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Structured Abstract

**Background:** Menopausal hormone therapy to prevent chronic conditions, such as cardiovascular disease and cancer, is currently not recommended because of its adverse effects.

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

**Data Sources:** We searched MEDLINE (January 2002 to November 30, 2011), Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through third quarter 2011), Scopus, and reference lists.

**Study Selection:** We included English-language, randomized, placebo-controlled trials that evaluated the prevention of new conditions rather than treatment of existing conditions and reported health outcomes.

**Data Extraction:** We abstracted details about participants, study design, analysis, followup, and results; study quality was rated using established criteria.

**Data Synthesis:** Nine fair-quality trials provided data for outcomes. The Women’s Health Initiative (WHI) reported most of the results, had 11 years of followup, and was most applicable to the target population. Participants in the WHI estrogen only trial had more risk factors for cardiovascular disease and fewer for breast cancer than those in the estrogen plus progestin trial. In WHI, compared with placebo, estrogen plus progestin reduced fractures (46/10,000 women-years) and increased invasive breast cancer (8/10,000), stroke (9/10,000), deep vein thrombosis (12/10,000), pulmonary embolus (9/10,000), lung cancer death (5/10,000), gallbladder disease (20/10,000), dementia (22/10,000), and urinary incontinence (872/10,000). Estrogen only reduced fractures (56/10,000) and invasive breast cancer incidence (8/10,000) and death (2/10,000), and increased stroke (11/10,000), deep vein thrombosis (7/10,000), gallbladder disease (33/10,000), and urinary incontinence (1271/10,000). Among subgroup analyses, there were no consistent differences by age and comorbidities.

**Limitations:** Few trials or subgroup analyses were powered for prevention outcomes; 40 to 50 percent of WHI participants discontinued their medications by the end of the trial.

**Conclusions:** Both hormone therapy regimens decreased fractures but increased stroke, thromboembolic events, gallbladder disease, and urinary incontinence. Estrogen plus progestin increased breast cancer and probable dementia, while estrogen alone decreased breast cancer.
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CHAPTER 1. INTRODUCTION

Purpose of Review and Prior USPSTF Recommendation

This systematic evidence review is an update for the U.S. Preventive Services Task Force (USPSTF) recommendations on use of menopausal hormone therapy for postmenopausal women to prevent chronic health conditions such as cardiovascular disease, types of cancer, and osteoporotic fractures. Use of menopausal hormone therapy for treatment of menopausal symptoms, such as vasomotor hot flashes or urogenital atrophy, or for other indications is outside the scope of this review. Menopausal hormone therapy includes use of various forms, doses, and regimens of estrogen with or without progestin. Estrogen combined with progestin is used by women who have not had previous hysterectomies to prevent endometrial proliferation and endometrial cancer, whereas women with previous hysterectomies use estrogen only. (Abbreviations are listed in Appendix A.)

In 2002, the USPSTF recommended against the routine use of combined estrogen and progestin hormone therapy for the prevention of chronic conditions in postmenopausal women who have not had hysterectomies because the harmful effects were likely to exceed the chronic disease prevention benefits in most women (D recommendation). Based on the results of systematic reviews and early findings of the Women’s Health Initiative (WHI) trial of estrogen plus progestin, the USPSTF found good evidence that combined hormone therapy results in both benefits and harms. Benefits included reduced risk for fracture (good evidence) and colorectal cancer (fair evidence). Combined estrogen and progestin had no beneficial effect on coronary heart disease and suggested an increased risk (good evidence). Other harms included increased risk for breast cancer (good evidence), venous thromboembolism (good evidence), stroke (fair evidence), cholecystitis (fair evidence), dementia (fair evidence), and lower global cognitive function (fair evidence). Because of insufficient evidence, the USPSTF could not assess effects on the incidence of ovarian cancer, mortality from breast cancer or coronary heart disease, or all-cause mortality.

In 2005, the USPSTF recommended against the routine use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had previous hysterectomies based on results of the WHI trial of estrogen only in women with hysterectomies (D recommendation). The USPSTF found good evidence that the use of unopposed estrogen resulted in both benefits and harms. The benefits included reduced risk for fracture (good evidence), and harms included increased risk for venous thromboembolism (fair evidence), stroke (fair evidence), dementia (fair evidence), and lower global cognitive function (fair evidence). There was fair evidence that unopposed estrogen had no beneficial effect on coronary heart disease. The USPSTF could not assess the effects of unopposed estrogen on the incidence of breast cancer, ovarian cancer, or colorectal cancer, as well as breast cancer mortality or all-cause mortality.
Prevalence and Burden of Condition

Women transitioning through menopause and postmenopausal women are the target populations for hormone therapy use. For many years, hormone therapy was used by large numbers of women to treat menopausal symptoms, such as hot flashes, as well as to prevent chronic conditions such as cardiovascular disease, cognitive decline, and osteoporosis. Results from WHI, a large U.S.-based randomized, controlled trial (RCT) of hormone therapy compared with placebo, indicated that hormone therapy was associated with important adverse health effects. As a result, the U.S. Food and Drug Administration (FDA) changed the indications for use to now include only short-term treatment of menopausal symptoms and prevention of osteoporosis.  

Recommendations of Other Groups and Current Clinical Practice

The American Academy of Family Physicians, American Congress of Obstetricians and Gynecologists, American Heart Association, North American Menopause Society, and Canadian Task Force on Preventive Health Care recommend against use of menopausal hormone therapy for the prevention of chronic conditions in postmenopausal women (Table 1). The American College of Physicians directs individuals to the USPSTF recommendations. No professional organizations recommend use of hormone therapy outside the FDA indications.
CHAPTER 2. METHODS

Key Questions and Analytic Framework

A standard protocol was developed and followed for this review. Based on evidence from the previous review and using the methods of the USPSTF, USPSTF members and Agency for Healthcare Research and Quality (AHRQ) scientific staff determined the key questions for this update. Investigators created an analytic framework incorporating the key questions and outlining the patient populations, interventions, outcomes, and harms of menopausal hormone therapy (Figure 1). Key questions include:

1. What are the benefits of menopausal hormone therapy when used to prevent chronic conditions?
2. What are the harms of menopausal hormone therapy when used to prevent chronic conditions?
3. Do benefits and harms differ by subgroups? Subgroups include women with premature menopause; surgical menopause; age of use; types, doses, and modes of delivery of hormones; and presence of comorbidities.

The target population includes adult postmenopausal women eligible for use of estrogen with or without progestin. Women with known contraindications, such as thrombotic disorders, hormone sensitive cancer, and others, would be ineligible and are outside the scope of this review. Outcomes include cardiovascular disease such as coronary heart disease (CHD), stroke, and thromboembolic disease; cancer of the breast, colon, lung, endometrium, and ovaries; fractures at various sites; cognition and dementia; disease-specific and all-cause mortality, and new findings reported by the trials. This update includes health outcomes, such as fractures, rather than intermediate outcomes, such as bone mineral density, and emphasizes medications, health care settings, and populations of postmenopausal women applicable to U.S. primary care practice.

Search Strategies

In conjunction with a research librarian, investigators searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the third quarter of 2011), MEDLINE (2002 to November 30, 2011), reference lists of papers, and Scopus for relevant English-language studies and systematic reviews. Search strategies are described in Appendix B1.

Study Selection

Investigators selected studies on the basis of inclusion and exclusion criteria developed for each key question (Appendix B2). For all key questions, RCTs of postmenopausal hormone therapy versus placebo were included to determine its effectiveness in reducing risks for chronic conditions (key question 1), its harms (key question 2), and differences among the defined
population subgroups (key question 3). Trials were included that enrolled participants matching
the target population, were designed to prevent new conditions rather than treat existing
conditions, and provided results estimating risk reduction or elevation compared with placebo.
Estimates based on individual hormone therapy regimens rather than those that pooled results
from different regimens were included. For trials that enrolled participants with a preexisting
condition, such as CHD in the Heart and Estrogen/Progestin Replacement Study (HERS), data
were used for all outcomes except the preexisting condition and conditions related to it.

Some studies reported outcomes at multiple time points in the trial, including after the
postintervention phase. In these cases, results were selected based on specific outcome measures.
For conditions known to be related to ongoing exposure to hormone therapy, such as
thromboembolic disease and osteoporotic fractures, results reported at the end of the trial
intervention phase were used. For conditions initiated during exposure but continuing to accrue
after the intervention phase, such as cancer, results reported at the end of the trial
postintervention phase were used, if available. Investigators reviewed their selection of results
from the WHI trials with WHI investigators. Nominal, rather than adjusted, estimates were used
because they were considered the main results by the WHI investigators.

Observational studies were not included because of the existence of published RCTs designed to
address the key questions directly, and the known biases inherent in observational studies of
menopausal hormone use.

Data Abstraction and Quality Rating

From the included studies, an investigator abstracted details about the patient population, study
design, analysis, followup, and results. Essential data elements were confirmed by a second
investigator. Investigators used criteria developed by the USPSTF to rate the quality of each
study as good, fair, or poor (Appendix B3). Two investigators independently rated the quality of
studies and resolved discrepancies by consensus.

Data Synthesis

Results from WHI were used as the main estimates for each outcome rather than a meta-analysis
of all trials because the trials were heterogeneous, WHI was the most applicable to the key
questions, and results from WHI would dominate a meta-analysis because of its large enrollment.
As a group, the research team assessed the overall quality of the body of evidence for each key
question (good, fair, poor) using methods developed by the USPSTF based on the number,
quality, and size of studies; consistency of results between studies; and directness of effect.22

External Review

The draft report was reviewed by content experts, USPSTF members, AHRQ Program Officers,
and collaborative partners (Appendix B4).
CHAPTER 3. RESULTS

Description of Trials

A total of 4,524 abstracts were identified by the searches; of these, 704 full-text articles were reviewed, and 51 articles met inclusion criteria (Appendix B5, see Appendix B6 for a list of excluded full-text articles). Included articles provided data from nine RCTs of postmenopausal women comparing the effects of estrogen, either in combination with progestin or alone, against placebo for the prevention of chronic conditions. These include the WHI estrogen plus progestin trial,\(^\text{12,23-41}\) WHI estrogen only trial,\(^\text{29,35,39,42-50}\) Women’s Health Initiative Memory Study (WHIMS),\(^\text{51-55}\) Women’s Health Initiative Study of Cognitive Aging (WHISCA),\(^\text{56-58}\) HERS,\(^\text{59-65}\) Women’s International Study of Long Duration Oestrogen After Menopause (WISDOM),\(^\text{66}\) Oestrogen in the Prevention of Reinfarction Trial (ESPRIT),\(^\text{67}\) Estrogen Memory Study (EMS),\(^\text{68}\) and Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA)\(^\text{69-72}\) (Table 2). An additional article with new results from WHI\(^\text{73}\) that was published after the literature search was also included. Trial designs are described in Figures 2–5, and outcome measures in Table 3.

All trials met criteria for fair quality (quality ratings are provided in Table 2 and Appendix C1). Six trials were limited by attrition or low adherence to medications, including two main WHI trials, WHIMS, WHISCA, HERS, and ESPRIT. WHI and WISDOM were discontinued prematurely because of adverse events or concerns for adverse events. HERS II was discontinued early because it was determined that no useful information was likely to result from continuing. No trials rated poor quality were included in this review.

Women’s Health Initiative

The two main WHI trials were designed as randomized, double-blind trials comparing estrogen plus progestin or estrogen only against placebo.\(^\text{74}\) The primary outcome for both trials was CHD, and invasive breast cancer was the primary adverse event. Secondary outcomes included hip and other types of fractures; additional cardiovascular disease outcomes such as stroke and thromboembolic disease; endometrial, colorectal, and other types of cancer; and mortality. A global index was developed to estimate the effect of hormone therapy on overall health and included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

Participants were recruited by population-based direct mailing campaigns and media awareness programs to one of 40 clinical centers in the United States between 1993 and 1998. Eligibility criteria included postmenopausal status, aged 50 to 79 years at initial assessment, having an intact uterus for the estrogen plus progestin trial or a previous hysterectomy for the estrogen only trial, plans to reside in the area for 3 years, and ability to provide written informed consent. Women were excluded if they had a medical condition associated with a predicted survival of less than 3 years, breast cancer or other cancer within the last 10 years, alcoholism, dementia, or transportation limitations. Participants using hormone therapy at the baseline assessment were required to go through a 3-month washout period prior to randomization.
Participants enrolled in the two trials had different cardiovascular and breast cancer risk factors at baseline (Table 4). Those in the estrogen only trial had more risk factors for cardiovascular disease. These included high body mass index (BMI); history of previous myocardial infarction (MI), stroke, and thromboembolic events; high systolic and diastolic blood pressure; treatment for hypertension; high cholesterol levels requiring medication; and treatment for diabetes. Participants in the estrogen only trial also had characteristics that reduce risk for breast cancer, including more women with previous hysterectomies and bilateral oophorectomies, less with nulliparity, and fewer first pregnancies at age 30 years and older. However, more participants in the estrogen only trial had relatives with breast cancer and high BMI—factors that increase risk for breast cancer. Interpretation of results requires consideration of these differences, and acknowledgement that WHI was not a head-to-head trial of estrogen only versus estrogen plus progestin.

Participants were followed by telephone 6 weeks after randomization and every 6 months thereafter, with in-clinic visits each year to assess outcomes and adverse events. At each 6-month visit, reports of outcomes were obtained using self-administered questionnaires. Participants had mammography and clinical breast examinations annually, and electrocardiography at baseline and at 3 and 6 years. Adherence to study medication was assessed by weighing returned pill bottles, and study medications were withheld from participants who did not follow the protocol. Permanent discontinuation of study medications was required for participants who developed breast cancer, endometrial pathology, deep vein thrombosis (DVT), PE, malignant melanoma, meningioma, or triglyceride level >1000 mg/dL or received prescriptions of estrogen, testosterone, or selective estrogen receptor modulator medications from their personal physicians.

WHI estrogen plus progestin trial. The estrogen plus progestin trial randomized 16,608 participants; 8,506 received 0.625 mg per day of conjugated equine estrogen (CEE) plus 2.5 mg per day of medroxyprogesterone acetate (MPA) in a single tablet and 8,102 received matching placebo. There were no significant differences in baseline characteristics between groups. The mean age of participants was 63.3 years, the majority were white (84 percent in both groups), and most had never used hormone therapy in the past (74 percent in both groups).

Study participants, physicians, and outcome assessors were blinded to the assignment of medication throughout the trial. However, clinic gynecologists were unblinded when managing adverse effects, such as persistent vaginal bleeding for 3,444 (40.5 percent) participants in the estrogen plus progestin group and 548 (6.8 percent) in the placebo group. Participants who had a hysterectomy after randomization for reasons other than cancer were switched to estrogen only or placebo without unblinding (248 [2.9 percent] using estrogen plus progestin and 183 [2.3 percent] using placebo). A small imbalance in the number of participants in each group was a consequence of an early protocol change eliminating an estrogen only intervention for participants with a uterus.

The trial was planned for 8.5 years; however, it was stopped early in 2002 by the Data and Safety Monitoring Board after an average of 5.2 years. The Board concluded that increases in breast cancer, CHD, stroke, and PE outweighed reductions in fractures and colon cancer. At the time
the trial was stopped, vital status was known for 16,025 participants (96.5 percent), 449 (2.7 percent) had died, and 583 (3.5 percent) were lost to followup or stopped providing outcomes data for more than 18 months. Forty-two percent of participants in the treatment group and 38 percent in the placebo group had stopped taking study medications at some time during the trial. Data from these participants were included in the intention-to-treat analysis.

After discontinuation of the trial, assessment of outcomes continued until 2005, the end of the predefined trial period.\textsuperscript{33} Postintervention data were available for 8,052 participants from the original 8,506 participants randomized to receive estrogen plus progestin (95 percent), and for 7,678 of 8,102 participants in the original placebo group (95 percent). Participants lacking postintervention data did not differ by treatment group or from participants providing data. Participants were followed for an average of 2.4 years during the postintervention trial.

After the postintervention trial ended, participants provided consent for the extension trial for continued assessment of breast cancer incidence until 2009.\textsuperscript{25} Data were available for 6,545 participants from the estrogen plus progestin group and 6,243 from the placebo group who consented (83 percent of surviving participants from the original cohort). Baseline characteristics of participants consenting to the extension phase were similar to characteristics of the original WHI cohort. Participants who consented were slightly younger and more likely to be white compared with those who did not consent.

Only data from participants in the postintervention and extension phases of the WHI estrogen plus progestin trial that were analyzed based on originally assigned medication groups using an intention-to-treat analysis were used for this report.

\textbf{WHI estrogen only trial.} The estrogen only trial randomized 10,739 participants; 5,310 received 0.625 mg per day of CEE and 5,429 received matching placebo.\textsuperscript{42} There were no significant differences in baseline characteristics between groups. The mean age of participants was 63.6 years, most were white (75 percent in both groups), and approximately half had never used hormone therapy in the past (52 percent in both groups). As with the estrogen plus progestin trial, participants, physicians, and outcome assessors were blinded throughout the trial.

The trial was planned for 9 years; however, it was stopped early in 2004 by the Data and Safety Monitoring Board after an average of 6.8 years because of increased incidence of stroke in the estrogen group. At the time the trial was stopped, vital status was known for 95 percent of participants, 5.4 percent had died, and 54 percent had stopped taking their study medication.

After discontinuation of the trial, assessments of outcomes continued until 2005, the end of the predefined trial period.\textsuperscript{49} Postintervention data were available for 4,794 participants from the original 5,310 participants randomized to receive estrogen (90 percent), and for 4,877 of 5,429 participants in the original placebo group (90 percent). Participants lacking postintervention data did not differ by treatment group or from participants providing data. Participants were followed for an average of 3.9 years during the postintervention trial.

After the postintervention trial ended, participants provided consent for the extension trial for continued assessment of breast cancer incidence until 2009.\textsuperscript{49} Data were available for 3,778
participants from the estrogen group and 3,867 from the placebo group who consented (75 percent of surviving participants from the original cohort). Baseline characteristics of participants consenting to the extension phase were similar to the characteristics of the original WHI cohort. However, there were slight differences between groups, with more participants in the estrogen only group having no previous pregnancies (9.3 vs. 8.0 percent; p=0.04) and fewer with bilateral oophorectomies (39.0 vs. 41.8 percent; p=0.01) than in the placebo group.

Only data from participants in the postintervention and extension phases of the WHI estrogen only trial that were analyzed based on originally assigned medication groups using an intention-to-treat analysis were used for this report.

**Women’s Health Initiative Memory Study**

WHIMS was a concurrent trial of participants enrolled in either the WHI estrogen plus progestin trial or the WHI estrogen only trial. The primary outcome was all-cause dementia. Secondary outcomes included mild cognitive impairment and global cognitive function. Enrollment was limited to women age 65 years or older and free of probable dementia.

In addition to the measures and laboratory tests required for the main WHI trials, participants in WHIMS completed the Modified Mini-Mental State Examination (3MSE) at baseline and annually thereafter. The 3MSE has 15 parts with 46 items and scores ranging from 0 to 100, with a higher score reflecting better cognitive function. WHIMS used the 3MSE to screen for global cognitive impairment and track changes. If participants scored at or below education-adjusted cut-off points, they completed an expanded neuropsychological battery. This included the modified Consortium to Establish a Registry for Alzheimer’s Disease and a clinical examination. These participants were also examined by a physician with experience diagnosing dementia, who reviewed all data and classified the participants as having no dementia, mild cognitive impairment, or probable dementia based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Participants diagnosed with probable dementia had an unenhanced computed tomography scan of the brain and laboratory blood tests to rule out possible reversible causes. If dementia was present after these tests, the physician diagnosed the most probable etiology based on reviewing all data. The diagnosis of vascular dementia, Alzheimer’s disease, and other dementia-related classifications was based on DSM-IV criteria. A panel of adjudicators independently reviewed all cases of probable dementia, as well as 50 percent of cases of mild cognitive impairment and a random sample of 10 percent of cases without dementia. All cases were discussed until a consensus was reached.

Of the 4,894 eligible participants from the WHI estrogen plus progestin trial, 4,532 (93 percent) agreed to participate in WHIMS; 2,229 in the estrogen plus progestin group and 2,303 in the placebo group. Nearly half of the participants were aged 65 to 69 years (47 percent in both groups) and most had never used hormone therapy in the past (78 percent in both groups). After 6 years of followup, only 32.3 percent of participants in the estrogen plus progestin group and 61.4 percent in the placebo group still adhered to their study medication. Of the 3,200 eligible participants from the WHI estrogen only trial, 2,947 (92 percent) agreed to participate in WHIMS; 1,464 in the estrogen group and 1,483 in the placebo group. Most participants were white (83 percent in estrogen group and 84 percent in placebo group), nearly half were aged 65
to 69 years (44 percent in estrogen group and 45 percent in placebo group), and half had never used hormone therapy in the past (54 percent in estrogen group and 55 percent in placebo group). After 7 years of followup, only 36.8 percent of participants in the estrogen group and 45.1 percent in the placebo group still adhered to their study medication.

Data were analyzed according to assigned groups at WHI enrollment and until the trial stopped in 2002 for the estrogen plus progestin trial and 2004 for the estrogen only trial. WHIMS did not include any postintervention or extension trial data.

**Women’s Health Initiative Study of Cognitive Aging**

WHISCA was a concurrent trial of women enrolled in either the WHIMS estrogen plus progestin trial or the estrogen only trial. The primary outcome was age-related changes in specific cognitive function. Enrollment was limited to English-speaking women without probable dementia at 14 of the 39 WHIMS centers. WHISCA was initiated 3 years after WHI randomization. In addition to the WHI and WHIMS measures, participants in WHISCA completed a battery of cognitive tests consisting of the Primary Mental Abilities scale, the Benton Visual Retention Test, the California Verbal Learning Test (CVLT), the Positive and Negative Affect Schedule, the Geriatric Depression Scale, verbal fluency (letter and semantic), attention and working memory ability (digits forward and backward), spatial rotation ability (card rotations), and fine motor speed (finger tapping).

Of the 2,089 eligible participants from the WHIMS estrogen plus progestin trial, 1,416 (67.8 percent) agreed to participate in WHISCA; 690 in the estrogen plus progestin group and 726 in the placebo group. The mean age of participants was 74 years, the majority were white (92 percent in estrogen plus progestin group and 93 percent in placebo group), and most had never used hormone therapy in the past (79 percent in estrogen plus progestin group and 77 percent in placebo group). After 3 years of followup, 42.2 percent in the estrogen plus progestin group and 44.1 percent in the placebo group completed final assessments. Of the 1,361 eligible participants from the WHIMS estrogen only trial, 866 (64 percent) agreed to participate in WHISCA; 434 in the estrogen group and 452 in the placebo group. The mean age of participants was 74 years, the majority were white (86 percent in estrogen group and 87 percent in placebo group), and half had never used hormone therapy in the past (50 percent in estrogen group and 54 percent in placebo group). After 4 years of followup, 75.1 percent in the estrogen group and 71.9 percent in the placebo group completed final assessments.

Data were analyzed according to assigned groups at WHI enrollment and until the trial stopped in 2002 for the estrogen plus progestin trial and 2004 for the estrogen only trial. WHISCA did not include any postintervention or extension trial data.

**Heart and Estrogen/Progestin Replacement Study**

HERS was a randomized, double-blinded, secondary prevention trial of estrogen plus progestin compared with placebo in women with established coronary artery disease. The primary outcome was the occurrence of nonfatal MI or CHD death. Secondary outcomes included other CHD outcomes, vascular disease, cancer, thromboembolism, gallbladder disease, fractures,
Participants were recruited from outpatient and community settings at 20 clinical centers in the United States between 1993 and 1994. Postmenopausal women younger than age 80 years with an intact uterus were eligible. Women were excluded if they reported a CHD event within 6 months of randomization, hormone therapy was contraindicated or used within 3 months of recruitment, they were participating in another trial, or they were thought to be unlikely to adhere to the protocol.

Participants were followed every 4 months to assess compliance, obtain data, and refill medications. Evaluations included annual general and cardiac examinations with electrocardiography; blood tests at first, third, and final visits; annual breast examinations, screening mammography, and pelvic examinations with Papanicolaou tests; and endometrial evaluations at second and final annual visits. Permanent discontinuation of study medications was required for participants who developed endometrial pathology; endometrial, cervical, breast, or ovarian cancer; DVT, PE, or prolonged immobilization; or active gallbladder disease.

There were 2,763 participants randomized; 1,380 received 0.625 mg per day of CEE and 2.5 mg per day of MPA in a single tablet and 1,383 received matching placebo. Baseline characteristics did not differ significantly between groups. The mean age of participants was 66.7 years, the majority were white (88 percent in estrogen plus progestin group and 90 percent in placebo group), and most had never used estrogen in the past (76 percent in estrogen plus progestin group and 77 percent in placebo group). Participants, physicians, and outcome assessors were blinded throughout the trial. Symptoms were addressed by separate medical staff.

During the middle years of the trial, the incidence of venous thromboembolic events in the estrogen plus progestin group exceeded safety thresholds. The Data Safety and Monitoring Board recommended against extending the trial beyond its scheduled closeout date. HERS ended in 1998 after 4.1 years of followup. Participants were informed of their treatment assignment and the main trial results. Blinded medication was stopped and participants were advised to make individual decisions about using open-label hormone therapy after discussing it with their personal physicians.

At the time the trial ended, vital status was available for all 2,763 participants. Self-reported adherence to study medications was 75 percent in the hormone group and 81 percent in the placebo group after 3 years, and pill counts indicated that 70 percent of participants in the hormone group were 80 percent adherent to their medications at the end of year 3. There were 36 (3 percent) participants in the estrogen plus progestin group and 110 (8 percent) in the placebo group who had discontinued their study medication and reported taking estrogen outside of the study. Closeout assessments were completed by 1,222 participants in the estrogen plus progestin group and 1,228 in the placebo group. Unadjusted intention-to-treat analysis was performed for the primary analysis. Secondary analyses using multivariate hazard models were adjusted to examine possible confounders by controlling for baseline covariates.

Of the surviving HERS participants, 2,321 (93 percent) agreed to enroll in HERS II followup and provided consent; 1,156 participants in the estrogen plus progestin group and 1,165 participants
in the placebo group. Baseline characteristics of participants in HERS II were not significantly different between groups. The mean age of participants was 67 years, the majority were white (89 percent in estrogen plus progestin group and 91 percent in placebo group), and a small proportion had used estrogen in the past (25 percent in estrogen plus progestin group and 23 percent in placebo group). Open-label followup continued in HERS II to collect additional data about CHD events. Documentation of clinical events in HERS II was the same as for HERS. Participants were contacted by telephone every 4 months and asked about health outcomes and their use of medications and hormones. Final telephone contacts were completed with 99 percent of survivors. Only data analyzed according to the original HERS assigned medication groups were included in this review.

HERS II was planned to continue for 4 years. Data were reviewed annually by a review committee who decided to discontinue HERS II after the second review because they determined that no useful information was likely to result from continuing until the end of the fourth year. The mean duration of followup in HERS II was 2.7 years. Among participants in the estrogen plus progestin group, 81 percent adhered to medications during the first year, declining to 45 percent during the sixth year, compared with none in the first year and 8 percent in the sixth year for participants in the placebo group taking open-label hormone therapy.

**Women’s International Study of Long Duration Oestrogen After Menopause**

WISDOM was a randomized, placebo-controlled and head-to-head, double-blind trial comparing estrogen plus progestin with placebo and estrogen only. This review uses results comparing estrogen plus progestin against placebo, because WISDOM did not report results comparing estrogen only against placebo, and comparisons of estrogen plus progestin against estrogen only are limited by baseline differences between participants. Primary outcomes were major cardiovascular disease, osteoporotic fractures, and breast cancer. Secondary outcomes included other types of cancer, death from all causes, venous thromboembolism, cerebrovascular disease, dementia, and quality of life. Outcomes were subsequently changed to exclude stroke and to include unstable angina.

Postmenopausal women aged 50 to 69 years were recruited from general medical practices in the United Kingdom (384 sites), Australia (91 sites), and New Zealand (24 sites) between 1999 and 2001. Women were excluded for hormone therapy use within 6 months; MI or cardiovascular event within 6 months; DVT or PE; history of cancer; renal impairment; liver or gallbladder disease; history of hepatitis B, hepatitis C, or HIV; current pregnancy; contraceptive use within 12 months; fasting triglyceride level >5.5 mmol/L; using selective estrogen receptor modulator medications; and any other conditions or circumstances limiting informed consent or trial procedures.

Participants were followed at 4, 14, 27, 40, and 52 weeks and every 6 months thereafter to assess outcomes and adverse events using a validated questionnaire administered by study nurses. At the annual visit, risk factors were also assessed and participants’ continued eligibility was
confirmed.

There were 4,385 participants randomized; 2,196 received 0.625 mg per day of CEE and 2.5 to 5.0 mg per day of MPA in a single tablet and 2,189 received matching placebo. Baseline characteristics did not differ significantly between groups. The mean age of participants was 63.3 years, almost all were white (99 percent in both groups), and half had never used hormone therapy previously (53 percent in estrogen plus progestin group and 54 percent in placebo group).

Participants, physicians, and outcome assessors were blinded throughout the trial. Unblinding occurred to manage adverse effects such as persistent vaginal bleeding for 712 (38 percent) participants in the estrogen plus progestin group and 66 (4 percent) participants in the placebo group.

While 10 years of treatment was planned, the trial was prematurely closed after publication of early results from WHI in 2002 showed increased risks with estrogen plus progestin. The median followup time was 11.9 months (interquartile range, 7.1 to 19.6). Because the trial closed early, the study was not adequately powered for most outcomes and dementia was never assessed.

Oestrogen in the Prevention of Reinfarction Trial

ESPRIT was a randomized, double-blind trial of estradiol valerate compared with placebo in women with recent MI. The primary outcomes were first nonfatal reinfarction, cardiac death, or death from another cause within 2 years of study entry. Secondary outcomes included uterine bleeding, endometrial cancer, breast cancer, stroke, other thromboembolic events, fractures, and compliance with treatment.

Participants were recruited by trained research nurses from coronary care units or general medical wards in participating hospitals in England and Wales between 1996 and 2000. Postmenopausal women aged 50 to 69 years who were recently discharged from the hospital after a MI, within 31 days of admission, and had had no previous MI were eligible. Exclusion criteria included use of hormone therapy; vaginal bleeding 12 months before admission; history of breast, ovarian, or endometrial carcinoma; active thrombophlebitis; history of DVT or PE; and acute or chronic liver disease, Rotor syndrome, Dubin-Johnson syndrome, or severe renal disease.

Participants were followed at 3, 6, 12, and 18 months to assess outcomes and adverse events using a questionnaire administered by their physicians. When a potential reinfarction was noted, trained research nurses obtained medical records to ascertain whether or not a reinfarction had occurred.

There were 1,017 participants randomized; 513 received 2 mg per day of estradiol valerate, while 504 received matching placebo. Baseline characteristics were similar between groups. The mean age of participants was 62.6 years, almost all were white (97 percent), and most had never used hormone therapy in the past (88 percent in estrogen group and 90 percent in placebo group). Participants, physicians, and outcome assessors were blinded throughout the trial. A separate
team of clinicians investigated uterine bleeding and other adverse effects. Participants were followed for 2 years after randomization and assessed using an intention-to-treat analysis.

**Estrogen Memory Study**

EMS was a randomized, double-blind trial of estrogen plus progestin given in a cyclical regimen with estrogen alone compared with placebo. The primary outcome was short-delay verbal recall (scored 0–16) on the CVLT. Secondary outcomes included immediate recall (sum of five immediate recall trials), new list recall (scored 0–16), cued recall (sum of four cued recall trials), recognition memory of the CVLT (true positives plus true negatives divided by total number of words), as well as the 3MSE.

Postmenopausal women aged 60 years or older who had their last menstrual cycle at least 12 months earlier were recruited from a single center in Toronto between 2000 and 2006. The trial included women with normal to below normal scores on the short-delay recall trial of the Rey Auditory Verbal Learning Test to increase the probability of detecting cognitive decline. Exclusion criteria included women with dementia or a clinical history of a neurological, systemic, or psychiatric condition that affects cognition, as well as any conditions that could be exacerbated by estrogen. Participants were followed annually to assess outcomes and adverse events, measure serum estradiol levels, and assess adherence to study medications. Participants who took less than 80 percent of their study medication were considered to have discontinued it.

There were 142 participants randomized; 70 received 1 mg of 17-β estradiol micronized per day for 4 days followed by 1 mg of 17-β estradiol plus 0.35 mg norethindrone per day in a single tablet for 3 days, repeated in this cycle every week, and 72 received matching placebo. Baseline characteristics did not differ significantly between groups. The mean age of participants was 75 years, the majority were white (96 percent in treatment group and 90 percent in placebo group), and most had never used hormone therapy in the past (69 percent in treatment group and 76 percent in placebo group).

Participants, physicians, and outcome assessors were blinded throughout the 2-year trial. A total of 62 (88.6 percent) participants in the treatment group and 66 (91.6 percent) in the placebo group completed 2-year assessments, and outcomes were assessed using an intention-to-treat analysis.

**Ultra-Low-Dose Transdermal Estrogen Assessment**

ULTRA was a randomized, double-blind trial of transdermal estradiol compared with placebo. Primary outcomes were bone mineral density and endometrial hyperplasia, both intermediate outcomes not meeting eligibility criteria for this review. However, clinical fractures were secondary outcomes. Cognitive function was measured, but not identified as an a priori outcome, and assessed by the 3MSE, Modified Boston Naming Test, Brief Visuospatial Memory Test, Logical Memory Immediate and Delayed, Word List Memory, Trails B, and verbal fluency. Participant recruitment was not reported. Postmenopausal women aged 60 to 80 years with an intact uterus, at least 5 years postmenopausal, and with osteoporosis but normal bone mineral density for their age were included. Exclusion criteria included unexplained uterine bleeding;
abnormal mammography suggestive of breast cancer; history of metabolic bone disease; cancer; CHD; venous thromboembolism; uncontrolled hypertension; thyroid disease; liver disease; fasting triglyceride of >300 mg/dL; fasting glucose of >180 mg/dL; prior use of fluoride, calcitonin, or bisphosphonates; or estrogen or progestin use within 3 months. Participants were followed every 4 months for 2 years and cognitive function was assessed at annual visits.

There were 417 participants randomized; 208 received 0.014 mg per day of estradiol transdermally and 209 received matching placebo. All participants received oral supplements of 400 mg calcium twice daily and 400 IU vitamin D once daily. Baseline characteristics did not differ between groups, except that participants in the treatment group had baseline bone mineral density at the lumbar spine that was 2 percent lower than the placebo group. Mean age of participants was 67 years and the majority were white (93 percent in treatment group and 92 percent in placebo group). Participants, physicians, and outcome assessors were blinded throughout the trial.

At the end of the trial, 191 (91.8 percent) participants in the treatment group and 185 (88.5 percent) in the placebo group completed the trial; of these, 18 (9.4 percent) in the treatment group and 24 (13 percent) in the placebo group had stopped taking their study medications.

Key Question 1. What Are the Benefits of Menopausal Hormone Therapy When Used to Prevent Chronic Conditions?

Summary

Results of trials indicated benefits for hormone therapy that vary by regimen. For participants using estrogen and progestin in WHI, hip, vertebral, and total fractures and diabetes were significantly reduced compared with placebo. For participants using estrogen only in WHI, invasive breast cancer incidence and death and hip, vertebral, and total fractures were reduced. Participants in HERS using estrogen and progestin had reduced diabetes, but not fractures.

Evidence

Benefits of hormone therapy are summarized in Table 5 according to regimen (estrogen with progestin [E+P] or estrogen only [E]), trial (WHI or other trials), and outcome (cancer, diabetes, and fractures). Results are expressed as hazard ratios (HRs) or rate ratios (RRs), with 95 percent confidence intervals (CIs). Results are further described in evidence tables in Appendices C2–C12.

Participants using estrogen only in WHI had reduced invasive breast cancer incidence (HR, 0.77 [95% CI, 0.62 to 0.95])\(^{49}\) and mortality (HR, 0.37 [95% CI, 0.13 to 0.91]).\(^{73}\) Colorectal cancer was reduced for participants using estrogen plus progestin (HR, 0.75 [95% CI, 0.57 to 1.00]),\(^{33}\) although results were of borderline statistical significance. Colorectal cancer was not reduced for participants using estrogen only in WHI\(^{49}\) or in the HERS trial of estrogen plus progestin.\(^{61}\)
The incidence of diabetes was reduced for participants using estrogen plus progestin in WHI (HR, 0.79 [95% CI, 0.67 to 0.93])\(^{38}\) and HERS (HR, 0.65 [95% CI, 0.48 to 0.89]),\(^{63}\) but not for estrogen only in WHI.\(^{43}\) Diabetes diagnosis was based on self-report in WHI and by fasting glucose levels in HERS (≥6.9 mmol/L).

Both estrogen plus progestin and estrogen only reduced hip, vertebral, and total fractures in WHI\(^{12,24,42,75}\) but not HERS.\(^{61}\) For estrogen plus progestin, estimates included a hazard ratio of 0.67 (95% CI, 0.47 to 0.95) for hip, 0.68 (95% CI, 0.48 to 0.96) for vertebral, and 0.76 (95% CI, 0.69 to 0.83) for total fractures. Results for the estrogen only trial were similar (Table 5). For most fracture outcomes in WHI, the confidence intervals included 1.00 when estimates were adjusted for multiple outcomes.

**Key Question 2. What Are the Harms of Menopausal Hormone Therapy When Used to Prevent Chronic Conditions?**

**Summary**

Results of trials indicated several important harms for hormone therapy that vary by regimen. For participants using estrogen and progestin in WHI, CHD, stroke, thromboembolic events (DVT and PE), invasive breast cancer, death from breast cancer, death from lung cancer, gallbladder disease, probable dementia, and urinary incontinence were significantly increased compared with placebo. For participants using estrogen only in WHI, stroke, thromboembolic events (DVT), gallbladder disease, and urinary incontinence were significantly increased compared with placebo. Participants in HERS using estrogen and progestin had increased urinary incontinence. Results are further described in evidence tables in Appendixes C2–C12.

**Evidence**

Harms of hormone therapy are summarized in Table 5 according to regimen (estrogen with progestin [E+P] or estrogen only [E]), trial (WHI or other trials), and outcome (cardiovascular events, thromboembolic events, cancer, death, gallbladder disease, cognitive function, and urinary incontinence). Results are expressed as hazard or rate ratios with 95 percent confidence intervals.

Contrary to the cardioprotective effects initially hypothesized, participants randomized to estrogen plus progestin in WHI had increased CHD, including nonfatal MI and CHD death, although results were of borderline statistical significance (HR, 1.22 [95% CI, 0.99 to 1.51]).\(^{33}\) CHD was not increased for participants randomized to estrogen only.\(^{49}\)

Stroke was significantly increased for both estrogen plus progestin (HR, 1.34 [95% CI, 1.05 to 1.71])\(^{33}\) and estrogen only (HR, 1.36 [95% CI, 1.08 to 1.71])\(^{59}\) in WHI. Thromboembolic events,
DVT and PE, were also increased in both WHI trials, but to higher levels for estrogen plus progestin\textsuperscript{33} than estrogen only.\textsuperscript{49}

Although breast cancer was reduced among participants in WHI using estrogen only, incidence was increased among participants using estrogen plus progestin (HR, 1.25 [95% CI, 1.07 to 1.46]).\textsuperscript{25} Other types of cancer, including lung, endometrial, ovarian, and cervical, were not significantly increased in the estrogen plus progestin trial.\textsuperscript{23,27,33} The estrogen only trial reported results for lung cancer that were not significantly increased.\textsuperscript{45} Invasive breast, lung, and endometrial cancer were not increased in HERS II.\textsuperscript{61}

All-cause mortality was not significantly increased in the WHI estrogen plus progestin, WHI estrogen only, HERS II, or ESPRIT trials. Death from breast cancer (HR, 1.96 [95% CI, 1.00 to 4.04])\textsuperscript{45} and lung cancer (HR, 1.71 [95% CI, 1.16 to 2.52])\textsuperscript{27} were increased for participants using estrogen plus progestin in WHI, although results for breast cancer mortality were of borderline statistical significance.

Gallbladder disease, cholecystectomy, and cholecystitis were all significantly increased in WHI for participants using estrogen plus progestin and estrogen only.\textsuperscript{29} Incidence was higher for estrogen only users (gallbladder disease: HR, 1.79 [95% CI, 1.44 to 2.22]).\textsuperscript{29}

Measures of impaired cognitive function were significantly increased for participants in WHI using estrogen plus progestin for probable dementia (HR, 2.05 [95% CI, 1.21 to 3.48]), but not mild cognitive impairment.\textsuperscript{55} These measures were not significantly increased for estrogen only.\textsuperscript{54}

Studies evaluating urinary incontinence used self-reported measures. The incidence of overall urinary incontinence was increased for participants using estrogen plus progestin (RR, 1.39 [95% CI, 1.27 to 1.52]) and estrogen only (RR, 1.53 [95% CI, 1.37 to 1.71]) after 1 year of treatment in WHI.\textsuperscript{35} Further analysis indicated increased risk for different types of urinary incontinence, including stress, urgency, and mixed for both the estrogen plus progestin and the estrogen only trials. In a subsample of estrogen plus progestin users continent at baseline, incontinence persisted during 3 years of followup.\textsuperscript{35} Weekly, stress, and urge incontinence were increased among estrogen plus progestin users in HERS (weekly odds ratio [OR], 1.6 [95% CI, 1.3 to 1.9]),\textsuperscript{54} but urinary incontinence was not significantly increased in ULTRA.\textsuperscript{71}

### Key Question 3. Do Benefits and Harms Differ by Subgroups?

### Summary

Subgroups defined by the key question include women with premature menopause; women with surgical menopause; age of use; types, doses, and modes of delivery of hormone; and presence of comorbidities. Trials did not report results for most of these subgroups, and post hoc subgroup analyses of trial results based on these characteristics were restricted to age and a limited number of comorbidities (Appendix C13). These included increased risk for breast cancer for
participants randomized to estrogen plus progestin with prior oral contraceptive use, prior estrogen plus progestin use, or smoking; increased CHD risk for participants randomized to estrogen plus progestin with high low-density lipoprotein (LDL) cholesterol levels or randomized to estrogen only with high C-reactive protein levels; increased thromboembolic disease for participants randomized to estrogen plus progestin who were older, obese, or possessed Factor V Leiden; and increased urinary incontinence for older participants using either regimen.

Evidence

**Breast cancer.** In the WHI estrogen plus progestin trial, invasive breast cancer incidence was reported by baseline characteristics for age (50–59, 60–69, and 70–79 years), BMI (normal, overweight, and obese categories), Gail risk score, prior estrogen plus progestin use, and time since menopause. Among these analyses, there were no significant differences based on age, BMI, or Gail risk score. However, breast cancer incidence was increased for participants who entered the study with prior estrogen plus progestin use (HR, 1.85 [95% CI, 1.25 to 2.80]) compared with participants with no prior use (HR, 1.16 [95% CI, 0.98 to 1.37]).

A separate analysis of the estrogen plus progestin trial reported subgroup analyses by prior estrogen plus progestin use, age, Gail risk score, prior oral contraceptive use, recency of hormone use, BMI, smoking status, and use of nonsteroidal anti-inflammatory drugs (NSAIDs). Among the subgroup analyses, participants who received estrogen plus progestin had higher rates of invasive breast cancer if they had prior use of oral contraceptives for less than 5 years, prior use of menopausal estrogen plus progestin for 5 or more years, or were current smokers. Another analysis of estrogen plus progestin subgroups based on first-degree family history of breast cancer found no significant interactions.

An evaluation of the effect of age on breast cancer incidence in the estrogen only trial indicated no significant differences by age.

**Colorectal cancer.** A subgroup analysis of the WHI estrogen plus progestin trial showed no differences in invasive colorectal cancer incidence by age, race or ethnic group, family history of colorectal cancer, prior use of menopausal estrogen plus progestin, BMI, waist circumference, smoking status, current alcohol use, dietary selenium, diabetes, use of NSAIDs, or history of polyp removal.

An analysis of the estrogen only trial indicated that subgroup analyses based on history of polyp removal, height, and waist circumference yielded statistically significant interactions. There were no statistically significant results based on age, race or ethnic group, family history of colorectal cancer, BMI, smoking status, alcohol intake, dietary selenium, treated diabetes, use of NSAIDs, previous use of menopausal hormones, previous use of oral contraceptives, and bilateral oophorectomy.

**Cardiovascular disease.** Subgroup analyses in the WHI estrogen plus progestin trial indicated no significant interactions for CHD, except for participants with elevated LDL cholesterol at baseline. Many risk factors related to CHD and other baseline characteristics were evaluated.
and found to not be significantly related. CHD events were significantly increased during the first year of the trial compared with later years (year 1: HR, 1.81 [95% CI, 1.09 to 3.01] vs. year 6 or later: HR, 0.70 [95% CI, 0.42 to 1.14]). Similar analyses for the estrogen only trial indicated that participants with elevated levels of C-reactive protein at baseline had a greater risk for CHD with estrogen only, but all other analyses were not significant.

An additional subgroup analysis of the WHI estrogen plus progestin and estrogen only trials indicated that participants initiating hormone therapy closer to menopause had reduced CHD risk compared with participants initiating later. Although the reduction in risk for women within 10 years of menopause was not statistically significant, the trend of increasing risk with increasing duration of time from menopause was.

Risk for stroke was similar in all subgroups evaluated for the WHI estrogen plus progestin and estrogen only trials. For thromboembolic disease, use of estrogen plus progestin increased the risks associated with older age, being overweight or obese, or possessing Factor V Leiden. Analysis of subgroups in the WHI estrogen only trial indicated no associations with venous thrombosis.

Fractures. The protective effect of estrogen plus progestin in WHI did not differ by age, BMI, smoking status, history of falls, personal and family history of fracture, calcium intake, prior hormone therapy, bone mineral density, or fracture risk score.

Cognitive function and dementia. In WHIMS, analyses were conducted on 17 subgroups using adjusted models that indicated no significant subgroup differences between estrogen plus progestin and placebo. For estrogen only, 17 subgroups were also analyzed. Results indicated that participants at or below the screening cut-off point for 3MSE scores at baseline in the estrogen only group had significantly lower changes in 3MSE scores compared with placebo (difference, -1.52 [95% CI, -2.29 to -0.75]; p=0.006).

Urinary incontinence. In WHI, participants differed significantly at baseline for parity in the estrogen only trial, and emphysema in the estrogen plus progestin trial. Adjusting for these baseline differences did not change results for urinary incontinence outcomes. Further subgroup analysis did not show a significant effect for race or ethnicity. In the estrogen plus progestin trial, older age, increasing duration since menopause, prior menopausal hormone therapy use, and beta blocker use were significantly associated with stress urinary incontinence for estrogen plus progestin users. The absence of diabetes was significantly associated with urge urinary incontinence. In the estrogen only trial, older age and increasing duration since menopause were significantly associated with stress urinary incontinence, and increasing age with urge and mixed urinary incontinence for estrogen users. A significant interaction was also found between smoking, estrogen only use, and mixed urinary incontinence.

In HERS, participants assigned to placebo were older and further from menopause than participants taking hormone therapy at baseline, but were otherwise similar. Adjusting for these differences did not change results. Participants taking estrogen plus progestin were more likely to report weekly, urge, and stress urinary incontinence compared with those taking placebo. The adverse effect on urge urinary incontinence increased with time. However, for participants
younger than age 60 years, the effect of estrogen plus progestin on urinary incontinence was minimal and not significantly elevated (OR, 1.31 [95% CI, 0.85 to 2.04]).
CHAPTER 4. DISCUSSION

Summary of Review Findings

Nine trials comparing the effects of estrogen plus progestin or estrogen only against placebo for the prevention of chronic conditions in postmenopausal women have been published since 2002 and provided data for this review. A summary of the evidence is provided in Table 6. Trials included the WHI trials of estrogen plus progestin and estrogen only, two trials enrolling subsamples from WHI—WHIMS and WHISCA—and EMS, HERS, ESPRIT, ULTRA, and WISDOM. WHI is the only trial designed and powered to evaluate the effectiveness of hormone therapy for primary prevention of the multiple conditions that are the focus of this review. WHI met criteria for fair quality, provided most of the estimates of benefits and harms, had 11 years of followup, and was most applicable to the target population. Results of the other trials, such as HERS, were consistent with WHI for selected outcomes, such as diabetes. However, most outcomes of the other trials were either not measured or were inadequately powered to detect significant differences between groups.

Results of WHI indicated some benefits with hormone therapy (key question 1). For women using estrogen plus progestin, fractures (hip: 6/10,000; vertebral: 6/10,000; total: 46/10,000) and diabetes (15/10,000) were significantly reduced compared with placebo. For women using estrogen only, fractures (hip: 7/10,000 women-years; vertebral: 6/10,000; total: 56/10,000) and invasive breast cancer incidence (8/10,000) and death (2/10,000) were reduced. While fractures were a major secondary outcome of the trials and were determined by clinical and radiographic criteria, diabetes was based on post hoc analysis of self-reports. In comparison, women in HERS using estrogen plus progestin also had reduced risk for diabetes based on blood glucose levels, but not reduced fractures.

Several harms were also demonstrated by WHI (key question 2). For women using estrogen plus progestin, invasive breast cancer (8/10,000), stroke (9/10,000), DVT (12/10,000) and PE (9/10,000), lung cancer death (5/10,000), gallbladder disease (20/10,000), probable dementia (22/10,000), and urinary incontinence (872/10,000) were significantly increased compared with placebo. For women using estrogen only, stroke (11/10,000), DVT (7/10,000), gallbladder disease (33/10,000), and urinary incontinence (1271/10,000) were increased. Women in HERS using estrogen plus progestin also had increased risk for urinary incontinence.

Trials did not report results for subgroups of women with premature menopause, women with surgical menopause, or using various types, doses, and modes of delivery of hormones (key question 3). Subgroup analyses based on age and comorbidities were limited by lack of power for many of the comparisons, and indicated few statistically significant differences. These included increased risk for breast cancer for women randomized to estrogen plus progestin with prior oral contraceptive use, prior estrogen plus progestin use, or who smoke; increased CHD risk for women randomized to estrogen plus progestin with high LDL cholesterol levels, or women randomized to estrogen only with high C-reactive protein levels; increased thromboembolic disease for women randomized to estrogen plus progestin who were older, obese, or possessed Factor V Leiden; and increased urinary incontinence for older women using
either regimen. Other than these findings, trials provided few results applicable to clinical
decisions about selecting hormone therapy based on individual patient characteristics.

Limitations and Future Research

This review was limited by the small number of trials that met inclusion criteria, although the
number of participants was large. The review was also limited to trials published in English-
language journals, although no relevant trials were identified from English-language abstracts of
non-English journals, additional citation searches, or expert reviewers.

Few outcomes were reported in more than two trials. Some outcomes were especially affected by
potential bias, such as diabetes, based on post hoc analysis, and cognitive function, limited by
disparate adherence rates (WHIMS, 61.4 percent for placebo vs. 32.3 percent for estrogen plus
progestin). Trials often used different measures for ascertaining outcomes, limiting comparisons
across trials. For cognitive function, WHIMS was the only trial to use a thorough adjudication
process for probable dementia and mild cognitive impairment, while other trials used batteries of
cognitive tests. For diabetes, WHI relied on participants’ self-reports of new diagnoses or new
treatment for diabetes, while HERS used fasting glucose levels. For urinary incontinence, all
trials relied on self-reported measures.

Most trials had high attrition or low adherence to medications, including WHI, in which 40 to 50
percent of participants discontinued their medications during the course of the trial. Although
trials of various forms of hormone therapy have been published, results for most outcomes have
been derived from large trials using CEE and MPA, restricting comparative effectiveness
evaluations. Use of post hoc analysis and small subgroup comparisons provided limited
additional findings.

The average age of participants in the trials was generally in the mid 60s, restricting the
applicability of the findings. Research directed at women transitioning through menopause or
immediately postmenopausal would be useful to women in these age groups who now make up
the majority of hormone users.

Continuing research on long-term outcomes, such as cancer and mortality, will be important to
fully understand the implications of hormone therapy. In the WHI estrogen only trial, a
significant reduction in invasive breast cancer among estrogen users was only recently reported
after nearly 11 years of followup. The results of the estrogen plus progestin trial indicated the
opposite effect—a significant increase in breast cancer. Whether this discrepancy can be
explained by the concomitant use of progestin, the differences in characteristics of women who
had a hysterectomy or not, or other reasons is unclear at this point.

Conclusions

Evidence from trials published since 2002 indicated that both hormone therapy regimens
decreased fractures but increased stroke, thromboembolic events, gallbladder disease, and
urinary incontinence. Estrogen plus progestin also increased breast cancer and probable dementia, while estrogen alone decreased breast cancer.
REFERENCES


Figure 1. Analytic Framework and Key Questions

**Key Questions**

1. What are the benefits of menopausal hormone therapy when used to prevent chronic conditions? Potential benefits include reduced fractures and colorectal cancer.
2. What are the harms of menopausal hormone therapy when used to prevent chronic conditions? Potential harms include coronary heart disease events, stroke, cognitive decline, venous thromboembolism, breast cancer, endometrial cancer, ovarian cancer, and cholecystitis.
3. Do benefits and harms differ by subgroups? Subgroups include women with premature menopause; women with surgical menopause; age of use; types, doses, and modes of delivery of hormones; and presence of comorbidities.
Figure 2. Design of the Women’s Health Initiative Hormone Therapy Trials

Abbreviations: CHD=coronary heart disease; DVT=deep vein thrombosis; E=estrogen; HT=hormone therapy; P=progestin; PE=pulmonary embolus.
Figure 3. Design of the Women’s Health Initiative Hormone Therapy Subtrials

WHI Subtrials

WHI Memory Study (WHIMS)
E+P vs. Placebo
E vs. Placebo
4.1 years
Outcome = cognitive function

WHI Study of Cognitive Aging (WHISCA)
E+P vs. Placebo
E vs. Placebo
1.4 years
Outcome = cognitive function

Abbreviations: E=estrogen; HT=hormone therapy; P=progestin; WHI=Women’s Health Initiative.
**Abbreviations**: CHD=coronary heart disease; DVT=deep vein thrombosis; E=estrogen; HERS/HERS II=Heart and Estrogen/Progestin Replacement Study; P=progestin; PE=pulmonary embolus.
**Abbreviations:** E=estrogen; EMS=Estrogen Memory Study; ESPRIT=Oestrogen in the Prevention of Reinfarction Trial; P=progestin; ULTRA=Ultra-Low-Dose Transdermal Estrogen Assessment; WISDOM=Women’s International Study of Long Duration Oestrogen After Menopause.
Table 1. Recommendations of Other Groups

<table>
<thead>
<tr>
<th>Organization, year</th>
<th>Recommendations</th>
</tr>
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<tbody>
<tr>
<td>American College of Physicians&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Recommends the U.S. Preventive Services Task Force Web site and the Canadian Task Force on Preventive Health Care.</td>
</tr>
<tr>
<td>American Academy of Family Physicians, 2005&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Recommends against the routine use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women (Grade: D recommendation). AAFP recommends against the routine use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy (Grade: D recommendation).</td>
</tr>
<tr>
<td>American Congress of Obstetricians and Gynecologists, 2004&lt;sup&gt;17&lt;/sup&gt;</td>
<td>The risks of hormone therapy exceed the benefits for prevention of chronic diseases in postmenopausal women and the benefits and risks should be discussed with patients before initiating therapy.</td>
</tr>
<tr>
<td>American Heart Association, 2011&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Recommends against the use of hormone therapy for primary and secondary prevention of cardiovascular disease in women (Class III, Level of Evidence A).</td>
</tr>
<tr>
<td>North American Menopause Society, 2010&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Supports the initiation of hormone therapy around the time of menopause to treat menopause-related symptoms, to treat or reduce the risk for osteoporosis in select postmenopausal women, or both. The benefit-risk ratio for menopausal hormone therapy is positive for women who begin therapy close to the start of menopause and decreases in older women. This position statement has been endorsed by the American Medical Women’s Association, the Asociacion Mexicana para el Estudio del Climaterio, the Endocrine Society, HealthyWomen, the National Association of Nurse Practitioners in Women’s Health, and the Society of Obstetricians and Gynecologists of Canada.</td>
</tr>
<tr>
<td>Canadian Task Force on Preventive Health Care, 2004&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Given the balance of harms and benefits, the Task Force recommends against the use of combined estrogen–progestin therapy and estrogen-only therapy for the primary prevention of chronic diseases in menopausal women (grade D recommendation).</td>
</tr>
</tbody>
</table>
### Table 2. Randomized, Controlled Trials and Quality Ratings

<table>
<thead>
<tr>
<th>Trial</th>
<th>Author, year</th>
<th>Intervention</th>
<th>Participants</th>
<th>Quality Rating/Limitations</th>
</tr>
</thead>
</table>
Aged 50-79 years  
Intact uterus  
3-month washout period for women using hormone therapy at baseline | Fair  
Low adherence: 42% of E+P and 38% of placebo group stopped study medications during the trial; drop-in and drop-out rates exceeded design projections |
| WHI E+P Post-intervention Phase                                      | Chlebowski, 2009;* Gramling, 2009;* Heiss, 2008;* | CEE 0.625 mg/d, plus MPA 2.5 mg/d (N=8052) Placebo (N=7678) | Women from the intervention trial who provided followup information | Fair |
| WHI E+P Extension Phase                                              | Chlebowski, 2010;* | CEE 0.625 mg/d, plus MPA 2.5 mg/d (N=8506) Placebo (N=8102) | Women from the intervention trial who consented to the extension phase | Fair |
| Women’s Health Initiative Memory Study (WHIMS) E+P                   | Culhane, 2003;* Rapp, 2003;* Shumaker, 2003;* | CEE 0.625 mg/d plus MPA 2.5 mg/d (N=2229) Placebo (N=2303) | WHI participants enrolled in the E+P trial  
Age >65 years  
Free of probable dementia  
Able and willing to undergo annual cognitive assessment | Fair  
High attrition and differences between groups at baseline |
| Women’s Health Initiative Study of Cognitive Aging (WHISCA) E+P      | Espeland, 2010;* Resnick, 2006;* | CEE 0.625 mg/d plus MPA 2.5 mg/d (N=690) Placebo (N=726) | WHI E+P trial participants  
Free of probable dementia  
At 1 of 14 WHIMS centers | Fair  
High attrition |
Aged 50-79 years  
Prior hysterectomy  
3-month washout required for women using hormone therapy at baseline | Fair  
Low adherence: 53.8% of all participants stopped study medications during the trial; drop-out rates exceeded design projections |
| WHI Extension Phase                                                  | Chlebowski, 2010;* LaCroix, 2011;* | CEE 0.625 mg/d (N=5310) Placebo (N=5429) | 7645 surviving participants from WHI (78%) consented to this followup | Fair |
| WHIMS E                                                             | Espeland, 2004;* Shumaker, 2004;* | CEE 0.625 mg/d (N=1464) Placebo (N=1483) | WHI participants enrolled in the E only trial  
Age >65 years  
Free of probable dementia  
Able and willing to undergo annual cognitive assessment | Fair  
High attrition and differences between groups at baseline |
| WHISCA E                                                            | Espeland, 2010;* Resnick, 2009;* | CEE 0.625 mg/d plus MPA 2.5 mg/d (N=434) Placebo (N=452) | WHIMS E only trial participants  
Free of probable dementia  
At 1 of 14 WHIMS centers | Fair  
High attrition and differences between groups at baseline |
| Heart and Estrogen/Progestin Replacement Study (HERS)               | Grady, 1998;* Hulley, 1998;* Kanaya, 2003;* Steinauer, 2005;* | CEE 0.625 mg/d plus MPA 2.5 mg (N=1380) Placebo (N=1383) | Age ≤80 years  
Intact uterus  
Postmenopausal  
Established coronary artery disease | Fair  
Low adherence rates as study years progressed, and differences between groups at baseline for some outcomes |
Table 2. Randomized, Controlled Trials and Quality Ratings

<table>
<thead>
<tr>
<th>Trial</th>
<th>Author, year</th>
<th>Intervention</th>
<th>Participants</th>
<th>Quality Rating/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart and Estrogen/ Progestin Replacement Study Phase II (HERS II)</td>
<td>Grady, 2002; Hulley, 2002</td>
<td>CEE 0.625 mg/d plus MPA 2.5 mg (N=1156) Placebo (N=1165)</td>
<td>Women from the original HERS who consented to followup</td>
<td>Fair</td>
</tr>
<tr>
<td>Oestrogen in the Prevention of Reinfarction Trial (ESPRIT)</td>
<td>Cherry, 2002</td>
<td>Estradiol valerate 2 mg/d (N=513) Placebo (N=504)</td>
<td>• Aged 50-60 years • Admitted to coronary care units or general medical wards in participating hospitals • Met diagnostic criteria for initial myocardial infarction • Discharged from hospital within 31 days of admission</td>
<td>Fair</td>
</tr>
<tr>
<td>Estrogen Memory Study (EMS)</td>
<td>Tierney, 2009</td>
<td>17-β estradiol 1 mg/d for 4 days then 17-β estradiol 1 mg plus norethindrone 0.35 mg/d for 3 days, repeated every week (N=70) Placebo (N=72)</td>
<td>• Age &gt;60 years • Last menstrual cycle &gt;12 months before screening • Fluent in English and could read normal print and hear normal speech</td>
<td>Good</td>
</tr>
<tr>
<td>Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA)</td>
<td>Ettinger, 2004; Johnson, 2005; Waetjen, 2005; Yaffe, 2006</td>
<td>Unopposed transdermal estradiol 0.014 mg/d (N=208) Placebo (N=209)</td>
<td>• Aged 60-80 years • Intact uterus • At least 5 years past menopause • Bone mineral density normal for age</td>
<td>Fair</td>
</tr>
<tr>
<td>Women’s International Study of Long Duration Oestrogen After Menopause (WISDOM)</td>
<td>Vickers 2007</td>
<td>CEE 0.625 mg/d plus MPA 2.5-5.0 mg/d (N=2196) Placebo (N=2189)</td>
<td>• Aged 50-69 years • Postmenopausal</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Abbreviations: CEE=conjugated equine estrogen; E=estrogen only; E+P=estrogen plus progestin; mg/d=milligrams per day; MPA=medroxyprogesterone acetate; N=number of subjects.
### Table 3. Outcomes Reported in Randomized, Controlled Trials

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Placebo-Controlled Trials Reporting Outcomes</th>
<th>Results for E+P vs. Placebo</th>
<th>Results for E vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>EMS, ESPRIT, HERS, HERS II, ULTRA, WHI, WISDOM</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>ESPRIT, HERS, HERS II, ULTRA, WHI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>ESPRIT, HERS, HERS II, ULTRA, WHI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>ESPRIT, HERS, HERS II, ULTRA, WHI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>ESPRIT, HERS, HERS II, WHI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fractures</td>
<td>HERS, WHI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>EMS, ESPRIT, HERS, HERS II, ULTRA, WHI, WISDOM</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>WHI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>WHI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>WHI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Coronary heart events</td>
<td>WHI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Stroke</td>
<td>WHI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Diabetes</td>
<td>HERS,WHI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>WHI</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>EMS, HERS, ULTRA, WHI, WHIMS, WHISCA</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>HERS, WHI, ULTRA</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviations: E=estrogen; EMS=Estrogen Memory Study; ESPRIT=Oestrogen in the Prevention of Reinfarction Trial; HERS=Heart and Estrogen/Progestin Replacement Study; P=progestin; ULTRA=Ultra-Low-Dose Transdermal Estrogen Assessment; WHI=Women’s Health Initiative; WHIMS=Women’s Health Initiative Memory Study; WHISCA=Women’s Health Initiative Study of Cognitive Aging; WISDOM=Women’s International Study of Long Duration Oestrogen After Menopause.
Table 4. Baseline Characteristics of Participants in Randomized, Controlled Trials

<table>
<thead>
<tr>
<th>Characteristic (Hormone Therapy; Placebo)</th>
<th>WHI E+P</th>
<th>WHI E</th>
<th>WHIMS E+P</th>
<th>WHIMS E</th>
<th>WHISCA E</th>
<th>WHISCA E</th>
<th>HERS E+P</th>
<th>ESPRIT E</th>
<th>EMS E+P</th>
<th>WISDOM E</th>
<th>ULTRA E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal age (yrs)</td>
<td>8506;8102</td>
<td>5310;5429</td>
<td>2229;2303</td>
<td>1464;1483</td>
<td>690;726</td>
<td>434;452</td>
<td>1380;1383</td>
<td>513;504</td>
<td>70;72</td>
<td>2196;2189</td>
<td>191;185</td>
</tr>
<tr>
<td>Age (mean yrs)</td>
<td>63.2;63.3</td>
<td>63.6;63.6</td>
<td>63.2;63.3</td>
<td>63.6;63.6</td>
<td>73.69;73.86</td>
<td>74.01;74.02</td>
<td>67.67</td>
<td>62.3;62.9</td>
<td>75.74;5</td>
<td>63.3;63.3</td>
<td>66.8;66.7</td>
</tr>
<tr>
<td>Nonwhite race (%)</td>
<td>16.1;16.0</td>
<td>24.5;24.9</td>
<td>-</td>
<td>17.3;16.4</td>
<td>8.4;7.0</td>
<td>14.09;13.08</td>
<td>12.10</td>
<td>3.3</td>
<td>4.3;9.7</td>
<td>1.1;4</td>
<td>7.2;8.1</td>
</tr>
<tr>
<td>Previous or current HT (%)</td>
<td>26.1;25.6</td>
<td>47.8;48.9</td>
<td>21.8;22.4</td>
<td>45.8;44.7</td>
<td>21.2;22.6</td>
<td>49.54;46.24</td>
<td>1.7;1.7</td>
<td>12.10</td>
<td>31.4;23.6</td>
<td>55.54;3</td>
<td>-</td>
</tr>
<tr>
<td>Hysterectomy age &lt;40 yr (%)</td>
<td>-</td>
<td>39.8;39.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hysterectomy age 40-49 yrs (%)</td>
<td>-</td>
<td>43.2;42.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bilateral oophorectomy (%)</td>
<td>-</td>
<td>39.5;42.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Never pregnant (%)</td>
<td>10.1;10.3</td>
<td>9.3;3.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>First pregnancy age ≥30 yrs (%)</td>
<td>10.6;9.7</td>
<td>49.5;9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female relative with breast cancer (%)</td>
<td>16.0;15.3</td>
<td>18.0;17.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8.9</td>
<td>-</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>10.5;10.5</td>
<td>10.3;10.6</td>
<td>6.7;6.9</td>
<td>7.3;8.0</td>
<td>6.2;5.0</td>
<td>3.72;7.59</td>
<td>13;13</td>
<td>54;52</td>
<td>-</td>
<td>12;14</td>
<td>7.7;6.2</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>28.5;28.5</td>
<td>30.1;30.1</td>
<td>-</td>
<td>28.5;28.1</td>
<td>29.40;29.21</td>
<td>57.55</td>
<td>26.8;26.7</td>
<td>27.26;6</td>
<td>27.9;28.0</td>
<td>28.3;28.0</td>
<td></td>
</tr>
<tr>
<td>History of MI (%)</td>
<td>1.6;1.9</td>
<td>3.1;3.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.2;1.2</td>
<td>-</td>
<td>5.7;4.2</td>
<td>2.1</td>
<td>-</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>0.7;1.0</td>
<td>1.4;1.7</td>
<td>1;1.9</td>
<td>1.8;2.1</td>
<td>1.1</td>
<td>1.15;1.77</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.2</td>
<td>-</td>
</tr>
<tr>
<td>History of DVT or PE (%)</td>
<td>0.9;0.8</td>
<td>1.6;1.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean SBP (mm Hg)</td>
<td>127.6;127.8</td>
<td>130.4;130.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>135;135</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean DBP (mm Hg)</td>
<td>75.6;75.8</td>
<td>76.5;76.5</td>
<td>-</td>
<td>73.73</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean SBP (mm Hg)</td>
<td>35.7;36.4</td>
<td>48.0;47.4</td>
<td>-</td>
<td>47.3;42.3</td>
<td>44.4;46.0</td>
<td>53.69;51.11</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Elevated cholesterol requiring medication (%)</td>
<td>12.5;12.9</td>
<td>14.5;15.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prior aspirin use or use at baseline (%)</td>
<td>19.1;20.1</td>
<td>19.4;19.7</td>
<td>28.1;29.6</td>
<td>28.0;30.9</td>
<td>-</td>
<td>-</td>
<td>5.6;5.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>History of or treatment for diabetes (%)</td>
<td>4.4;4.4</td>
<td>7.7;7.6</td>
<td>7.6;5.5</td>
<td>11.3;10.6</td>
<td>5.4;6.2</td>
<td>10.14;10.84</td>
<td>19;18</td>
<td>15;15</td>
<td>7.1;11.1</td>
<td>3.4</td>
<td>-</td>
</tr>
<tr>
<td>Fracture age ≥55 yrs (%)</td>
<td>13.5;13.6</td>
<td>14.0;13.2</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: BMI=body mass index; BP=blood pressure; CVD=cardiovascular disease; DBP=diastolic blood pressure; DVT=deep vein thrombosis; E=estrogen; E+P=estrogen with progestin; EMS=Estrogen Memory Study; ESPRIT=Estrogen in the Prevention of Reinfarction Trial; HERS=Heart and Estrogen/Progestin Replacement Study; HT=hormone therapy; MI=myocardial infarction; P=progestin; PE=pulmonary embolism; SBP=systolic blood pressure; ULTRA=Ultra-Low-Dose Transdermal Estrogen Assessment; WHI=Women’s Health Initiative; WHIMS=Women’s Health Initiative Memory Study; WHISCA=Women’s Health Initiative Study of Cognitive Aging; WISDOM=Women’s International Study of Long Duration Oestrogen After Menopause.
Table 5. Results of Hormone Therapy Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>E+P vs. Placebo</th>
<th>E vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>Differences in events per 10,000 women-years (95% CI)*</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive breast</td>
<td>1.25 (1.07-1.46)**</td>
<td>8 (3-14) more</td>
</tr>
<tr>
<td>Colorectal</td>
<td>0.75 (0.57-1.00)**</td>
<td>Not significant</td>
</tr>
<tr>
<td>Lung</td>
<td>1.23 (0.92-1.63)**</td>
<td>Not significant</td>
</tr>
<tr>
<td>Endometrial</td>
<td>0.78 (0.52-1.16)**</td>
<td>Not significant</td>
</tr>
<tr>
<td>Cervical</td>
<td>1.58 (0.77-3.24)**</td>
<td>Not significant</td>
</tr>
<tr>
<td>Coronary heart disease (CHD death and total MI)</td>
<td>1.22 (0.99-1.51)**</td>
<td>Not significant</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.34 (1.05-1.71)**</td>
<td>9 (2-15) more</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.88 (1.38-2.55)**</td>
<td>12 (6-17) more</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1.98 (1.36-2.87)**</td>
<td>9 (4-14) more</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reported new diagnosis requiring treatment with drugs</td>
<td>0.79 (0.67-0.93)**</td>
<td>15 (4-26) less</td>
</tr>
<tr>
<td>Hip</td>
<td>0.67 (0.47-0.95)**</td>
<td>6 (1-10) less</td>
</tr>
<tr>
<td>Vertebral</td>
<td>0.68 (0.48-0.96)**</td>
<td>6 (1-11) less</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.76 (0.69-0.83)**</td>
<td>46 (29-63) less</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.04 (0.91-1.18)**</td>
<td>Not significant</td>
</tr>
<tr>
<td>Breast cancer mortality</td>
<td>1.96 (1.00-4.04)**</td>
<td>Not significant</td>
</tr>
<tr>
<td>Lung cancer mortality</td>
<td>1.71 (1.16-2.52)**</td>
<td>5 (1-8) more</td>
</tr>
<tr>
<td>Gallbladder disease (cholecystitis and cholelithiasis)</td>
<td>1.61 (1.30-2.00)**</td>
<td>20 (11-29) more</td>
</tr>
<tr>
<td>Cognitive function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable dementia</td>
<td>2.05 (1.21-3.48)**</td>
<td>22 (5-39) more</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>1.07 (0.74-1.55)**</td>
<td>Not significant</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>1.39 (1.27-1.52)**</td>
<td>872 (591-1153) more</td>
</tr>
</tbody>
</table>

### Abbreviations:
- CHD = coronary heart disease
- CI = confidence interval
- E = estrogen
- HR = hazard ratio
- MI = myocardial infarction
- P = progestin
- RR = relative risk
- WHI = Women’s Health Initiative

*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).
# Table 6. Summary of Evidence

<table>
<thead>
<tr>
<th>Key Question 1. What are the benefits of menopausal hormone therapy when used to prevent chronic conditions?</th>
<th>Number of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Overall quality</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 main trials</td>
<td>RCT</td>
<td>High attrition rates; differential loss to followup; low adherence</td>
<td>Consistent</td>
<td>High</td>
<td>Fair</td>
<td>In the WHI estrogen plus progestin trial, hip, vertebral, and total fractures and diabetes were significantly reduced compared with placebo. In the WHI estrogen only trial, invasive breast cancer and hip, vertebral, and total fractures were reduced. Women in HERS using estrogen plus progestin had reduced diabetes but not fractures.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Key Question 2. What are the harms of menopausal hormone therapy when used to prevent chronic conditions?</th>
<th>Number of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Overall quality</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 main trials</td>
<td>RCT</td>
<td>High attrition rates; differential loss to followup; low adherence</td>
<td>Consistent</td>
<td>High</td>
<td>Fair</td>
<td>In the WHI estrogen plus progestin trial, invasive breast cancer, stroke, thromboembolic events, lung cancer death, gallbladder disease, probable dementia, and urinary incontinence were significantly increased compared with placebo. In the WHI estrogen only trial, stroke, deep vein thrombosis, gallbladder disease, and urinary incontinence were increased. Women in HERS using estrogen plus progestin had increased urinary incontinence.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Key Question 3. Do benefits and harms differ by subgroups?</th>
<th>Number of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Overall quality</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 main trials</td>
<td>RCT</td>
<td>Most subgroups were not evaluated in trials</td>
<td>Not relevant</td>
<td>Not relevant</td>
<td>Varied</td>
<td>Subgroup comparisons were limited and inconclusive.</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** HERS=Heart and Estrogen/Progestin Replacement Study; RCT=randomized, controlled trial; WHI=Women’s Health Initiative.
### Appendix A. List of Acronyms and Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>3MSE</td>
<td>Modified Mini-Mental State Examination</td>
</tr>
<tr>
<td>AAFP</td>
<td>American Academy of Family Physicians</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ACOG</td>
<td>American Congress of Obstetricians and Gynecologists</td>
</tr>
<tr>
<td>ACP</td>
<td>American College of Physicians</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse events</td>
</tr>
<tr>
<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>BVRT</td>
<td>Benton Visual Retention Test</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass graft</td>
</tr>
<tr>
<td>CEE</td>
<td>Conjugated equine estrogen</td>
</tr>
<tr>
<td>CERAD</td>
<td>Consortium to Establish a Registry for Alzheimer’s Disease</td>
</tr>
<tr>
<td>CES-D</td>
<td>Center for Epidemiologic Studies Depression Scale</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>CVLT</td>
<td>California Verbal Learning Test</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep venous thrombosis</td>
</tr>
<tr>
<td>E</td>
<td>Estrogen</td>
</tr>
<tr>
<td>E + P</td>
<td>Estrogen with progestin</td>
</tr>
<tr>
<td>EMS</td>
<td>Estrogen Memory Study</td>
</tr>
<tr>
<td>ERA</td>
<td>Estrogen Replacement and Atherosclerosis</td>
</tr>
<tr>
<td>ESPRIT</td>
<td>Oestrogen in the Prevention of Reinfarction Trial</td>
</tr>
<tr>
<td>ET</td>
<td>Evidence table</td>
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<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>f/u</td>
<td>Followup</td>
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<tr>
<td>GDS</td>
<td>Geriatric Depression Scale</td>
</tr>
<tr>
<td>GED</td>
<td>General Education Development</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
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<tr>
<td>HERS</td>
<td>Heart and Estrogen/Progestin Replacement Study</td>
</tr>
<tr>
<td>HERS II</td>
<td>Heart and Estrogen/Progestin Replacement Study Phase II</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>HT</td>
<td>Hormone therapy</td>
</tr>
<tr>
<td>HTN</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Hx</td>
<td>History</td>
</tr>
<tr>
<td>ICD 9</td>
<td>International Classification of Diseases–9th Division</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat</td>
</tr>
<tr>
<td>IU</td>
<td>International unit</td>
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</table>
## Appendix A. List of Acronyms and Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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</thead>
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<tr>
<td>KQ</td>
<td>Key question</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td>MBNT</td>
<td>Modified Boston Naming Test</td>
</tr>
<tr>
<td>MCI</td>
<td>Mild cognitive impairment</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MPA</td>
<td>Medroxyprogesterone acetate</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>n</td>
<td>Sample size</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
</tr>
<tr>
<td>NR</td>
<td>Not reported</td>
</tr>
<tr>
<td>NS</td>
<td>Not significant</td>
</tr>
<tr>
<td>NSAID</td>
<td>Nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>P</td>
<td>Progestin</td>
</tr>
<tr>
<td>PANAS</td>
<td>Positive and Negative Affect Schedule</td>
</tr>
<tr>
<td>Pap</td>
<td>Papanicolau</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>PD</td>
<td>Probable dementia</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>PMA</td>
<td>Primary mental abilities</td>
</tr>
<tr>
<td>PO</td>
<td>Per os (by mouth)</td>
</tr>
<tr>
<td>PTCA</td>
<td>Percutaneous transluminal coronary angioplasty</td>
</tr>
<tr>
<td>RAVLT</td>
<td>Rey Auditory Verbal Learning Test</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized, controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>Rx</td>
<td>Prescription</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SE</td>
<td>Standard error</td>
</tr>
<tr>
<td>SF-36</td>
<td>36-Item Short-Form Health Survey</td>
</tr>
<tr>
<td>Tx</td>
<td>Treatment</td>
</tr>
<tr>
<td>UI</td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>ULTRA</td>
<td>Ultra Low-Dose Transdermal Estrogen Replacement Assessment</td>
</tr>
<tr>
<td>USPSTF</td>
<td>U.S. Preventive Services Task Force</td>
</tr>
<tr>
<td>VT</td>
<td>Venous thrombosis</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>WHI</td>
<td>Women’s Health Initiative</td>
</tr>
<tr>
<td>WHIMS</td>
<td>Women’s Health Initiative Memory Study</td>
</tr>
<tr>
<td>WHISCA</td>
<td>Women’s Health Initiative Study of Cognitive Aging</td>
</tr>
<tr>
<td>WISDOM</td>
<td>Women’s International Study of Long-Duration Oestrogen After Menopause</td>
</tr>
</tbody>
</table>
Appendix B1. Search Strategies

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1947 to November Week 3 2011>

Search Strategy:

1. exp Hormone Replacement Therapy/ (18014)
2. ((oestrogen$ or estrogen$ or hormon$) adj3 (replac$ or treat$ or therap$ or interven$)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (61635)
3. exp Estrogens/ad, tu, ae, to (30285)
4. exp Estradiol Congeners/ad, tu, ae, to (16224)
5. 1 or 2 or 3 or 4 (83066)
6. exp climaacteric/ (42184)
7. (menopaus$ or postmenopaus$ or premenopaus$ or perimenopaus$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (71436)
8. 6 or 7 (73433)
9. 5 and 8 (21705)
10. limit 5 to yr="2002 -Current" (30216)
11. limit 10 to randomized controlled trial (2532)
12. systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or (systematic review.ti,ab. and review.pt.) or consensus development conference.pt. or practice guideline.pt. or cochrane database syst rev.jn. or aep journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. (62504)
13. evidence based.ti. or exp Evidence-Based Medicine/ or best practice$.ti. or evidence synthesis.ti,ab. (43717)
14. review.pt. or exp "diseases (non mesh)"/ or exp "behavior and behavior mechanisms"/ or exp therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. (12073345)
15. 13 and 14 (35235)
16. (systematic or systematically).mp. or critical.ti,ab. or study selection.mp. or ((predetermined or inclusion) and criteri$).mp. or exclusion criteri$mp. or main outcome measures.mp. or standard of care.mp. or standards of care.mp. (493608)
17. (survey or surveys).ti,ab. or overview$.mp. or review.ti,ab. or reviews.ti,ab. or search$.mp. or handsearch.mp. or analysis.ti,ab. or critique.ti,ab. or appraisal.mp. or (reduction.mp. and (exp risk/ or risk.mp.) and (exp death/ or death.mp. or exp recurrence/ or recurrence.mp.)) (2675017)
18. (literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or unpublished.mp. or citation.mp. or citations.mp. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.mp. or scales.mp. or papers.mp. or datasets.mp. or trials.ti,ab. or meta-analy$.mp. or (clinical and studies).ti,ab. or exp treatment outcome/ or treatment outcome.mp. (1559459)
19. 16 and 17 and 18 (74949)
20. 12 or 15 or 19 (143395)
21. (letter or newspaper article or comment).pt. (861393)
22. 20 not 21 (137375)
23. 10 and 22 (1119)
24. 11 or 23 (3629)
25. exp Randomized Controlled Trials as Topic/ (69462)
26. 10 and 25 (1384)
Appendix B1. Search Strategies

27  24 or 26 (4709)
28  exp Mental Processes/ (611118)
29  exp Cognition Disorders/ (45056)
30  exp Dementia/ (94310)
31  exp memory/ (77691)
32  exp Memory Disorders/ (17597)
33  28 or 29 or 30 or 31 or 32 (721314)
34  27 and 33 (319)
35  exp Breast Neoplasms/ (176281)
36  27 and 35 (762)
37  exp Cardiovascular Diseases/ (1598559)
38  heart disease$.tw. (100444)
39  (cardiovascular disease$ or myocardial infarct$).tw. (176571)
40  37 or 38 or 39 (1639524)
41  27 and 40 (1055)
42  exp Osteoporosis/ (37080)
43  exp Fractures, Bone/ (119047)
44  fractur$.tw. (135977)
45  bone density.mp. (38276)
46  42 or 43 or 44 or 45 (212984)
47  27 and 46 (685)
48  exp Cerebrovascular Disorders/ (226197)
49  stroke.mp. (127016)
50  48 or 49 (286153)
51  27 and 50 (215)
52  (tamoxifen or raloxifene).mp. (19548)
53  Bone density/ or "bone density".mp. (38276)
54  exp osteoporosis/ or "osteoporosis".mp. (47690)
55  exp fractures/ or fracture$.mp. (175011)
56  53 or 54 or 55 (223064)
57  27 and 56 (748)
58  34 or 36 or 41 or 47 or 51 or 57 (2353)
59  limit 58 to engish language (2184)
60  limit 58 to abstracts (2022)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2011>
Search Strategy:
--------------------------------------------------------------------------------
1  ((oestrogen$ or estrogen$ or hormon$) adj3 (replac$ or treat$ or therap$ or interven$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (7834)
2  (menopaus$ or postmenopaus$ or premenopaus$ or perimenopaus$ or climacter$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (10925)
3  (mental$ or cognit$ or dement$ or alzheim$ or memor$ or amnes$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (35737)
Appendix B1. Search Strategies

4  ((breast$ or mamma$) adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcinom$ or adenocarcinom$ or malig$ or metastas$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (11801)
5  (heart$ or cardi$ or myocardi$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (76479)
6  (osteopor$ or fractur$ or ((bone$ or osteo$) adj3 dens$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (9454)
7  (cerebrovasc$ or stroke$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (17295)
8  (tamoxifen or raloxifene).mp. (3103)
9  1 and 2 (3940)
10  3 and 9 (180)
11  4 and 9 (596)
12  5 and 9 (748)
13  6 and 9 (771)
14  7 and 9 (76)
15  8 and 9 (479)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2011>
Search Strategy:

1  ((oestrogen$ or estrogen$ or hormon$) adj3 (replac$ or treat$ or therap$ or interven$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (7834)
2  (menopaus$ or postmenopaus$ or premenopaus$ or perimenopaus$ or climacter$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (10925)
3  (mental$ or cognit$ or dement$ or alzheim$ or memor$ or amnes$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (35737)
4  ((breast$ or mamma$) adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcinom$ or adenocarcinom$ or malig$ or metastas$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (11801)
5  (heart$ or cardi$ or myocardi$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (76479)
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2  (menopaus$ or postmenopaus$ or premenopaus$ or perimenopaus$ or climacter$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (10925)
3  (mental$ or cognit$ or dement$ or alzheim$ or memor$ or amnes$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (35737)
4  ((breast$ or mamma$) adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcinom$ or adenocarcinom$ or malig$ or metastas$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (11801)
5  (heart$ or cardi$ or myocardi$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (76479)
6  (osteopor$ or fractur$ or ((bone$ or osteo$) adj3 dens$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (9454)
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Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2011>
Search Strategy:
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3  (mental$ or cognit$ or dement$ or alzheim$ or memor$ or amnes$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (35737)
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Appendix B1. Search Strategies

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15 8 and 9 (479)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2011>

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3  (mental$ or cognit$ or dement$ or alzheim$ or memor$ or amnes$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (35737)
4  ((breast$ or mamma$) adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcinom$ or adenocarcinom$ or malig$ or metastas$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (11801)
5  (heart$ or cardi$ or myocardi$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (76479)
6  (osteopor$ or fractur$ or ((bone$ or osteo$) adj3 dens$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (9454)
7  (cerebrovasc$ or stroke$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (17295)
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9  1 and 2 (3940)
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15 8 and 9 (479)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2011>

Search Strategy:
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2  (menopaus$ or postmenopaus$ or premenopaus$ or perimenopaus$ or climacter$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (10925)
3  (mental$ or cognit$ or dement$ or alzheim$ or memor$ or amnes$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (35737)
Appendix B1. Search Strategies

4  ((breast$ or mamma$) adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcinom$ or adenocarcinom$ or malig$ or metastas$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (11801)
5   (heart$ or cardi$ or myocardi$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (76479)
6   (osteopor$ or fractur$ or ((bone$ or osteo$) adj3 dens$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (9454)
7   (cerebrovasc$ or stroke$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (17295)
8   (tamoxifen or raloxifene).mp. (3103)
9   1 and 2 (3940)
10  3 and 9 (180)
11  4 and 9 (596)
12  5 and 9 (748)
13  6 and 9 (771)
14  7 and 9 (76)
15  8 and 9 (479)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2011>
Search Strategy:

1   ((oestrogen$ or estrogen$ or hormon$) adj3 (replac$ or treat$ or therap$ or interven$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (7834)
2   (menopaus$ or postmenopaus$ or premenopaus$ or perimenopaus$ or climacter$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (10925)
3   (mental$ or cognit$ or dement$ or alzheim$ or memor$ or amnes$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (35737)
4   ((breast$ or mamma$) adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcinom$ or adenocarcinom$ or malig$ or metastas$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (11801)
5   (heart$ or cardi$ or myocardi$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (76479)
6   (osteopor$ or fractur$ or ((bone$ or osteo$) adj3 dens$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (9454)
7   (cerebrovasc$ or stroke$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (17295)
8   (tamoxifen or raloxifene).mp. (3103)
9   1 and 2 (3940)
10  3 and 9 (180)
11  4 and 9 (596)
12  5 and 9 (748)
13  6 and 9 (771)
14  7 and 9 (76)
15  8 and 9 (479)
Appendix B1. Search Strategies

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 2011>

Search Strategy:
--------------------------------------------------------------------------------
1  ((oestrogen$ or estrogen$ or hormon$) adj3 (replac$ or treat$ or therap$ or interven$)).mp. [mp=title, abstract, full text, keywords, caption text] (401)
2  (menopaus$ or postmenopaus$ or premenopaus$ or perimenopaus$ or climacter$).mp. [mp=title, abstract, full text, keywords, caption text] (294)
3  (mental$ or cognit$ or dement$ or alzheim$ or memor$ or amnes$).mp. [mp=title, abstract, full text, keywords, caption text] (1913)
4  ((breast$ or mamma$) adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcinom$ or adenocarcinom$ or malig$ or metastas$)).mp. [mp=title, abstract, full text, keywords, caption text] (265)
5  (heart$ or cardi$ or myocardi$).mp. [mp=title, abstract, full text, keywords, caption text] (2665)
6  (osteopor$ or fractur$ or ((bone$ or osteo$) adj3 dens$)).mp. [mp=title, abstract, full text, keywords, caption text] (738)
7  (cerebrovasc$ or stroke$).mp. [mp=title, abstract, full text, keywords, caption text] (959)
8  (tamoxifen or raloxifene).mp. (64)
9  1 and 2 (164)
10  3 and 9 (48)
11  4 and 9 (64)
12  5 and 9 (72)
13  6 and 9 (62)
14  7 and 9 (35)
15  8 and 9 (33)
16  10 or 11 or 12 or 13 or 14 or 15 (130)

Database: EBM Reviews - Cochrane Methodology Register <3rd Quarter 2011>

Search Strategy:
--------------------------------------------------------------------------------
1  ((oestrogen$ or estrogen$ or hormon$) adj3 (replac$ or treat$ or therap$ or interven$)).mp. [mp=title, abstract, subject heading word] (92)
2  (menopaus$ or postmenopaus$ or premenopaus$ or perimenopaus$ or climacter$).mp. [mp=title, abstract, subject heading word] (86)
3  (mental$ or cognit$ or dement$ or alzheim$ or memor$ or amnes$).mp. [mp=title, abstract, subject heading word] (364)
4  ((breast$ or mamma$) adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcinom$ or adenocarcinom$ or malig$ or metastas$)).mp. [mp=title, abstract, subject heading word] (418)
5  (heart$ or cardi$ or myocardi$).mp. [mp=title, abstract, subject heading word] (721)
6  (osteopor$ or fractur$ or ((bone$ or osteo$) adj3 dens$)).mp. [mp=title, abstract, subject heading word] (83)
7  (cerebrovasc$ or stroke$).mp. [mp=title, abstract, subject heading word] (197)
8  (tamoxifen or raloxifene).mp. (43)
9  1 and 2 (40)
10  3 and 9 (1)
Appendix B1. Search Strategies

11  4 and 9 (10)
12  5 and 9 (15)
13  6 and 9 (7)
14  7 and 9 (4)
15  8 and 9 (2)
16  10 or 11 or 12 or 13 or 14 or 15 (24)
### Appendix B2. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Generally healthy postmenopausal women eligible for menopausal hormone therapy. Characteristics of enrolled participants are applicable to the U.S. primary care population.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Estrogen only or combined with progestin for prevention of chronic conditions. Medications are available for use in the United States.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Health outcomes include mortality, fractures; coronary heart disease; stroke; venous thromboembolism; breast, colorectal, endometrial, and ovarian cancer; cholecystitis, cognition; urinary incontinence; and others.</td>
</tr>
<tr>
<td><strong>Study types and designs</strong></td>
<td>English-language randomized, controlled trials published in 2002 or later.</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>1 year of treatment.</td>
</tr>
</tbody>
</table>
Appendix B3. U.S. Preventive Services Task Force Quality Rating Criteria for Randomized, Controlled Trials

Randomized, Controlled Trials (RCTs)

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 RCTs, 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 percent); 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 exists: 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, 200122
Appendix B4. List of Reviewers of Draft Report

Outside Experts

JoAnn Manson, M.D., M.P.H., Dr.P.H., Chief, Division of Preventive Medicine; Co-Director, Connors Center for Women’s Health and Gender Biology; Elizabeth F. Brigham Professor of Women’s Health and Professor of Medicine, Harvard Medical School

Elizabeth Barrett-Connor, M.D., Professor and Division Chief of Epidemiology, Department of Family and Preventive Medicine, University of California, San Diego School of Medicine

Diana Petitti, M.D., M.P.H., Professor of Biomedical Informatics, Arizona State University

Collaborative Partners

Jacques Rossouw, M.D., Chief, Women’s Health Initiative Branch, National Heart, Lung and Blood Institute

Leslie Ford, M.D., Associate Director for Clinical Research, Division of Cancer Prevention, National Cancer Institute

Worta McCaskill-Stevens, M.D., Program Director, Division of Cancer Prevention, Community Oncology and Prevention Trials Research Group, National Cancer Institute

Joseph Chin, M.D., M.S., Medical Officer, Coverage and Analysis Group, Centers for Medicare and Medicaid Services
Appendix B5. Literature Flow Diagram

Abstracts of potentially relevant articles identified through MEDLINE, Cochrane*, and other sources† (N=4,524)

Excluded abstracts and background articles (n=3,820)

Full-text articles reviewed for relevance to key questions (n=704)

Excluded articles (n=653)

Included articles‡ (n=51)

WHI 29
WHIMS 5
WHISCA 3
HERS 7
ESPRIT 1
EMS 1
ULTRA 4
WISDOM 1

* Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
† Identified from reference lists, suggested by experts.
‡ Studies that provided data and contributed to the body of evidence were considered “included.”

**Abbreviations:** EMS=Estrogen Memory Study; ESPRIT=Oestrogen in the Prevention of Reinfarction Trial; HERS=Heart and Estrogen/Progestin Replacement Study; ULTRA=Ultra-Low-Dose Transdermal Estrogen Replacement Assessment; WHI=Women's Health Initiative; WHIMS=Women's Health Initiative Memory Study; WHISCA=Women's Health Initiative Study of Cognitive Aging; WISDOM=Women’s International Study of Long-Duration Oestrogen After Menopause.
Appendix B6. List of Excluded Full-Text Articles

Key to exclusion codes
2 Background
3 Wrong population
4 Wrong intervention
5 Wrong outcome
6 Wrong study design
7 Wrong publication type
8 Wrong indication
9 Conducted prior to 2002
10 Foreign language
11 Focus on intermediate outcomes
12 Superseded by review; no new data
13 Followup less than 1 year
14 Less than 100 subjects

List of excluded articles

Exclusion code: 7

Hormone therapy is no heart helper. The latest chapter in the sage of hormone replacement therapy warns that it may harm, not help, the heart. *Harv Heart Lett.* 2002;13(2):2-3. Exclusion code: 7


Exclusion code: 7

Exclusion code: 7


Appendix B6. List of Excluded Full-Text Articles


Estrogen raises risk of blood clots and stroke. Replacing this powerful hormone after menopause has more risks than first thought. *Heart Advis.* 2008;11(10):7. Exclusion code: 7


Adis International Ltd. ALX 111: ALX1-11, parathyroid hormone (1-84)—NPS Allelix, PREOS, PTH, recombinant human parathyroid hormone, rhPTH (1-84). *Drugs R D.* 2003;4(4):231-235. Exclusion code: 4


Al-Azzawi F, Thompson J, Stevenson J. Which progestogen is more likely to increase the risk of fatal myocardial infarction: a combination of epidemiological and trial evidence. *Maturitas.* 2006;54(2):154-163. Exclusion code: 11

Albert MA, Glynn RJ, Buring J, Ridker PM. C-reactive protein levels among women of various ethnic groups living in the United States (from the Women’s Health Study). *Am J Cardiol.* 2004;93(10):1238-1242. Exclusion code: 11


Appendix B6. List of Excluded Full-Text Articles


Alpert MA. Hormone replacement therapy to reduce cardiovascular risk: a concept whose time has passed? *South Med J.* 2002;95(9):959-961. Exclusion code: 7


American Association of Clinical Endocrinologists Reproductive Medicine Committee. Position statement on hormone replacement therapy (HRT) and cardiovascular risk. 2008. Exclusion code: 2


Appendix B6. List of Excluded Full-Text Articles


Hormone therapy with oestrogen or oestrogen plus progesterone does not reduce the risk of dementia or mild cognitive impairment in older postmenopausal women. *Evid Based Healthcare Pub Health.* 2004;8(6):396-397. Exclusion code: 7


Appendix B6. List of Excluded Full-Text Articles

menopause: a possible role for hormone replacement therapy. *Int J Cardiol.* 2008;130(2):140-146. Exclusion code: 7


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


Bjarnason NH, Alexandersen P, Christiansen C. Number of years since menopause: spontaneous bone loss is dependent but response to hormone replacement therapy is independent. *Bone.* 2002;30(4):637-642. Exclusion code: 11


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles

Exclusion code: 7


Exclusion code: 7


Appendix B6. List of Excluded Full-Text Articles


Decensi A, Omodei U, Robertson C, et al. Effect of transdermal estradiol and oral
Appendix B6. List of Excluded Full-Text Articles


Ding EL, Mehta S, Fawzi WW, Giovannucci EL. Interaction of estrogen therapy with calcium and vitamin D supplementation on colorectal cancer risk: reanalysis of Women’s Health Initiative randomized trial. *Int J Cancer.* 2008;122(8):1690-1694. Exclusion code: 5


Dobey RK, Imthurn B, Barton M, Jackson EK. Vascular consequences of menopause
Appendix B6. List of Excluded Full-Text Articles


Espie M, Daures JP, Chevallier T, et al. Breast cancer incidence and hormone
Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


Garbe E, Levesque L, Suissa S. Variability of breast cancer risk in observational studies of hormone replacement therapy: a meta-


Appendix B6. List of Excluded Full-Text Articles

Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation.* 2006;113(24):e873-923. Exclusion code: 2


Guaschino S, Grimaldi E, Sartore A, et al. Visual function in menopause: the role of...
Appendix B6. List of Excluded Full-Text Articles


Hoibraaten E, Qvigstad E, Arnesen H, et al. Increased risk of recurrent venous thromboembolism during hormone replacement therapy.
Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


MacLennan A, Sturdee DW. The end of WISDOM. *Climacteric*. 2002;5:313-316. Exclusion code: 7


Merz CN, Olson MB, McClure C, et al. A randomized controlled trial of low-dose
Appendix B6. List of Excluded Full-Text Articles

hormone therapy on myocardial ischemia in postmenopausal women with no obstructive coronary artery disease: results from the National Institutes of Health/National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE). Am Heart J. 2010;159(6):987.e981-987. Exclusion code: 5


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


Park A. Clarifying the hazards of HRT. *Time.* 2010;176(18):20. Exclusion code: 7


Perez-Lopez FR, Chedraui P, Gilbert JJ, Perez-Roncero G. Cardiovascular risk in menopausal women and prevalent related co-morbid conditions: facing the post-


Pines A, Sturdee DW, Birkhauser M; International Menopause Society. More data on hormone therapy and coronary artery disease: comments on recent publications from the WHI and Nurses’ Study. *Climacteric.* 2006;9(2):75-76. Exclusion code: 7


Appendix B6. List of Excluded Full-Text Articles


Prentice RL, Langer R, Stefanick ML, et al. Combined postmenopausal hormone therapy and cardiovascular disease: toward resolving the discrepancy between observational studies and the Women’s Health Initiative
Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles

*Clin Endocrinol Metab.* 2010;95(7 Suppl 1):s1-s66. Exclusion code: 2


Shapiro S. Risk of cardiovascular disease in relation to the use of combined postmenopausal hormone therapy: detection bias and resolution of discrepant findings in two Women’s Health Initiative studies.
Appendix B6. List of Excluded Full-Text Articles


Sherwin BB. Estrogen and memory in women: how can we reconcile the findings? Horm Behav. 2005;47(3):371-375. Exclusion code: 7


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


Appendix B6. List of Excluded Full-Text Articles


van de Weijer PH. Risks of hormone therapy in the 50-59 year age group. Maturitas. 2008;60(1):59-64. Exclusion code: 7


Vogelvang TE, van der Mooren MJ, Mijatovic V. Hormone replacement therapy, selective estrogen receptor modulators, and tissue-specific compounds: cardiovascular
Appendix B6. List of Excluded Full-Text Articles


Waetjen LE, Dwyer PL. Estrogen therapy and urinary incontinence: what is the evidence and what do we tell our patients? Int Urogynecol J Pelvic Floor Dysfunct. 2006;17:541-545. Exclusion code: 6


Windler E. Cardiovascular risks under hormone replacement therapy. Internist
Appendix B6. List of Excluded Full-Text Articles

Berl). 2004;45(7):826-834. Exclusion code: 10


Appendix B6. List of Excluded Full-Text Articles


## Appendix C1. Quality Assessment of Randomized, Controlled Trials

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<td>Anderson, 2004**</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Anderson, 2003**</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Compliance rates similar</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Cherry, 2002**</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Greater noncompliance in treatment group</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Ettinger, 2004**</td>
<td>Yes</td>
<td>Yes</td>
<td>Mostly: 2% lower lumbar spine BMD in treatment group compared with placebo group</td>
<td>Unclear</td>
<td>Yes</td>
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<td>Heiss, 2008**</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Hulley, 2002**</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>LaCroix, 2011**</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Yes</td>
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<td>Resnick, 2006**</td>
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<td>Yes</td>
<td>Yes</td>
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<td>No</td>
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<td>No</td>
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<td>National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services</td>
<td>Good</td>
<td>Fair</td>
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<tr>
<td>Anderson, 2003**</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
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<td>National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services</td>
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<td>Fair</td>
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<td>Cherry, 2002**</td>
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<td>Schering AG</td>
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<td>Yes: attrition and adherence No: crossovers and contamination</td>
<td>No</td>
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<td>No</td>
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<td>Berlex Laboratories, Inc</td>
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<td>No</td>
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<td>Yes</td>
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<td>National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services</td>
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<td>Fair</td>
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<tr>
<td>Resnick, 2006**</td>
<td>Yes</td>
<td>Completion rates at year 3: 42.2% E+P vs. 44.1% placebo</td>
<td>Yes</td>
<td>No</td>
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<td>National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services</td>
<td>Good</td>
<td>Fair</td>
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</table>
### Appendix C1. Quality Assessment of Randomized, Controlled Trials

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<td>Resnick, 2009</td>
<td>Yes</td>
<td>Yes</td>
<td>Mostly, except for smoking status</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Completion rates at year 4: 75.1% estrogen vs. 71.9% placebo</td>
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<td>Yes</td>
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<td>National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services</td>
<td>Good</td>
<td>Fair</td>
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<td>Rossouw, 2002</td>
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<td>Yes</td>
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<td>National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services</td>
<td>Good</td>
<td>Fair</td>
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<td>Shumaker, 2003</td>
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<td>Yes</td>
<td>Mostly, except for history of stroke and prior statins use</td>
<td>NR</td>
<td>Yes</td>
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<td>National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services</td>
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<td>NR</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services</td>
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<td>Fair</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services</td>
<td>Good</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Vickers, 2007</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear; prematurely closed trial</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services</td>
<td>Not reported</td>
<td>Fair</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** BMD=bone mineral density; E+P=estrogen and progestin; EMS=Estrogen Memory Study; ESPRIT=Oestrogen in the Prevention of Reinfarction Trial; HERS/HERS II=Heart and Estrogen/Progestin Replacement Study; ULTRA= Ultra-Low-Dose Transdermal Estrogen Assessment; WHI=Women's Health Initiative; WHIMS=Women's Health Initiative Memory Study; WHISCA=Women's Health Initiative Study of Cognitive Aging; WISDOM=Women's International Study of Long Duration Oestrogen After Menopause.
### Appendix C2. Evidence Table of Trials Reporting Incidence of Breast Cancer

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Menopausal Hormone Therapy</strong></td>
<td></td>
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</tr>
<tr>
<td>Chlebowski, 2010;** Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. **WHI Estrogen plus progestin trial</td>
<td>Women enrolled in WHI trial: <strong>Estrogen plus progestin</strong> 8,506 Intervention phase 8,056 Post-intervention phase 8,506 Extension phase <strong>Placebo</strong> 8,102 Intervention phase 7,682 Post-intervention phase 8,102 Extension phase</td>
<td>Incidence of breast cancer 385 (0.42% per year) vs. 293 (0.34% per year); HR, 1.25 (95% CI, 1.07 to 1.46); p=0.004 <strong>Overall mortality per year</strong> 25 vs. 12; HR, 1.96 (95% CI, 1.00 to 4.04); p=0.049 <strong>Rates when analyses limited to 80% adherence</strong> 14 vs.5; HR, 2.96 (95% CI, 1.00 to 8.77); p=0.053</td>
</tr>
<tr>
<td>Chlebowski, 2003;** Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women’s Health Initiative randomized trial. **WHI Estrogen plus progestin trial</td>
<td>Women enrolled in WHI trial: 16,608 Enrolled 8,506 Estrogen plus progestin 8,102 Placebo</td>
<td>Invasive breast cancer 199 (0.41%) vs. 150 (0.33%); HR, 1.24 (95% CI, 1.01 to 1.54); p=0.003 Sensitivity analyses examining impact of nonadherence suggested a stronger effect on invasive breast cancer incidence when events in nonadherent women are excluded (HR, 1.49; p=0.001) <strong>Without prior menopausal hormone use</strong> Treatment (n=6,277) vs. Placebo (n=6,020) Year 1 after entry: 7 (0.11%) vs. 14 (0.23%); HR, 0.48 (95% CI, 0.19 to 1.20) Year 2 after entry: 15 (0.24%) vs. 22 (0.37%); HR, 0.65 (95% CI, 0.34 to 1.25) Year 3 after entry: 19 (0.31%) vs. 19 (0.33%); HR, 0.96 (95% CI, 0.51 to 1.82) Year 4 after entry: 35 (0.58%) vs. 23 (0.40%); HR, 1.45 (95% CI, 0.85 to 2.45) Year 5 after entry: 28 (0.54%) vs. 17 (0.34%); HR, 1.61 (95% CI, 0.88 to 2.94) Year 6 or more after entry: 37 (0.69%) vs. 26 (0.56%); HR, 1.24 (95% CI, 0.75 to 2.05) <strong>Overall</strong> Year 1 after entry: 12 (0.14%) vs. 19 (0.24%); HR, 0.60 (95% CI, 0.29 to 1.23) Year 2 after entry: 26 (0.31%) vs. 32 (0.40%); HR, 0.77 (95% CI, 0.46 to 1.30) Year 3 after entry: 29 (0.35%) vs. 22 (0.28%); HR, 1.26 (95% CI, 0.73 to 2.20) Year 4 after entry: 44 (0.54%) vs. 27 (0.35%); HR, 1.54 (95% CI, 0.95 to 2.49) Year 5 after entry: 43 (0.61%) vs. 21 (0.32%); HR, 1.99 (95% CI, 1.18 to 3.35) Year 6 or more after entry: 45 (0.61%) vs. 29 (0.45%); HR, 1.35 (95% CI, 0.85 to 2.16)</td>
</tr>
<tr>
<td>Rossouw, 2002;** Risks and benefits of estrogen plus progestin in healthy postmenopausal women. **WHI Estrogen plus progestin trial</td>
<td>Women enrolled in WHI trial: 8,506 Estrogen plus progestin 8,102 Placebo</td>
<td>Invasive breast cancer 166 (0.38 annualized %) vs. 124 (0.30 annualized %); HR, 1.26 (95% CI, 1.00 to 1.59) <strong>Breast cancer mortality</strong> 3 (0.01 annualized %) vs. 2 (&lt;0.01 annualized %)</td>
</tr>
<tr>
<td>Gramling, 2009;** Hormone replacement therapy, family history, and breast cancer risk among postmenopausal women (longitudinal follow-up). **WHI Estrogen plus progestin trial</td>
<td>Women enrolled in WHI trial: 16,608 Enrolled 8,506 Estrogen plus progestin 8,102 Placebo</td>
<td>Those with a first-degree family history of breast cancer Total: 1,009 vs. 895 Invasive breast cancer: 35 vs. 25 Women-years: 5,596 vs. 4,900 <strong>Those without a first-degree family history of breast cancer</strong> Total: 7,497 vs. 7,202 Invasive breast cancer: 164 vs. 125 Woman-years: 41,998 vs. 37,798</td>
</tr>
<tr>
<td>Heiss, 2008;** Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. **WHI Estrogen plus progestin trial</td>
<td>All women included in WHI: 8,052 Estrogen plus progestin (analyzed 95% of original 8,506) 7,678 Placebo (analyzed 95% of original 8,102)</td>
<td>Intervention phase 206 (0.43 annualized %) vs. 153 (0.34 annualized %); HR, 1.26 (95% CI, 1.02 to 1.55) <strong>Postintervention phase</strong> 79 (0.42 annualized %) vs. 60 (0.33 annualized %); HR, 1.27 (95% CI, 0.91 to 1.78) p-value for difference between phases=0.97 <strong>Overall combined phase data</strong> 285 (0.43 annualized %) vs. 213 (0.34 annualized %); HR, 1.27 (95% CI, 1.06 to 1.51)</td>
</tr>
</tbody>
</table>
# Appendix C2. Evidence Table of Trials Reporting Incidence of Breast Cancer

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Breast cancer incidence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention stage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postintervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td>LaCroix, 2011;*57</td>
<td>Women enrolled in WHI trial: 10,739 Enrolled 5,310 Estrogen 5,429 Placebo</td>
<td>104 vs. 135; HR, 0.79 (95% CI, 0.61 to 1.02); p=0.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47 vs. 64; HR, 0.75 (95% CI, 0.51 to 1.09); p=0.76</td>
</tr>
<tr>
<td>Anderson, 2004;*57</td>
<td>Women enrolled in WHI trial: 10,739 Enrolled 5,310 Estrogen 5,429 Placebo</td>
<td>151 vs. 199; HR, 0.77 (95% CI, 0.62 to 0.95); p=0.76</td>
</tr>
<tr>
<td>Hulley, 2002;*59</td>
<td>Women from original HERS trial who consented to followup: 2,321 (93% of surviving participants from HERS)</td>
<td>49 (5.9 per 1,000 person-years) vs. 39 (4.7 per 1,000 person-years); HR, 1.27 (95% CI, 0.84 to 0.94); p=0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34 (6.2 per 1,000 person-years) vs. 25 (4.5 per 1,000 person-years); HR, 1.38 (95% CI, 0.82 to 2.31); p=0.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 (5.3 per 1,000 person-years) vs. 14 (4.9 per 1,000 person-years); HR, 1.08 (95% CI, 0.52 to 2.31); p=0.83</td>
</tr>
<tr>
<td>Cherry (ESPRIT Team), 2002;*67</td>
<td>Postmenopausal women aged 50-69 years who had survived a first myocardial infarction: 1,017 Enrolled 513 Estrogen 504 Placebo</td>
<td>Cases by 24 months</td>
</tr>
<tr>
<td>Vickers, 2007;*66</td>
<td>4,385 Enrolled (estrogen plus progestin vs. placebo trial only) 2,196 Estrogen plus progestin 2,189 Placebo</td>
<td>Breast cancer incidence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality from breast cancer</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI=confidence interval; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HERS=Heart and Estrogen/Progestin Replacement Study; HERS II=Heart and Estrogen/Progestin Replacement Study Phase II; HR=hazard ratio; ITT=intention-to-treat; WHI=Women's Health Initiative; WISDOM=Women's International Study of Long-Duration Oestrogen After Menopause.
### Appendix C3. Evidence Table of Trials Reporting Incidence of Colorectal Cancer

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heiss 2008; HERS II: Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin.</td>
<td>Women in the post-intervention phase of WHI: 16,608 Enrolled 8,506 Estrogen plus progestin 8,102 Placebo</td>
<td>Clinical Trial Phase 50 vs.75; HR, 0.62 (95% CI, 0.43 to 0.89)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-intervention phase 34 vs.30; HR, 1.08 (95% CI, 0.66 to 1.77); p=0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Within colorectal cancer</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colon cancer: 49 vs.74; HR, 0.61 (95% CI, 0.42 to 0.87); p=0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Invasive colorectal cancer: 43 vs. 72; HR, 0.56 (95% CI, 0.38 to 0.81); p= 0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rectal cancer: 5 vs.10; HR, 0.54 (95% CI, 0.36 to 0.82); p= 0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rectal cancer: 8 vs.11; HR, 0.66 (95% CI, 0.26 to 0.65); p=0.37</td>
</tr>
<tr>
<td>Chlebowski, 2004; WHI Estrogen plus progestin and colorectal cancer in postmenopausal women.</td>
<td>Women enrolled in WHI trial: 16,608 Enrolled 8,506 Estrogen + progestin 8,102 Placebo</td>
<td><strong>Annualized rate of colorectal cancer</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colorectal cancer: 49 vs.74; HR, 0.61 (95% CI, 0.42 to 0.87); p=0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Invasive colorectal cancer: 43 vs. 72; HR, 0.56 (95% CI, 0.38 to 0.81); p= 0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rectal cancer: 5 vs.10; HR, 0.54 (95% CI, 0.36 to 0.82); p= 0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rectal cancer: 8 vs.11; HR, 0.66 (95% CI, 0.26 to 0.65); p=0.37</td>
</tr>
<tr>
<td>Rossouw, 2002; WHI Estrogen plus progestin in healthy postmenopausal women.</td>
<td>Women enrolled in WHI trial: 16,608 Enrolled 8,506 Estrogen + progestin 8,102 Placebo</td>
<td><strong>Colorectal cancer</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 vs. 67; HR, 0.63 (nominal 95% CI, 0.43 to 0.92) (adjusted 95% CI, 0.32 to -1.24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Colorectal cancer by followup year</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Year 1: 10 vs.15; HR, 0.64</td>
</tr>
<tr>
<td></td>
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<td>Year 2: 11 vs. 9; HR, 1.17</td>
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<tr>
<td></td>
<td></td>
<td>Year 3: 6 vs. 8; HR, 0.72</td>
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<tr>
<td></td>
<td></td>
<td>Year 4: 9 vs. 20; HR, 0.43</td>
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<tr>
<td></td>
<td></td>
<td>Year 5: 4 vs. 8; HR, 0.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Year 6 and later: 5 vs. 7; HR, 0.59</td>
</tr>
<tr>
<td>LaCroix, 2011; WHI Estrogen only trial</td>
<td>Women enrolled in WHI trial: 10,739 Enrolled 5,310 Estrogen 5,429 Placebo</td>
<td><strong>Colorectal cancer</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention stage: 65 vs. 58; HR, 1.15 (95% CI, 0.81 to 1.64); p= 0.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postintervention: 24 vs. 24; HR, 1.01 (95% CI, 0.58 to 1.79); p=0.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall: 89 vs. 82; HR, 1.11 (95% CI, 0.82 to 1.50); p=0.71</td>
</tr>
<tr>
<td>Ritenbaugh, 2008; Conjugated equine estrogens and colorectal cancer incidence and survival: the Women’s Health Initiative randomized clinical trial.</td>
<td>Women enrolled in WHI trial: 10,739 Enrolled 5,310 Estrogen 5,429 Placebo</td>
<td><strong>Incidence of invasive colorectal cancer</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>58 vs. 53; HR, 1.12 (95% CI, 0.77 to 1.63); p=0.55</td>
</tr>
<tr>
<td></td>
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<td><strong>Within invasive colorectal cancer</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colon cancer: 53 vs. 43; HR, 1.26 (95% CI, 0.84 to1.88); p=0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rectal cancer: 5 vs.10; HR, 0.53 (95% CI, 0.18 to 1.56); p=0.25</td>
</tr>
<tr>
<td>Anderson, 2004; Effects of conjugated equine estrogen in postmenopausal women with hysterectomy.</td>
<td>Women enrolled in WHI trial: 10,739 Enrolled 5,310 Estrogen 5,429 Placebo</td>
<td><strong>Colorectal cancer</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>61 vs. 58; HR, 1.08 (nominal 95% CI, 0.75 to 1.55); (adjusted 95% CI, 0.63 to 1.86)</td>
</tr>
<tr>
<td>Hulley 2002; Noncardiovascular disease outcomes during 6.8 years of hormone therapy (Heart and Estrogen/Progestin Replacement Study Follow-Up, HERS II).</td>
<td>Women from original HERS trial who consented to followup: 2,321 (93% of surviving patients from HERS)</td>
<td><strong>Colon cancer (events per 1,000 person-years)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HERS: 2.0 vs. 2.9; HR, 0.69 (95% CI, 0.32 to 1.49); p=0.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HERS II: 10/3.4 vs. 10/3.4; HR, 1.01 (95% CI, 0.42 to 2.43); p=0.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total: 21/2.5 vs. 26/3.1; HR, 0.81 (95% CI, 0.46 to 1.45); p=0.48</td>
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<tr>
<td></td>
<td></td>
<td>p-value for treatment-time interaction = 0.52</td>
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<tr>
<td></td>
<td></td>
<td><strong>Unadjusted ITT vs. adjusted ITT vs. adjusted as-treated</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR, 0.81 (95% CI, 0.46 to 1.45) vs. HR, 0.82 (95% CI, 0.46 to 1.47) vs. HR, 0.58 (95% CI, 0.25 to 1.35)</td>
</tr>
</tbody>
</table>
## Appendix C3. Evidence Table of Trials Reporting Incidence of Colorectal Cancer

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tierney, 2009;[68] A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women. EMS Estrogen plus progestin trial</td>
<td>Within the greater Toronto area; enrolled between April 2000 and January 2004; aged &gt;60 years; last menstrual cycle &gt;12 months before screening; fluent in English and could read normal print and hear normal speech. 142 Enrolled 70 Estrogen + progestin 72 Placebo</td>
<td>Colorectal cancer 0 vs. 0</td>
</tr>
<tr>
<td>Vickers 2007;[66] Main morbidities recorded in the Women’s International Study of Long Duration Oestrogen After Menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women. WISDOM Estrogen plus progestin trial</td>
<td>4,385 Enrolled 2,196 Estrogen plus progestin 2,189 Placebo</td>
<td>Colorectal Cancer 2 vs. 2; HR, not reported Mortality 1 vs. 0; HR, not reported</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI=confidence interval; EMS=Estrogen Memory Study; HERS=Heart and Estrogen/Progestin Replacement Study; HERS II=Heart and Estrogen/Progestin Replacement Study Phase II; HR=hazard ratio; ITT=intention-to-treat; WHI=Women’s Health Initiative; WISDOM=Women’s International Study of Long-Duration Oestrogen After Menopause.
## Appendix C4. Evidence Table of Trials Reporting Incidence of Diabetes

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Margolis, 2004:</strong> Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women’s Health Initiative Hormone Trial. <strong>WHI Estrogen plus progestin trial</strong></td>
<td>Excluded women with self-reported diabetes at baseline: 15,641 Enrolled 8,014 Estrogen plus progestin 7,627 Placebo</td>
<td>Incident diabetes 277 (3.5%) vs. 324 (4.2%); HR, 0.79 (95% CI, 0.67 to 0.93); p=0.006 Absolute reduction of 1.5 cases/1,000 women/year with estrogen plus progestin 21% relative reduction in the risk for incident treated diabetes 143 women would need to be treated with estrogen plus progestin to prevent 1 case of diabetes over 5.6 years</td>
</tr>
<tr>
<td><strong>Bonds, 2006:</strong> The effect of conjugated equine oestrogen on diabetes incidence: the Women’s Health Initiative randomised trial. <strong>WHI Estrogen only trial</strong></td>
<td>Excluded women with self-reported diabetes at baseline: 9,712 Enrolled 4,806 Estrogen 4,906 Placebo</td>
<td>Incident diabetes overall 397 (8.3%) vs. 455 (9.3%); HR, 0.88 (95% CI, 0.77 to 1.01); p=not significant Of those who adhered to ≥80% of medication 27% reduction in risk for new, treated diabetes in estrogen group compared with placebo group; HR, 0.73 (95% CI, 0.60 to 0.88)</td>
</tr>
<tr>
<td><strong>Kanay, 2003:</strong> Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/Progestin Replacement Study. <strong>HERS Estrogen plus progestin trial</strong></td>
<td>Excluded women with self-reported diabetes at baseline: 2,763 Enrolled 1,380 Estrogen plus progestin 1,383 Placebo</td>
<td>Cumulative incidence of new diabetes diagnosis Overall: 62/999 (6.2%) vs. 98/1030 (9.5%); NNT, 30 (95% CI, 18 to 103); p=0.006 Baseline normal glucose: 38/904 (4%) vs. 52/907 (6%); p=0.13 Baseline impaired fasting glucose: 24/95 (25%) vs. 46/123 (37%); p=0.06 Risk for incident diabetes Unadjusted: HR, 0.65 (95% CI, 0.48 to 0.89) Adjusted for BMI, weight, change in weight, and waist circumference: HR, 0.66 (95% CI, 0.48 to 0.93) Adjusted for triglyceride and HDL levels: HR, 0.69 (95% CI, 0.50 to 0.95) Adjusted for hypertension: HR, 0.65 (95% CI, 0.47 to 0.89) Adjusted for smoking: HR, 0.65 (95% CI, 0.47 to 0.89) Adjusted for medications (diuretics, β-blockers, ACE inhibitors, statins): HR, 0.63 (95% CI, 0.46 to 0.87) Adjusted for all above: HR, 0.67 (95% CI, 0.49 to 0.93)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACE=angiotensin-converting enzyme; BMI=body mass index; CI=confidence interval; HDL=high-density lipoprotein; HERS=Heart and Estrogen/Progestin Replacement Study; HR=hazard ratio; NNT=number needed to treat; WHI=Women’s Health Initiative.
### Appendix C5. Evidence Table of Trials Reporting Incidence of Cardiovascular Disease

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo) Cardiovascular disease incidence during intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heiss, 2008;** Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin (WHI, post-treatment). **WHI Estrogen plus progestin trial</td>
<td>Women enrolled in WHI E+P trial: 8,052 Estrogen plus progestin 7,678 Placebo</td>
<td><strong>Overall CHD</strong>&lt;br&gt;196 vs. 154; HR, 1.22 (95% CI, 0.99 to 1.51)&lt;br&gt;<strong>CHD death</strong>&lt;br&gt;40 vs. 36; HR, 1.04 (95% CI, 0.67 to 1.64)&lt;br&gt;<strong>Total MI</strong>&lt;br&gt;168 vs. 127; HR, 1.26 (95% CI, 1.00 to 1.59)&lt;br&gt;<strong>Stroke</strong>&lt;br&gt;159 vs. 110; HR, 1.34 (95% CI, 1.05 to 1.71)&lt;br&gt;<strong>DVT</strong>&lt;br&gt;122 vs. 61; HR, 1.88 (95% CI, 1.38 to 2.55)&lt;br&gt;<strong>PE</strong>&lt;br&gt;87 vs. 41; HR, 1.98 (95% CI, 1.36 to 2.87)&lt;br&gt;<strong>All CVD events</strong>&lt;br&gt;785 vs. 660; HR, 1.13 (95% CI, 1.02 to 1.25)</td>
</tr>
<tr>
<td>Manson, 2003;** Estrogen plus progestin and the risk of coronary heart disease. **WHI Estrogen plus progestin trial</td>
<td>Women enrolled in WHI E+P trial: 8,052 Estrogen plus progestin 7,678 Placebo</td>
<td><strong>Overall CHD</strong>&lt;br&gt;188 vs. 147; HR, 1.24 (95% CI, 1.00 to 1.54)&lt;br&gt;<strong>Nonfatal MI</strong>&lt;br&gt;151 vs. 114; HR, 1.28 (95% CI, 1.00 to 1.63)&lt;br&gt;<strong>CHD death</strong>&lt;br&gt;39 vs. 34; HR, 1.10 (95% CI, 0.70 to 1.75)&lt;br&gt;<strong>CHF</strong>&lt;br&gt;113 vs. 109; HR, 0.99 (95% CI, 0.76 to 1.29)&lt;br&gt;<strong>Subgroups not associated with HT and outcomes</strong>&lt;br&gt;Age, years since menopause, vasomotor symptoms, BMI, aspirin use, statin use, serum lipid levels except for LDL cholesterol, fibrinogen, Factor VIII:C, C-reactive protein, race or ethnic group, education level, current smoking, hypertension, diabetes, number of CHD risk factors, CVD at baseline, CHD at baseline.&lt;br&gt;<strong>Subgroups associated with HT and outcomes</strong>&lt;br&gt;LDL cholesterol level; also risk highest and most significant during the first year of the trial.</td>
</tr>
<tr>
<td>Wassertheil-Smoller, 2003;** Effect of estrogen plus progestin on stroke in postmenopausal women: the Women’s Health Initiative: a randomized trial. **WHI Estrogen plus progestin trial</td>
<td>Women enrolled in WHI E+P trial: 8,052 Estrogen plus progestin 7,678 Placebo</td>
<td><strong>All stroke</strong>&lt;br&gt;151 vs. 107; HR, 1.31 (95% CI, 1.02 to 1.68)&lt;br&gt;<strong>Ischemic stroke</strong>&lt;br&gt;125 vs. 81; HR, 1.44 (95% CI, 1.09 to 1.90)&lt;br&gt;<strong>Hemorrhagic stroke</strong>&lt;br&gt;18 vs. 20; HR, 0.82 (95% CI, 0.43 to 1.56)&lt;br&gt;<strong>Subgroups not associated with HT and outcomes</strong>&lt;br&gt;Prior oral contraceptive use.&lt;br&gt;<strong>Subgroups associated with HT and outcomes</strong>&lt;br&gt;Current smoking, hypertension, diabetes, high Framingham stroke score, high white cell count or hematocrit, biomarkers of inflammation—but these did not modify the effect of HT on stroke. Reduced risk with vitamin C use and increased physical activity.</td>
</tr>
</tbody>
</table>
### Appendix C5. Evidence Table of Trials Reporting Incidence of Cardiovascular Disease

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
<th>Cardiovascular disease incidence during intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushman, 2004&lt;sup&gt;10&lt;/sup&gt; Estrogen plus progestin and risk of venous thrombosis. <strong>WHI Estrogen plus progestin trial</strong></td>
<td>Women enrolled in WHI trial: 8,052 Estrogen plus progestin 7,678 Placebo</td>
<td>VT 167 vs. 76; HR, 2.06 (95% CI, 1.57 to 2.70)</td>
<td><strong>Subgroups not associated with HT and outcomes</strong> Genetic variants except Factor V Leiden. <strong>Subgroups associated with HT and outcomes</strong> Age, BMI, Factor V Leiden.</td>
</tr>
<tr>
<td>Rossouw, 2007&lt;sup&gt;13&lt;/sup&gt; Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. <strong>WHI Estrogen plus progestin and estrogen only trials</strong></td>
<td>Women enrolled in WHI trial: 8,052 Estrogen plus progestin 7,678 Placebo 5,310 Estrogen 5,429 Placebo</td>
<td>Overall CHD Combined trials: 396 vs. 379; HR, 1.07 (95% CI, 0.92 to 1.23) E+P: 195 vs. 153; HR, 1.23 (95% CI, 0.99 to 1.53) Estrogen only: 201 vs. 217; HR, 0.95 (95% CI, 0.78 to 1.16) Stroke Combined trials: 327 vs. 239; HR, 1.32 (95% CI, 1.12 to 1.56) E+P: 159 vs. 112; HR, 1.31 (95% CI, 1.03 to 1.68) Estrogen only: 169 vs. 127; HR, 1.33 (95% CI, 1.05 to 1.68) <strong>Subgroups not associated with HT and outcomes</strong> Age, years since menopause for stroke. <strong>Subgroups associated with HT and outcomes</strong> Years since menopause for CHD. Interaction with CHD and vasomotor symptoms at baseline.</td>
<td></td>
</tr>
<tr>
<td>LaCroix, 2011&lt;sup&gt;17&lt;/sup&gt; Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy post-intervention. <strong>WHI Estrogen only trial</strong></td>
<td>Women enrolled in WHI trial: 5,310 Estrogen 5,429 Placebo</td>
<td>Overall CHD 203 vs. 221; HR, 0.95 (95% CI, 0.78 to 1.15) CHD death 63 vs. 66; HR, 0.98 (95% CI, 0.70 to 1.39) Total MI 164 vs. 173; HR, 0.98 (95% CI, 0.79 to 1.21) Stroke 169 vs. 129; HR, 1.36 (95% CI, 1.08 to 1.71) DVT 85 vs. 59; HR, 1.47 (95% CI, 1.06 to 2.05) PE 52 vs. 39; HR, 1.37 (95% CI, 0.90 to 2.07) <strong>All CVD events</strong> 874 vs. 811; HR, 1.11 (95% CI, 1.01 to 1.23)</td>
<td></td>
</tr>
<tr>
<td>Hsia, 2006&lt;sup&gt;20&lt;/sup&gt; Conjugated equine estrogens and coronary heart disease: the Women’s Health Initiative. <strong>WHI Estrogen only trial</strong></td>
<td>Women enrolled in WHI trial: 5,310 Estrogen 5,429 Placebo</td>
<td>CHD outcomes not significantly different between estrogen vs. placebo MI or CHD death, nonfatal MI, coronary death, CABG or PCI, angina, CHF, acute coronary syndrome, combinations of outcomes. <strong>Subgroups not associated with CEE and CHD outcomes</strong> Race or ethnic group, level of education, smoking, hypertension, diabetes, high cholesterol requiring medication, coronary risk factors, CVD at baseline, CHD at baseline, age, vasomotor symptoms, years since bilateral oophorectomy, years since hysterectomy, BMI, waist circumference, statin use at baseline, aspirin use at baseline, serum lipid levels, fibrinogen levels, Factor VIII:C. <strong>Significant association</strong> High C-reactive protein levels.</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix C5. Evidence Table of Trials Reporting Incidence of Cardiovascular Disease

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo) Cardiovascular disease incidence during intervention</th>
</tr>
</thead>
</table>
| **Hendrix, 2006:** Effects of conjugated equine estrogen on stroke in the Women’s Health Initiative. **WHI Estrogen only trial** | Women enrolled in WHI trial: 5,310 Estrogen 5,429 Placebo | All stroke  
168 vs. 127; HR, 1.37 (95% CI, 1.09 to 1.73)  
Ischemic stroke  
142 vs. 95; HR, 1.55 (95% CI, 1.19 to 2.01)  
Hemorrhagic stroke  
17 vs. 27; HR, 0.64 (95% CI, 0.35 to 1.18)  
Subgroups not associated with HT and outcomes  
Age, race or ethnicity, years since menopause, prior CVD, hypertension, diabetes, BMI, smoking, prior HT use and duration, statin use, aspirin use, vasomotor symptoms, Framingham risk score.  
Subgroups not associated with HT and outcomes  
None. |
| **Curb, 2006:** Venous thrombosis and conjugated equine estrogen in women without a uterus.  
**WHI Estrogen only trial** | Women enrolled in WHI trial: 5,310 Estrogen 5,429 Placebo | VT  
111 vs. 86; HR, 1.32 (95% CI, 0.99 to 1.75)  
DVT  
85 vs. 59; HR, 1.47 (95% CI, 1.06 to 2.06)  
PE  
52 vs. 39; HR, 1.37 (95% CI, 0.90 to 2.07)  
Subgroups not associated with HT and outcomes  
Age, BMI, race or ethnicity, smoking, prior HT use, prior oral contraceptives, physical activity level (borderline significance), dietary fatty acid intake, dietary fish intake, treatment for hypertension, aspirin use, statin use, history of CVD, time in the study, multiple genetic variants, serum cholesterol levels except HDL.  
Subgroups associated with HT and outcomes  
HDL cholesterol level, but no estimates were statistically significant. |

**Abbreviations:** BMI=body mass index; CABG=coronary artery bypass graft; CEE=conjugated equine estrogen; CHD=coronary heart disease; CHF=coronary heart failure; CI=confidence interval; CVD=cardiovascular disease; DVT=deep vein thrombosis; E+P=estrogen with progestin; HDL=high-density lipoprotein; HR=hazard ratio; HT=hormone therapy; LDL=low-density lipoprotein; MI=myocardial infarction; PCI=percutaneous coronary intervention; PE=pulmonary embolism; VT=venous thrombosis; WHI=Women's Health Initiative.
## Appendix C6. Evidence Table of Trials Reporting Incidence of Fractures

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
</tr>
</thead>
</table>
| **Cauley, 2003;**— Effects of estrogen plus progestin on risk of fracture and bone mineral density. WHI Estrogen plus progestin trial | Women enrolled in WHI trial: 8,506 Estrogen plus progestin 8,102 Placebo | Hip  
52 vs. 73; HR, 0.67 (95% CI, 0.47 to 0.96)  
No significant interactions with age, years since menopause, BMI, smoking, number of recent falls, parental history of fracture, previous HT, history of fracture, or fracture risk score; improved effect with calcium intake >1200 mg/d.  
Total  
733 vs. 896; HR, 0.76 (95% CI, 0.69 to 0.83)  
No significant interactions with age, years since menopause, BMI, smoking, number of recent falls, total calcium intake, parental history of fracture, previous HT, race or ethnicity, history of fracture, fracture risk score, or low baseline BMD. |
| **Rossouw, 2002;**— Risks and benefits of estrogen plus progestin in healthy postmenopausal women. WHI Estrogen plus progestin trial | Women enrolled in WHI trial: 8,506 Estrogen plus progestin 8,102 Placebo | Hip  
44 vs. 62; HR, 0.66 (95% CI, 0.45 to 0.98)  
Vertebral  
41 vs. 60; HR, 0.66 (95% CI, 0.44 to 0.98)  
Other osteoporotic  
579 vs. 701; HR, 0.77 (95% CI, 0.69 to 0.86)  
Total  
650 vs. 788; HR, 0.76 (95% CI, 0.69 to 0.85) |
| **LaCroix, 2011;**— Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy post-intervention. WHI Estrogen only trial | Women enrolled in WHI trial: 5,310 Estrogen 5,429 Placebo | Hip intervention  
48 vs. 74; HR, 0.67 (95% CI, 0.46 to 0.96)  
Hip postintervention  
66 vs. 53; HR, 1.27 (95% CI, 0.88 to 1.82)  
Hip overall  
114 vs. 127; HR, 0.92 (95% CI, 0.71 to 1.18) |
| **Anderson, 2004;**— Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. WHI Estrogen only trial | Women enrolled in WHI trial: 5,310 Estrogen 5,429 Placebo | Hip  
38 vs. 64; HR, 0.61 (95% CI, 0.41 to 0.91)  
Vertebral  
39 vs. 64; HR, 0.62 (95% CI, 0.42 to 0.93)  
Total  
503 vs. 724; HR, 0.70 (95% CI, 0.63 to 0.79)  
No significant interactions with age. |
| **Hulley, 2002;**— Noncardiovascular disease outcomes during 6.8 years of hormone therapy (Heart and Estrogen/Progestin Replacement Study follow-up, HERS II). HERS II Estrogen plus progestin trial | Women from original HERS trial who consented to followup: 2,321 | Hip  
40 vs. 25; HR, 1.61 (95% CI, 0.98 to 2.66)  
Wrist  
42 vs. 43; HR, 0.98 (95% CI, 0.64 to 1.50)  
Vertebral  
26 vs. 30; HR, 0.87 (95% CI, 0.52 to 1.48)  
Other  
144 vs. 154; HR, 0.94 (95% CI, 0.75 to 1.18)  
Any  
230 vs. 222; HR, 1.04 (95% CI, 0.87 to 1.25) |

**Abbreviations:** BMD=bone mineral density; BMI=body mass index; CI=confidence interval; HERS=Heart and Estrogen/Progestin Replacement Study; HR=hazard ratio; HT=hormone therapy; WHI=Women’s Health Initiative.
### Appendix C7. Evidence Table of Trials Reporting Incidence of Lung Cancer

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
<th>Lung cancer incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlebowski, 2009;27</td>
<td>Women enrolled in WHI trial: 16,608 Enrolled 8,506 Estrogen plus progestin 8,102 Placebo</td>
<td>Lung cancer incidence 109 vs. 85; HR, 0.23 (95% CI, 0.92 to 1.63); p=0.16</td>
<td><strong>Lung cancer incidence</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung cancer mortality</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality from lung cancer: 73 vs. 40; HR, 1.71 (95% CI, 1.6 to 2.52); p=0.01</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Non-small cell: 62 vs. 31; HR, 1.67 (95% CI, 1.22 to 2.88); p=0.004</td>
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<tr>
<td></td>
<td></td>
<td>Small cell: 11 vs. 9; HR, 1.16 (95% CI, 0.48 to 2.79); p=0.75</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality after diagnosis: 78 vs. 49; HR, 1.50 (95% CI, 1.05 to 2.14); p=0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-small cell: 67 vs. 39; HR, 1.61; (95% CI, 1.09 to 2.39); p=0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small cell: 11 vs. 10; HR, 1.04 (95% CI, 0.44 to 2.46); p=0.92</td>
<td></td>
</tr>
</tbody>
</table>

| Chlebowski, 2010;45 | Women enrolled in WHI trial: 10,739 Enrolled 5,310 Estrogen 5,429 Placebo | Lung cancer incidence 61 vs. 54; HR, 1.17 (95% CI, 0.81 to 1.69); p =0.39 |                       |
|                     |            | Lung cancer mortality            |                       |
|                     |            | Hulley 2002;61 Noncardiovascular disease outcomes during 6.8 years of hormone therapy (Heart and Estrogen/Progestin Replacement Study follow-up, HERS II). |                       |
|                     |            | HERS II Estrogen plus progestin trial |                       |
|                     |            | Women who agreed to be followed after HERS termination: 2,321 (93% of surviving patients from HERS) |                       |
|                     |            | Lung cancer HERS: 24 vs. 19; HR, 1.28 (95% CI, 0.70 to 2.33); p=0.43 |                       |
|                     |            | HERS II: 13 vs. 8; HR, 1.64 (95% CI, 0.68 to 3.96); p=0.27 |                       |
|                     |            | Total: 37 vs. 27; HR, 1.39 (95% CI, 0.84 to 2.28); p=0.20 |                       |
|                     |            | Treatment-time interaction: p=0.64 |                       |
|                     |            | Unadjusted ITT vs. adjusted as-treated |                       |
|                     |            | 1.39 vs. 1.43 vs. 1.73 |                       |

| Tierney, 2009;68 | Women enrolled in EMS trial: 142 Enrolled 70 Estrogen plus progestin 72 Placebo | Lung cancer 1 (1.4%) vs. 0 |                       |
|                  |            | Lung cancer mortality 1 vs. 0 |                       |

**Abbreviations**: CI=confidence interval; EMS=Estrogen Memory Study; HERS=Heart and Estrogen/Progestin Replacement Study; HERS II=Heart and Estrogen/Progestin Replacement Study Phase II; HR=hazard ratio; ITT=intention to treat; WHI=Women’s Health Initiative.
### Appendix C8. Evidence Table of Trials Reporting Incidence of Gynecological Cancers

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
<th>Other outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heiss, 2008;¹⁹²⁰</td>
<td>Women enrolled in WHI trial: 15,730 Analyzed 8,052 Estradiol plus progestin 7,678 Placebo</td>
<td><strong>Endometrial cancer (postintervention phase only)</strong>:&lt;br&gt;17 (0.09 annualized %) vs. 21 (0.11 annualized %); HR, 0.75 (95% CI, 0.40 to 1.43); p=0.83&lt;br&gt;<strong>Endometrial cancer (intervention and postintervention phases combined)</strong>:&lt;br&gt;44 (0.07 annualized %) vs. 52 (0.08 annualized %); HR, 0.78 (95% CI, 0.52 to 1.16)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Anderson, 2004;²¹²²</td>
<td>Women enrolled in WHI trial: 16,608 Enrolled 8,506 Estradiol plus progestin 8,102 Placebo</td>
<td><strong>Ovarian cancer</strong>&lt;br&gt;20 (0.04 annualized %) vs. 12 (0.03 annualized %); HR, 1.58 (95% CI, 0.77 to 3.24)&lt;br&gt;Mortality: 9 vs. 3; HR, 2.70 (95% CI, 0.73 to 10.0)&lt;br&gt;Observed annual incidence rate: 34 per 100,000 person-years&lt;br&gt;Rate of diagnosis: 27 per 100,000 person-years&lt;br&gt;<strong>Endometrial cancer</strong>&lt;br&gt;27 (0.06 annualized %) vs. 31 (0.07 annualized %); HR, 0.81 (95% CI, 0.48 to 1.36)&lt;br&gt;Observed incidence rate: 62 per 100,000 person-years&lt;br&gt;Rate of diagnosis: 56 per 100,000 person-years&lt;br&gt;<strong>Cervical cancer</strong>&lt;br&gt;8 (0.02 annualized %) vs. 5 (0.01 annualized %); HR, 1.44 (95% CI, 0.47 to 4.42)&lt;br&gt;<strong>Other gynecological cancer (including fallopian, primary peritoneum cancers)</strong>&lt;br&gt;27 (0.06 annualized %) vs. 31 (0.07 annualized %); HR, 0.81 (95% CI, 0.48 to 1.36)</td>
<td>Followup endometrial biopsy&lt;br&gt;Routine biopsy subgroup and endometrial cancer: 0 vs. 0&lt;br&gt;Usual care subgroup and endometrial cancer: 7 (0.3%) vs. 7 (1.6%)</td>
</tr>
<tr>
<td>Hulley, 2002;²³²⁴</td>
<td>Women reconsenting to followup period of HERS study: 2,485 Eligible from HERS II 1,156 Estradiol plus progestin 1,165 Placebo</td>
<td><strong>Endometrial cancer</strong>&lt;br&gt;HERS II: 0 vs. 3 (1.0 events per 1,000 person-years)&lt;br&gt;HERS: 2 (0.4 events per 1,000 person-years)&lt;br&gt;Interaction between HERS and HERS II: p=0.99&lt;br&gt;HERS and HERS II combined: 2 (0.2 events per 1,000 person-years) vs. 8 (0.9 events per 1,000 person-years); HR, 0.25 (95% CI, 0.05 to 1.18); p=0.08</td>
<td>Not reported</td>
</tr>
<tr>
<td>Cherry, 2002;²⁶²⁷</td>
<td>Women enrolled in ESPRIT trial: 1,017 Enrolled 513 Estradiol 504 Placebo</td>
<td><strong>Endometrial cancer</strong>&lt;br&gt;0 vs.0</td>
<td>Not reported</td>
</tr>
<tr>
<td>Johnson, 2005;²⁸²⁹</td>
<td>Women enrolled in ULTRA trial: 417 Enrolled 208 Estradiol 209 Placebo</td>
<td><strong>Endometrial cancer</strong>&lt;br&gt;0.0% (95% CI, 0 to 1.9) vs. 0.0% (95% CI, 0.0 to 2.1); difference=0.0 (95% CI, -4.2 to 3.1); p=1.000</td>
<td>Benign or atrophic endometrium: 83.5% vs. 86.4%; p=0.5&lt;br&gt;Proliferative endometrium: 8.5% vs. 11.1%; p=0.06&lt;br&gt;Of 11 women in estradiol group who had biopsy showing proliferation, none had progressively higher histological diagnoses and 9 (82%) reverted to benign, nonproliferative histology. All 11 women had...</td>
</tr>
</tbody>
</table>

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¹⁹ Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. WHI Estrogen plus progestin trial.
²⁰ ESPRIT Estrogen alone randomised placebo controlled trial.
²¹ Postmenopausal women: for prevention of reinfarction in the Women's Heart and Estrogen Therapy (WHI) study: HERS II Estrogen plus progestin on gynecological cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. WHI Estrogen plus progestin trial.
²² HERS II Estrogen plus progestin trial: Estrogen/Progestin Replacement of hormone therapy: Heart and disease outcomes during 6.8 years of hormone therapy: Heart and disease outcomes during 6.8 years of Hulley, 2002; Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Hulley, 2002; Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. ESPRIT Estrogen alone.
²³ HERS Estrogen alone randomised placebo controlled trial.
²⁴ HERS Estrogen plus progestin trial: Study Follow-up.
²⁵ WHI Estrogen plus progestin trial: Estrogen plus progestin on gynecological cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. WHI Estrogen plus progestin trial.
²⁶ Cherry, 2002; Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. ESPRIT Estrogen alone.
²⁷ Johnson, 2005; Ulterine and vaginal effects of unopposed ultralow-dose transdermal estradiol. ULTRA Estrogen alone.
Appendix C8. Evidence Table of Trials Reporting Incidence of Gynecological Cancers

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
<th>Other outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Gynecological cancer incidence</td>
<td>continued on estradiol therapy. Women with vaginal bleeding 90 days prior to biopsy were more likely to have proliferation than those without bleeding (OR, 9.5 [95% CI, 1.1 to 84]; p=0.04).</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI=confidence interval; EMS=Estrogen Memory Study; ESPRIT=Oestrogen in the Prevention of Reinfarction Trial; HERS=Heart and Estrogen/Progestin Replacement Study; HERS II=Heart and Estrogen/Progestin Replacement Study Phase II; HR=hazard ratio; OR=odds ratio; ULTRA=Ultra-Low-Dose Transdermal Estrogen Replacement Assessment; WHI=Women's Health Initiative.
<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo) Mortality incidence</th>
</tr>
</thead>
</table>
| Heiss, 2008; 33     | All women enrolled in WHI trial followed through postintervention phase | All-cause mortality No differences between groups  
During treatment  
250 (2.9%) vs. 239 (3%); HR, 0.97 (95% CI, 0.81 to 1.16)  
Annualized rate: 0.52 vs. 0.53  
Posttreatment  
233 (2.9%) vs. 196 (2.5%); HR, 1.15 (95% CI, 0.95 to 1.39)  
Annualized rate: 1.20 vs. 1.06  
Overall  
483 (5.7%) vs. 435 (5.4%); HR, 1.04 (95% CI, 0.91 to 1.18)  
Annualized rate: 0.71 vs. 0.68 |
| LaCroix, 2011; 49    | All women enrolled in WHI trial followed through postintervention extension phase | All-cause mortality No differences between groups  
During treatment  
300 (5.6%) vs. 297 (5.5%); HR, 1.04 (95% CI, 0.89 to 1.22)  
Annualized rate: 0.80 vs. 0.77  
Posttreatment  
277 (5.8%) vs. 284 (5.8%); HR, 1.00 (95% CI, 0.84 to 1.18)  
Annualized rate: 1.47 vs. 1.48  
Overall  
577 (10.9%) vs. 581 (10.7%); HR, 1.02 (95% CI, 0.91 to 1.15)  
Annualized rate: 1.02 vs. 1.00 |
| Hulley, 2002; 61     | All women enrolled in HERS trial followed through HERS II | All-cause mortality No differences between groups  
During treatment  
130 (9.4%) vs. 123 (8.9%); HR, 1.06 (95% CI, 0.83 to 1.36); p=0.62  
23.5 per 1,000 person-years vs. 22.1 per 1,000 person-years  
Posttreatment  
131 (11.3%) vs. 116 (9.9%); HR, 1.14 (95% CI, 0.89 to 1.46); p=0.31  
43.4 per 1,000 person-years vs. 38.1 per 1,000 person-years  
Overall  
261 (18.9%) vs. 239 (17.3%); HR, 1.10 (95% CI, 0.92 to 1.31); p=0.29  
30.6 per 1,000 person-years vs. 27.8 per 1,000 person-years |
| Cherry, 2002; 67     | All women enrolled in ESPRIT trial followed through trial completion | All-cause mortality  
Rate ratio, 0.79 (95% CI, 0.50 to 1.27); p=0.34 |

**Abbreviations:** CI=confidence interval; ESPRIT=Oestrogen in the Prevention of Reinfarction Trial; HERS=Heart and Estrogen/Progestin Replacement Study; HERS II=Heart and Estrogen/Progestin Replacement Study Phase II; HR=hazard ratio; WHI=Women’s Health Initiative.
## Appendix C10. Evidence Table of Trials Reporting Incidence of Gallbladder Disease

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
<th>Other outcomes</th>
</tr>
</thead>
</table>
| Cicullo, 2005;* Effect of estrogen therapy on gallbladder disease. WHI Estrogen plus progestin and estrogen only trials | Excluded women with cholecystectomy at baseline. 14,203 (85.5%) Eligible from WHI estrogen plus progestin trial: 7,308 Estrogen plus progestin 6,895 Placebo 8,376 (77.99%) Eligible from WHI estrogen only trial: 4,141 Estrogen 4,235 Placebo | **Annual incidence rate for any gallbladder event**  
E+P: 5.5/1,000 person-years vs. 3.5/1,000 person-years  
E: 7.8/1,000 person-years vs. 4.7/1,000 person-years | **Cholecystectomy**  
E+P: 190 (2.6%) vs. 107 (1.5%); HR, 1.67 (95% CI, 1.32 to 2.11); p<0.001  
E: 192 (4.6%) vs. 104 (2.4%); HR, 1.93 (95% CI, 1.52 to 2.44); p<0.001  
**Global gallbladder disease**  
E+P: 223 (3.0%) vs. 130 (1.9%); HR, 1.61 (95% CI, 1.30 to 2.00); p<0.001  
E: 223 (5.4%) vs. 130 (3.1%); HR, 1.79 (95% CI, 1.44 to 2.22); p<0.001  
**Cholecystitis**  
E+P: 192 (2.6%) vs. 117 (1.7%); HR, 1.54 (95% CI, 1.22 to 1.94); p<0.001  
E: 186 (4.5%) vs. 107 (2.5%); HR, 1.80 (95% CI, 1.42 to 2.28); p<0.001 |

**Abbreviations:** CI=confidence interval; E=estrogen; E+P=estrogen with progestin; HR=hazard ratio; WHI=Women’s Health Initiative.
### Appendix C11. Evidence Table of Trials Reporting Incidence of Cognitive Functioning

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
<th>Other dementia diagnosis outcomes</th>
<th>3MSE Scores</th>
<th>Other measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shumaker, 2003</strong>&lt;sup&gt;114&lt;/sup&gt; Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. <strong>WHIMS Estrogen plus progestin trial</strong></td>
<td>Women enrolled in WHI trial aged ≥65 years without probable dementia: 4,532 Enrolled 2,229 Estrogen plus progestin 2,303 Placebo</td>
<td>PD incidence: 40 (1.8%) vs. 21 (0.9%) 4.5 vs. 2.2 per 1,000 person-years HR, 2.05 (95% CI, 1.21 to 3.48); p=0.01 MCI incidence: 56 (2.5%) vs. 55 (2.4%) 6.3 vs. 5.9 per 1,000 person-years HR, 1.07 (95% CI, 0.74 to 1.55); p=0.72</td>
<td>PD or MCI: 85 (3.8%) vs. 66 (2.9%) PD or MCI per 1,000 person-years: 9.5 vs. 7.1 HR, 1.37 (95% CI, 0.99 to 1.89); p=NR No differences between groups in type of dementia diagnosed, with majority being diagnosed AD: 20 (50%) vs. 12 (57.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rapp, 2003</strong>&lt;sup&gt;53&lt;/sup&gt; Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. <strong>WHIMS Estrogen plus progestin trial</strong></td>
<td>Women enrolled in WHI trial aged ≥65 years without probable dementia and with &gt;1 postrandomization 3MSE score: 4,381 Enrolled 2,145 Estrogen plus progestin 2,236 Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Espeland, 2004</strong>&lt;sup&gt;52&lt;/sup&gt; Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. <strong>WHIMS Estrogen plus progestin and estrogen only trial</strong></td>
<td>Women enrolled in WHI trial aged ≥65 years without probable dementia, enrolled in WHIMS &gt;6 months after initiation of assigned WHI therapy and with &gt;1 post-randomization 3MSE score: 4,344 Enrolled 2,131 Estrogen plus progestin 2,213 Placebo 1,387 Estrogen 1,421 Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Resnick, 2006</strong>&lt;sup&gt;58&lt;/sup&gt; Effects of combination estrogen plus progestin hormone treatment on cognition and affect. <strong>WHISCA Estrogen plus progestin trial</strong></td>
<td>Women enrolled in WHIMS trial, limited to 14 of 39 WHIMS locations: 1,416 Enrolled 690 Estrogen plus progestin 726 Placebo</td>
<td>5 (0.7%) vs. 6 (0.8%) 6 (0.9%) vs. 13 (1.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<sup>114</sup> Oregon Evidence-based Practice Center
<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>PD incidence</th>
<th>MCI incidence</th>
<th>Other dementia diagnosis outcomes</th>
<th>3MSE Scores</th>
<th>Other measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Espeland, 2010;¹⁶ Long-term effects of conjugated equine estrogen therapies on domain-specific cognitive function: results from the Women's Health Initiative Study of Cognitive Aging Extension. <strong>WHISCA Estrogen plus progestin trial</strong></td>
<td>Women enrolled in WHISCA and participated in extension after termination of trial</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>On trial Global cognitive function: -0.080 (SE, 0.034); p=0.02</td>
</tr>
<tr>
<td>Shumaker, 2004;¹⁷ Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. <strong>WHIMS Estrogen only trial</strong></td>
<td>Women enrolled in WHI trial aged ≥65 years without probable dementia: 2947 Enrolled 1464 Estrogen 1483 Placebo</td>
<td>28 (1.9%) vs. 19 (1.3%) 3.7 vs. 2.5 per 1,000 person-years HR, 1.49 (95% CI, 0.83 to 2.66); p=0.18</td>
<td>7.6 vs. 5.8 per 1,000 person-years HR, 1.34 (95% CI, 0.95 to 1.89); p=NS</td>
<td>PD or MCI: 93 (6.4%) vs. 69 (4.7%) PD or MCI per 1,000 person-years: 12.6 vs. 9.1 HR, 1.38 (95% CI, 1.01 to 1.89); p=0.04 No differences between groups in type of dementia diagnosed with majority being diagnosed AD: 13 (46.4%) vs. 9 (47.4%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Resnick, 2009;¹⁸ Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. <strong>WHISCA Estrogen only trial</strong></td>
<td>Women enrolled in WHIMS trial, limited to 14 of 39 WHIMS locations: 866 Enrolled 434 Estrogen 452 Placebo</td>
<td>4 (0.9%) vs. 2 (0.4%)</td>
<td>18 (4.1%) vs. 15 (3.3%)</td>
<td>NR</td>
<td>NR</td>
<td>Differences in change Card rotations: 1.26 (SE, 0.48); p=0.008 No other differences on any measures</td>
</tr>
<tr>
<td>Espeland, 2010;¹⁶ Long-term effects of conjugated equine estrogen therapies on domain-specific cognitive function: results from the Women's Health Initiative Study of Cognitive Aging Extension. <strong>WHISCA Estrogen only trial</strong></td>
<td>Women enrolled in WHISCA and participated in extension after termination of trial</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Intervention Global cognitive function: -0.092 (SE, 0.039); p=0.02 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 Fine motor speed: -0.171 (SE, 0.053); p=0.001 Postintervention Spatial ability: -0.179 (SE, 0.063); p=0.004</td>
</tr>
</tbody>
</table>
## Appendix C11. Evidence Table of Trials Reporting Incidence of Cognitive Functioning

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
<th>Other dementia diagnosis outcomes</th>
<th>3MSE Scores</th>
<th>Other measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grady, 2002; Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/Progestin Replacement Study. HERS Estrogen plus progestin trial</td>
<td>Completed HERS trial at any 1 of 10 out of 20 centers: 1,063 Enrolled 662 Estrogen plus progestin 666 Placebo</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No differences between groups</td>
</tr>
<tr>
<td>Tierney, 2009; A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women. EMS Estrogen plus progestin trial</td>
<td>Women aged ≥60 years with last menstrual period ≥12 months before, with normal to just below normal scores on cognitive battery tests, but free of dementia: 142 Enrolled 70 Estrogen plus progestin 72 Placebo</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No differences between groups</td>
</tr>
<tr>
<td>Yaffe, 2006; Effects of ultra-low-dose transdermal estradiol on cognition and health-related quality of life. ULTRA Estrogen only trial</td>
<td>Women aged 60-80 years with an intact uterus and ≥5 years beyond menopause with normal BMD: 417 Enrolled 208 Estrogen 209 Placebo</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Mean difference between groups (estradiol tertile 1 vs. 2 vs. 3) 3MSE: -2.01 (p&lt;0.001) vs. 0.01 (p=0.99) vs. -0.22 (p=0.73); overall p=0.05 No other differences between groups on any tests</td>
</tr>
</tbody>
</table>

**Abbreviations:** 3MSE=Modified Mini-Mental State Examination; AD=Alzheimer’s Disease; BMD=bone mineral density; BVRT=Benton Visual Retention Test; CI=confidence interval; CVLT=California Verbal Learning Test; EMS=Estrogen Memory Study; HERS=Heart and Estrogen/Progestin Replacement Study; HR=hazard ratio; MCI=mild cognitive impairment; NR=not reported; NS=not significant; PD=probable dementia; SD=standard deviation; SE=standard error; WHI=Women’s Health Initiative; WHIMS=Women’s Health Initiative Memory Study; WHISCA=Women’s Health Initiative Study of Cognitive Aging; ULTRA=Ultra Low-Dose Transdermal Estrogen Replacement Assessment.
### Appendix C12. Evidence Table of Trials Reporting Incidence of Urinary Incontinence

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
</tr>
</thead>
</table>
| **Hendrix, 2005** | Analysis focused on women with urinary incontinence data at baseline and 1 year: 7,247 Estrogen plus progestin (2,675 continent at baseline) 7,056 Placebo (2,507 continent at baseline) | **Results at 1 year**  
Urinary incontinence incidence  
Estrogen and progestin  
Incident UI: 834 vs. 563; RR, 1.39 (95% CI, 1.27 to 1.52)  
Stress UI: 429 (16.0%) vs. 218 (8.7%); RR, 1.87 (95% CI, 1.61 to 2.18); p<0.001  
Urge UI: 304 (11.4%) vs. 272 (10.8%); RR, 1.15 (95% CI, 0.99 to 1.34); p=0.06  
Mixed UI: 99 (3.7%) vs. 69 (2.8%); RR, 1.49 (95% CI, 1.10 to 2.01); p=0.01  
Estrogen only  
Incident UI: 557 vs. 368; RR, 1.53 (95% CI, 1.37 to 1.71)  
Stress UI: 266 (17.4%) vs. 131 (8.5%); RR, 2.15 (95% CI, 1.77 to 2.62); p<0.001  
Urge UI: 210 (13.8%) vs. 184 (11.9%); RR, 1.32 (95% CI, 1.10 to 1.58); p=0.003  
Mixed UI: 76 (5.0%) vs. 50 (3.2%); RR, 1.79 (95% CI, 1.26 to 2.53); p=0.01 |
| **Steinauer, 2005** | Analysis focused on women reporting no episodes of incontinence in the past week at baseline: 1,208 Enrolled 597 Estrogen plus progestin 611 Placebo | **Results at 3 years**  
Estrogen and progestin  
39/153 (25.5%) vs. 26/185 (14.1%) of continent women at baseline and 1 year reported incident UI at 3 years (RR, 1.81 [95% CI, 1.16 to 2.84])  
51/172 (70.8%) vs. 40/57 (70.2%) of women with incident UI at 1 year still had UI at 3 years (p=0.94)  
Estrogen only  
27/96 (28.1%) vs. 26/136 (19.1%) of continent women at baseline and 1 year reported incident UI at 3 years (RR, 1.47 [95% CI, 0.92 to 2.36])  
43/60 (71.7%) vs. 26/38 (68.4%) of women with incident UI at 1 year still had UI at 3 years (p=0.73) |
| **Waeljen, 2005** | Women enrolled in ULTRA trial who were continent at baseline: 605 Eligible 208 Estrogen 209 Placebo | **Odds ratio**  
Weekly UI: OR, 1.6 (95% CI, 1.3 to 1.9); p<0.001  
Urge UI: OR, 1.5 (95% CI, 1.2 to 1.8); p<0.001  
Stress UI: OR, 1.7 (95% CI, 1.5 to 2.1); p<0.00  
**Cumulative 4-year risk**  
Weekly UI: 64% vs. 49%; excess risk, 15%  
Urge UI: 48% vs. 36%; excess risk, 12%  
Stress UI: 54% vs. 38%; excess risk, 16%  
**Number needed to harm**  
Weekly UI: 6.9 (95% CI, 5.0 to 11.1)  
Urge UI: 8.6 (95% CI, 5.8 to 16.6)  
Stress UI: 6.2 (95% CI, 4.6 to 9.4) |

**Abbreviations:** CI=confidence interval; HERS=Heart and Estrogen/Progestin Replacement Study; HERS II=Heart and Estrogen/Progestin Replacement Study Phase II; HR=hazard ratio; OR=odds ratio; RR=relative risk; UI=urinary incontinence; ULTRA=Ultra Low-Dose Transdermal Estrogen Replacement Assessment; WHI=Women's Health Initiative.
### Appendix C13. Evidence Table of Trials Reporting Outcomes by Subgroups

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Ritenbaugh, 2008;[13] Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. **WHI Estrogen only trial** | Excluded women with history of breast cancer and medical conditions likely to result in death in the next 3 years. 10,739 Enrolled 5,310 Estrogen 5,429 Placebo | **Incidence (annualized rate) of invasive colorectal cancer**  
Overall: 58 (0.15%) vs. 53 (0.14%); HR, 1.12 (95% CI, 0.77 to 1.63)  
**History of polyp removal**  
No: 40 (0.13%) vs. 46 (0.15%); HR, 0.87 (95% CI, 0.57 to 1.33)  
Yes: 9 (0.29%) vs. 0 (0.00); HR, not reported  
**Height (cm); p=0.03**  
96.0-158.6: 26 (0.21%) vs. 12 (0.10%); HR, 1.12 (95% CI, 0.64 to 2.52)  
158.7-163.9: 14 (0.11%) vs. 26 (0.20%); HR, 0.57 (95% CI, 0.29 to 1.10)  
164.0-188.3: 14 (0.11%) vs. 26 (0.20%); HR, 0.57 (95% CI, 0.29 to 1.10)  
**Waist circumference (cm); p=0.03**  
37.1-84.9: 22 (0.17%) vs. 11 (0.09%); HR, 2.03 (95% CI, 0.98 to 4.19)  
85.0-96.9: 18 (0.15%) vs. 17 (0.13%); HR, 1.14 (95% CI, 0.59 to 2.22)  
97.0-191.6: 18 (0.14%) vs. 25 (0.20%); HR, 0.68 (95% CI, 0.37 to 1.25) |
| LaCroix, 2011;[14] Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy postintervention. **WHI Estrogen only trial** | All women enrolled in WHI trial followed after completion of trial (postintervention phase): 10,739 Enrolled 5,310 Estrogen 5,429 Placebo | **Cumulative annualized rates for colorectal cancer**  
Age at screening (years); p=0.04  
50-59: 14 vs. 18; HR, 0.80 (95% CI, 0.40 to 1.61); p=0.04  
60-69: 37 vs. 43; HR, 0.90 (95% CI, 0.58 to 1.39); p =0.04  
70-79: 38 vs. 21; HR, 1.83 (95% CI, 1.08 to 3.12); p=0.04 |
| Anderson, 2004;[15] Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. **WHI Estrogen only trial** | Women enrolled in WHI trial (intervention phase): 10,739 Enrolled 5,310 Estrogen 5,429 Placebo | **Colorectal cancer**  
Age at screening (years); p=0.048  
50-59: 8 vs. 14; HR, 0.59 (95% CI, 0.25 to 1.41)  
60-69: 26 vs. 31; HR, 0.88 (95% CI, 0.52 to 1.48)  
70-79: 27 vs. 13; HR, 2.09 (95% CI, 1.08 to 4.04) |
| Chlebowski, 2010;[16] Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. **WHI Estrogen plus progestin trial** | All women enrolled in WHI trial followed after completion of trial (postintervention and extension phase). 8,506 Estrogen plus progestin 8,056 Placebo  
**Resulted** | Prior menopausal hormone therapy use (annualized %)  
No prior use: 312 (0.42%) vs. 257 (0.36%); HR, 1.16 (95% CI, 0.98 to 1.37)  
Prior use (current/past): 73 (0.44%) vs. 36 (0.23%); HR,1.85 (95% CI, 1.25 to 2.80); p=0.03 |
### Appendix C13. Evidence Table of Trials Reporting Outcomes by Subgroups

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
</tr>
</thead>
</table>
| **Chlebowski, 2003:** Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. **WHI Estrogen plus progestin trial** | Women enrolled in WHI trial: 16,608 Enrolled 8,506 Estrogen plus progestin 8,102 Placebo | **Invasive breast cancer**  
Without prior menopausal hormone therapy use  
Treatment (6,277) vs. placebo (6,020)  
Year 1 after entry: 7 (0.11%) vs. 14 (0.23%); HR, 0.48 (95% CI, 0.19 to 1.20)  
Year 2 after entry: 15 (0.24%) vs. 22 (0.37%); HR, 0.65 (95% CI, 0.34 to 1.25)  
Year 3 after entry: 19 (0.31%) vs. 19 (0.33%); HR, 0.96 (95% CI, 0.51 to 1.82)  
Year 4 after entry: 35 (0.58%) vs. 23 (0.40%); HR, 1.45 (95% CI, 0.85 to 2.45)  
Year 5 after entry: 28 (0.54%) vs. 17 (0.34%); HR, 1.61 (95% CI, 0.88 to 2.94)  
Year 6 or more after entry: 37 (0.69%) vs. 26 (0.56%); HR, 1.24 (95% CI, 0.75 to 2.05)  
z score=2.31  
**With prior menopausal hormone therapy use**  
Treatment (6,225) vs. placebo (2,079)  
Year 1 after entry: 5 (0.23%) vs. 5 (0.24%); HR, 0.90 (95% CI, 0.26 to 3.15)  
Year 2 after entry: 11 (0.50%) vs. 10 (0.49%); HR, 1.10 (95% CI, 0.47 to 2.61)  
Year 3 after entry: 10 (0.46%) vs. 3 (0.15%); HR, 3.09 (95% CI, 0.84 to 11.27)  
Year 4 after entry: 9 (0.42%) vs. 4 (0.20%); HR, 2.16 (95% CI, 0.66 to 7.05)  
Year 5 after entry: 15 (0.82%) vs. 4 (0.23%); HR, 3.56 (95% CI, 1.18 to 10.73)  
Year 6 or more after entry: 8 (0.39%) vs. 3 (0.17%); HR, 1.99 (95% CI, 0.52 to 7.60)  
z score=1.62  
**Overall**  
Year 1 after entry: 12 (0.14%) vs. 19 (0.24%); HR, 0.60 (95% CI, 0.29 to 1.23)  
Year 2 after entry: 26 (0.31%) vs. 32 (0.40%); HR, 0.77 (95% CI, 0.46 to 1.30)  
Year 3 after entry: 29 (0.35%) vs. 22 (0.28%); HR, 1.26 (95% CI, 0.73 to 2.20)  
Year 4 after entry: 44 (0.54%) vs. 27 (0.35%); HR, 1.54 (95% CI, 0.95 to 2.49)  
Year 5 after entry: 43 (0.61%) vs. 21 (0.32%); HR, 1.99 (95% CI, 1.18 to 3.35)  
Year 6 or more after entry: 45 (0.61%) vs. 29 (0.45%); HR, 1.35 (95% CI, 0.85 to 2.16)  
z score=2.56  
All p values >0.05 for: Age at screening, Gail risk assessment, prior oral contraceptive use, prior menopausal hormone use, prior estrogen only use, prior estrogen plus progestin use, recency of hormone use, BMI, smoking, NSAID use  
(Note: prior menopausal hormone therapy use ≥ 5 years: HR, 2.27 (95% CI, 1.00 to 5.15); border significance) |
| **LaCroix, 2011:** Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy postintervention. **WHI Estrogen only trial** | All women enrolled in WHI trial followed up after completion of trial (postintervention phase): 10,739 Enrolled 5,310 Estrogen 5,429 Placebo | **Cumulative annualized rates for invasive breast cancer**  
Age at screening (years)  
50-59: 43 vs 54; HR, 0.80 (95% CI, 0.53 to 1.19); p=0.96  
60-69: 68 vs. 95; HR, 0.73 (95% CI, 0.54 to 1.00); p=0.96  
70-79: 40 vs. 50; HR, 0.81 (95% CI, 0.53 to 1.23); p=0.96  
**Rossouw, 2002:** Risks and benefits of estrogen plus progestin in healthy postmenopausal women. **WHI Estrogen plus progestin trial** | Women enrolled in WHI trial (intervention phase): 16,608 Enrolled 8,506 Estrogen plus progestin 8,102 Placebo | **Invasive breast cancer (annualized %)**  
By followup year  
Year 1: 11 (0.13) vs. 17 (0.21); HR, 0.62  
Year 2: 26 (0.31) vs. 30 (0.38); HR, 0.83  
Year 3: 28 (0.34) vs. 23 (0.29); HR, 1.16  
Year 4: 40 (0.50) vs. 22 (0.29); HR, 1.73  
Year 5: 34 (0.57) vs. 12 (0.22); HR, 2.64  
Year 6 and later: 27 (0.53) vs. 20 (0.47); HR, 1.12 |
### Appendix C13. Evidence Table of Trials Reporting Outcomes by Subgroups

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anderson, 2004,</strong> Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. <strong>WHI Estrogen only trial</strong></td>
<td>Women enrolled in WHI trial (intervention phase): 10,739 Enrolled 5,310 Estrogen 5,429 Placebo</td>
<td>Invasive breast cancer  Age at screening (years); p=0.51  50-59: 25 vs. 35; HR, 0.72 (95% CI, 0.43 to 1.21)  60-69: 42 vs. 60; HR, 0.72 (95% CI, 0.49 to 1.07)  70-79: 27 vs. 29; HR, 0.94 (95% CI, 0.56 to 1.60)</td>
</tr>
<tr>
<td><strong>Gramling, 2009,</strong> Hormone replacement therapy, family history, and breast cancer risk among postmenopausal women. <strong>WHI Estrogen plus progestin trial</strong></td>
<td>Women enrolled in WHI trial (longitudinal followup): 16,608 Enrolled 8,506 Estrogen plus progestin 8,102 Placebo</td>
<td>Incidence of invasive breast cancer in those with first-degree family member with breast cancer (n=1,009 vs. 895) Overall: 35 (3.5%) vs. 25 (2.7%) Incidence of invasive breast cancer in those without first-degree family member with breast cancer (n=7,497 vs. 7,202) Overall: 164 (2.2%) vs. 125 (1.7%)</td>
</tr>
<tr>
<td><strong>Hendrix, 2005,</strong> Effects of estrogen with and without progestin on urinary incontinence. <strong>WHI Estrogen plus progestin trial</strong></td>
<td>Analysis focused on women with urinary incontinence data at baseline and 1 year: 16,608 Enrolled in WHI 7,247 Estrogen plus progestin (2,675 continent at baseline) 7,056 Placebo (2,507 continent at baseline)</td>
<td>Stress urinary incontinence  Age at screening (years)  50-54: RR, 0.90 (95% CI, 0.58 to 1.40)  55-59: RR, 1.63 (95% CI, 1.18 to 2.27); p&lt;0.001  60-69: RR, 2.11 (95% CI, 1.70 to 2.62); p&lt;0.001  70-79: RR, 2.59 (95% CI, 1.77 to 3.81); p&lt;0.001  Duration since menopause (years)  &lt;5: RR, 1.21 (95% CI, 0.83 to 1.77)  5 to &lt;10: RR, 1.70 (95% CI, 1.19 to 2.44); p=0.005  10 to &lt;15: RR, 2.00 (95% CI, 1.45 to 2.77); p=0.005  ≥15: RR, 2.33 (95% CI, 1.79 to 3.03); p=0.005  Menopausal hormone therapy use  Never: RR, 1.87 (95% CI, 1.57 to 2.24); p=0.008  Past: RR, 2.41 (95% CI, 1.71 to 3.41); p=0.008  Current: RR, 0.85 (95% CI, 0.48 to 1.50)  Beta blocker use  Absent: RR, 1.81 (95% CI, 1.55 to 2.11); p=0.03  Present: RR, 6.69 (95% CI, 2.03 to 22.05); p=0.03  Urge urinary incontinence  Age at screening (years)  50-54: RR, 1.18 (95% CI, 0.75 to 1.88)  55-59: RR, 0.90 (95% CI, 0.63 to 1.30)  60-69: RR, 1.26 (95% CI, 1.01 to 1.58)  70-79: RR, 1.20 (95% CI, 0.89 to 1.61)  Duration since menopause (years)  &lt;5: RR, 1.25 (95% CI, 0.80 to 1.93)  5 to &lt;10: RR, 1.17 (95% CI, 0.80 to 1.70)  10 to &lt;15: RR, 1.17 (95% CI, 0.81 to 1.67)  ≥15: RR, 1.17 (95% CI, 0.93 to 1.46)  Menopausal hormone therapy use  Never: RR, 1.14 (95% CI, 0.96 to 1.36)  Past: RR, 1.16 (95% CI, 0.83 to 1.62)  Current: RR, 1.38 (95% CI, 0.85 to 2.96)  Diabetes  Absent: RR, 1.21 (95% CI, 1.21 to 1.03); p=0.03  Present: RR, 0.59 (95% CI, 0.32 to 1.09)</td>
</tr>
</tbody>
</table>
## Appendix C13. Evidence Table of Trials Reporting Outcomes by Subgroups

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hendrix, 2005;* Effects of estrogen with and without progestin on urinary incontinence. <strong>WHI Estrogen only trial</strong></td>
<td>Analysis focused on women with urinary incontinence data at baseline and 1 year: 10,739 Enrolled in WHI 4,476 Estrogen (1,526 continent at baseline) 4,517 Placebo (1,547 continent at baseline)</td>
<td><strong>Mixed urinary incontinence</strong>&lt;br&gt;Age at screening (years)&lt;br&gt;50-54: RR, 2.11 (95% CI, 0.55 to 8.06)&lt;br&gt;55-59: RR, 1.05 (95% CI, 0.58 to 1.91)&lt;br&gt;60-69: RR, 1.46 (95% CI, 0.94 to 2.26)&lt;br&gt;70-79: RR, 2.24 (95% CI, 1.17 to 4.30); p=0.26&lt;br&gt;&lt;br&gt;Duration since menopause (years)&lt;br&gt;&lt;5: RR, 1.32 (95% CI, 0.59 to 2.96)&lt;br&gt;5 to &lt;10: RR, 1.53 (95% CI, 0.71 to 3.29)&lt;br&gt;10 to &lt;15: RR, 1.31 (95% CI, 0.67 to 2.56)&lt;br&gt;&gt;15: RR, 1.58 (95% CI, 0.99 to 2.50); p=0.73&lt;br&gt;&lt;br&gt;Menopausal hormone therapy use&lt;br&gt;Never: RR, 1.43 (95% CI, 1.01 to 2.02); p=0.49&lt;br&gt;Past: RR, 1.39 (0.69 to 2.79)&lt;br&gt;Current: RR, 3.64 (0.79 to 16.79)</td>
</tr>
</tbody>
</table>
## Appendix C13. Evidence Table of Trials Reporting Outcomes by Subgroups

<table>
<thead>
<tr>
<th>Author, year; title</th>
<th>Population</th>
<th>Results (Treatment vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>60-69: RR, 2.05 (95% CI, 1.25 to 3.35); p=0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70-79: RR, 2.63 (95% CI, 1.32 to 5.25); p=0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration since menopause (years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;5: RR, 2.62 (95% CI, 0.94 to 7.30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 to &lt;10: RR, 0.36 (95% CI, 0.7 to 1.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 to &lt;15: RR, 0.89 (95% CI, 0.36 to 2.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥15: RR, 2.11 (95% CI, 1.35 to 3.30); p=0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Menopausal hormone therapy use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Never: RR, 1.36 (95% CI, 0.85 to 2.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Past: RR, 2.65 (95% CI, 1.47 to 4.79); p=0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Current: RR, 1.75 (95% CI, 0.57 to 5.35)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smoking status</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Never: RR, 2.57 (95% CI, 1.55 to 4.27); p=0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Past: RR, 1.51 (95% CI, 0.89 to 2.58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Current: RR, 0.38 (0.08 to 1.86)</td>
</tr>
</tbody>
</table>

### Diabetes

<table>
<thead>
<tr>
<th>Margolis, 2004;13</th>
<th>Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative hormone trial. Estrogen plus progestin trial</th>
<th>Excluded women with self-reported diabetes at baseline: 15,641 Eligible from WHI 8,014 Estrogen plus progestin 7,627 Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence of new diabetes diagnosis</td>
<td>BMI &lt;25: 32 vs. 34; HR, 1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI 25-29: 57 vs. 75; HR, 1.77 (95% CI, 1.32 to 2.38); p=0.0002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI ≥30: 123 vs. 143; HR, 4.06 (95% CI, 3.09 to 5.35); p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Waist circumference &gt;88 cm: 138 vs. 189; HR, 3.57 (95% CI, 2.90 to 4.39); p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Change in waist circumference from baseline to year 1 of &gt;2.0 cm: 59 vs. 78; HR, 1.31 (95% CI, 1.04 to 1.65); p=0.020</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bonds, 2006;14</th>
<th>The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. Estrogen only trial</th>
<th>Excluded women with self-reported diabetes at baseline: 9,712 Eligible from WHI 4,806 Estrogen 4,906 Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence of new diabetes diagnosis</td>
<td>Current smoker: 31 (0.6%) vs. 59 (1.2%); HR, 0.54 (95% CI, 0.35 to 0.84); p=0.02</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI=body mass index; CI=confidence interval; HERS=Heart and Estrogen/Progestin Replacement Study; HERS II=Heart and Estrogen/Progestin Replacement Study Phase II; HR=hazard ratio; ITT=intention-to-treat; NSAID=nonsteroidal anti-inflammatory drug; RR=relative risk; WHI=Women's Health Initiative; WISDOM=Women’s International Study of Long-Duration Oestrogen After Menopause.