Cumulative followup: Median 17.7 years**[88] **Breast cancer mortality** 22 (0.025% annualized) vs. 41 (0.046% annualized); HR, 0.55 (95% CI, 0.33 to 0.92); p=0.02 *Subgroups:* No significant difference by age at randomization

Appendix F Table 1. Outcomes From Trials Reporting Incidence of Breast Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial Anderson, 2004;[37] Anderson, 2012;[109] LaCroix, 2011;[108] Prentice, 2009;[110] Manson, 2013;[67] Chlebowski, 2015;[111] Manson, 2019;[89] Chlebowski, 2016;[90] Chlebowski, 2020;[87] Chlebowski, 2017;[95] Prentice, 2019;[101] Prentice, 2020;[91] Manson, 2017[88] (continued)		**Cumulative followup: Median 18.0 years**[91] **Invasive breast cancer** 231 (0.30% annualized) vs. 291 (0.38% annualized); no HR reported; p=NR *Subgroups:* No significant difference by age[91] or oophorectomy status[89] **Cumulative followup: Median 19.4 years**[101] **Invasive breast cancer** 231 (4.4% calculated) vs. 291 (5.4% calculated); HR, 0.80 (95% CI, 0.68 to 0.95); p=NR **Cumulative followup: Median 20.7 years*†**[87] **Invasive breast cancer** 238 (0.30%) vs. 296 (0.37%); HR, 0.78 (95% CI, 0.65 to 0.93); p=0.005 **Breast cancer mortality** 30 (0.031%) vs. 46 (0.046%); HR, 0.60 (95% CI, 0.37 to 0.97); p=0.04 *Subgroups:* No significant differences by age, race/ethnicity, and oophorectomy status *Risk based on timing of intervention:* No significant differences by timing of intervention
WHI Estrogen plus progestin trial Writing Group for the WHI, 2002;[36] Heiss, 2008;[132] Chlebowski, 2003;[133] Chlebowski, 2010;[134] Gramling, 2009;[135] Prentice, 2009[110]; Manson, 2013;[67] Chlebowski, 2015;[111] Chlebowski, 2016;[90] Chlebowski, 2020;[87] Prentice, 2019;[101] Prentice, 2020[88, 91]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention extension followup: 6,545 Estrogen plus progestin 6,243 Placebo Cumulative followup[87, 88, 90] 8506 Estrogen plus progestin 8,102 Placebo	**Intervention followup: Median 5.6 years**[67] **Invasive breast cancer** 206 (0.43% annualized) vs. 155 (0.35% annualized); HR, 1.24 (95% CI, 1.01 to 1.53); p=0.04 *Subgroups:* No significant difference by age *Risk based on timing of intervention:* No significant differences by timing of intervention **Breast cancer mortality[88]** 5 (0.010% annualized) vs. 4 (0.009%); HR, 1.08 (95% CI, 0.29 to 4.03); p=0.91 **Postintervention followup: Mean 2.4 years**[132] **Invasive breast cancer** HR, 1.27 (95% CI, 0.91 to 1.78) **Postintervention followup: Median 8.2 years**[67] **Invasive breast cancer** 228 (0.43% annualized) vs. 168 (0.33% annualized); HR, 1.32 (95% CI, 1.08 vs. 1.61); p=0.007

Appendix F Table 1. Outcomes From Trials Reporting Incidence of Breast Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Writing Group for the WHI, 2002;[36] Heiss, 2008;[132] Chlebowski, 2003;[133] Chlebowski, 2010;[134] Gramling, 2009;[135] Prentice, 2009[110]; Manson, 2013;[67] Chlebowski, 2015;[111] Chlebowski, 2016;[90] Chlebowski, 2020;[87] Prentice, 2019;[101] Prentice, 2020[88, 91] (continued)		**Postintervention followup: Median 12.5 years**[88] **Breast cancer mortality** 56 (0.060% annualized) vs. 36 (0.041%); HR, 1.50 (95% CI, 0.98 to 2.27); p=0.06 *Subgroups:* No significant difference by age at randomization **Cumulative followup: Mean 11.0 years** **Invasive breast cancer** *Risk based on timing of intervention:*[110] 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=0.03 for gap time interaction *Subgroups:* *Time since randomization (p=0.008 for trend)*[111] 2 years since randomization: HR, 0.71 (95% CI, 0.47 to 1.08) 4 years since randomization: HR, 1.36 (95% CI, 0.95 to 1.94) 6 years since randomization: HR, 1.65 (95% CI, 1.17 to 2.32) **Breast cancer mortality**[134] 25 (0.03% annualized) vs. 12 (0.02% annualized); HR, 1.96 (95% CI, 1.00 to 4.04); p=0.049 **Cumulative followup: 13.2 years** **Invasive breast cancer** 434 (0.43% annualized) vs. 323 (0.34% annualized); HR, 1.28 (95% CI, 1.11 to 1.48); p<0.001[90] *Subgroups:* No significant difference by age[67] or race[90] **Cumulative followup: Median 17.7 years**[88] **Breast cancer mortality** 61 (0.043% annualized) vs. 40 (0.030%); HR, 1.44 (95% CI, 0.97 to 2.15); p=0.07 *Subgroups:* No significant difference by age at randomization **Cumulative followup: Median 18.0 years**[91] **Invasive breast cancer** 574 (0.45% annualized) vs. 432 (0.36% annualized) *Subgroups:* No significant difference by age

Appendix F Table 1. Outcomes From Trials Reporting Incidence of Breast Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Writing Group for the WHI, 2002;[36] Heiss, 2008;[132] Chlebowski, 2003;[133] Chlebowski, 2010;[134] Gramling, 2009;[135] Prentice, 2009[110]; Manson, 2013;[67] Chlebowski, 2015;[111] Chlebowski, 2016;[90] Chlebowski, 2020;[87] Prentice, 2019;[101] Prentice, 2020[88, 91] (continued)		**Cumulative followup: Median 18.9 years**[87] **Invasive breast cancer** 584 (0.45%) vs. 447 (0.36%); HR, 1.28 (95% CI, 1.13 to 1.45); p<0.001 *Subgroups:* No significant differences by age and race/ethnicity *Risk based on timing of intervention:* No significant differences by timing of intervention **Cumulative followup: Median 19.4 years**[101] **Invasive breast cancer** 574 (6.7% calculated) vs. 432 (5.3% calculated); HR, 1.28 (95% CI, 1.13 to 1.45); p=NR **Cumulative followup: Median 20.3 years**[87] **Breast cancer mortality** 71 (0.045%) vs. 53 (0.035%); HR, 1.35 (95% CI, 0.94 to 1.95); p=0.11
WISDOM Estrogen plus progestin trial Vickers, 2007[138]	2,196 Estrogen plus progestin 2,189 Placebo	**Intervention followup: Mean 1 year** **Breast cancer incidence** 5 (0.2%) vs. 7 (0.3%) **Breast cancer mortality** 0 vs. 0

***** Intervention dosages are listed in Table 3 by trial.

† It was 20.7 years for participants who consented to extended followup beyond September 30, 2010 (i.e., extension II), but 16.2 years overall when including patients who did not consent to participate in extension II. These data reflect both those who consented and did not consent to extended followup.

Abbreviations: CI=confidence interval; 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; EPAT=Estrogen in the Prevention of Atherosclerosis; EPHT=Estonian Postmenopausal Hormone Therapy Trial; HERS=Heart and Estrogen/Progestin Replacement Study; HR=hazard ratio;; PEPI=Postmenopausal Estrogen and Progestin Interventions Trial; 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 F Table 2. Outcomes From Trials Reporting Incidence of Cervical Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Anderson, 2003[126]	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)

* Intervention dosages are listed in Table 3 by trial.

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

Appendix F Table 3. Outcomes From Trials Reporting Incidence of Colorectal Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
EMS Estrogen plus progestin trial Tierney, 2009[141]	70 Estrogen plus progestin 72 Placebo	**Intervention Followup: 2 years** 0 vs. 0
Greenspan, et al Estrogen-only and estrogen plus progestin trial Greenspan, 2005[107]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Intervention Followup: 3 years** *Analysis did not stratify by treatment regimen* 3 vs. 1; p=0.62
HERS Estrogen plus progestin trial† Hulley, 2002[136]	1,380 Estrogen plus progestin 1,383 Placebo Cumulative followup: 1,156 Estrogen plus progestin 1,383 Placebo	**Intervention 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, 0.82 (95% CI, 0.46 to 1.47); p=NR
Multiethnic Cohort Study Park, 2016[103]	46,723 Hormone therapy ever users 39,011 Never users	**Followup: 16 years** Ever used estrogen only: 547 (1.2% calculated) vs. 903 (2.3% calculated); HR, 0.85 (95% CI, 0.76 to 0.94) Currently use estrogen only: 214 vs. 903 (2.3% calculated); HR, 0.77 (95% CI, 0.66 to 0.89) Ever used estrogen plus progestin: 405 vs. 903 (2.3% calculated); HR, 0.76 (95% CI, 0.68 to 0.86) Currently use estrogen plus progestin: 214 vs. 903 (2.3% calculated); HR, 0.72 (95% CI, 0.62 to 0.84)
PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995[32]	175 Estrogen only 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Intervention 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[106]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Intervention followup: 3 years** *Analysis did not stratify by treatment regimen* 1 (hormone therapy with or without calcitriol) vs. 6 (calcitriol only and placebo)

Appendix F Table 3. Outcomes From Trials Reporting Incidence of Colorectal Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial Anderson, 2004;[37] Ritenbaugh, 2008;[114] Prentice, 2009;[110] LaCroix, 2011;[108] Manson, 2013;[67] Manson, 2019;[89] Chlebowski, 2017;[95] Prentice, 2020;[91] Manson, 2017;[88] Prentice, 2020[91]	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	**Intervention followup: Median 7.2 years** **Colorectal cancer** 65 (1.22%) vs. 58 (1.07%); HR, 1.15 (95% CI, 0.81 to 1.64); p=0.44[67] *Subgroups*: No significant difference by race or ethnic group,‡[95, 114] bilateral oophorectomy status, family history of colorectal cancer, or treated diabetes status‡[114] *Age at randomization* (p=0.02 for trend)[67, 91] 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) *Risk based on timing of intervention*:[110] No significant association by timing of the intervention **Invasive colorectal cancer**‡[114] HR, 1.12 (95% CI, 0.77 to 1.63); p=0.55 **Invasive colon cancer**‡[114] HR, 1.26 (95% CI, 0.84 to 1.88); p=0.26 **Invasive rectal cancer**‡[114] HR, 0.53 (95% CI, 0.18 to 1.56); p=0.25 **Colorectal cancer mortality**[88] 16 (0.041% annualized) vs. 17 (0.043%); HR, 0.98 (95% CI, 0.50 to 1.95); p=0.96 *Subgroups* No significant difference by age **Postintervention only followup: Median 6.6 years**[67] **Colorectal cancer** HR, 1.10 (95% CI, 0.68 to 1.78); p=0.69 **Intervention and postintervention Followup: Median 10.8 years**[88] **Colorectal cancer mortality** 31 (0.064% annualized) vs. 23 (0.046%); HR, 1.36 (95% CI, 0.79 to 2.34); p=0.26 *Subgroups* No significant difference by age

Appendix F Table 3. Outcomes From Trials Reporting Incidence of Colorectal Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial Anderson, 2004;[37] Ritenbaugh, 2008;[114] Prentice, 2009;[110] LaCroix, 2011;[108] Manson, 2013;[67] Manson, 2019;[89] Chlebowski, 2017;[95] Prentice, 2020;[91] Manson, 2017;[88] Prentice, 2020[91] (continued)		**Cumulative followup: Median 13.0 years**[67] **Colorectal cancer** HR, 1.13 (95% CI, 0.85 to 1.51); p=0.39 *Subgroups*: No significant difference by age at randomization;[67] no significant difference by race[95] **Cumulative followup: Median 17.7 years** **Colorectal cancer mortality**[88] 47 (0.054% annualized) vs. 40 (0.045%); HR, 1.21 (95% CI, 0.79 to 1.84); p=0.38 *Subgroups:* *Age at randomization* (p=0.03) 50–59: 5 (0.017% annualized) vs. 8 (0.027%); HR, 0.65 (95% CI, 0.21 to 2.00) 60–69: 15 (0.038%) vs. 19 (0.047%); HR, 0.81 (95% CI, 0.41 to 1.60) 70–79: 27 (0.14%) vs. 13 (0.068%); HR, 2.13 (95% CI, 1.10 to 4.12) **Cumulative followup: Median 18.0 years** **Colorectal cancer** *Subgroups*: No significant difference by oophorectomy status within any age group at randomization[89, 91]
WHI Estrogen plus progestin trial Writing Group for the Women's Health Initiative Investigators, 2002;[36] Chlebowski, 2004;[140] Heiss, 2008;[132] Prentice, 2009;[110] Manson, 2013;[67] Prentice, 2020;[91] Manson, 2017[88]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,060 Estrogen plus progestin 7,687 Placebo Postintervention extension followup:[§] 6,545 Estrogen plus progestin 6,243 Placebo	**Intervention followup: Median 5.6 years** **Colorectal cancer** 50 (0.59%) vs. 75 (0.93%); HR, 0.62 (95% CI, 0.43 to 0.89); p=0.009[67] *Subgroups*: No significant difference by age at randomization,[67, 91] race or ethnic group, family history of colorectal cancer[l,110, 140] *Risk based on timing of intervention:*[110] No significant association by timing of the intervention **Invasive colorectal cancer**[l,140] HR, 0.56 (95% CI, 0.38 to 0.81); p=0.003 **Invasive colon cancer**[l,140] HR, 0.54 (95% CI, 0.36 to 0.82); p=0.004 **Invasive rectal cancer**[l,140] HR, 0.66 (95% CI, 0.26 to 1.64); p=0.37 **Colorectal cancer mortality**[88] 11 (0.022% annualized) vs. 12 (0.026%); HR, 0.87 (95% CI, 0.38 to 1.98); p=0.74 *Subgroups:* No difference by age at randomization

Appendix F Table 3. Outcomes From Trials Reporting Incidence of Colorectal Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Writing Group for the Women's Health Initiative Investigators, 2002;[36] Chlebowski, 2004;[140] Heiss, 2008;[132] Prentice, 2009;[110] Manson, 2013;[67] Prentice, 2020;[91] Manson, 2017[88] (continued)		**Postintervention followup: Median 8.2 years**[67] **Colorectal cancer** HR, 0.97 (95% CI, 0.70 to 1.33); p=0.83 **Intervention and postintervention phase followup: Median 12.5 years**[88] **Colorectal cancer mortality** 42 (0.045% annualized) vs. 38 (0.043%); HR, 1.06 (95% CI, 0.68 to 1.64); p=0.80 *Subgroups:* No difference by age at randomization **Cumulative followup: Median 13.2 years**[67] **Colorectal cancer** HR, 0.80 (95% CI, 0.63 to 1.01); p=0.06 *Subgroups:*[67] No significant difference by age at randomization **Cumulative followup: Median 17.7 years**[88] **Colorectal cancer mortality** 53 (0.037% annualized) vs. 50 (0.037%); HR, 1.01 (95% CI, 0.69 to 1.49); p=0.96 *Subgroups:* No difference by age at randomization **Cumulative followup: Median 18.0 years**[91] **Colorectal cancer** *Subgroups:* No difference by age at randomization
WISDOM Estrogen plus progestin trial Vickers, 2007[138]	2,196 Estrogen plus progestin¶ 2,189 Placebo¶	**Intervention followup: Median 11.9 months** 2 vs. 2

***** Intervention dosages are listed in Table 3 by trial.

† HERS was a blinded randomized, controlled trial, that had a mean followup of 4.1 years. At the end of HERS, participants were unblinded and 93 percent reenrolled in HERS2, an open label study, for an additional 2.7 years.

‡ The mean followup for some of these analyses (Ritenbaugh, 2008[114] and Prentice, 2009[110]) 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).[67]

§ 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).[67]

‖ 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.

¶ The estrogen plus progestin arm included 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.

Appendix F Table 3. Outcomes From Trials Reporting Incidence of Colorectal Cancer

Abbreviations: CI=confidence interval; EMS=Estrogen Memory Study; HERS=Heart and Estrogen/Progestin Replacement Study; HR=hazard ratio; NR=not reported; PEPI=Postmenopausal Estrogen/Progestin Interventions Trial; 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 F Table 4. Outcomes From Trials Reporting Incidence of Endometrial Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
EPAT Estrogen-only trial Hodis, 2001[112]	133 (60%) of enrolled women had an intact uterus 111 Estrogen only 111 Placebo	**Intervention followup: Mean 2 years**† 0 (0.0%) vs. 0 (0.0%)
ERA Estrogen only and estrogen plus progestin trial Herrington, 2000[113]	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	**Intervention followup: Mean 3.2 years** 0 (0.0%) vs. 0 (0.0%)
Greenspan, et al Estrogen-only and estrogen plus progestin trial Greenspan, 2005[107]	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	**Intervention followup: Mean 3 years** 1 vs. 0; p=1.0‡
HERS Estrogen plus progestin trial Hulley, 2002[136]	All enrolled women had an intact uterus 1,380 Estrogen plus progestin 1,383 Placebo Cumulative followup: 1156 Estrogen plus progestin 1165 Placebo	**Intervention 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

Appendix F Table 4. Outcomes From Trials Reporting Incidence of Endometrial Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
Danish Sex Hormone Register Study Morch, 2016[102]	Women with an intact uterus from the Danish Sex Hormone Register Study 22,853 Continuous combined estrogen plus progestin 25,209 Cyclic combined estrogen plus progestin 2,071 Long cyclic combined estrogen plus progestin 593,207 Never hormone use	**Followup: Mean 9.8 years** Estrogen only: adjusted RR, 2.70 (95% CI, 2.41 to 3.02) Estrogen plus progestin: adjusted RR, 1.71 (95% CI, 1.58 to 1.86) Continuous combined estrogen plus progestin: adjusted RR, 1.02 (95% CI, 0.87 to 1.20) Cyclic combined regimen: adjusted RR, 2.06 (95% CI, 1.88 to 2.27) Long cyclic combined regimen: adjusted RR, 2.89 (95% CI, 2.27 to 3.67) *Subgroups:* No significant differences by age, hypertension, or diabetes.
PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995[32]	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	**Intervention followup: Mean 3 years** 0 (estrogen plus progestin) vs. 0 (estrogen plus micronized progestin) vs. 0 (placebo)
STOP-IT Estrogen only and estrogen plus progestin Gallagher, 2001[106]	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	**Intervention followup: Mean 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[115]	All enrolled women had an intact uterus 208 Estrogen only 209 Placebo	**Intervention followup: Mean 2 years** 0 (0.0%) vs. 0 (0.0%); difference, 0.0 (95% CI, -4.2 to 3.1); p=1.000

Appendix F Table 4. Outcomes From Trials Reporting Incidence of Endometrial Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Writing Group for the Women's Health Initiative Investigators, 2002;[36] Anderson, 2003;[126] Heiss, 2008;[132] Prentice, 2009;[110] Chlebowski, 2010;[116] Manson, 2013;[67, 94] Chlebowski, 2016;[94] Prentice, 2020[91]	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:§ 6,545 Estrogen plus progestin 6,243 Placebo	**Intervention followup: Median 5.6 years**[67] 27 (0.32%) vs. 30 (0.37%); HR, 0.83 (95% CI, 0.49 to 1.40); p=0.49 *Subgroups*:[67] No significant difference by age at randomization **Postintervention followup: Median 8.2 years**[94] 41 (0.08% annualized) vs. 65 (0.13% annualized); HR, 0.59 (95% CI, 0.40 to 0.88); p=0.008 **Cumulative followup: Median 13.2 years**[94] 66 (0.06% annualized) vs. 95 (0.10% annualized); HR, 0.65 (95% CI, 0.48 to 0.89); p=0.007 *Subgroups:*[67, 94] No significant differences by age at randomization,[67] race,[94] diabetes,[94] or hypertension[94] *Risk based on timing of intervention:*[94] No significant difference by time since menopause **Cumulative followup: Median 18.0 years**[91] *Subgroups:* No significant difference by age

***** Intervention dosages are listed in Table 3 by trial.

† 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).

‡ 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.

§ 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; HERS=Heart and Estrogen/Progestin Replacement Study; HR=hazard ratio; PEPI=Postmenopausal Estrogen/Progestin Interventions Trial; RR=relative risk; 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 F Table 5. Outcomes From Trials Reporting Incidence of Lung Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
EMS Estrogen plus progestin trial Tierney, 2009[141]	70 Estrogen plus progestin 72 Placebo	**Intervention followup: 2 years** 1 (1.4%) vs. 0 (0.0%)
HERS Estrogen plus progestin trial† Hulley, 2002[136]	1,380 Estrogen plus progestin 1,383 Placebo Cumulative followup: 1156 Estrogen plus progestin 1383 Placebo	**Intervention followup: Mean 4.1 years** 24 (1.74% calculated) vs. 19 (1.37% calculated); HR, 1.28 (95% CI, 0.70 to 2.33); p=0.43 **Cumulative followup: Mean 6.8 years** 37 (3.2% calculated) vs. 27 (2.0% calculated) 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[32]	175 Estrogen only 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Intervention followup: 3 years** *Analysis did not stratify by treatment regimen* 2 lung cancer cases

Appendix F Table 5. Outcomes From Trials Reporting Incidence of Lung Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial Chlebowski, 2010;[116] Manson, 2013[67]	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	**Intervention followup: Median 7.2 years**[67] 62 (0.16% annualized) vs. 61 (0.16% annualized); HR, 1.05 (95% CI, 0.74 to 1.49); p=0.79 *Subgroups*:[67] No significant difference by age at randomization **Intervention and partial postintervention followup: Mean 7.9 years**[116,‡] **Lung cancer** 61 (0.15% annualized) vs. 54 (0.13% annualized); HR, 1.17 (95% CI, 0.81 to 1.69); p=0.39 **NSCLC** 51 (0.12% annualized) vs. 48 (0.11% annualized); HR, 1.10 (95% CI, 0.74 to 1.64); p=0.62 **SCLC** 9 (0.02% annualized) vs. 6 (0.01% annualized); HR, 1.57 (95% CI, 0.56 to 4.41); p=0.39 **Mortality from lung cancer** 34 (0.08% annualized) vs. 33 (0.08% annualized); HR, 1.07 (95% CI, 0.66 to 1.72); p=0.79 **Mortality from NSCLC** 25 (0.06% annualized) vs. 29 (0.07% annualized); HR, 0.89 (95% CI, 0.52 to 1.52); p=0.67 **Mortality from SCLC** 8 (0.02% annualized) vs. 4 (0.01% annualized); HR, 2.11 (95% CI, 0.62 to 7.01); p=0.22 *Subgroups*:[116] No significant difference by age at randomization, race, or ethnicity *Risk based on timing of intervention:*[116] No significant differences by timing of intervention **Postintervention followup: Median 6.6 years**[67] 47 (0.20% annualized) vs. 53 (0.22% annualized); HR, 0.90 (95% CI, 0.61 to 1.34); p=0.61 **Cumulative followup: Median 13.0 years**[67] 109 (0.18% annualized) vs. 114 (0.18% annualized); HR, 0.98 (95% CI, 0.75 to 1.27); p=0.87 *Subgroups*:[67] No significant difference by age at randomization

Appendix F Table 5. Outcomes From Trials Reporting Incidence of Lung Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Chlebowski, 2009;[142] Manson, 2013;[67] Chlebowski, 2019[98]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,060 Estrogen plus progestin 7,687 Placebo Postintervention extension followup:[§] 6,545 Estrogen plus progestin 6,243 Placebo	**Intervention followup: Median 5.6 years**[67] 78 (0.92%) vs. 70 (0.86%); HR, 1.05 (95% CI, 0.76 to 1.45); p=0.78 *Subgroups*:[67] No significant difference by age at randomization **Intervention and postintervention followup: Mean 7.9 years**[‡142] **Lung cancer** 109 (0.16% annualized) vs. 85 (0.13% annualized); HR, 1.23 (95% CI, 0.92 to 1.63); p=0.16 **NSCLC** 96 (0.14% annualized) vs. 72 (0.11% annualized); HR, 1.28 (95% CI, 0.94 to 1.73); p=0.12 **SCLC** 13 (0.02% annualized) vs. 13 (0.02% annualized); HR, 0.96 (95% CI, 0.44 to 2.07); p=0.91 **Postintervention followup: Median 8.2 years**[67] 120 (0.22% annualized) vs. 101 (0.19% annualized); HR, 1.13 (95% CI, 0.86 to 1.47); p=0.38 **Cumulative followup: Median 13.2 years**[67] 198 (0.19% annualized) vs. 171 (0.18% annualized); HR, 1.10 (95% CI, 0.89 to 1.35); p=0.38 *Subgroups*:[67] No significant difference by age at randomization **Cumulative followup: Median 14 years**[98] **Lung cancer** 219 (0.19% annualized) vs. 184 (0.17% annualized); HR, 1.12 (95% CI, 0.92 to 1.37); p=0.24 **NSCLC** 160 (0.14% annualized) vs. 125 (0.11% annualized); HR, 1.23 (95% CI, 0.97 to 1.55); p=0.08 **SCLC** 20 (0.02% annualized) vs. 23 (0.02% annualized); HR, 1.09 (95% CI, 0.60 to 1.98); p=0.78 **Mortality from lung cancer** 153 (0.13% annualized) vs. 132 (0.12% annualized); HR, 1.09 (95% CI, 0.87 to 1.38); p=0.45 **Mortality from NSCLC** 109 (0.09% annualized) vs. 85 (0.08% annualized); HR, 1.23 (95% CI, 0.92 to 1.63); p=0.16 **Mortality from SCLC** 17 (0.02% annualized) vs. 21 (0.02% annualized); HR, 1.16 (95% CI, 0.61 to 2.21); p=0.64 Significant linear trend over time in lung cancer mortality (p=0.042), suggesting that the nonsignificant increase in risk of mortality in the hormone therapy group through year 9 decreased after both randomization groups stopped taking study pills after active intervention (median 5.6 years)

* Intervention dosages are listed in Table 3 by trial.

Appendix F Table 5. Outcomes From Trials Reporting Incidence of Lung Cancer

† HERS was a blinded randomized, controlled trial that had a mean followup of 4.1 years. At the end of HERS, participants were unblinded and 93 percent re-enrolled in HERS2, an open-label study, for an additional 2.7 years.
‡ Authors state ascertainment of lung cancer cases is through 3/31/2005, which is the end of the postintervention phase according to Manson[67]; this would mean these results are for trial and posttrial phases combined together.
§ 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; NSCLC=non-small cell lung cancer; PEPI=Postmenopausal Estrogen/Progestin Interventions; SCLC=small-cell lung cancer; vs.=versus; WHI=Women's Health Initiative.

Appendix F Table 6. Outcomes From Trials Reporting Incidence of Non-Hodgkin's Lymphoma

Study Author, Year	Population	Results (Treatment* vs. Placebo)
Women's Health Initiative, Estrogen-only trial[96]	5,283 Estrogen 5,402 Placebo	**Intervention followup: Median 7.2 years** **Incidence of non-Hodgkin's lymphoma** HR, 0.89 (95% CI, 0.56 to 1.42) **Cumulative followup: Median 12.9 years** **Incidence of non-Hodgkin's lymphoma** 80 (0.117% annualized) vs. 80 (0.115% annualized); HR, 1.02 (95% CI, 0.74 to 1.39)
Women's Health Initiative, Estrogen plus progestin trial[96]	8,469 Estrogen and progestin 8,075 Placebo	**Intervention followup: Median 5.6 years** **Incidence of non-Hodgkin's lymphoma** HR, 0.81 (95% CI, 0.51 to 1.29) **Cumulative followup: Median 13.5 years** **Incidence of non-Hodgkin's lymphoma** 113 (0.099% annualized) vs. 110 (0.101% annualized); HR, 0.98 (95% CI, 0.76 to 1.28)

* Intervention dosages are listed in Table 3 by trial.

Abbreviations: CI=confidence interval; HR=hazard ratio; vs.=versus.

Appendix F Table 7. Outcomes From Trials Reporting Incidence of Ovarian Cancer

Study Author, Year	Population	Results (Treatment* vs. Placebo)
Black Women's Health Study Bethea, 2017[104]	2,477 Estrogen only 1,836 Estrogen plus progestin 4,689 Never used or used <1 year	**Followup: 18 years** 17 (0.7% calculated) vs. 14 (0.8% calculated) vs. 61 (1.3% calculated) Estrogen only: HR, 1.66 (95% CI, 0.90 to 3.07) Estrogen plus progestin: HR, 1.37 (95% CI, 0.73 to 2.55)
WHI Estrogen plus progestin trial Anderson, 2003;[126] Manson, 2013[67]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,060 Estrogen plus progestin 7,687 Placebo Postintervention extension followup:† 6,545 Estrogen plus progestin 6,243 Placebo	**Intervention followup: Median 5.6 years**[67] 24 (0.28%) vs.16 (0.20%); HR, 1.41 (95% CI, 0.75 to 2.66); p=0.28 *Subgroups:* No significant difference by age at randomization **Postintervention followup: Median 8.2 years**[67] HR, 1.12 (95% CI, 0.65 to 1.90); p=0.69 **Cumulative followup: Median 13.2 years**[67] HR, 1.24 (95% CI, 0.83 to 1.87); p=0.30 *Subgroups:* *Age (p=0.005 for trend)* 50–59 years: HR, 0.55 (95% CI, 0.24 to 1.25) 60–69 years: HR, 1.25 (95% CI, 0.72 to 2.18) 70–79 years: HR, 3.82 (95% CI, 1.27 to 11.52)

***** Intervention dosages are listed in Table 3 by trial.

† 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; HR=hazard ratio; vs.=versus; WHI=Women's Health Initiative.

Appendix F Table 8. Outcomes From Trials Reporting Incidence Total Cancer Mortality

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial Manson, 2013;[67] Manson, 2019;[89] Manson, 2017[88]	5,310 Estrogen 5,429 Placebo Postintervention followup: 5,009 Estrogen 5,130 Placebo Cumulative followup (intervention plus postintervention phases): 5,310 Estrogen 5,429 Placebo	**Intervention followup: Mean 7.2 years**[88] 126 (0.33% annualized) vs. 136 (0.34% annualized); HR, 0.96 (95% CI, 0.75 to 1.22); p=0.72 *Subgroups:* No significant difference by age group **Postintervention followup: Median 10.8 years**[88] 298 (0.61% annualized) vs. 303 (0.61% annualized); HR, 1.00 (95% CI, 0.85 to 1.17); p=1.00 *Subgroups:* No significant difference by age group **Cumulative followup: Median 13.0 years**[67] 260 (0.42% annualized) vs. 278 (0.44% annualized); HR, 0.95 (95% CI, 0.81 to 1.13); p=0.58 *Subgroups:* No significant difference by age **Cumulative followup: Median 17.7 years**[88] 424 (0.49% annualized) vs. 439 (0.49% annualized); HR, 0.99 (95% CI, 0.86 to 1.13); p=0.86 *Subgroups:* No significant difference by age group **Cumulative followup: Median 18.0 years**[89] *Subgroups:* No significant difference by oophorectomy status by age group

Appendix F Table 8. Outcomes From Trials Reporting Incidence Total Cancer Mortality

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Manson, 2013;[67] Manson, 2017[88]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention extension followup: 8,256 Estrogen plus progestin 7,864 Placebo Cumulative followup (intervention plus postintervention phases): 8,506 Estrogen plus progestin 8,102 Placebo	**Intervention followup: Median 5.6 years**[88] 133 (0.27% annualized) vs. 111 (0.24% annualized); HR, 1.10 (95% CI, 0.86 to 1.42); p=0.44 *Subgroups:* No significant difference by age group **Postintervention followup: Median 12.5 years**[88] 573 (0.62% annualized) vs. 527 (0.59% annualized); HR, 1.05 (95% CI, 0.93 to 1.18); p=0.43 *Subgroups:* No significant difference by age group **Cumulative followup: Median 13.2 years**[67] 428 (0.42% annualized) vs. 379 (0.39% annualized); HR, 1.07 (95% CI, 0.93 to 1.23); p=0.32 *Subgroups:* No significant difference by age **Cumulative followup: Median 17.7 years**[88] 706 (0.50% annualized) vs. 638 (0.47% annualized); HR, 1.06 (95% CI, 0.95 to 1.18); p=0.31 *Subgroups:* No significant difference by age group

* Intervention dosages are listed in Table 3 by trial.

Abbreviations: CI=confidence interval; HR=hazard ratio; NR=not reported; vs.=versus; WHI=Women's Health Initiative.

Appendix F Table 9. Outcomes From Trials Reporting COPD Mortality

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial Manson, 2017[88]	5,310 Estrogen 5,429 Placebo	**Intervention phase followup: Median 7.2 years** **COPD-specific mortality** 6 (0.016% annualized) vs. 8 (0.020% annualized); HR, 0.76 (95% CI, 0.26 to 2.20); p=0.62 *Subgroups:* No significant difference by age at randomization **Postintervention phase followup: Median 10.8 years** **COPD-specific mortality** 77 (0.16% annualized) vs. 71 (0.14% annualized); HR, 1.09 (95% CI, 0.79 to 1.51); p=0.60 *Subgroups:* *Age at randomization (p=0.002)* 50–59: 4 (0.024% annualized) vs. 16 (0.095% annualized); HR, 0.24 (95% CI, 0.08 to 0.73) 60–69: 35 (0.16% annualized) vs. 32 (0.14% annualized); HR, 1.12 (95% CI, 0.69 to 1.81) 70–79: 38 (0.39% annualized) vs. 23 (0.23% annualized); HR, 1.65 (95% CI, 0.98 to 2.77) **Cumulative followup: Median 17.7 years** **COPD-specific mortality** 83 (0.095% annualized) vs. 79 (0.088% annualized); HR, 1.07 (95% CI, 0.78 to 1.45); p=0.68 *Subgroups:* *Age at randomization (p=0.005)* 50–59: 6 (0.020% annualized) vs. 17 (0.057% annualized); HR, 0.35 (95% CI, 0.14 to 0.88) 60–69: 36 (0.092% annualized) vs. 36 (0.089% annualized); HR, 1.04 (95% CI, 0.65 to 1.64) 70–79: 41 (0.22% annualized) vs. 26 (0.14% annualized); HR, 1.59 (95% CI, 0.97 to 2.60)
WHI Estrogen plus progestin trial Manson, 2017[88]	8,506 Estrogen plus progestin 8,102 Placebo	**Intervention phase followup: Median 5.6 years** **COPD-specific mortality** 1 (0.002% annualized) vs. 8 (0.017% annualized); HR, 0.12 (95% CI, 0.01 to 0.93); p=0.01 **Postintervention phase followup: Median 12.5 years** **COPD-specific mortality** 107 (0.12% annualized) vs. 92 (0.10% annualized); HR, 1.13 (95% CI, 0.85 to 1.49); p=0.41 *Subgroups:* No difference by age at randomization **Cumulative followup: Median 17.7 years** **COPD-specific mortality** 108 (0.076% annualized) vs. 100 (0.074% annualized); HR, 1.03 (95% CI, 0.79 to 1.36); p=0.81 *Subgroups:* No difference by age at randomization

* Intervention dosages are listed in Table 3 by trial.

Abbreviations: CI=confidence interval; COPD=chronic obstructive pulmonary disease; HR=hazard ratio; vs.=versus; WHI=Women's Health Initiative.

Appendix F Table 10. Outcomes From Trials Reporting Incidence of Coronary Heart Disease

Study Author, Year	Population	Results (Treatment* vs. Placebo)
EMS Estrogen plus progestin trial Tierney, 2009[141]	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[112]	111 Estrogen 111 Placebo	**Followup: Mean 2 years** **Cardiovascular events** 3 (2.7%) vs. 4 (3.6%); p>0.2 Nonfatal or fatal myocardial infarction 1 (0.9%) vs. 2 (0.9%); p=NR
EPHT Estrogen plus progestin trial Veerus, 2006[137]	404 Estrogen plus progestin 373 Placebo Timing of intervention analysis: 251 total (analysis did not report by regimen)	**Followup: Mean 3.4 years** **CHD** 66 (16.3%) vs. 62 (16.6%); HR, 1.03 (95% CI, 0.73 to 1.46) *Risk based on timing of intervention:* No significant difference among women within 3 years of menopause Myocardial infarction only 2 (0.5%) vs. 0 (0%)
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[113]	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[107]	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[32]	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[106]	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%)

Appendix F Table 10. Outcomes From Trials Reporting Incidence of Coronary Heart Disease

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WAVE Estrogen-only and estrogen plus progestin trial Waters, 2002[105]	Women with a coronary stenosis of 15%–75% 124 Estrogen (with or without vitamin C and E) 86 Estrogen plus progestin (with or without vitamin C and E) 213 Placebo (with or without vitamin 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%)
WHI Estrogen-only trial Anderson, 2004;[37] Rossouw, 2007;[52] Hsia, 2006;[117] Prentice, 2009;[110] LaCroix, 2011;[108] Manson, 2013;[67] Manson, 2019;[89] Liu, 2020;[99] Chlebowski, 2017;[95] Prentice, 2020;[101] Manson, 2017[88]	5,310 Estrogen 5,429 Placebo Postintervention Followup: 3,778 Estrogen 3,867 Placebo	**Intervention followup: Mean 7.1 years/Median 7.2 years** **Overall CHD (nonfatal myocardial infarction or coronary death)**[117] 201 (annualized 0.53%) vs. 217 (annualized 0.56%); HR, 0.95 (95% CI, 0.79 to 1.16) *Subgroups:*[67, 117] No significant difference by race/ethnicity, age, years since bilateral oophorectomy, diabetes, hypertension, high cholesterol requiring medication, coronary risk factors, CVD at baseline, or CHD at baseline *Risk based on timing of intervention:*[67, 110] No significant difference by timing of intervention **CHD** ***Subgroups:*** No significant difference by race,[95] by oophorectomy status in the overall sample,[89] or within any age group at randomization.[89] Among those age <60 years at randomization, no significant difference among those having had oophorectomy regardless of whether it was performed at age <45 years or ≥45 years.[89] Among those age ≥60 years at randomization, no significant difference among those having had oophorectomy regardless of whether it was performed at age <45 years or ≥45 years[89] All cardiovascular events[67] 877 (2.51% annualized) vs. 813 (2.24%); HR, 1.11 (95% CI, 1.01 to 1.22); p=0.03 *Subgroups:* No significant difference by age group Myocardial infarction[67] 164 (0.44% annualized) vs. 173 (0.45); HR, 0.97 (95% CI, 0.79 to 1.21); p=0.81 *Subgroups:* *Age (p=0.02)* 50–59 years: 17 (0.14% annualized) vs. 31 (0.25%); HR, 0.55 (95% CI, 0.31 to 1.00) 60–69 years: 76 (0.46%) vs. 82 (0.48%); HR, 0.95 (95% CI, 0.69 to 1.30) 70–79 years: 71 (0.83%) vs. 60 (0.69%); HR, 1.24 (95% CI, 0.88 to 1.75)

Appendix F Table 10. Outcomes From Trials Reporting Incidence of Coronary Heart Disease

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial Anderson, 2004;[37] Rossouw, 2007;[52] Hsia, 2006;[117] Prentice, 2009;[110] LaCroix, 2011;[108] Manson, 2013;[67] Manson, 2019;[89] Liu, 2020;[99] Chlebowski, 2017;[95] Prentice, 2020;[101] Manson, 2017[88] (continued)		*Risk based on timing of intervention:* No significant difference by timing of intervention Total HF[99] 120 (2.30%) vs. 119 (2.22%); HR, 1.04 (95% CI, 0.81 to 1.34) *Subgroups:* No significant difference in total hospitalized HF by age at randomization Hospitalized HFrEF 38 (0.75%) vs. 43 (0.82%); HR, 0.91 (95% CI, 0.59 to 1.41) Hospitalized HFpEF 49 (0.96%) vs. 50 (0.95%); HR, 1.01 (95% CI, 0.68 to 1.50) CHD mortality[88] 66 (0.17%) vs. 67 (0.17%); HR, 1.02 (95% CI, 0.72 to 1.43); p=0.92 *Subgroups*: No significant difference by age group **Postintervention followup: Mean 3.9 years** Overall CHD (nonfatal myocardial infarction or coronary death)[108] HR, 0.97 (95% CI, 0.75 to 1.25) **Postintervention followup: Median 10.8 years**[88] CHD mortality 174 (0.36%) vs. 210 (0.42%); HR, 0.84 (95% CI, 0.69 to 1.03); p=0.09 *Subgroups*: No significant difference by age group **Cumulative followup: Median 13.0 years** **Overall CHD** (nonfatal myocardial infarction or coronary death)[67] 363 (0.60% annualized) vs. 393 (0.63% annualized); HR, 0.94 (95% CI, 0.82 to 1.09); p=0.43 *Subgroups:* No significant difference by race[95] or age[67] All cardiovascular events[67] 1,267 (2.30% annualized) vs. 1,227 (2.15%); HR, 1.06 (95% CI, 0.98 to 1.15); p=0.12 *Subgroups:* No significant difference by age group **Myocardial infarction**[67] 285 (0.47% annualized) vs. 288 (0.47%); HR, 1.01 (95% CI, 0.86 to 1.19); p=0.90 *Subgroups:* *Age (p=0.007)*[67] 50–59 years: 35 (0.17% annualized) vs. 58 (0.29%); HR, 0.60 (95% CI, 0.39 to 0.91) 60–69 years: 140 (0.52%) vs. 139 (0.49%); HR, 1.03 (95% CI, 0.82 to 1.31) 70–79 years: 110 (0.82%) vs. 91 (0.67%); HR, 1.25 (95% CI, 0.95 to 1.65)

Appendix F Table 10. Outcomes From Trials Reporting Incidence of Coronary Heart Disease

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial Anderson, 2004;[37] Rossouw, 2007;[52] Hsia, 2006;[117] Prentice, 2009;[110] LaCroix, 2011;[108] Manson, 2013;[67] Manson, 2019;[89] Liu, 2020;[99] Chlebowski, 2017;[95] Prentice, 2020;[101] Manson, 2017[88] (continued)		**Cumulative followup: Median 17.7 years** **CHD mortality**[88] 240 (0.28%) vs. 277 (0.31%); HR, 0.89 (95% CI, 0.75 to 1.05), p=0.17 *Subgroups*: No significant difference by age group **Cumulative followup: Median 18.0 years**[89] **CHD** *Subgroups:* No significant difference by oophorectomy status in the overall sample (p=0.31 for interaction) or within any age group at randomization (p values ranged from 0.44 to 0.55 for interaction trend). Among women age <60 years at randomization, no significant difference among those having had oophorectomy regardless of whether it was performed at age <45 years or ≥45 years (p=0.51 for trend). Among women age ≥60 years at randomization, no significant difference among those having had oophorectomy regardless of whether it was performed at age <45 years or ≥45 years (p=0.86 for trend). No significant difference by oophorectomy status, regardless of prior menopausal hormone therapy use (p values ranged from 0.60 to 0.72 for interaction) Myocardial infarction *Subgroups:* No significant difference by oophorectomy status within any age group at randomization (p ranged from 0.053 to 0.27 for interaction trend) **Total CVD mortality** *Subgroups:* No significant difference by oophorectomy status within any age group at randomization **Cumulative followup: Median 18.9 years**[99] **Total HF** 359 (6.9%) vs. 353 (6.6%); HR, 1.04 (95% CI, 0.90 to 1.20) *Subgroups:* No significant difference in by age at randomization **Hospitalized HFrEF** 108 (2.2%) vs. 127 (2.5%); HR, 0.87 (95% CI, 0.67 to 1.13) *Subgroups:* No significant difference in by age at randomization **Hospitalized HFpEF** 168 (3.3%) vs. 151 (2.9%); HR, 1.13 (95% CI, 0.91 to 1.41) *Subgroups:* No significant difference by age at randomization **Cumulative followup: Median 19.4 years**[101] **Overall CHD (nonfatal myocardial infarction or coronary death)** 521 (9.8% calculated) vs. 550 (10.1%); HR, 0.97 (95% CI, 0.86 to 1.09); p=NR

Appendix F Table 10. Outcomes From Trials Reporting Incidence of Coronary Heart Disease

WHI Estrogen plus progestin trial Writing Group for the WHI, 2002;[36] Manson, 2003;[174] Rossouw, 2007;[52] Heiss, 2008;[132] Prentice, 2009;[110] Manson, 2013;[67] Liu, 2020;[99] Prentice, 2020;[101] Manson, 2017[88]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,052 Estrogen plus progestin 7,678 Placebo	**Intervention followup: Mean 5.2 years/Median 5.6 years** **Overall CHD (nonfatal myocardial infarction or coronary death)**[67] 196 (0.41% annualized) vs. 159 (0.35% annualized); HR, 1.18 (95% CI, 0.95 to 1.45) *Subgroups*: No significant difference by age group[67, 174] *Risk based on timing of intervention:* No significant difference by timing of intervention[67, 110, 174] **All cardiovascular events**[67] 786 (1.7% annualized) vs. 663 (1.52%); HR, 1.13 (95% CI, 1.02 to 1.25); p=0.02 *Subgroups:* No significant difference by age **Myocardial infarction**[67] 168 (0.35% annualized) vs. 129 (0.29%); HR, 1.24 (95% CI, 0.98 to 1.56); p=0.07 *Subgroups*: No significant difference by age group *Risk for based on timing of intervention (p=0.01 for trend):* <10 years after menopause: HR, 0.91 (95% CI and p=NR) 10 to <20 years after menopause: HR, 1.16 (95% CI and p=NR) ≥20 years after menopause: HR, 1.99 (95% CI and p=NR) **Total HF**[99] 89 (1.05%) vs. 82 (1.02%); HR, 1.01 (95% CI, 0.75 to 1.37) *Subgroups:* No significant difference by age at randomization **Hospitalized HFrEF**[99] 32 (0.38%) vs. 28 (0.35%); HR, 1.06 (95% CI, 0.64 to 1.76) Hospitalized HFpEF[99] 31 (0.37%) vs. 31 (0.39%); HR, 0.93 (95% CI, 0.57 to 1.53) **CHD mortality**[88] 40 (0.082% annualized) vs. 40 (0.087%); HR, 0.94 (95% CI, 0.60 to 1.45); p=0.77 *Subgroups*: No significant difference by age group **Postintervention followup: Mean 2.4 years**[132] **Overall CHD** HR, 1.04 (95% CI, 0.89 to 1.21) **Postintervention followup: Median 12.5 years** **CHD mortality**[88] 270 (0.29%) vs. 245 (0.28%); HR, 1.08 (95% CI, 0.91 to 1.28); p=0.39 *Subgroups*: No significant difference by age group

Appendix F Table 10. Outcomes From Trials Reporting Incidence of Coronary Heart Disease

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Writing Group for the WHI, 2002;[36] Manson, 2003;[174] Rossouw, 2007;[52] Heiss, 2008;[132] Prentice, 2009;[110] Manson, 2013;[67] Liu, 2020;[99] Prentice, 2020;[101] Manson, 2017[88] (continued)		**Cumulative followup: Median 13.0 years**[67] **Overall CHD (nonfatal myocardial infarction or coronary death)** 487 (0.48% annualized) vs. 430 (0.45%); HR, 1.09 (95% CI, 0.96 to 1.24); p=0.19 *Subgroups:* No significant difference by age group **All cardiovascular events**[67] 1,606 (1.7% annualized) vs. 1,446 (1.6% annualized); HR, 1.08 (95% CI, 1.00 to 1.15); p=0.05 *Subgroups:* No significant difference by age **Myocardial infarction** 389 (0.39% annualized) vs. 324 (0.34%); HR, 1.15 (95% CI, 0.99 to 1.34); p=0.06 *Subgroups:* No significant difference by age group **Cumulative followup: Median 17.7 years** **CHD mortality**[88] 310 (0.22%) vs. 285 (0.21%); HR, 1.05 (95% CI, 0.89 to 1.23); p=0.57 *Subgroups*: No significant difference by age group **Cumulative followup: Median 18.9 years**[99] **Total HF** 433 (5.1%) vs. 418 (5.2%); HR, 0.98 (95% CI, 0.86 to 1.13) *Subgroups:* No significant difference by age at randomization **Hospitalized HFrEF** 139 (1.7%) vs. 143 (1.8%); HR, 0.93 (95% CI, 0.73 to 1.17) *Subgroups:* No significant difference by age at randomization **Hospitalized HFpEF** 205 (2.5%) vs. 196 (2.5%); HR, 0.99 (95% CI, 0.82 to 1.21) *Subgroups:* No significant difference by age at randomization **Cumulative followup: Median 19.4 years**[101] **Overall CHD (nonfatal myocardial infarction or coronary death)** 710 (8.3% calculated) vs. 652 (8.0%); HR, 1.05 (95% CI, 0.95 to 1.17); p=NR

Appendix F Table 10. Outcomes From Trials Reporting Incidence of Coronary Heart Disease

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WISDOM Estrogen plus progestin trial Vickers, 2007[138]	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

* Intervention dosages are listed in Table 3 by trial.

Abbreviations: CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; EMS=Estrogen Memory Study; EPAT=Estrogen in the Prevention of Atherosclerosis Trial; EPHT=Estonian Postmenopausal Hormone Therapy Trial; ERA=Estrogen Replacement and Atherosclerosis; HF=heart failure; HFpEF=HF with preserved ejection fraction; HFrEF=HF with reduced ejection fraction; HR=hazard ratio; NR=not reported; PEPI=Postmenopausal Estrogen/Progestin Interventions Trial; 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; WISDOM=Women's International Study of Long Duration Oestrogen After Menopause.

Appendix F Table 11. Outcomes From Trials Reporting Incidence of Peripheral Arterial Disease

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial Hsia, 2006[79]	5,310 Estrogen 5,429 Placebo	**Followup: Mean 7.1 years** **Peripheral arterial disease** 82 vs. 62; HR, 1.35 (95% CI, 0.97 to 1.88) *Subgroups:* No significant difference by age, ethnicity, diabetes, or body mass index
WHI Estrogen plus progestin trial Hsia, 2004[80]	58,506 Estrogen plus progestin 8,102 Placebo	**Followup: Mean 5.6 years** **Peripheral arterial disease** 48 vs. 50; HR, 0.89 (95% CI, 0.60 to 1.32); p=0.57 *Subgroups:* No significant difference by age, ethnicity, diabetes, or body mass index

* Intervention dosages are listed in Table 3 by trial.

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

Appendix F Table 12. Outcomes From Trials Reporting Incidence of Dementia

Study Author, Year	Population	Results (Treatment* vs. Placebo)		
		Probable Dementia Incidence	MCI Incidence	Other Dementia Diagnosis Outcomes
WHIMS Estrogen-only trial Shumaker, 2004[119]	Women without probable dementia Dementia outcomes, WHI:[119] 1,464 Estrogen 1,483 Placebo	**Intervention followup: 5.2 years**[119] **Probable dementia** 28 (1.9%) vs. 19 (1.3%); cumulative HR, 1.49 (95% CI, 0.83 to 2.66); p=0.18 ***Subgroups:***[119] No difference in the hazard rate for probable dementia by race or history of cardiovascular disease, diabetes, hypertension, or stroke.	**Intervention followup: 5.2 years**[119] 76 (5.2%) vs. 58 (3.9%); cumulative HR, 1.34 (95% CI, 0.95 to 1.89); p=NS	**Intervention followup: 5.2 years**[119] **Probable dementia or MCI** 93 (6.4%) vs. 69 (4.7%); cumulative HR, 1.38 (95% CI, 1.01 to 1.89); p=0.04
WHIMS Estrogen plus progestin trial Shumaker, 2003;[143] Shumaker, 2004[119]	Women without probable dementia Dementia and cognitive impairment outcomes:[143] 2,229 Estrogen plus progestin 2,303 Placebo	**Intervention followup: ~4 years**[143] **Probable dementia** 40 (1.8%) vs. 21 (0.9%); cumulative HR, 2.05 (95% CI, 1.21 to 3.48); p=0.01 ***Subgroups:***[143] No difference in the hazard rate for probable dementia by race or history of cardiovascular disease, diabetes, hypertension, or stroke.	**Intervention followup: ~4 years**[143] 56 (2.5%) vs. 55 (2.4%); cumulative HR, 1.07 (95% CI, 0.74 to 1.55); p=0.72	**Intervention followup: ~4 years**[143] **Probable dementia or MCI** 85 (3.8%) vs. 66 (2.9%); cumulative HR, 1.37 (95% CI, 0.99 to 1.89)
WHISCA Estrogen-only trial Resnick, 2009[120]	Dementia outcomes, WHISCA:[120] 434 Estrogen 452 Placebo	**Intervention followup: 2.7 years** (during WHISCA, after being enrolled in WHI for 3 years)[120] **Probable dementia** 4 (0.9%) vs. 2 (0.4%); calculated RR, 2.08 (95% CI, 0.38 to 11.31); p=0.40	**Intervention followup: 2.7 years** (during WHISCA, after being enrolled in WHI for 3 years)[120] 18 (4.1%) vs. 15 (3.3%); calculated RR, 1.25 (95% CI, 0.64 to 2.45); p=0.52	NR
WHISCA Estrogen plus progestin trial Resnick, 2006[144]	Probable dementia or cognitive impairment, WHIMS:[144] 690 Estrogen plus progestin 726 Placebo	**Intervention followup: 1.4 years** (during WHISCA, after being enrolled in WHI for 3 years)[144] **Probable dementia** 5 (0.7%) vs. 6 (0.8%); calculated RR, 0.88 (95% CI, 0.27 to 2.86); p=0.83	**Intervention followup: 1.4 years** (during WHISCA, after being enrolled in WHI for 3 years)[144] 6 (0.9%) vs. 13 (1.8%); calculated RR, 0.49 (95% CI, 0.19 to 1.27); p=0.14	NR

Appendix F Table 12. Outcomes From Trials Reporting Incidence of Dementia

Study Author, Year	Population	Results (Treatment* vs. Placebo)		
		Probable Dementia Incidence	MCI Incidence	Other Dementia Diagnosis Outcomes
WHI Estrogen-only trial Manson, 2017[88]	5,310 Estrogen 5,429 Placebo	**Intervention followup: Median 7.2 years** **Alzheimer's disease or other dementia mortality** 5 (0.013% annualized) vs. 6 (0.015%); HR, 0.90 (95% CI, 0.27 to 2.95); p=0.86 **Postintervention followup: Median 10.8 years** **Alzheimer's disease or other dementia mortality** 122 (0.25% annualized) vs. 169 (0.34%); HR, 0.73 (95% CI, 0.58 to 0.92); p=0.008 ***Subgroups***: No difference by age at randomization. **Cumulative followup: Median 17.7 years** **Alzheimer's disease or other dementia mortality** 127 (0.15% annualized) vs. 175 (0.20%); HR, 0.74 (95% CI, 0.59 to 0.94); p=0.01 ***Subgroups***: No difference by age at randomization.	NR	NR
WHI Estrogen plus progestin trial Manson, 2017[88]	8,506 Estrogen plus progestin 8,102 Placebo	**Intervention followup: Median 5.6 years** **Alzheimer's disease or other dementia mortality** 0 (0% annualized) vs. 0 (0%); HR not estimatable **Postintervention followup: Median 12.5 years** **Alzheimer's disease or other dementia mortality** 223 (0.24% annualized) vs. 233 (0.26%); HR, 0.94 (95% CI, 0.78 to 1.13); p=0.52 ***Subgroups***: No difference by age at randomization. **Cumulative followup: Median 17.7 years** **Alzheimer's disease or other dementia mortality** 223 (0.16% annualized) vs. 233 (0.17%); HR, 0.93 (95% CI, 0.77 to 1.11); p=0.42 ***Subgroups:*** No difference by age at randomization.	NR	NR

* Intervention dosages are listed in Table 3 by trial.

Abbreviations: CI=confidence interval; HR=hazard ratio; MCI=mild cognitive impairment; NR=not reported; NS=not significant; RR=relative risk; vs.=versus; WHI=Women's Health Initiative; WHIMS=Women's Health Initiative Memory Study; WHISCA=Women's Health Initiative Study of Cognitive Aging.

Appendix F Table 13. Outcomes From Trials Reporting Incidence of Cognitive Function Scores

Study Author, Year	Population	Results (Treatment* vs. Placebo)	
		Global Cognitive Function (3MS Scores or TICS-m Scores)	Other Cognitive Measures
ELITE-Cog Henderson, 2016[92]	323 Estrogen 320 Placebo	NR	**Followup: Mean 4.8 years** **Change in verbal episodic memory** 0.33 (SE, 0.06) vs. 0.40 (SE, 0.07); difference, -0.07 (95% CI, -0.25 to 0.10); p=0.25 ***Subgroups:*** No difference for women with surgical vs. natural menopause. ***Risk based on timing of intervention:*** No difference by timing of intervention.† **Change in executive functions** -0.08 (SE, 0.04) vs. -0.05 (SE, 0.05); difference, -0.03 (95% CI, -0.15 to 0.10); p=0.085 ***Subgroups:*** No difference for women with surgical vs. natural menopause. ***Risk based on timing of intervention:*** No difference by timing of intervention. **Change in global cognition** 0.36 (SE, 0.06) vs. 0.39 (SE, 0.07); difference, -0.03 (95% CI, -0.21 to 0.15); p=0.75 ***Subgroups:*** No difference for women with surgical vs. natural menopause. ***Risk based on timing of intervention:*** No difference by timing of intervention. **Neuropsychological test scores** No significant treatment effect.
EMS Estrogen plus progestin trial Tierney, 2009[141]	Women with normal to just below normal scores on cognitive battery tests, but free of dementia: 70 Estrogen plus progestin 72 Placebo	NR	**Followup: 1 year** **CVLT short-delay verbal recall** No significant differences by group. **Followup: 2 years** **CVLT short-delay verbal recall** No significant differences by group.

Appendix F Table 13. Outcomes From Trials Reporting Incidence of Cognitive Function Scores

Study Author, Year	Population	Results (Treatment* vs. Placebo)	
		Global Cognitive Function (3MS Scores or TICS-m Scores)	Other Cognitive Measures
HERS Estrogen plus progestin trial Grady, 2002[145]	662 Estrogen plus progestin 666 Placebo	**Followup: 4.2 years** **3MS** 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** 15.9 (SD, 4.8) vs. 16.6 (SD, 4.8); difference, -0.7 (95% CI, -1.3 to -0.1); p=0.02 **Boston Naming Test** No significant differences by group. **Word List Memory** No significant differences by group. **Word List Recall** No significant differences by group. **Trials B** No significant differences by group.
KEEPS-Cog Estrogen plus progestin trial Gleason, 2015[146]	220 Estrogen (oral) plus progesterone 211 Estrogen (transdermal) plus progesteroone 262 Placebo	**Followup: 4 years** **3MS** Oral estrogen: Beta estimate, 1.02 x 10^{-2} (95% CI, -4.45 x 10^{-3} to 2.48 x 10^{-2}); p=0.178 Transdermal estrogen: Beta estimate, -9.40 x 10^{-4} (95% CI, -1.57 x 10^{-2} to 1.38 x 10^{-2}); p=0.840	NR
KEEPS-MRI Kantarci, 2016[100]	31 Estrogen (oral) plus progesterone 31 Estrogen (transdermal) plus progesterone 39 Placebo	**Followup: 4 years** **3MS** No significant differences in changes in global cognitive function.‡	NR

Appendix F Table 13. Outcomes From Trials Reporting Incidence of Cognitive Function Scores

Study Author, Year	Population	Results (Treatment* vs. Placebo)	
		Global Cognitive Function (3MS Scores or TICS-m Scores)	Other Cognitive Measures
ULTRA Estrogen-only trial Yaffe, 2006[124]	417 Enrolled 208 Estrogen 209 Placebo	**Followup: 2 years** **Baseline 3MS ≤90** 5.90 vs. 7.10; difference, -1.21 (95% CI, -5.05 to 2.64); p=0.53 **Baseline 3MS >90** 0.57 vs. 0.87; difference, -0.30 (95% CI, -0.74 to 0.14); p=0.18	**Followup: 2 years** **Logical Memory** No significant differences by group. **Brief Visuospatial Memory Test** No significant differences by group. **Word List** No significant differences by group. **Trials B** No significant differences by group. **Modified Boston Naming Test** No significant differences by group. **Verbal Fluency** No significant differences by group.
WHIMS-ECHO Espeland, 2017[93]	1,402 Hormone therapy 1,478 Placebo	**Postintervention followup: 6.4 years** *Analysis did not stratify by treatment regimen* **Global cognitive function** TICS-m: 33.93 (SE, 0.11) vs. 34.30 (SE, 0.11); difference, -0.37 (SE, 0.15); p=0.01	**Postintervention followup: 6.4 years** *Analysis did not stratify by treatment regimen* **Executive function** OTMT-B: 57.49 (SE, 0.69) vs. 55.24 (SE, 0.67); difference, 2.25 (SE, 0.96); p=0.02 **DST forward for working memory** 7.44 (SE, 0.05) vs. 7.61 (SE, 0.04); difference -0.17 (SE, 0.06); p=0.008 **DST backward for working memory** No significant differences by group. **Verbal Fluency** No significant differences by group. **Verbal Memory** No significant differences by group. **Attention** No significant differences by group. ***Subgroups:*** No difference by CEE-alone and CEE + MPA therapy, for diabetes.

Appendix F Table 13. Outcomes From Trials Reporting Incidence of Cognitive Function Scores

Study Author, Year	Population	Results (Treatment* vs. Placebo)	
		Global Cognitive Function (3MS Scores or TICS-m Scores)	Other Cognitive Measures
WHIMS Estrogen-only trial Espeland, 2004[121]	Women without probable dementia General cognitive function, enrolled in WHIMS >6 months after initiation of assigned WHI therapy and with >1 postrandom-ization 3MS score:[121] 1,387 Estrogen 1,421 Placebo Subgroup analysis: 1,464 Estrogen 1,483 Placebo	**Followup: Mean 5.4 years** **3MS** Mean difference in change from baseline, -0.26 (95% CI, -0.52 to 0.00); p=0.04	NR
WHIMS Estrogen plus progestin trial Rapp, 2003;[147] Espeland, 2004[121]	Women without probable dementia Cognitive function outcomes:[121] 2,131 Estrogen plus progestin 2,213 Placebo	**Followup: 5.4 years**[121] **3MS** Mean difference in change from baseline, -0.18 (95% CI, -0.37 to 0.00); p=0.055 ***Subgroups:***[147] No difference in the rate of change by race, length of use, or history of cardiovascular disease, diabetes, or hypertension. ***Risk based on timing of intervention:***[147] No difference in the rate of change by time to initiation of therapy after last menstrual period.	NR

Appendix F Table 13. Outcomes From Trials Reporting Incidence of Cognitive Function Scores

Study Author, Year	Population	Results (Treatment* vs. Placebo)	
		Global Cognitive Function (3MS Scores or TICS-m Scores)	Other Cognitive Measures
WHIMSY Estrogen-only trial Espeland, 2013;[123] Espeland, 2017[93]	696 Hormone therapy[§] 630 Placebo	**Postintervention followup: 7.2 years** **TICS-m** 37.67 (SE, 0.26) vs. 37.28 (SE, 0.27); p=NR	**Postintervention followup: 7.2 years** **Verbal Fluency** No significant differences by group. **Verbal Memory** No significant differences by group. **Attention** No significant differences by group. **Executive function** No significant differences by group. **Working Memory** No significant differences by group. **East Boston Memory Test** No significant differences by group. **Composite cognitive function** No significant differences by group.
WHIMSY Estrogen plus progestin trial Espeland, 2013;[123] Espeland, 2017[93]	696 Hormone therapy[§] 630 Placebo[‖]	**Postintervention followup: 7.2 years** **TICS-m:** 38.08 (SE, 0.20) vs. 38.26 (SE, 0.21); p=NR	**Postintervention followup: 7.2 years** **Verbal Fluency** No significant differences by group. **Verbal Memory** No significant differences by group. **Attention** No significant differences by group. **Executive function** No significant differences by group. **Working Memory** No significant differences by group. **East Boston Memory Test** No significant differences by group. **Composite cognitive function** No significant differences by group.

Appendix F Table 13. Outcomes From Trials Reporting Incidence of Cognitive Function Scores

Study Author, Year	Population	Results (Treatment* vs. Placebo)	
		Global Cognitive Function (3MS Scores or TICS-m Scores)	Other Cognitive Measures
WHISCA Estrogen-only trial Espeland, 2010[122]	Cognitive measures, WHISCA extension:[122] 601 Hormone therapy 612 Placebo	**Followup: 3.6 years** (during WHISCA, after being enrolled in WHI for 3 years)[122] **Mean decrement in global cognitive function, 3MS** -0.092 (SE, 0.039); p=0.02 **Postintervention followup: Mean 2.4 years** (after being enrolled in WHI for 3 years and WHISCA for 3.6 years)[122] **Mean decrement in global cognitive function, 3MS** -0.081 (SE, 0.047); p=0.09	**Followup: Mean 3.6 years**[122] **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** No significant differences by group. **Attention** No significant differences by group. **Working Memory** No significant differences by group. **Postintervention followup: 2.4 years**[122] **Spatial ability** -0.179 (SE, 0.063); p=0.004 **Verbal Knowledge** No significant differences by group. **Verbal Fluency** No significant differences by group. **Verbal Memory** No significant differences by group. **Figural Memory** No significant differences by group. **Attention** No significant differences by group. **Working Memory** No significant differences by group.

Appendix F Table 13. Outcomes From Trials Reporting Incidence of Cognitive Function Scores

Study Author, Year	Population	Results (Treatment* vs. Placebo)	
		Global Cognitive Function (3MS Scores or TICS-m Scores)	Other Cognitive Measures
WHISCA Estrogen plus progestin trial Espeland, 2010[122]	Cognitive measures, WHISCA extension[122] 601 Hormone therapy 612 Placebo	**Followup: Mean 2 years** (during WHISCA, after being enrolled in WHI for 3 years)[122] **Mean decrement in global cognitive function, 3MS** -0.080 (SE, 0.034); p=0.02 **Postintervention followup: Mean 4 years** (after being enrolled in WHI for 3 years and in WHISCA for 2 years)[122] **Mean decrement in global cognitive function, 3MS** -0.059 (SE, 0.032); p=0.06	**Followup: Mean 3 years** (pre-WHISCA, 2 years during WHISCA trial)[122] **Spatial Ability** No significant differences by group. **Verbal Knowledge** No significant differences by group. **Verbal Fluency** No significant differences by group. **Verbal Memory** No significant differences by group. **Figural Memory** No significant differences by group. **Attention** No significant differences by group. **Working Memory** No significant differences by group. **Postintervention followup: Mean 4 years**[122] **Spatial Ability** No significant differences by group. **Verbal Knowledge** No significant differences by group. **Verbal Fluency** No significant differences by group. **Verbal Memory** No significant differences by group. **Figural Memory** No significant differences by group. **Attention** No significant differences by group. **Working Memory** No significant differences by group.

* Intervention dosages are listed in Table 3 by trial.
† In the ELITE study, early-group women were within 6 years of a final menstrual period or surgical menopause. In the late group, women were at least 10 years beyond natural or surgical menopause.
ǂ Authors did not report absolute values of 3MS by group, visual display only.
§ CEE and CEE+MPA group numbers not reported.
ǀ N reported from Espeland.[123] Subsequent study[93] reports: 701 HT and 635 placebo. Unclear reason for discrepancy.

Abbreviations: 3MS=Modified Mini-Mental State Examination; CEE=conjugated equine estrogen; CI=confidence interval; DST=Digit Span Test; ELITE=Early versus Late Intervention Trial with Estradiol; EMS=Estrogen Memory Study; HERS=Heart and Estrogen/Progestin Replacement Study; HT=hormone therapy; KEEPS=Kronos Early Estrogen Prevention Study; KEEPS-MRI=Kronos Early Estrogen Prevention Study-MRI; MPA=medroxyprogesterone acetate; NR=not reported; OTMT-B=Oral Trail Making Test Part B;

Appendix F Table 13. Outcomes From Trials Reporting Incidence of Cognitive Function Scores

SD=standard deviation; SE=standard error; TICS=Telephone Interview for Cognitive Status; ULTRA=Ultra-Low-Dose Transdermal Estrogen Replacement Assessment; vs.=versus; WHI=Women's Health Initiative; WHIMS=Women's Health Initiative Memory Study; WHIMS-ECHO=Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes; WHIMSY=Women's Health Initiative Memory Study of Younger Women; WHISCA=Women's Health Initiative Study of Cognitive Aging.

Appendix F Table 14. Outcomes From Trials Reporting Incidence of Diabetes

Study Author, Year	Population	Results (Treatment* vs. Placebo)
Greenspan et al Estrogen-only and estrogen plus progestin trial Greenspan, 2005[107]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Intervention 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[148]	Women without self-reported diabetes at baseline 999 Estrogen plus progestin 1,030 Placebo	**Intervention followup: Mean 4.1 years** **Overall** 62 (6.2%) vs. 98 (9.5%); HR, 0.65 (95% CI, 0.48 to 0.89); p=0.006
WHI Estrogen-only trial Bonds, 2006;[125] Manson, 2013;[67] Prentice, 2020[101]	Women not receiving treatment for diabetes at baseline 4,900 Estrogen 5,017 Placebo	**Intervention followup: Mean 7.1/median 7.2 years** **Self-reported treated diabetes**[67] 449 (1.34% annualized) vs. 527 (1.55% annualized); HR, 0.86 (95% CI, 0.76 to 0.98); p=0.02 *Subgroups:*[125] No significant difference by race/ethnicity, age at screening, hypertension, or metabolic syndrome at baseline. **Postintervention followup: Median 6.6 years**[67] **Self-reported treated diabetes** 323 (1.64% annualized) vs. 306 (1.54% annualized); HR, 1.07 (95% CI, 0.92 to 1.25); p=0.39 **Cumulative followup: Median 13.0 years**[67] **Self-reported treated diabetes** 772 (1.45% annualized) vs. 833 (1.55% annualized); HR, 0.94 (95% CI, 0.85 to 1.04); p=0.22
WHI Estrogen plus progestin trial Margolis, 2004;[149] Manson, 2013;[67] Prentice, 2020[101]	Women not receiving treatment for diabetes at baseline 8,132 Estrogen plus progestin 7,742 Placebo	**Intervention followup: Mean 5.6 years** **Self-reported treated diabetes**[67] 328 (0.72% annualized) vs. 373 (0.88% annualized); HR, 0.81 (95% CI, 0.70 to 0.94); p=0.005 Subgroups:[149] No significant difference by race/ethnicity, age at screening, or hypertension at baseline. **Postintervention followup: Median 8.2 years**[67] **Self-reported treated diabetes** 603 (1.24% annualized) vs. 482 (1.04% annualized); HR, 1.19 (95% CI, 1.05 to 1.34); p=0.005 **Cumulative followup: Median 13.2 years**[67] **Self-reported treated diabetes** 931 (0.99% annualized) vs. 855 (0.96% annualized); HR, 1.02 (95% CI, 0.93 to 1.12); p=0.66

* Intervention dosages are listed in Table 3 by trial.

Abbreviations: CI=confidence interval; HERS=Heart and Estrogen/Progestin Replacement Study; HR=hazard ratio; vs.=versus; WHI=Women's Health Initiative.

Appendix F Table 15. Outcomes From Trials Reporting Incidence of Fractures

Study Author, Year	Population	Results (Treatment* vs. Placebo)
EMS Estrogen plus progestin trial Tierney, 2009[141]	70 Estrogen plus progestin 72 Placebo	**Intervention followup: 2 years** **Total** 3 (4.3%) vs. 7 (9.7%); p=NR **Hip** 0 (0.0%) vs. 1 (1.4%); p=NR
EPHT Estrogen plus progestin trial Veerus, 2006[137]	404 Estrogen plus progestin 373 Placebo Timing of intervention analysis: 251 total (analysis did not report by regimen)	**Intervention followup: 5 years** **Bone fractures†** 15 (3.7%) vs. 25 (6.7%); HR, 0.52 (95% CI, 0.27 to 0.98); p=NR *Risk based on timing of intervention:* No significant difference among women within 3 years of menopause.
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[113]	100 Estrogen 104 Estrogen plus progestin 105 Placebo	**Intervention followup: Mean 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[136]	1,380 Estrogen plus progestin 1,383 Placebo	**Intervention followup: Mean 4.1 years** **Any** 140 vs. 148; HR, 0.96 (95% CI, 0.76 to 1.20); p=0.70 **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 (i.e., not hip, wrist, or vertebral) 91 vs. 101; HR, 0.91 (95% CI, 0.69 to 1.21); p=0.52
STOP-IT Estrogen plus progestin trial Gallagher 2001[106]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Intervention followup: 3 years** **Vertebral** *Analysis did not stratify by regimen.* 2 (hormone therapy with or without calcitriol) vs. 1 (calcitriol only or placebo)

Appendix F Table 15. Outcomes From Trials Reporting Incidence of Fractures

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial LaCroix, 2011;[108] Anderson, 2004;[126] Manson, 2013;[67] Manson, 2019;[89] Watts, 2017;[97] Prentice, 2020;[101] Chlebowski, 2017;[95] Prentice, 2020[91]	5,310 Estrogen 5,429 Placebo Postintervention followup:[108] 3,778 Estrogen 3,867 Placebo Postintervention followup:[89] 2,521 Estrogen 2,532 Placebo	**Intervention followup: Median 7.2 years** **Total**[67] 544 (1.53% annualized) vs. 767 (2.14% annualized); HR, 0.72 (95% CI, 0.64 to 0.80); p<0.001 *Subgroups:* No significant difference by age.[67] **Hip**[67, 108] 48 (0.13% annualized) vs. 74 (0.19% annualized); HR, 0.67 (95% CI, 0.46 to 0.96); p=0.03 *Subgroups:* No significant difference by age or race.[67, 95, 126] *Risk based on timing of intervention (p=0.03):*[67] <10 years since menopause: 5 (0.08% annualized) vs. 1 (0.02% annualized); HR, 4.83 (95% CI, 0.56 to 41.41) 10–19 years since menopause: 9 (0.09% annualized) vs. 10 (0.09% annualized); HR, 0.97 (95% CI, 0.39 to 2.39) ≥20 years since menopause: 26 (0.17% annualized) vs. 49 (0.31% annualized); HR, 0.56 (95% CI, 0.35 to 0.90) **Vertebral**[67] 44 (0.12% annualized) vs. 70 (0.18% annualized); HR, 0.64 (95% CI, 0.44 to 0.93); p=0.02 *Subgroups:* No significant difference by age.[67, 126] **Postintervention followup: Mean 3.9 years**[108] **Hip** 66 (0.36% annualized) vs. 53 (0.28% annualized); HR, 1.27 (95% CI, 0.88 to 1.82); p=NR **Postintervention followup: Calculated mean 4.3 years**[97] **Total** 321 (3.11% annualized) vs. 378 (3.69% annualized); HR, 0.85 (95% CI, 0.73 to 0.98); p=0.03 *Subgroups:* No significant difference by age. **Hip** 30 (0.28% annualized) vs. 29 (0.27% annualized); HR, 1.04 (95% CI, 0.62 to 1.73); p=0.89 *Subgroups:* No significant difference by age.

Appendix F Table 15. Outcomes From Trials Reporting Incidence of Fractures

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial LaCroix, 2011;[108] Anderson, 2004;[126] Manson, 2013;[67] Manson, 2019;[89] Watts, 2017;[97] Prentice, 2020;[101] Chlebowski, 2017;[95] Prentice, 2020[91] (continued)		**Cumulative followup: Mean 10.7 years**[108] **Hip** 114 (0.20% annualized) vs. 127 (0.22% annualized); HR, 0.92 (95% CI, 0.71 to 1.18); p=NR *Subgroups:* No significant difference by age. **Cumulative followup: Median 13.0 years** **Hip** 134 (0.22% annualized) vs. 148 (0.24% annualized; HR, 0.91 (95% CI, 0.72 to 1.15); p=0.44[67] *Subgroups:* No significant difference by race.[95] **Cumulative followup: Median 18.0 years** **Hip** *Subgroups:* No significant difference by age or oophorectomy status within any age group at randomization.[89, 91] **Cumulative followup: Median 19.4 years**[101] **Hip** 208 (3.9% calculated) vs. 229 (4.2% calculated); HR, 0.92 (95% CI, 0.76 to 1.11); p=NR

Appendix F Table 15. Outcomes From Trials Reporting Incidence of Fractures

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Heiss, 2008;[132] Cauley, 2003;[150] Rossouw, 2002;[36] Manson, 2013;[67] Watts, 2017;[97] Prentice, 2020;[101] Prentice, 2020[91]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,052 Estrogen plus progestin 7,678 Placebo	**Intervention followup: Mean 5.6 years** **Total**[67] 741 (1.61% annualized) vs. 903 (2.12% annualized); HR, 0.76 (95% CI, 0.69 to 0.83); p<0.001 *Subgroups* No significant difference by age. **Hip**[67] 53 (0.11% annualized) vs. 75 (0.17% annualized); HR, 0.67 (95% CI, 0.47 to 0.96); p=0.03 *Subgroups* No significant difference by age. *Risk based on timing of intervention:* No significant difference by timing of intervention. **Vertebral**[67] 56 (0.12% annualized) vs. 78 (0.17% annualized); HR, 0.68 (95% CI, 0.48 to 0.96); p=0.03 *Subgroups* No significant difference by age. **Other osteoporotic fractures**[132] 650 (1.41% annualized) vs. 800 (1.87% annualized); HR, 0.75 (95% CI, 0.68 to 0.83); p=NR **Postintervention followup: Mean 2.4 years** **Total (hip, vertebral, or other osteoporotic fractures)**[132] 337 (1.95% annualized) vs. 346 (2.16% annualized); HR, 0.91 (95% CI, 0.78 to 1.06); p=0.06 **Hip** 54 (0.28% annualized) vs. 57 (0.31% annualized); HR, 0.92 (95% CI, 0.64 to 1.34); p=0.20[132] *Risk based on timing of intervention:* No significant difference by years since menopause.[67] **Vertebral**[132] 46 (0.24% annualized) vs. 47 (0.26% annualized); HR, 0.96 (95% CI, 0.64 to 1.44); p=0.23 **Other osteoporotic fractures**[132] 267 (1.52% annualized) vs. 285 (1.75% annualized); HR, 0.87 (95% CI, 0.74 to 1.03); p=0.16 **Postintervention followup: Calculated mean 4.2 years**[97] **Total** 572 (2.89% annualized) vs. 612 (2.99% annualized); HR, 0.97 (95% CI, 0.87 to 1.09); p=0.63 *Subgroups:* No significant difference by age. *Risk based on timing of intervention:* No significant difference in total fractures by years since menopause.

Appendix F Table 15. Outcomes From Trials Reporting Incidence of Fractures

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Heiss, 2008;[132], Cauley, 2003;[150] Rossouw, 2002;[36] Manson, 2013;[67] Watts, 2017;[97] Prentice, 2020;[101] Prentice, 2020[91] (continued)		**Hip** 50 (0.24% annualized) vs. 56 (0.26% annualized); HR, 0.93 (95% CI, 0.63 to 1.36); p=0.70 *Subgroups:* No significant difference by age. **Cumulative followup: Median 13.2 years**[67] **Hip** 232 (0.23% annualized) vs. 270 (0.28% annualized; HR, 0.81 (95% CI, 0.68 to 0.97); p=0.02 **Cumulative followup: Median 18.0 years**[91] **Hip** *Subgroups*[91] No significant difference by age. **Cumulative followup: Median 19.4 years**[101] **Hip** 394 (4.6% calculated) vs. 421 (5.2% calculated); HR, 0.90 (95% CI, 0.78 to 1.03); p=NR

* Intervention dosages are listed in Table 3 by trial.

† 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; ICD-10=10th revision of the International Statistical Classification of Diseases and Related Health Problems; NR=not reported; RR=relative risk; STOP-IT=Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs.=versus; WHI=Women's Health Initiative.

Appendix F Table 16. Outcomes From Trials Reporting Incidence of Gallbladder Disease

Study Author, Year	Population	Results (Treatment* vs. Placebo)
Greenspan, et al Estrogen-only and estrogen plus progestin trial Greenspan, 2005[107]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Intervention followup: 3 years**[107] **Gallstones** *Analysis did not stratify by regimen.* 1 (0.5%) vs. 1 (0.5%)
PEPI Estrogen-only and estrogen plus progestin trial PEPI, 1995[32]	175 Estrogen only 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Intervention followup: 3 years**[32] **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[106]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Intervention followup: 3 years**[106] **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;[127] LaCroix, 2011;[108] Manson, 2013;[67] Prentice, 2020[101]	Women without cholecystectomy or gallbladder disease at baseline 4,141 Estrogen 4,235 Placebo	**Intervention followup: Mean 7.1 years** **Gallbladder event incidence**[127] 228 (5.5%) vs. 143 (3.4%); HR, 1.67 (95% CI, 1.35 to 2.06); p<0.001 **Cholecystectomy**[127] 192 (4.6%) vs. 104 (2.5%); HR, 1.93 (95% CI, 1.52 to 2.44); p<0.001 **Global gallbladder disease**[67] 461 (1.64% annualized) vs. 312 (1.06% annualized); HR, 1.55 (95% CI, 1.34 to 1.79); p<0.001 **Cholecystitis**[127] 186 (4.5%) vs. 107 (2.5%); HR, 1.80 (95% CI, 1.42 to 2.28); p<0.001 *Subgroups:*[127] No significant difference by age. **Postintervention followup: Median 6.6 years**[67] **Gallbladder disease** 57 (1.65% annualized) vs. 61 (1.66% annualized); HR, 0.98 (95% CI, 0.68 to 1.41); p=0.92

Appendix F Table 16. Outcomes From Trials Reporting Incidence of Gallbladder Disease

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Cirillo, 2005;[127] Manson, 2013;[67] Prentice, 2020[101]	Women without cholecystectomy or gallbladder disease at baseline 7,308 Estrogen plus progestin 6,895 Placebo	**Intervention followup: Mean 5.6 years** **Gallbladder event incidence**[127] 228 (3.1%) vs. 135 (2.0%); HR, 1.59 (95% CI, 1.28 to 1.97); p<0.001 **Cholecystectomy**[127] 190 (2.6%) vs. 107 (1.6%); HR, 1.67 (95% CI, 1.32 to 2.11); p<0.001 **Global gallbladder disease**[67] 528 (1.31% annualized) vs. 319 (0.84% annualized); HR, 1.57 (95% CI, 1.36 to 1.80); p<0.001 **Cholecystitis**[127] 192 (2.6%) vs. 117 (1.7%); HR, 1.54 (95% CI, 1.22 to 1.94); p<0.001 *Subgroups:*[127] No significant difference by age. **Postintervention followup: Median 8.2 years**[67] **Gallbladder disease** 213 (1.27% annualized) vs. 166 (1.01% annualized); HR, 1.24 (95% CI, 1.01 to 1.52); p=0.04

* Intervention dosages are listed in Table 3 by trial.

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

Appendix F Table 17. Outcomes From Trials Reporting Incidence of Stroke

Study Author, Year	Population	Results (Treatment* vs. Placebo)
EMS Estrogen plus progestin trial Tierney, 2000[141]	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[112]	111 Estrogen† 111 Placebo†	**Followup: 2 years** **Cerebrovascular accidents** 0 vs. 1
EPHT Estrogen plus progestin trial Veerus, 2006[137]	404 Estrogen plus progestin 373 Placebo	**Followup: Mean 3.4 years** **Any cerebrovascular disease‡** 23 (5.7%) vs. 9 (2.4%); HR, 2.46 (95% CI, 1.14 to 5.34); p=NR **Stroke** 1 (0.2%) vs. 1 (0.3%); HR, 1.06 (95% CI, 0.07 to 17.2); p=NR
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[113]	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[106]	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[105]	Women with a coronary stenosis of 15%–75% 124 Estrogen (with or without vitamin C and E) 86 Estrogen plus progestin (with or without vitamin C and E) 213 Placebo (with or without vitamin 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

Appendix F Table 17. Outcomes From Trials Reporting Incidence of Stroke

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial Hendrix, 2006;[128] LaCroix, 2011;[108] Manson, 2013;[67] Prentice, 2009;[110] Manson, 2019;[89] Chlebowski, 2017;[95] Prentice, 2020;[101] Manson, 2017;[88] Prentice, 2020[91]	5,310 Estrogen 5,429 Placebo Postintervention followup: 3,778 Estrogen 3,867 Placebo Cumulative followup (intervention plus postintervention phases): 4,911 Estrogen 5,028 Placebo	**Intervention followup: Median 7.2 years** **Ischemic or hemorrhagic stroke**[67] 169 (3.2% calculated) vs. 129 (2.4%); HR, 1.35 (95% CI, 1.07 to 1.70); p=0.01 *Subgroups:* No significant difference by race/ethnicity, age, prior CVD, diabetes, hypertension.[95, 128] *Risk based on timing of intervention:*[67, 110] No significant difference by timing of intervention. **Stroke mortality**[88] 23 (0.060%) vs. 24 (0.060%); HR, 1.00 (95% CI, 0.57 to 1.78); p=0.99 **Postintervention followup: Mean 3.9 years**[108] **All stroke** 66 (0.36% annualized) vs. 77 (0.41%); HR, 0.89 (95% CI, 0.64 to 1.24); p=NR **Postintervention followup: Median 10.8 years**[88] **Stroke mortality** 103 (0.21%) vs. 108 (0.22%); HR, 0.98 (95% CI, 0.75 to 1.28); p=0.86 *Subgroups:* No significant difference by age. **Cumulative followup: Median 13.0 years**[67, 108] **All stroke** 278 (0.46% annualized) vs. 253 (0.41%); HR, 1.15 (95% CI, 0.97 to 1.37); p=0.10 **Cumulative followup: Median 17.7 years**[88] **Stroke mortality** 126 (0.14%) vs. 132 (0.15%); HR, 0.98 (95% CI, 0.77 to 1.26); p=0.89 *Subgroups:* No significant difference by age. **Cumulative followup: Median 18.0 years** **All stroke** *Subgroups:* No significant difference by race or oophorectomy status within any age group at randomization.[89, 95] No significant difference within age groups.[91] **Cumulative Followup: Median 19.4 years**[101] **Ischemic or hemorrhagic stroke** 399 (7.5% calculated) vs. 392 (7.2%); HR, 1.06 (95% CI, 0.92 to 1.22); p=NR

Appendix F Table 17. Outcomes From Trials Reporting Incidence of Stroke

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Wassertheil-Smoller, 2003;[151] Heiss, 2008;[132] Cushman, 2004;[153] Manson, 2013;[67] Prentice, 2020[101] Manson, 2017;[88] Prentice, 2020[91]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention Followup: 8,052 Estrogen plus progestin 7,678 Placebo	**Intervention followup: Mean 5.6 years** **Ischemic or hemorrhagic stroke**[67] 159 (1.9% calculated) vs. 109 (1.3%); HR, 1.37 (95% CI, 1.07 to 1.76); p=0.01[67] *Subgroups:* No significant difference by race/ethnicity, age, diabetes, or hypertension.[151] No significant difference within age groups.[91] *Risk based on timing of intervention:*[67, 110] No significant difference by timing of intervention. **Ischemic stroke**[151] 125 vs. 81; HR, 1.44 (95% CI, 1.09 to 1.90) **Hemorrhagic stroke**[151] 18 vs. 20; HR, 0.82 (95% CI, 0.43 to 1.56) **Stroke mortality**[88] 27 (0.055% annualized) vs. 16 (0.035%); HR, 1.58 (95% CI, 0.85 to 2.94); p=0.14 *Subgroups:* No significant difference by age. **Postintervention followup: Mean 2.4 years**[67] **All stroke** 217 (0.40% annualized) vs. 202 (0.39%); HR, 1.04 (95% CI, 0.86 to 1.26); p=0.67 **Postintervention followup: Median 12.5 years**[88] **Stroke mortality** 161 (0.17%) vs. 145 (0.16%); HR, 1.08 (95% CI, 0.86 to 1.35); p=0.52 *Subgroups:* No significant difference by age. **Cumulative followup: Median 13.2 years**[67] **All stroke** 376 (0.37% annualized) vs. 311 (0.32%); HR, 1.16 (95% CI, 1.00 to 1.35); p=0.06 **Cumulative followup: Median 17.7 years**[88] **Stroke mortality** 188 (0.13% annualized) vs. 161 (0.12%); HR, 1.12 (95% CI, 0.91 to 1.38); p=0.29 *Subgroups:* No significant difference by age.

Appendix F Table 17. Outcomes From Trials Reporting Incidence of Stroke

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Wassertheil-Smoller, 2003;[151] Heiss, 2008;[132] Cushman, 2004;[153] Manson, 2013;[67] Prentice, 2020[101] Manson, 2017;[88] Prentice, 2020[91] (continued)		**Cumulative followup: Median 18.0 years**[91] **Stroke** *Subgroups:* No significant difference within age groups. **Cumulative followup: Median 19.4 years**[101] **Ischemic or hemorrhagic stroke** 579 (6.8% calculated) vs. 492 (6.1%); HR, 1.13 (95% CI, 1.00 to 1.27); p=NR

***** Intervention dosages are listed in Table 3 by trial.
† Unopposed micronized 17V-estradiol (1 mg/d).
‡ 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, or 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; ICD-10=10th revision of the International Statistical Classification of Diseases and Related Health Problems; NR=not reported; NS=not significant; 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 F Table 18. Outcomes From Trials Reporting Incidence of Urinary Incontinence

Study Author, Year	Population	Results (Treatment* vs. Placebo)
HERS Estrogen plus progestin trial Steinauer, 2005[152]	Women reporting no episodes of incontinence in the past week at baseline 597 Estrogen plus progestin 611 Placebo	**Followup: 4.2 years** **Weekly total urinary incontinence** 382 vs. 302; OR, 1.6 (95% CI, 1.3 to 1.9); p<0.001 **Weekly stress urinary incontinence** OR, 1.7 (95% CI, 1.5 to 2.1); p<0.001 **Weekly urge urinary incontinence** OR, 1.5 (95% CI, 1.2 to 1.8); p<0.001
ULTRA Estrogen-only trial Waetjen, 2005[129]	Women who were continent at baseline 122 Estrogen (calculated) 117 Placebo (calculated)	**Followup: 2 years** **Weekly total urinary incontinence** 39.0% vs. 36.8%; OR, 1.2 (95% CI, 0.7 to 2.2); p=0.74
WHI Estrogen-only trial Hendrix, 2005;[130] Manson, 2013[67]	Women with urinary incontinence data at baseline and 1 year Intervention followup: 1 year for total urinary incontinence[67] 3,316 Estrogen (all continent at baseline)† 3,451 Placebo (all continent at baseline)† Intervention followup: 1 year for all outcomes, except total urinary incontinence[130] 1,526 Estrogen (all continent at baseline) 1,547 Placebo (all continent at baseline) Intervention followup: 3 years[130] 96 Estrogen (all continent at baseline and 1 year) 136 Placebo (all continent at baseline and 1 year) Postintervention followup: Median 6.6 years[67] 2,781 Estrogen (all continent at baseline) 2,863 Placebo (all continent at baseline)	**Intervention followup: 1 year** **Weekly total urinary incontinence**[67] 773 (22.6% annualized) vs. 499 (14.0% annualized); HR, 1.61 (95% CI, 1.46 to 1.79); p<0.001 **Incident urinary incontinence (≥1 episode/year)**[130] 557 (36.5%) vs. 368 (23.8%); RR, 1.53 (95% CI, 1.37 to 1.71); p=NR **Stress urinary incontinence (≥1 episode/year)**[130] 266 (17.4%) vs. 131 (8.5%); RR, 2.15 (95% CI, 1.77 to 2.62); p<0.001 **Urge urinary incontinence (≥1 episode/year)**[130] 210 (13.8%) vs. 184 (11.9%); RR, 1.32 (95% CI, 1.10 to 1.58); p=0.003 **Mixed urinary incontinence (≥1 episode/year)**[130] 76 (5.0%) vs. 50 (3.2%); RR, 1.79 (95% CI, 1.26 to 2.53); p=0.001 **Intervention followup: 3 years**[130] **Incident urinary incontinence (≥1 episode/year)** 27 (28.1%) vs. 26 (19.1%); RR, 1.47 (95% CI, 0.92 to 2.36); p=NR **Postintervention followup: Median 6.6 years**[67] **Weekly total urinary incontinence** 795 calculated (28.6%) vs. 661 calculated (23.1%); HR, 1.24 (95% CI, 1.13 to 1.35); p<0.001

Appendix F Table 18. Outcomes From Trials Reporting Incidence of Urinary Incontinence

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Hendrix, 2005;[130] Manson, 2013[67]	Women with urinary incontinence data at baseline and 1 year Intervention followup: 1 year for total urinary incontinence[67] 5,981 Estrogen plus progestin (all continent at baseline)† 5,597 Placebo (all continent at baseline)† Intervention followup: 1 year for all outcomes, except total urinary incontinence[130] 2,675 Estrogen plus progestin (all continent at baseline) 2,507 Placebo (all continent at baseline) Intervention followup: 3 years[130] 153 Estrogen plus progestin (all continent at baseline and 1 year) 185 Placebo (all continent at baseline and 1 year) Postintervention followup: Median 6.6 years[67] 5,194 Estrogen plus progestin (all continent at baseline) 4,879 Placebo (all continent at baseline)	**Intervention followup: 1 year** **Weekly total urinary incontinence**[67] 1,021 (16.6% annualized) vs. 641 (11.1% annualized); HR, 1.49 (95% CI, 1.36 to 1.63); p<0.001 **Incident urinary incontinence (≥1 episode/year)**[130] 834 (31.2%) vs. 563 (22.5%); RR, 1.39 (95% CI, 1.27 to 1.52) **Stress urinary incontinence (≥1 episode/year)**[130] 429 (16.0%) vs. 218 (8.7%); RR, 1.87 (95% CI, 1.61 to 2.18); p<0.001 **Urge urinary incontinence (≥1 episode/year)**[130] 304 (11.4%) vs. 272 (10.8%); RR, 1.15 (95% CI, 0.99 to 1.34); p=0.06 **Mixed urinary incontinence (≥1 episode/year)**[130] 99 (3.7%) vs. 69 (2.8%); RR, 1.49 (95% CI, 1.10 to 2.01); p=0.01 **Intervention followup: 3 years**[130] **Incident urinary incontinence (≥1 episode/year)** 39 (25.5%) vs. 26 (14.1%); RR, 1.81 (95% CI, 1.16 to 2.84); p=NR **Postintervention followup: Median 8.2 years**[67] **Weekly total urinary incontinence** 1,221 calculated (23.5%) vs. 990 calculated (20.3%); HR, 1.16 (95% CI, 1.08 to 1.25); p<0.001

***** Intervention dosages are listed in Table 3 by trial.

† The Ns of participants continent at baseline and included in the WHI trials' urinary incontinence analyses after 1 year of intervention followup were provided through a communication with the WHI Researcher Help Desk (July 2021).

Abbreviations: CI=confidence interval; HERS=Heart and Estrogen/Progestin Replacement Study; HR=hazard ratio; N=number; NR=not reported; OR=odds ratio; RR=relative risk; ULTRA=Ultra Low-Dose Transdermal Estrogen Replacement Assessment; vs.=versus; WHI=Women's Health Initiative.

Appendix F Table 19. Outcomes From Trials Reporting Incidence of Venous Thromboembolism

Study Author, Year	Population	Results (Treatment* vs. Placebo)
EMS Estrogen plus progestin trial Tierney, 2000[141]	70 Estrogen plus progestin 72 Placebo	**Followup: 2 years** **Deep vein thrombosis** 1 vs. 0; p=NS
EPAT Estrogen-only trial Hodis, 2001[112]	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[137]	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[113]	100 Estrogen 104 Estrogen plus progestin 105 Placebo	**Followup: 3.2 years** **Deep vein thrombosis or pulmonary embolism** 5 vs. 2 vs. 1; p=0.16 (For estrogen vs. placebo, p=0.11)
Greenspan, et al Estrogen-only and estrogen plus progestin trial Greenspan, 2005[107]	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
HERS Estrogen plus progestin trial† Hulley, 2002[136]	1,380 Estrogen plus progestin 1,383 Placebo Cumulative followup: 1,156 Estrogen plus progestin 1,383 Placebo	**Intervention followup: Mean 4.1 years** **Total thromboembolic events** 34 (2.5% calculated) vs. 13 (0.9% calculated); HR, 2.66 (95% CI, 1.41 to 5.04); p=0.003 **Deep vein thrombosis** 25 (1.8% calculated) vs. 9 (0.7% calculated); HR, 2.82 (95% CI, 1.32 to 6.04); p=0.008 **Pulmonary embolism** 11 (0.8% calculated) vs. 4 (0.3% calculated); HR, 2.78 (95% CI, 0.89 to 8.74); p=0.08 **Cumulative followup: Mean 6.8 years** **Total thromboembolic events** 49 (4.2% calculated) vs. 24 (1.7% calculated); HR, 2.06 (95% CI, 1.26 to 3.36); p=NR
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[106]	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)

Appendix F Table 19. Outcomes From Trials Reporting Incidence of Venous Thromboembolism

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WAVE Estrogen-only and estrogen plus progestin trial Waters, 2002[105]	Women with a coronary stenosis of 15%–75% 124 Estrogen (with or without vitamin C and E) 86 Estrogen plus progestin (with or without vitamin C and E) 213 Placebo (with or without vitamin 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;[108] Curb, 2006;[131] Prentice, 2009;[110] Manson, 2013;[67] Manson, 2019;[89] Chlebowski, 2017;[95] Prentice, 2020;[101] Prentice, 2020[91]	5,310 Estrogen 5,429 Placebo Postintervention followup: 3,778 Estrogen 3,867 Placebo Cumulative followup (intervention plus postintervention phases): 4,911 Estrogen 5,028 Placebo	**Intervention followup: Mean 7.1 years/Median 7.2 years** **Venous thromboembolism** 111 (2.1% calculated) vs. 86 (1.6%); HR, 1.32 (95% CI, 1.00 to 1.76); p=NR[101] *Subgroups:*[95] No significant difference by race. *Risk based on timing of intervention:*[110] No significant difference by timing of intervention. **Deep vein thrombosis** 85 (1.6%) vs. 59 (1.0%); HR, 1.48 (95% CI, 1.06 to 2.07); p=0.02[67, 108] *Subgroups:*[67, 131] No significant difference by race/ethnicity, age, or history of CVD. **Pulmonary embolism** 52 (0.14% annualized) vs. 39 (0.10%); HR, 1.35 (95% CI, 0.89 to 2.05); p=0.15[67] *Subgroups:*[91] No significant difference within any age group. *Risk based on timing of intervention:*[67] No significant difference by timing of intervention. **Postintervention followup: Mean 3.9 years** **Venous thromboembolism**[95] *Subgroups:* *Race (p=0.049)* White: 157 (0.34%) vs. 147 (0.31%); HR, 1.11 (95% CI, 0.88 to 1.39) Black: 23 (0.26%) vs. 40 (0.42%); HR, 0.63 (95% CI, 0.38 to 1.06) **Deep vein thrombosis**[108] HR, 0.63 (95% CI, 0.41 to 0.98); p=0.003 **Pulmonary embolism**[108] HR, 0.98 (95% CI, 0.62 to 1.55); p=0.29

Appendix F Table 19. Outcomes From Trials Reporting Incidence of Venous Thromboembolism

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial LaCroix, 2011;[108] Curb, 2006;[131] Prentice, 2009;[110] Manson, 2013;[67] Manson, 2019;[89] Chlebowski, 2017;[95] Prentice, 2020;[101] Prentice, 2020[91] (continued)		**<u>Cumulative followup: Median 13.0 years</u>**[67] **Deep vein thrombosis** 135 (0.22% annualized) vs. 133 (0.21%); HR, 1.05 (95% CI, 0.82 to 1.33); p=0.71 *Subgroups:* No significant difference by age group. **Pulmonary embolism** 107 (0.17% annualized) vs. 96 (0.15%); HR, 1.15 (95% CI, 0.87 to 1.51); p=0.34 *Subgroups:* No significant difference by age group. **<u>Cumulative followup: Median 18.0 years</u>** **Pulmonary embolism** *Subgroups:* No significant difference within any age group[91] or by oophorectomy status within any age group.[89] **<u>Cumulative followup: Median 19.4 years</u>**[101] **Venous thromboembolism** 270 (5.1% calculated) vs. 288 (5.3% calculated); HR, 0.97 (95% CI, 0.82 to 1.14); p=NR

Appendix F Table 19. Outcomes From Trials Reporting Incidence of Venous Thromboembolism

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Heiss, 2008;[132] Cushman, 2004;[153] Manson, 2013;[67] Prentice, 2009;[110] Prentice, 2020;[101] Prentice, 2020[91]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention followup: 8,052 Estrogen plus progestin 7,678 Placebo	**Intervention followup: Median 5.6 years** **Venous thrombosis**[153] 167 (1.96% calculated) vs. 76 (0.94%); HR, 2.06 (95% CI, 1.57 to 2.70) *Risk based on timing of intervention:*[110] No significant difference by timing of intervention. **Deep vein thrombosis**[67] 122 (1.4% calculated) vs. 61 (0.8%); HR, 1.87 (95% CI, 1.37 to 2.54); p<0.001 *Subgroups:* No significant difference by age.[67] **Pulmonary embolism**[67] 87 (1.0% calculated) vs. 41 (0.5%); HR, 1.98 (95% CI, 1.36 to 2.87); p<0.001 *Subgroups:* No significant difference by age.[67] *Age (p=NR)*[91] 50–59 years: HR, 2.15 (95% CI, 0.96 to 4.80) 60–69 years: HR, 1.69 (95% CI, 1.01 to 2.86) 70–79 years: HR, 2.48 (95% CI, 1.23 to 4.99) *Risk based on timing of intervention:*[67] No significant difference by timing of intervention. **Postintervention followup: Mean 2.4 years**[132] **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 13.2 years**[67] **Deep vein thrombosis** 212 (0.21% annualized) vs. 162 (0.17%); HR, 1.24 (95% CI, 1.01 to 1.53); p=0.04 *Subgroups:* No significant difference by age. **Pulmonary embolism** 172 (0.17% annualized) vs. 128 (0.13%); HR, 1.26 (95% CI, 1.00 to 1.59); p=0.05 *Subgroups:* No significant difference by age.

Appendix F Table 19. Outcomes From Trials Reporting Incidence of Venous Thromboembolism

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Heiss, 2008;[132] Cushman, 2004;[153] Manson, 2013;[67] Prentice, 2009;[110] Prentice, 2020;[101] Prentice, 2020[91]		**Cumulative followup: Median 18.0 years**[91] **Pulmonary embolism** *Subgroups:* No significant difference within any age group. **Cumulative followup: Median 19.4 years**[101] **Venous thromboembolism** 416 (4.9% calculated) vs. 348 (4.3%); HR, 1.14 (95% CI, 0.99 to 1.31); p=NR

* Intervention dosages are listed in Table 3 by trial.
† HERS was a blinded randomized, controlled trial that had a mean followup of 4.1 years. At the end of HERS, participants were unblinded and 93 percent reenrolled in the HERS II open-label study for an additional 2.7 years.

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; HERS=Heart and Estrogen/Progestin Replacement Study; HR=hazard ratio; NR=not reported; NS=not significant; 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 F Table 20. Outcomes From Trials Reporting Incidence of Quality of Life

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial Manson, 2013[67]	5,310 Estrogen 5,429 Placebo	**Followup: Mean 7.2 years**[67] SF-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 taking placebo had statistically significantly better scores than women taking estrogen-only therapy
WHI Estrogen plus progestin trial Manson, 2013;[67] Hays, 2003[172]	8,506 Estrogen plus progestin 8,102 Placebo	**Followup: Mean 5.6 years**[67] SF-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 taking hormone therapy had statistically significantly better scores than women taking placebo

* Intervention dosages are listed in Table 3 by trial.

Abbreviations: SF-36=36-Item Short Form Survey; vs.=versus; WHI=Women's Health Initiative.

Appendix F Table 21. Outcomes From Trials Reporting Incidence of All-Cause Mortality

Study Author, Year	Population	Results (Treatment* vs. Placebo)
ELITE-Cog Henderson, 2016[92]	323 Estrogen 320 Placebo	**Followup: Mean 4.8 years** **All-cause mortality** 1 (0.3%) vs. 1 (0.3%)
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[113]	100 Estrogen 104 Estrogen plus progestin 105 Placebo	**Followup: Mean 3.2 years** **All-cause mortality** 8 (8.0%) vs. 3 (2.9%) vs. 6 (5.7%); p=0.28
HERS Estrogen plus progestin trial Hulley, 2002[136]	1,380 Estrogen plus progestin 1,383 Placebo Cumulative followup: 1,156 Estrogen plus progestin 1,383 Placebo	**Followup: Mean 4.1 years** **All-cause mortality** 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** **All-cause mortality** 261 (22.6%) vs. 239 (17.3%); HR, 1.08 (95% CI, 0.91 to 1.29); p=NR
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[106]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Followup: 3 years** **All-cause mortality** *Analysis not stratified by hormone therapy 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[105]	124 Estrogen (with or without vitamin C and E) 86 Estrogen plus progestin (with or without vitamin C and E) 213 Placebo (with or without vitamin C and E)	**Followup: Mean 2.8 years** **All-cause mortality** *Analysis not stratified by hormone therapy regimen.* 14 (6.7%) vs. 8 (3.8%)

Appendix F Table 21. Outcomes From Trials Reporting Incidence of All-Cause Mortality

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial LaCroix, 2011;[108] Manson, 2013;[67] Prentice, 2009;[110] Manson, 2019;[89] Prentice, 2020;[101] Chlebowski, 2017;[95] Manson, 2017;[88] Prentice, 2020[91]	5,310 Estrogen 5,429 Placebo Postintervention followup: 3,778 Estrogen 3,867 Placebo Cumulative followup (intervention plus postintervention phases): 4,911 Estrogen 5,028 Placebo	**Intervention followup: Mean 7.2 years** **All-cause mortality**[108] 300 (5.6%) vs. 297 (5.5%); HR, 1.04 (95% CI, 0.89 to 1.22); p=NR *Subgroups:* No significant difference by race,[95] oophorectomy status in the overall sample or by age group, or by age at oophorectomy among younger or older women.[89] *Age (p=0.04)*[88, 91] 50–59 years: 35 (0.28% annualized) vs. 50 (0.39% annualized); HR, 0.71 (95% CI, 0.46 to 1.09) 60–69 years: 130 (0.76% annualized) vs. 134 (0.75% annualized); HR, 1.02 (95% CI, 0.80 to 1.30) 70–79 years: 136 (1.53% annualized) vs. 115 (1.27% annualized); HR, 1.22 (95% CI, 0.95 to 1.56) Comparing younger women (ages 50–59) to older women (ages 70–79): ratio of HRs, 0.58 (95% CI, 0.35 to 0.96) *Risk based on timing of intervention:* No significant difference by timing of intervention in the overall sample[67] or among women without prior hormone therapy use.[110] **Postintervention followup: Mean 3.9 years**[108] **All-cause mortality** 277 (1.47% annualized) vs. 284 (1.48% annualized); HR, 1.00 (95% CI, 0.84 to 1.18); p=NR **Postintervention followup: Median 10.8 years**[88] **All-cause mortality** 1,204 (2.48% annualized) vs. 1,331 (2.69%); HR, 0.92 (95% CI, 0.85 to 0.99); p=0.03 *Subgroup:* No significant difference by age group. **Cumulative followup: Mean 10.7 years**[108] **All-cause mortality** 577 (1.02% annualized) vs. 581 (1.00% annualized); HR, 1.02 (95% CI, 0.91 to 1.15); p=NR **Cumulative followup: Median 13.0 years** **All-cause mortality**[67] 704 (1.14% annualized) vs. 725 (1.14% annualized); HR, 0.99 (95% CI, 0.90 to 1.10); p=0.92 *Subgroups:* No significant difference by race[95] or age.[67]

Appendix F Table 21. Outcomes From Trials Reporting Incidence of All-Cause Mortality

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen-only trial LaCroix, 2011;[108] Manson, 2013;[67] Prentice, 2009;[110] Manson, 2019;[89] Prentice, 2020;[101] Chlebowski, 2017;[95] Manson, 2017;[88] Prentice, 2020[91] (continued)		**Cumulative followup: Median 17.7 years**[88] **All-cause mortality** 1,505 (1.73% annualized) vs. 1,630 (1.83% annualized); HR, 0.94 (95% CI, 0.88 to 1.01); p=0.11 *Subgroups:* No significant difference by age group. **Cumulative followup: Median 18.0 years** **All-cause mortality** *Subgroups:* No significant difference within age group[91] or by oophorectomy status in the overall sample or by prior hormone therapy use, by age at oophorectomy among younger or older women, or by age among women without oophorectomy.[89] ***Age among women with oophorectomy*** **(p=0.034)**[89] 50–59 years: 53 (0.56% annualized) vs. 84 (0.79% annualized); HR, 0.68 (95% CI, 0.48 to 0.96) 60–69 years: 225 (1.50% annualized) vs. 280 (1.71% annualized); HR, 0.88 (95% CI, 0.74 to 1.05) 70–79 years: 262 (3.65% annualized) vs. 284 (3.65% annualized); HR, 1.02 (95% CI, 0.86 to 1.21) **Cumulative followup: Median 19.4 years**[101] **All-cause mortality** 1,899 (35.8% calculated) vs. 2,004 (36.9% calculated); HR, 0.97 (95% CI, 0.91 to 1.03); p=NR

Appendix F Table 21. Outcomes From Trials Reporting Incidence of All-Cause Mortality

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Heiss, 2008;[132] Manson, 2013;[67] Prentice, 2009;[110] Prentice, 2020;[101] Manson, 2017;[88] Prentice, 2020[91]	8,506 Estrogen plus progestin 8,102 Placebo Postintervention extension followup: 6,545 Estrogen plus progestin 6,243 Placebo Cumulative followup 8,506 Estrogen plus progestin 8,102 Placebo	**Intervention followup: Median 5.6 years** **All-cause mortality** 250 (2.9% calculated) vs. 239 (2.9% calculated); HR, 0.97 (95% CI, 0.81 to 1.16)[88, 132] *Subgroups:*[88] No significant difference by age group. *Risk based on timing of intervention:* No significant difference by timing of intervention in the overall sample[67] or among women without prior hormone therapy use.[110] **Post intervention followup: Mean 2.4 years**[132] All-cause mortality 233 (1.20% annualized) vs. 196 (1.06% annualized); HR, 1.15 (95% CI, 0.95 to 1.39); p=0.27 **Postintervention followup: Median 8.2 years**[67] **All-cause mortality** 761 (1.39% annualized) vs. 728 (1.39% annualized); HR, 1.01 (95% CI, 0.91 to 1.11); p=0.90 **Postintervention followup: Median 12.5 years**[88] All-cause mortality 1,994 (2.15% annualized) vs. 1,872 (2.11% annualized); HR, 1.04 (95% CI, 0.97 to 1.10); p=0.28 *Subgroups:* No significant difference by age group. **Cumulative followup: Median 13.2 years**[67] All-cause mortality 1,011 (0.98% annualized) vs. 966 (0.99% annualized); HR, 0.99 (95% CI, 0.91 to 1.08); p=0.87 *Subgroups:* No significant difference by age. **Cumulative followup: Median 17.7 years**[88] **All-cause mortality** 2,244 (1.58% annualized) vs. 2,110 (1.57% annualized); HR, 1.02 (95% CI, 0.96 to 1.08); p=0.51 *Subgroups:* No significant difference by age group.

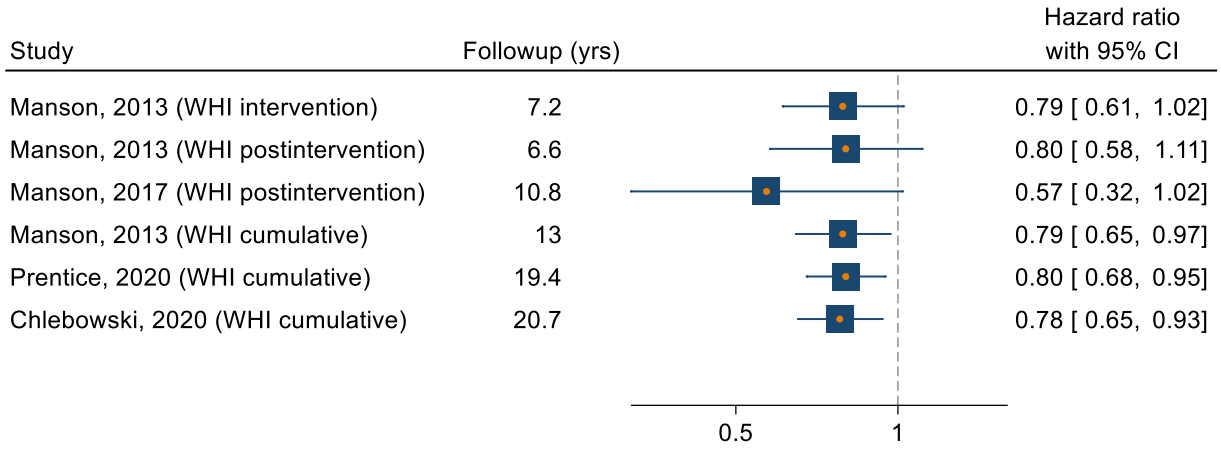
Appendix F Table 21. Outcomes From Trials Reporting Incidence of All-Cause Mortality

Study Author, Year	Population	Results (Treatment* vs. Placebo)
WHI Estrogen plus progestin trial Heiss, 2008;[132] Manson, 2013;[67] Prentice, 2009;[110] Prentice, 2020;[101] Manson, 2017;[88] Prentice, 2020[91] (continued)		**Cumulative followup: Median 18.0 years**[91] **All-cause mortality** *Subgroups:* No significant difference by age group. **Cumulative followup: Median 19.4 years**[101] **All-cause mortality** 2,802 (32.9% calculated) vs. 2,638 (32.6% calculated); HR, 1.02 (95% CI, 0.97 to 1.08); p=NR

* Intervention dosages are listed in Table 3 by trial.

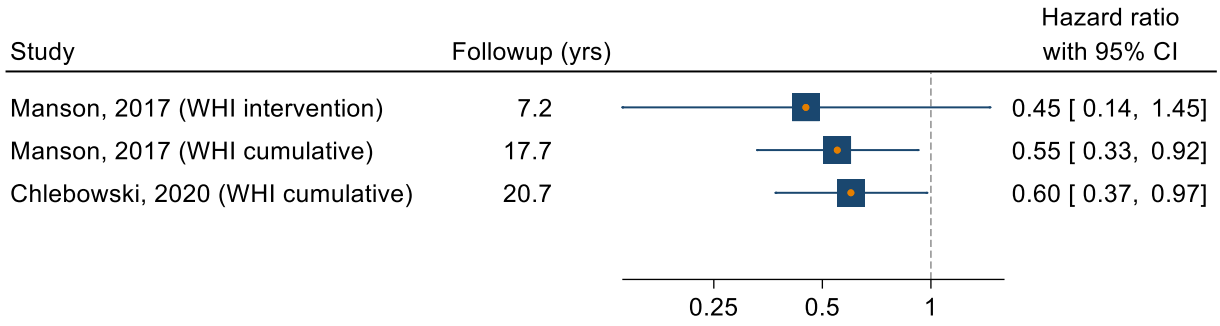
Abbreviations: BSO=bilateral salpingo-oophorectomy; CI=confidence interval; ELITE=Early vs. Late Intervention Trial with Estradiol; ERA=Estrogen Replacement and Atherosclerosis Trial; HERS=Heart and Estrogen/Progestin Replacement Study; HR=hazard ratio; HT=hormone therapy; NR=not reported; STOP-IT=Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs.=versus; WAVE=Women's Angiographic Vitamin and Estrogen Trial; WHI=Women's Health Initiative.

Appendix G Figure 1. Hazard Ratios for Invasive Breast Cancer for Estrogen-Only Trials



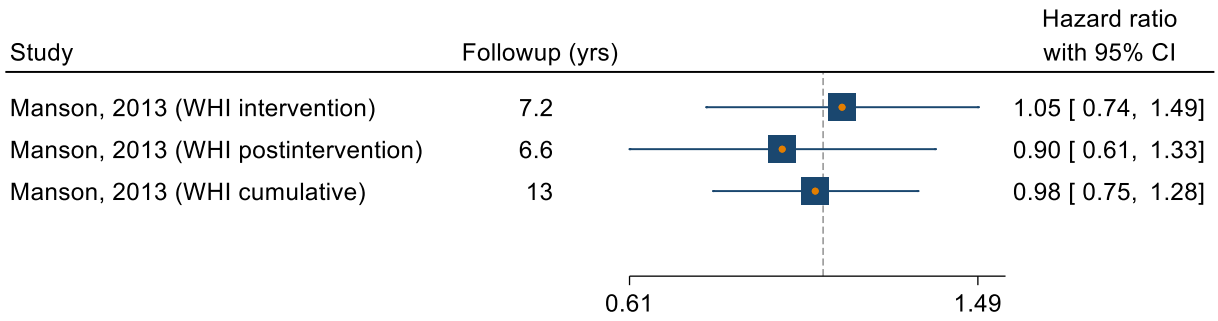
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 2. Hazard Ratios for Breast Cancer Mortality for Estrogen-Only Trials



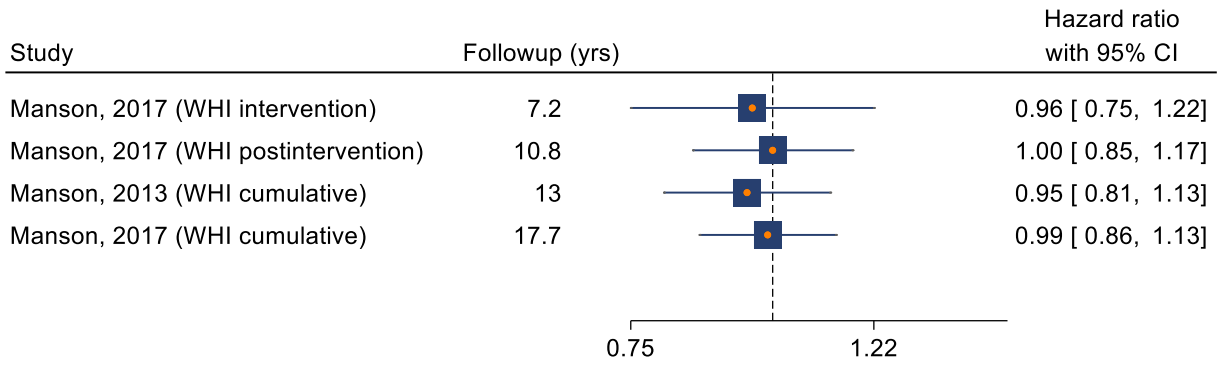
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 3. Hazard Ratios for Lung Cancer for Estrogen-Only Trials



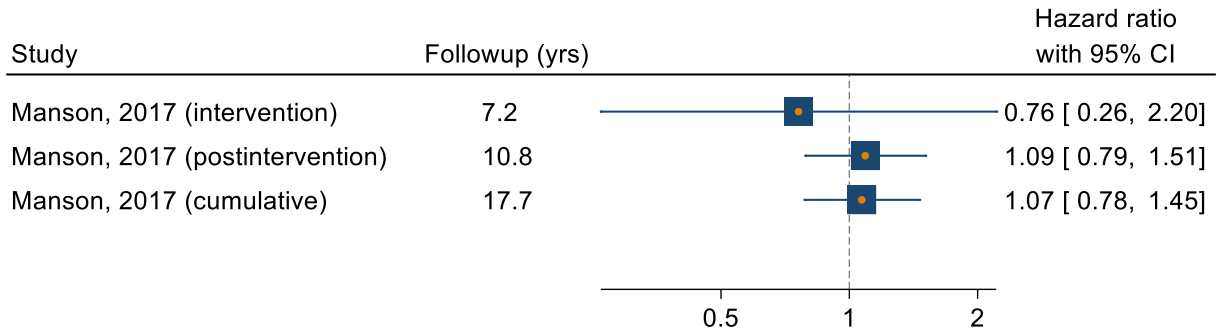
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 4. Hazard Ratios for Total Cancer Mortality for Estrogen-Only Trials



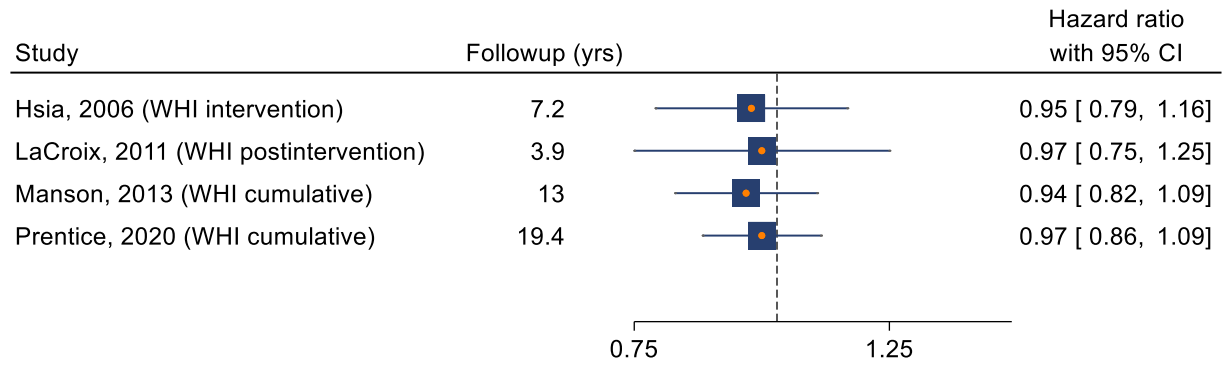
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 5. Hazard Ratios for COPD Mortality for Estrogen-Only Trials



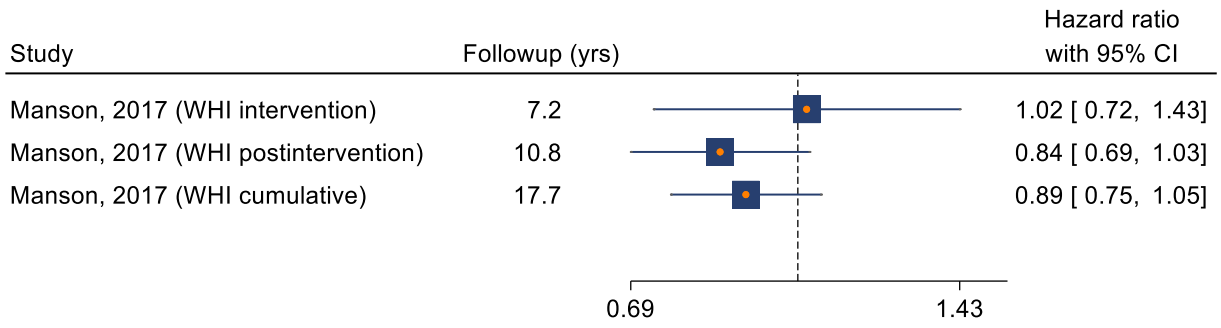
Abbreviations: CI=confidence interval; COPD=chronic obstructive pulmonary disease.

Appendix G Figure 6. Hazard Ratios for Coronary Heart Disease for Estrogen-Only Trials



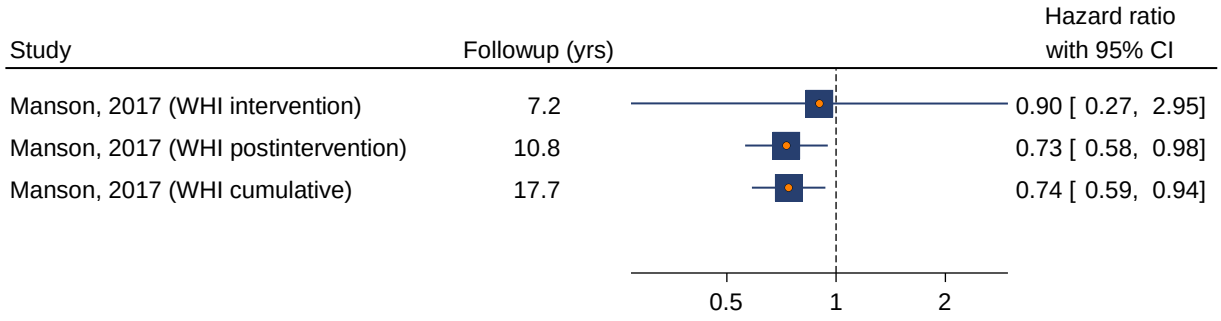
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 7. Hazard Ratios for Coronary Heart Disease Mortality for Estrogen-Only Trials



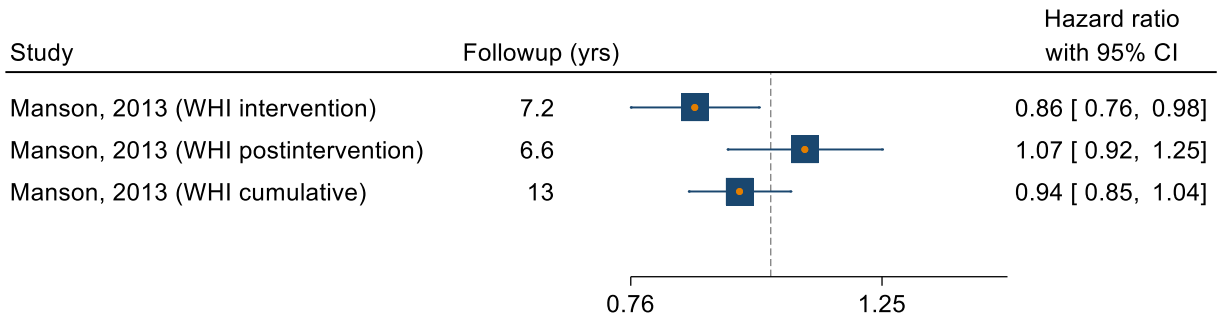
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 8. Hazard Ratios for Dementia-Related Mortality for Estrogen-Only Trials



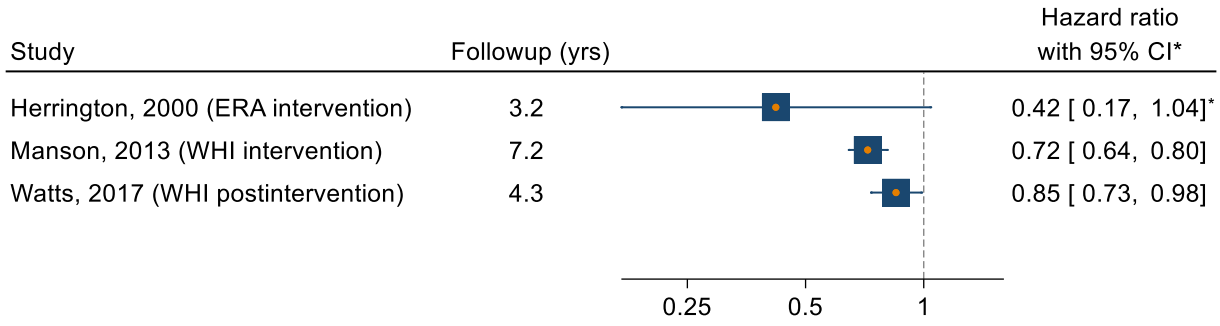
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 9. Hazard Ratios for Incident Diabetes for Estrogen-Only Trials



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

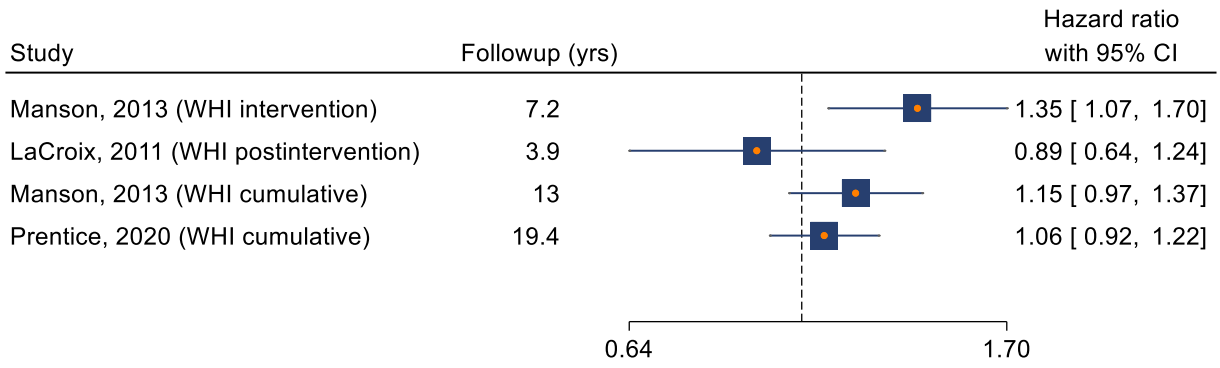
Appendix G Figure 10. Effect Estimates for Total Fractures for Estrogen-Only Trials



* The ERA trial's effect estimate was a calculated risk ratio.

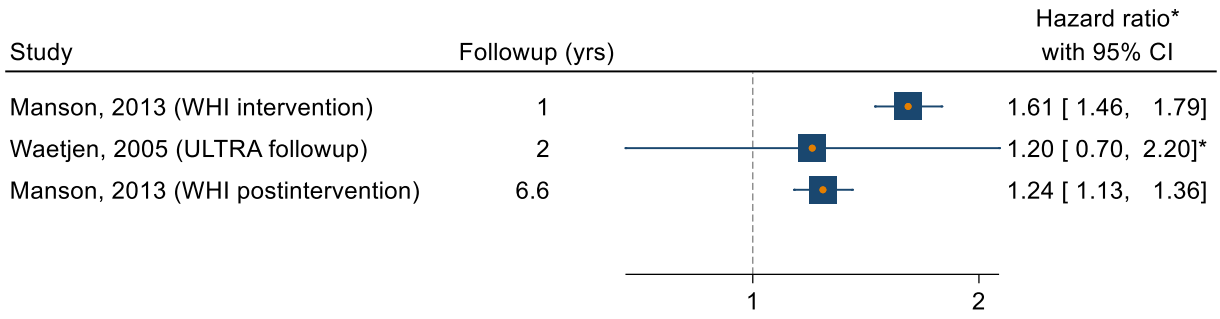
Abbreviations: CI=confidence interval; ERA=Estrogen Replacement and Atherosclerosis; WHI=Women's Health Initiative.

Appendix G Figure 11. Hazard Ratios for Stroke for Estrogen-Only Trials



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

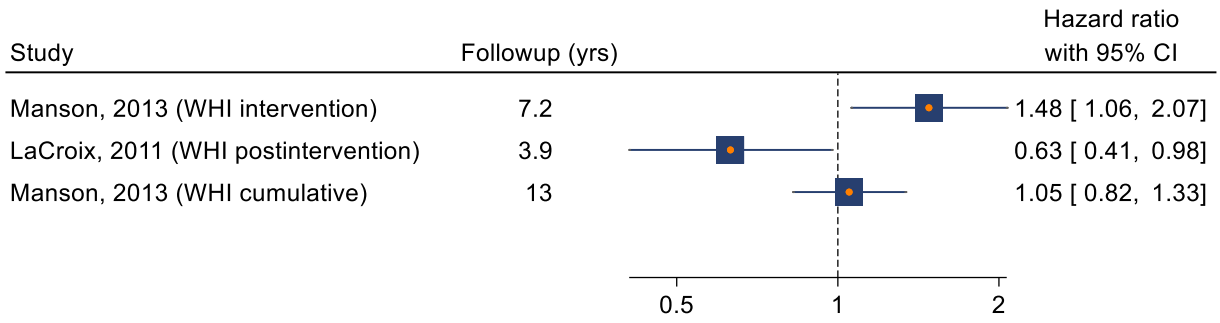
Appendix G Figure 12. Effect Estimates for Incident Weekly Urinary Incontinence for Estrogen-Only Trials



* The ULTRA trial's effect estimate was an odds ratio.

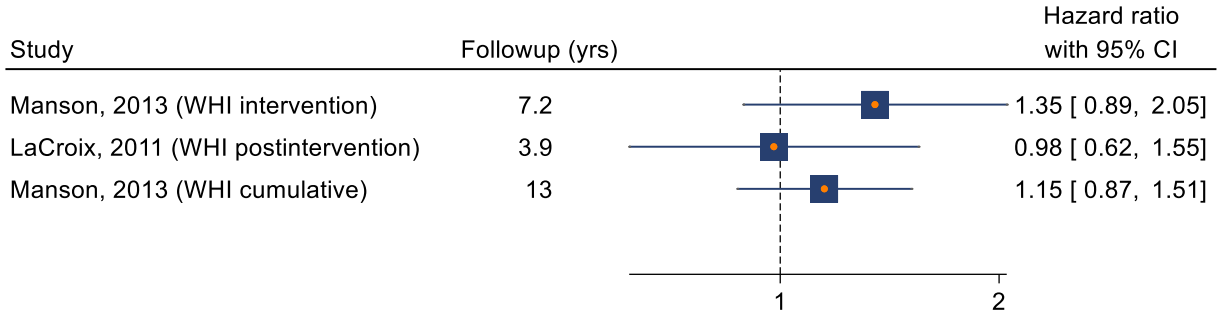
Abbreviations: CI=confidence interval; ULTRA=Ultra Low-Dose Transdermal Estrogen Replacement Assessment; WHI=Women's Health Initiative.

Appendix G Figure 13. Hazard Ratios for Deep Vein Thrombosis for Estrogen-Only Trials



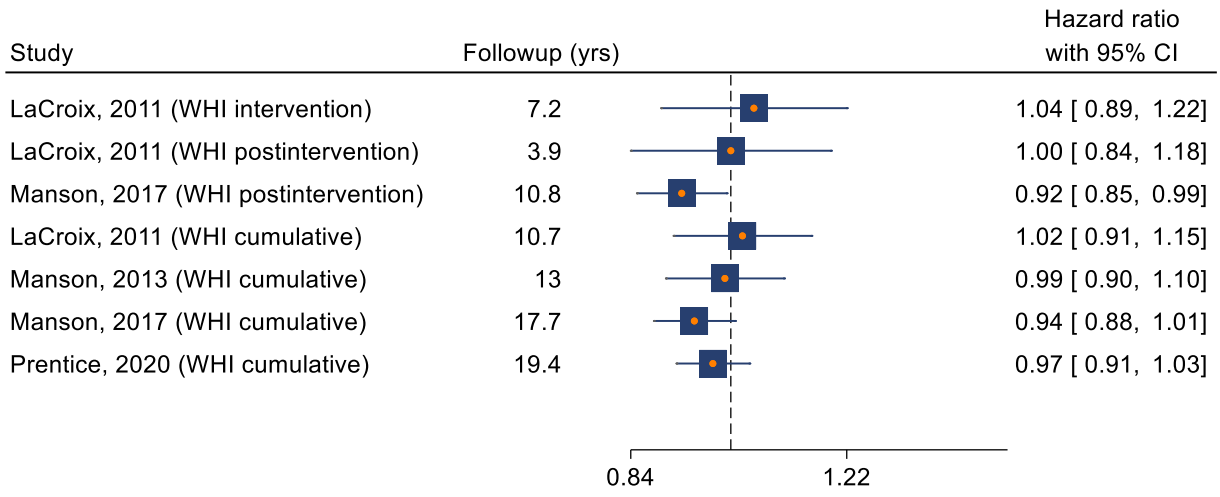
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 14. Hazard Ratios for Pulmonary Embolism for Estrogen-Only Trials



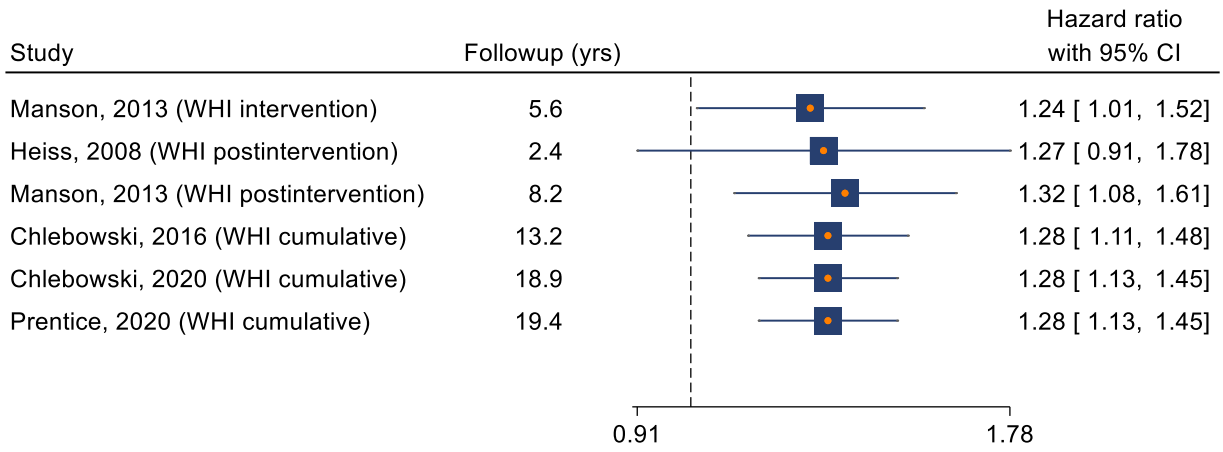
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 15. Hazard Ratios for All-Cause Mortality for Estrogen-Only Trials



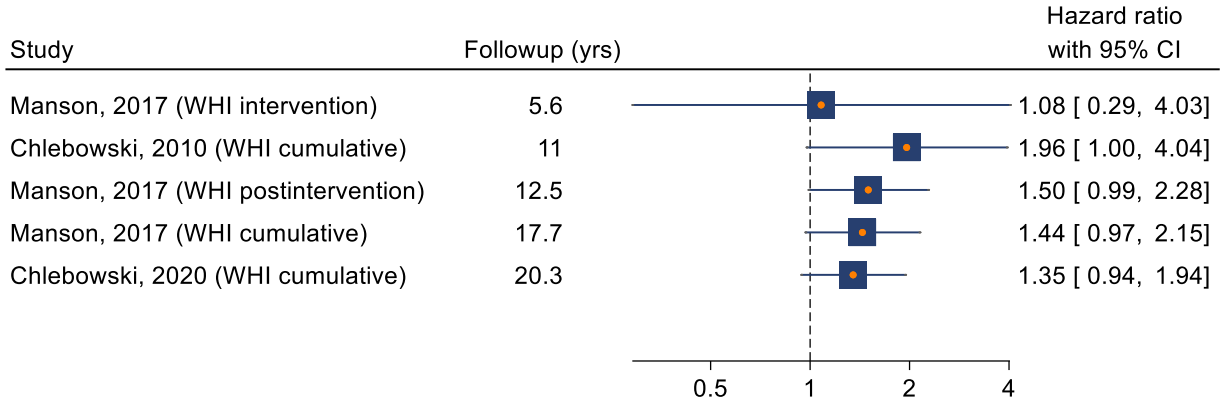
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 16. Hazard Ratios for Invasive Breast Cancer for Estrogen Plus Progestin Trials



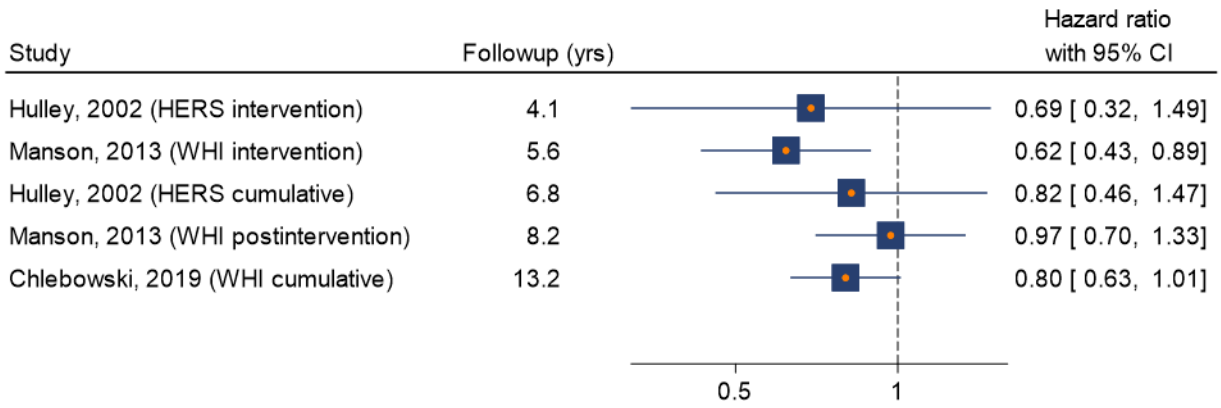
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 17. Hazard Ratios for Breast Cancer Mortality for Estrogen Plus Progestin Trials



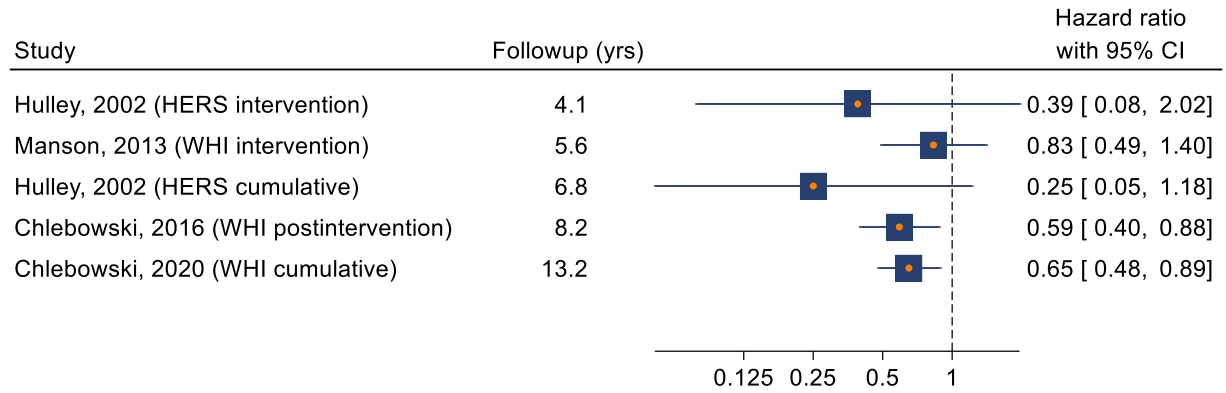
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 18. Hazard Ratios of Colorectal Cancer for Estrogen Plus Progestin Trials



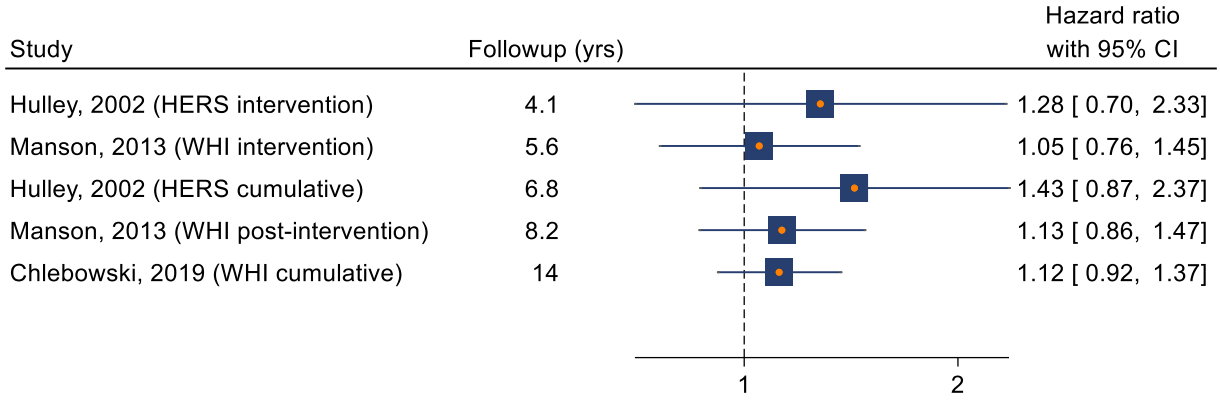
Abbreviations: CI=confidence interval; HERS=Heart and Estrogen/Progestin Replacement Study; WHI=Women's Health Initiative.

Appendix G Figure 19. Hazard Ratios for Endometrial Cancer for Estrogen Plus Progestin Trials



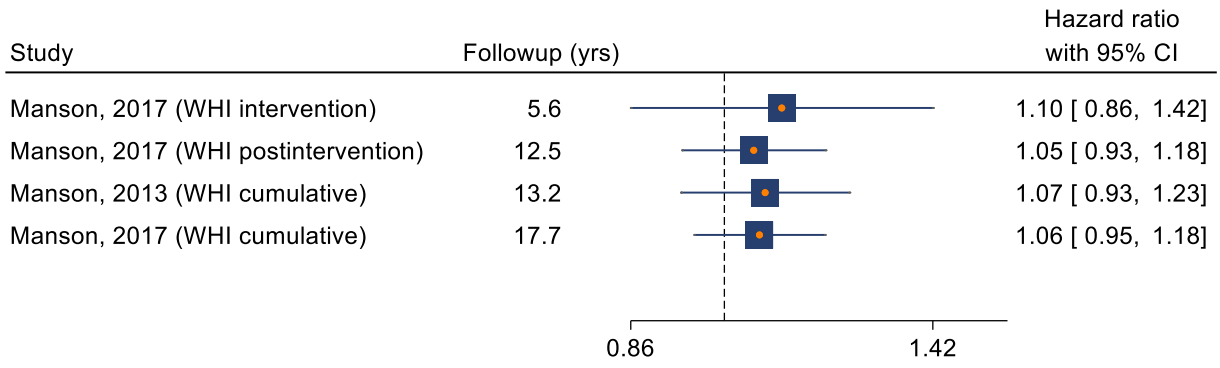
Abbreviations: CI=confidence interval; HERS=Heart and Estrogen/Progestin Replacement Study; WHI=Women's Health Initiative.

Appendix G Figure 20. Hazard Ratios for Lung Cancer for Estrogen Plus Progestin Trials



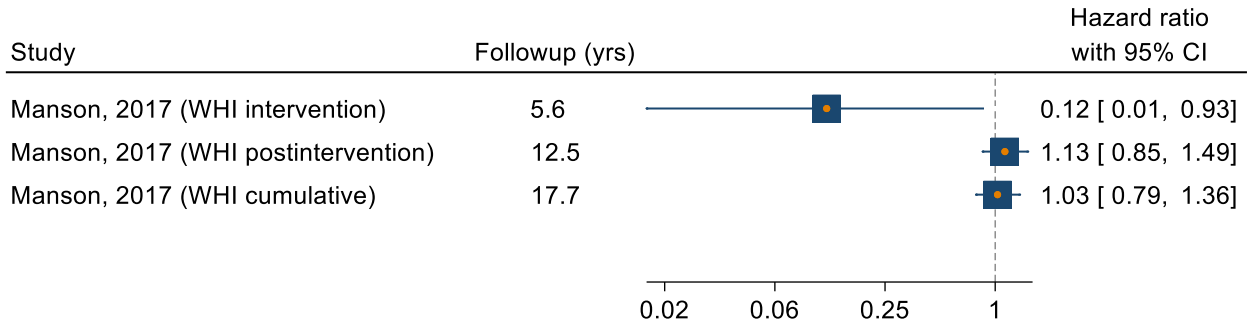
Abbreviations: CI=confidence interval; HERS=Heart and Estrogen/Progestin Replacement Study; WHI=Women's Health Initiatives.

Appendix G Figure 21. Hazard Ratios for Total Cancer Mortality for Estrogen Plus Progestin Trials



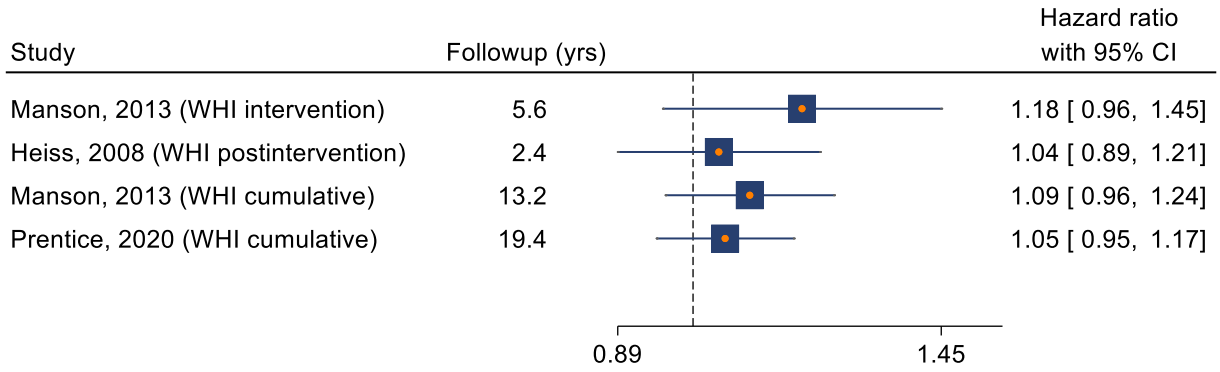
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 22. Hazard Ratios for COPD Mortality for Estrogen Plus Progestin Trials



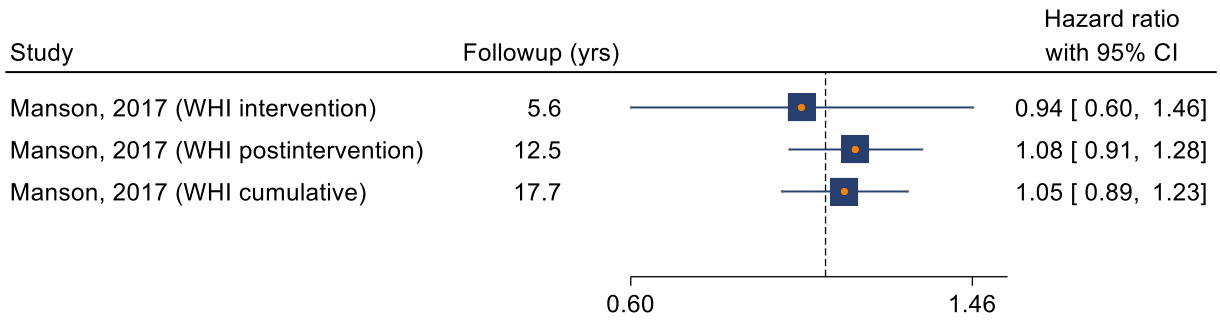
Abbreviations: CI=confidence interval; COPD=chronic obstructive pulmonary disease; WHI=Women's Health Initiative.

Appendix G Figure 23. Hazard Ratios for Coronary Heart Disease for Estrogen Plus Progestin Trials



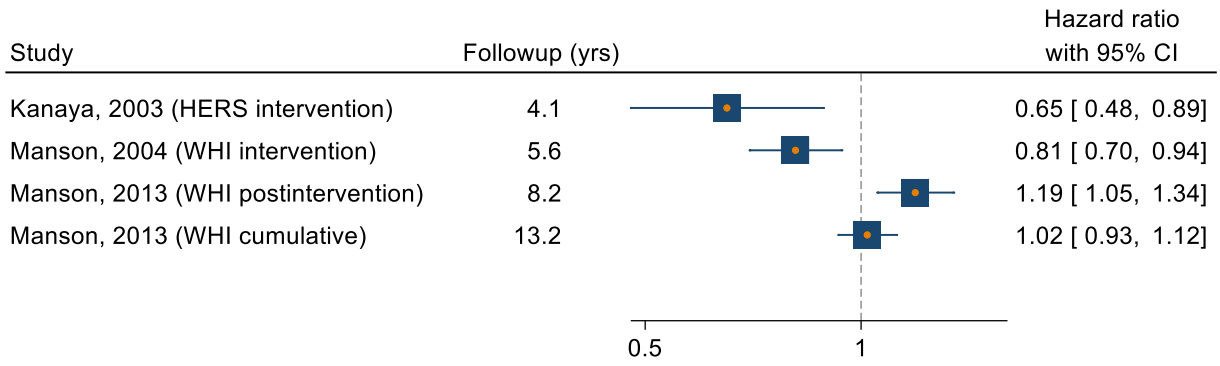
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 24. Hazard Ratios for Coronary Heart Disease Mortality for Estrogen Plus Progestin Trials



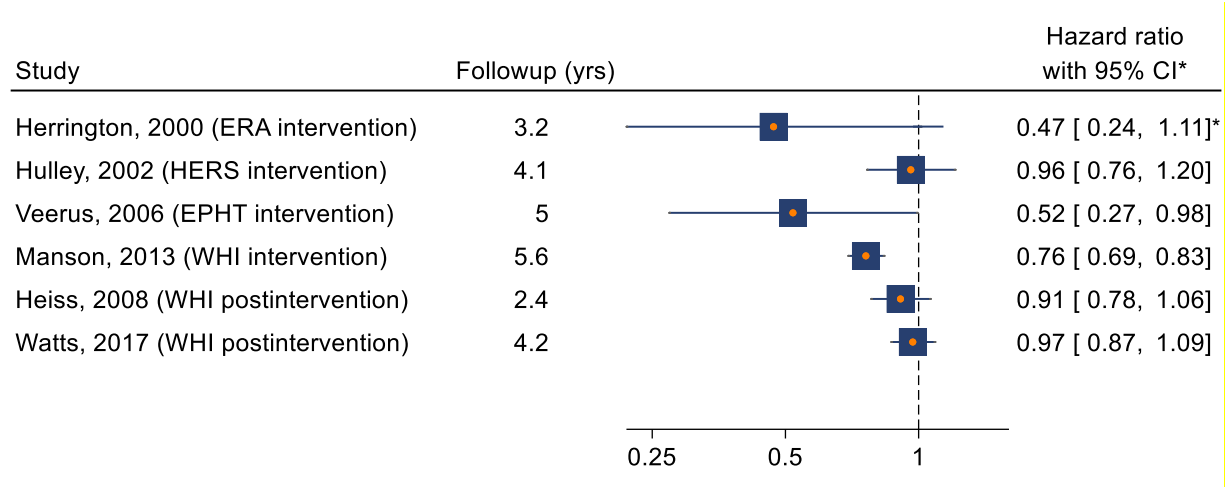
Abbreviations: CI=confidence interval; WHI=Women's Health Initiative.

Appendix G Figure 25. Hazard Ratios for Incident Diabetes for Estrogen Plus Progestin Trials



Abbreviations: CI=confidence interval; HERS=Heart and Estrogen/progestin Replacement Study; WHI=Women's Health Initiative.

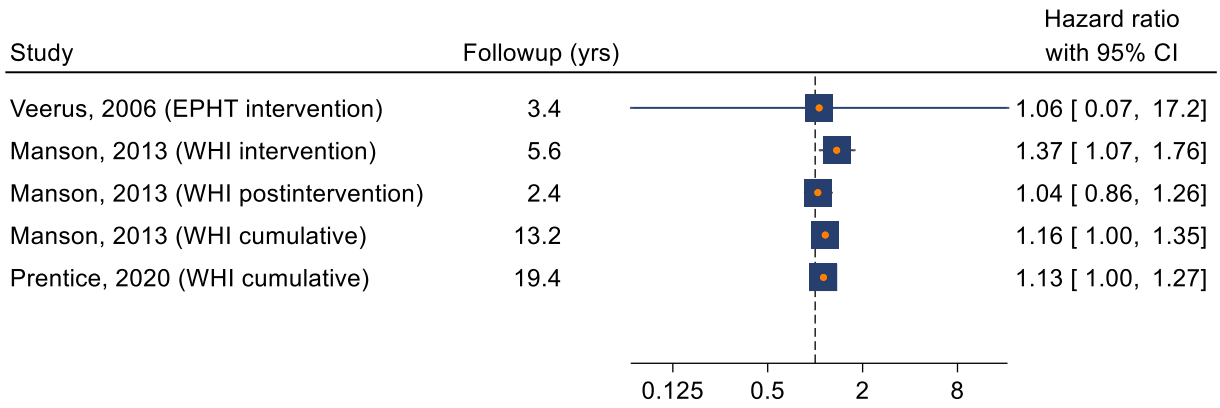
Appendix G Figure 26. Hazard Ratios for Total Fractures for Estrogen Plus Progestin Trials



* The ERA trial's effect estimate was a calculated risk ratio.

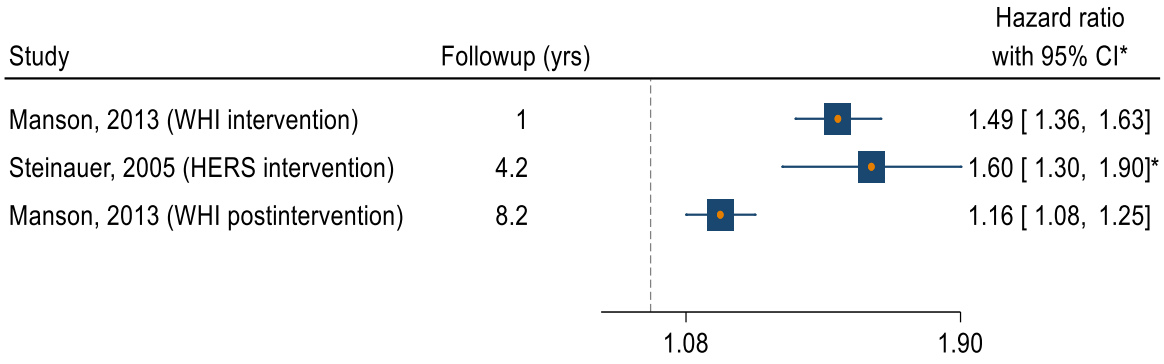
Abbreviations: CI=confidence interval; EPHT=Estonian Postmenopausal Hormones Therapy Trial; ERA=Estrogen Replacement and Atherosclerosis; HERS=Heart and Estrogen/progestin Replacement Study; WHI=Women's Health Initiative.

Appendix G Figure 27. Hazard Ratios for Stroke for Estrogen Plus Progestin Trials



Abbreviations: CI=confidence interval; EPHT=Estonian Postmenopausal Hormones Therapy Trial; WHI=Women's Health Initiative.

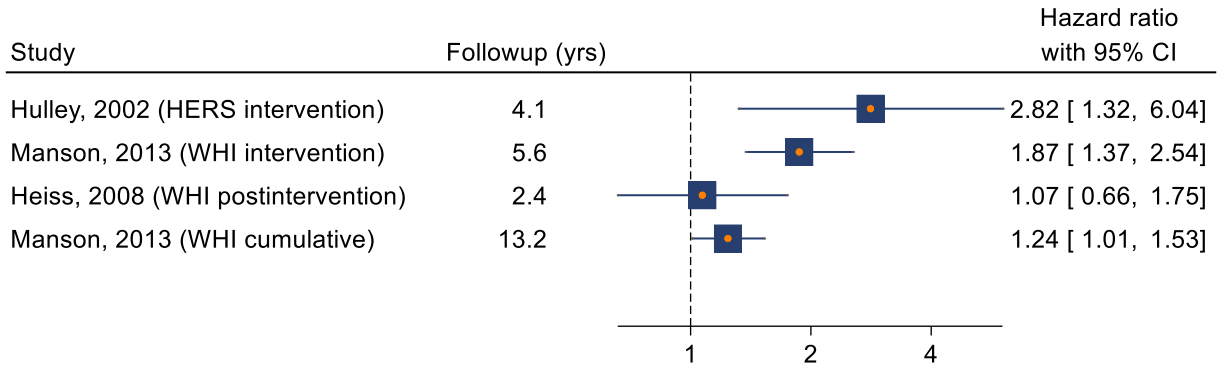
Appendix G Figure 28. Effect Estimates for Incident Weekly Urinary Incontinence for Estrogen Plus Progestin Trials



* The HERS trial's effect estimate was an odds ratio.

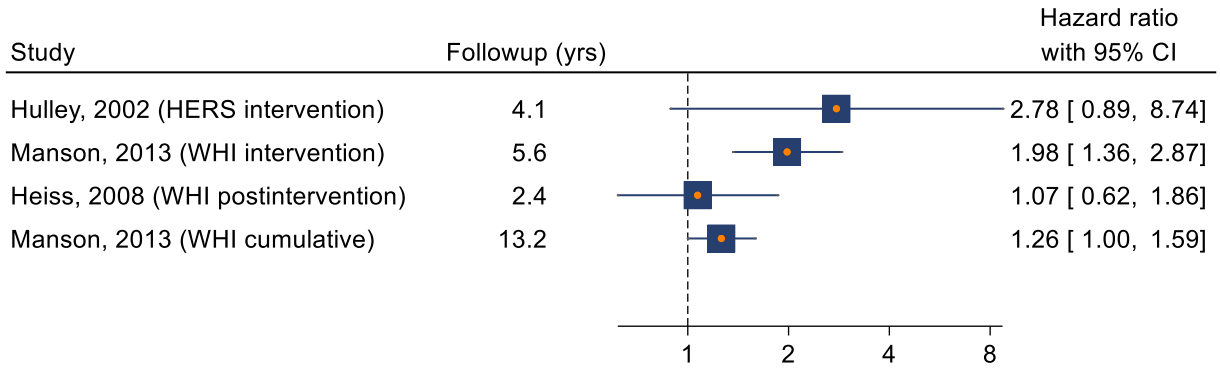
Abbreviations: CI=confidence interval; HERS=Heart and Estrogen/Progestin Replacement Study; WHI=Women's Health Initiative.

Appendix G Figure 29. Hazard Ratios for Deep Vein Thrombosis for Estrogen Plus Progestin Trials



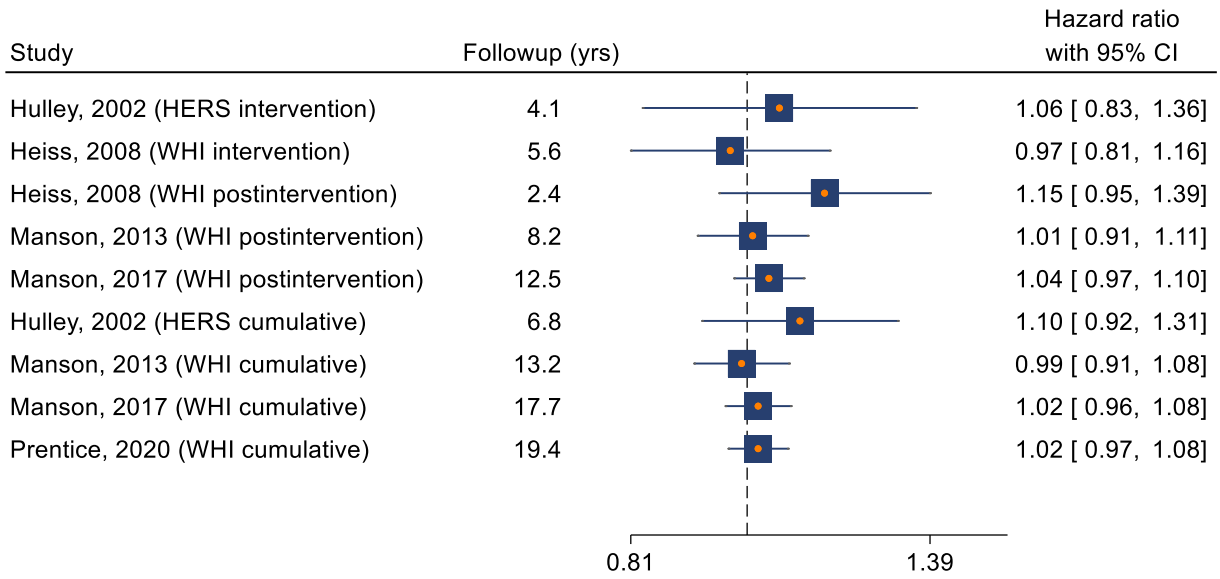
Abbreviations: CI=confidence interval; HERS=Heart and Estrogen/Progestin Replacement Study; WHI=Women's Health Initiative.

Appendix G Figure 30. Hazard Ratios for Pulmonary Embolism for Estrogen Plus Progestin Trials



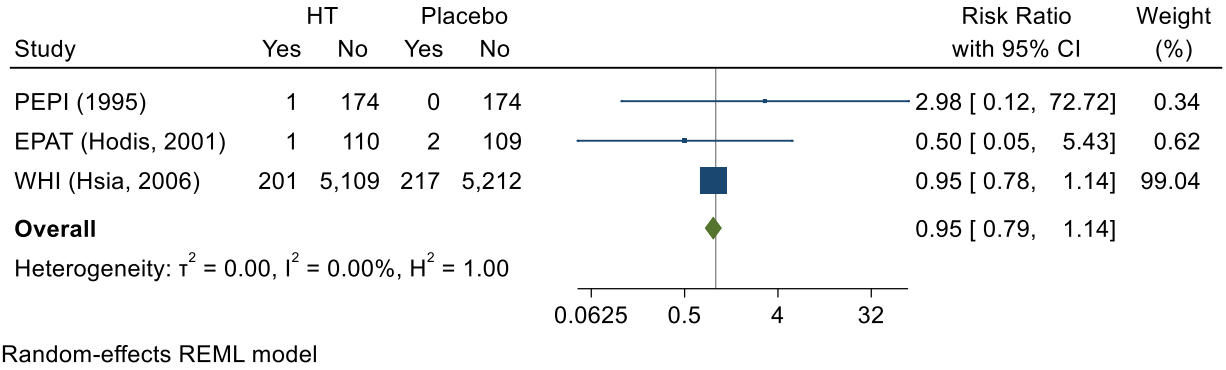
Abbreviations: CI=confidence interval; HERS=Heart and Estrogen/Progestin Replacement Study; WHI=Women's Health Initiative.

Appendix G Figure 31. Hazard Ratios for All-Cause Mortality for Estrogen Plus Progestin Trials



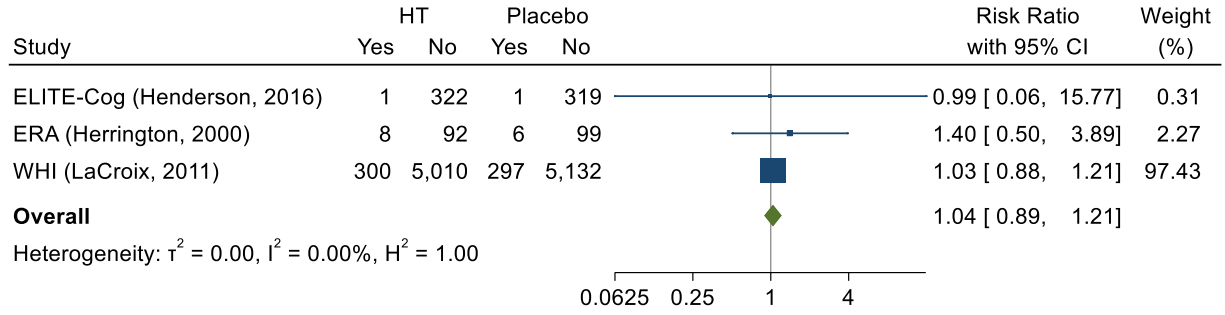
Abbreviations: CI=confidence interval; HERS=Heart and Estrogen/Progestin Replacement Study; WHI=Women's Health Initiative.

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



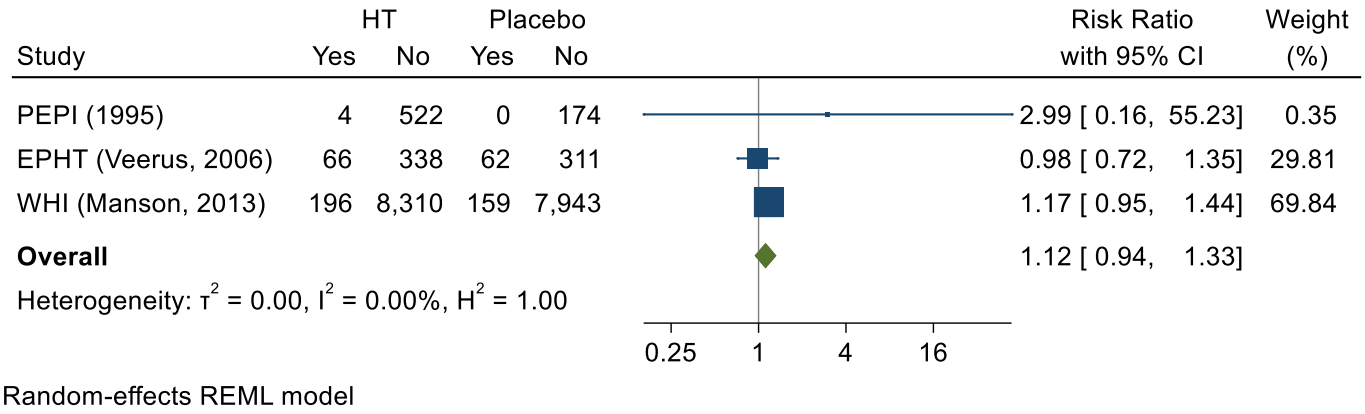
Abbreviations: CI=confidence interval; EPAT=Estrogen in the Prevention of Atherosclerosis; HT=hormone therapy; PEPI=Postmenopausal Estrogen and Progestin Interventions Trial; REML=restricted maximum likelihood; WHI=Women's Health Initiative.

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



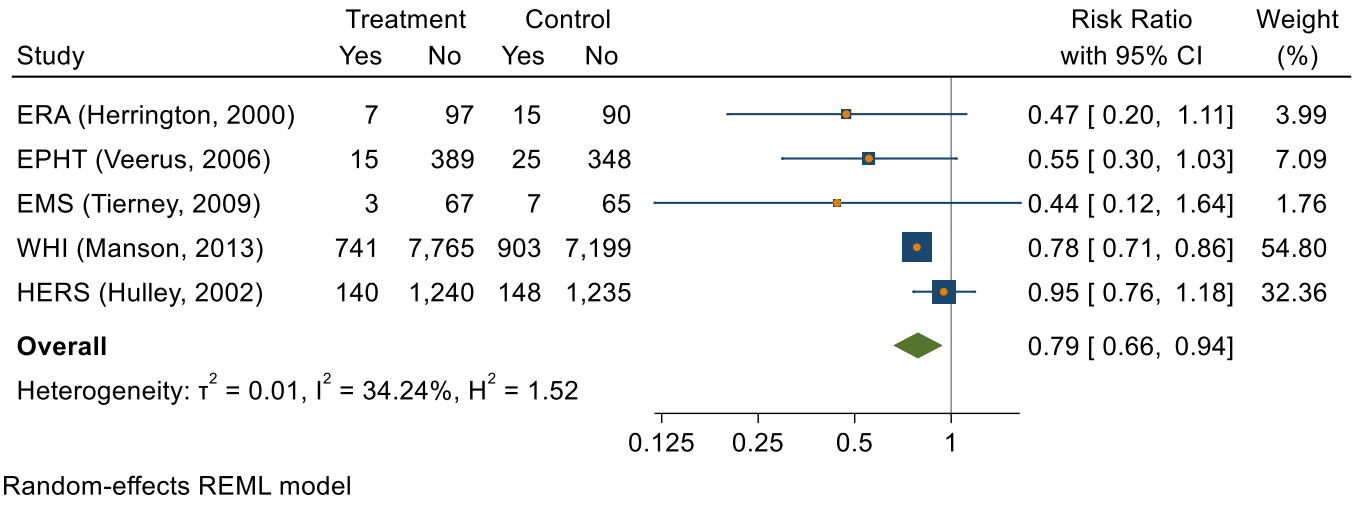
Abbreviations: CI=confidence interval; ELITE=Early versus Late Intervention Trial with Estradiol, Cognitive Endpoints; ERA=Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis; HT=hormone therapy; REML=restricted maximum likelihood; WHI=Women's Health Initiative.

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



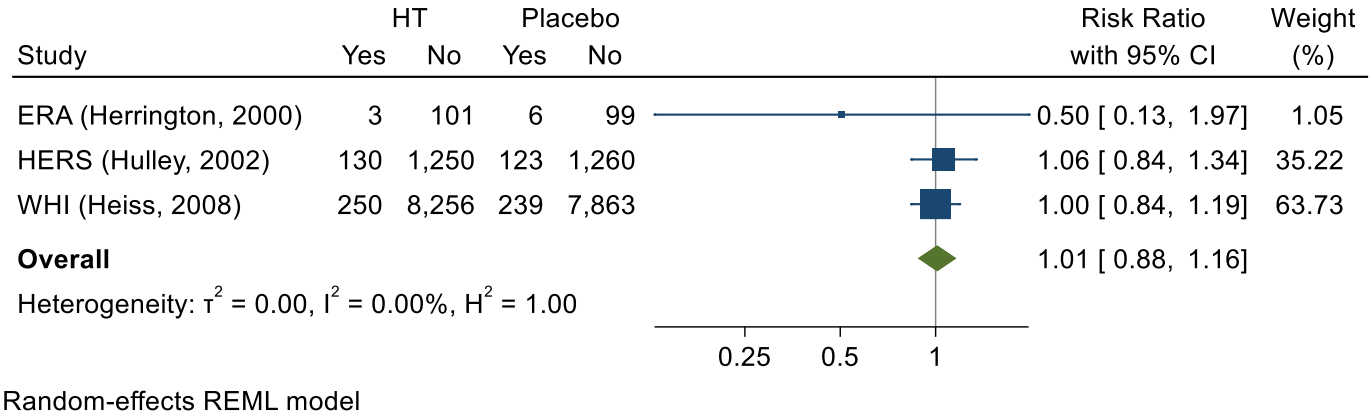
Abbreviations: CI=confidence interval; EPHT=Estonian Postmenopausal Hormone Therapy Trial; HT=hormone therapy; PEPI=Postmenopausal Estrogen and Progestin Interventions Trial; REML=restricted maximum likelihood; WHI=Women's Health Initiative.

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=Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis; HERS=Heart and Estrogen/Progestin Replacement Study; REML=restricted maximum likelihood; 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=Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis; HERS=Heart and Estrogen/Progestin Replacement Study; HT=hormone therapy; REML=restricted maximum likelihood; WHI=Women's Health Initiative.

Appendix I. Eligible Observational Studies

1. Bethea TN, Palmer JR, Adams-Campbell LL, et al. A prospective study of reproductive factors and exogenous hormone use in relation to ovarian cancer risk among Black women. *Cancer Causes Control*. 2017 May;28(5):385-91. doi: 10.1007/s10552-016-0840-4. PMID: 28025764.
2. Bhupathiraju SN, Grodstein F, Rosner BA, et al. Hormone therapy use and risk of chronic disease in the Nurses' Health Study: a comparative analysis with the Women's Health Initiative. *Am J Epidemiol*. 2017 Sep 15;186(6):696-708. doi: 10.1093/aje/kwx131. PMID: 28938710.
3. Botteri E, Støer NC, Sakshaug S, et al. Menopausal hormone therapy and colorectal cancer: a linkage between nationwide registries in Norway. *BMJ Open*. 2017 Nov 15;7(11):e017639. doi: 10.1136/bmjopen-2017-017639. PMID: 29146641.
4. Brusselaers N, Maret-Ouda J, Konings P, et al. Menopausal hormone therapy and the risk of esophageal and gastric cancer. *Int J Cancer*. 2017 Apr 1;140(7):1693-9. doi: 10.1002/ijc.30588. PMID: 28006838.
5. Cervenka I, Al Rahmoun M, Mahamat-Saleh Y, et al. Postmenopausal hormone use and cutaneous melanoma risk: a French prospective cohort study. *Int J Cancer*. 2019 Oct 1;145(7):1754-67. doi: 10.1002/ijc.32150. PMID: 30671928.
6. Curhan SG, Eliassen AH, Eavey RD, et al. Menopause and postmenopausal hormone therapy and risk of hearing loss. *Menopause*. 2017 Sep;24(9):1049-56. doi: 10.1097/gme.0000000000000878. PMID: 28486246.
7. Dartois L, Fagherazzi G, Baglietto L, et al. Proportion of premenopausal and postmenopausal breast cancers attributable to known risk factors: estimates from the E3N-EPIC cohort. *Int J Cancer*. 2016 May 15;138(10):2415-27. doi: 10.1002/ijc.29987. PMID: 26756677.
8. Eun Y, Jeon KH, Han K, et al. Menopausal factors and risk of seropositive rheumatoid arthritis in postmenopausal women: a nationwide cohort study of 1.36 million women. *Sci Rep*. 2020 Nov 27;10(1):20793. doi: 10.1038/s41598-020-77841-1. PMID: 33247198.
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10. Jeon KH, Shin DW, Han K, et al. Female reproductive factors and the risk of lung cancer in postmenopausal women: a nationwide cohort study. *Br J Cancer*. 2020 Apr;122(9):1417-24. doi: 10.1038/s41416-020-0789-7. PMID: 32203211.
11. Jiang Y, Xie Q, Chen R. Breast cancer incidence and mortality in relation to hormone replacement therapy use among postmenopausal women: results from a prospective cohort study. *Clin Breast Cancer*. 2021 Jun 26doi: 10.1016/j.clbc.2021.06.010. PMID: 34548240.
12. Jones ME, Schoemaker MJ, Wright L, et al. Menopausal hormone therapy and breast cancer: what is the true size of the increased risk? *Br J Cancer*. 2016 Aug 23;115(5):607-15. doi: 10.1038/bjc.2016.231. PMID: 27467055.
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15. Laaksonen MA, Arriaga ME, Canfell K, et al. The preventable burden of endometrial and ovarian cancers in Australia: a pooled cohort study. *Gynecol Oncol*. 2019 Jun;153(3):580-8. doi: 10.1016/j.ygyno.2019.03.102. PMID: 30935715.
16. Liu Q, Simin J, Debelius J, et al. Menopausal hormone therapies and risk of colorectal cancer: a Swedish matched-cohort study. *Aliment Pharmacol Ther*. 2021 Jun;53(11):1216-25. doi: 10.1111/apt.16362. PMID: 33857339.
17. Løkkegaard E, Nielsen LH, Keiding N. Risk of stroke with various types of menopausal hormone therapies: a national cohort study. *Stroke*. 2017 Aug;48(8):2266-9. doi: 10.1161/strokeaha.117.017132. PMID: 28626058.

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19. Nwaru BI, Shah SA, Tibble H, et al. Hormone replacement therapy and risk of severe asthma exacerbation in perimenopausal and postmenopausal women: 17-year national cohort study. *J Allergy Clin Immunol Pract*. 2021 Jul;9(7):2751-60.e1. doi: 10.1016/j.jaip.2021.02.052. PMID: 33705997.
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22. Peila R, Arthur R, Rohan TE. Risk factors for ductal carcinoma in situ of the breast in the UK Biobank cohort study. *Cancer Epidemiol*. 2020 Feb;64:101648. doi: 10.1016/j.canep.2019.101648. PMID: 31837535.
23. Qureshi AI, Malik AA, Saeed O, et al. Hormone replacement therapy and the risk of subarachnoid hemorrhage in postmenopausal women. *J Neurosurg*. 2016 Jan;124(1):45-50. doi: 10.3171/2014.12.Jns142329. PMID: 26162033.
24. Román M, Graff-Iversen S, Weiderpass E, et al. Postmenopausal hormone therapy and breast cancer prognostic characteristics: a linkage between nationwide registries. *Cancer Epidemiol Biomarkers Prev*. 2016;25(11):1464. doi: 10.1158/1055-9965.EPI-16-0240.
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26. Shah SA, Tibble H, Pillinger R, et al. Hormone replacement therapy and asthma onset in menopausal women: national cohort study. *J Allergy Clin Immunol*. 2020 Dec 3doi: 10.1016/j.jaci.2020.11.024. PMID: 33279576.
27. Simin J, Tamimi R, Lagergren J, et al. Menopausal hormone therapy and cancer risk: an overestimated risk? *Eur J Cancer*. 2017 Oct;84:60-8. doi: 10.1016/j.ejca.2017.07.012. PMID: 28783542.
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CQ 1: What Is the Average Treatment Duration of Hormone Therapy in Women Who Initiate Its Use for the Treatment of Menopausal Symptoms?

We did not identify any evidence to address this CQ.

CQ 2: Does the Use of Hormone Therapy Differ by Subgroup?

Five articles reported on the use of hormone therapy by subgroups of interest identified in KQ 3.[181-185]

Race or ethnicity. A secondary analysis of data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a large multicenter randomized trial from 1993 to 2001 with 75,587 women ages 55 to 74 years, found that more women who never used hormone therapy (estrogen only or estrogen plus progestin) were non-Hispanic Black compared with current hormone therapy users and former hormone therapy users (8.5% vs. 3.4% vs. 6.7%; $p<0.001$).[181]

Age. A retrospective cohort study with data from 353,173 perimenopausal and postmenopausal women (ages 45 to 70 years) from the Optimum Patient Care Research Database (OPCRD) in the United Kingdom found use of any hormone therapy, estrogen-only therapy, or estrogen plus progestin therapy was highest among women ages 51 to 55 years compared with use in other age groups.[184]

Comorbid condition. Five articles reported on the use of hormone therapy by BMI.[181-185] In the PLCO Cancer Screening Trial, the group of women who never used hormone therapy had the highest average BMI (kg/m^2) compared with current hormone therapy users and former hormone therapy users (27.9 vs. 26.5 vs. 27.5; $p<0.001$).[181] The WHI Observational Study of postmenopausal women with a hysterectomy similarly found that women who used hormone therapy tended to have a lower BMI.[182] In a national prescription register study in Finland among women ages 40 to 44 years, a larger proportion of women with a BMI less than 30 kg/m^2 started hormone therapy (estrogen, progesterone, or progesterone plus estrogen) compared with women with a BMI of 30 or greater.[185] In addition, the OPRCD retrospective cohort found the use of any hormone therapy was highest among women with a BMI less than 25 kg/m^2 compared with the use in women with a higher BMI score.[184] The WHI Observational Study found that a higher proportion of women with an intact uterus who used oral estradiol plus progestin (56%) and transdermal estradiol plus progestin (56%) had a BMI less than 25 kg/m^2 compared with women who used oral CEE plus progestin (50%).[183] Among women who had a prior hysterectomy, the proportion of women with a BMI less than 25 kg/m^2 was similar across groups: oral CEE alone (41%) vs. oral estradiol alone (43%) vs. transdermal estradiol alone (42%).[183]