Evidence Synthesis
Number 93

Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: Systematic Review to Update the 2002 and 2005 U.S. Preventive Services Task Force Recommendations

Prepared for:
Agency for Healthcare Research and Quality
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Contract No. HHSA-290-2007-10057-I-EPC3, Task Order No. 3

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AHRQ Publication No. 12-05168-EF-1
May 2012

This report is based on research conducted by the Oregon Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0024). The investigators involved have declared no conflicts of interest with objectively conducting this research. The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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Acknowledgements: The authors acknowledge Andrew Hamilton, MLS, MS, for assistance with literature searches, Rochelle (Rongwei) Fu, PhD, for statistical assistance, and Amanda Brunton, BS, for assistance with preparing this draft report; all are based at Oregon Health & Science University. We also thank AHRQ Officers Jennifer Croswell, MD, MPH, and Tess Miller, DrPH; USPSTF leads Kirsten Bibbins-Domingo, PhD, MD, Carolina Reyes, MD, and Sandy Schwartz, MD; and Mary Barton, MD, MPP, for their contributions to this report.

Suggested Citation: Nelson HD, Walker M, Zakher B, Mitchell J. Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: Systematic Review to Update the 2002 and 2005 U.S. Preventive Services Task Force Recommendations. Evidence Synthesis No. 93. AHRQ Pub No. 12-05168-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; May 2012.

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.

Table of Contents

Figures

Tables

Appendixes

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.[1] 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).[2] Based on the results of systematic reviews[3-11] and early findings of the Women's Health Initiative (WHI) trial of estrogen plus progestin,[12] 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).[13] 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.[12, 14,15] 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.[1]

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**).[16-20] The American College of Physicians directs individuals to the USPSTF recommendations.[21] 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[6] and using the methods of the USPSTF,[22] 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,[1] 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[22] 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,[12,23-41] WHI estrogen only trial,[29,35,39,42-50] Women's Health Initiative Memory Study (WHIMS),[51-55] Women's Health Initiative Study of Cognitive Aging (WHISCA),[56-58] HERS,[59-65] Women's International Study of Long Duration Oestrogen After Menopause (WISDOM),[66] Oestrogen in the Prevention of Reinfarction Trial (ESPRIT),[67] Estrogen Memory Study (EMS),[68] and Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA)[69-72] (**Table 2**). An additional article with new results from WHI[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.[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.[12] 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.[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.[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.

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.[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.[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.[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.[55] 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.[55] 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.[54] 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.[58] 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.[58] 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.[57] 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.[59,62] 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,

mortality, uterine bleeding, and side effects of hormone therapy.

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).[62] 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.[60,61]

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.[62] 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.[62]

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). [60]

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.[61,65]

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.[60] 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.[60,61]

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.[66] 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.[66] 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.[67] 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.[68] 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.[69] 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 **Appendixes 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])[49] in WHI. Thromboembolic events,

DVT and PE, were also increased in both WHI trials, but to higher levels for estrogen plus progestin[33] than estrogen only.[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]).[25] Other types of cancer, including lung, endometrial, ovarian, and cervical, were not significantly increased in the estrogen plus progestin trial.[23,27,33] The estrogen only trial reported results for lung cancer that were not significantly increased.[45] Invasive breast, lung, and endometrial cancer were not increased in HERS II.[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])[45] and lung cancer (HR, 1.71 [95% CI, 1.16 to 2.52])[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.[29] Incidence was higher for estrogen only users (gallbladder disease: HR, 1.79 [95% CI, 1.44 to 2.22]).[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.[55] These measures were not significantly increased for estrogen only.[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.[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.[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]),[64] but urinary incontinence was not significantly increased in ULTRA.[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.[25] 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).[26] 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.[31]

An evaluation of the effect of age on breast cancer incidence in the estrogen only trial indicated no significant differences by age.[42]

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.[28]

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.[50] 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.[37] 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]).[37] 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.[48]

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.[39] 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.[41,47] For thromboembolic disease, use of estrogen plus progestin increased the risks associated with older age, being overweight or obese, or possessing Factor V Leiden.[30] Analysis of subgroups in the WHI estrogen only trial indicated no associations with venous thrombosis.[46]

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.[24]

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.[53] For estrogen only, 17 subgroups were also analyzed.[52] 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.[35] 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]).[64]

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

1. U.S. Food and Drug Administration. Estrogen and Estrogen With Progestin Therapies for Postmenopausal Women. Silver Spring, MD: U.S. Food and Drug Administration; 2010. Accessed at http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135318.htm on 4 May 2012.
2. U.S. Preventive Services Task Force. Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: recommendations and rationale. *Ann Intern Med.* 2002;137(10):834-9.
3. LeBlanc ES, Janowsky J, Chan BK, Nelson HD. Hormone replacement therapy and cognition: systematic review and meta-analysis *JAMA.* 2001;285(11):1489-99.
4. Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002;136(9):680-90.
5. Humphrey LL. Hormone Replacement Therapy and Breast Cancer. Systematic Evidence Review No. 14. Rockville, MD: Agency for Healthcare Research and Quality; 2002. Accessed at http://www.ncbi.nlm.nih.gov/books/NBK42718/ on 4 May 2012.
6. Nelson HD, Humphrey LL, Nygren P, et al. Postmenopausal hormone replacement therapy: scientific review. *JAMA.* 2002;288(7):872-81.
7. Nelson HD. Assessing benefits and harms of hormone replacement therapy: clinical applications. *JAMA.* 2002;288(7):882-4.
8. LeBlanc ES, Chan BK, Nelson HD. Hormone Replacement Therapy and Cognition. Systematic Evidence Review No. 13. Rockville, MD: Agency for Healthcare Research and Quality; 2002. Accessed at http://www.ncbi.nlm.nih.gov/books/NBK42704/ on 4 May 2012.
9. Humphrey LL, Takano LM, Chan BK. Postmenopausal Hormone Replacement Therapy and Cardiovascular Disease. Systematic Evidence Review No. 10. Rockville, MD: Agency for Healthcare Research and Quality; 2002. Accessed at http://www.ncbi.nlm.nih.gov/books/NBK42645/ on 4 May 2012.
10. Miller J, Chan BK, Nelson HD. Hormone Replacement Therapy and Risk of Venous Thromboembolism. Systematic Evidence Review No. 11. Rockville, MD: Agency for Healthcare Research and Quality; 2002. Accessed at http://www.ncbi.nlm.nih.gov/books/NBK42678/ on 4 May 2012.
11. Nelson HD. Hormone Replacement Therapy and Osteoporosis. Systematic Evidence Review No. 12. Rockville, MD: Agency for Healthcare Research and Quality; 2002. Accessed at http://www.ncbi.nlm.nih.gov/books/NBK42693/ on 4 May 2012.
12. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288(3):321-33.
13. U.S. Preventive Services Task Force. Hormone therapy for the prevention of chronic conditions in postmenopausal women: recommendations from the U.S. Preventive Services Task Force. *Ann Intern Med.* 2005;142(10):855-60.
14. Management of osteoporosis in postmenopausal women: 2010 position statement of the North American Menopause Society. *Menopause.* 2010;17(1):25-54.

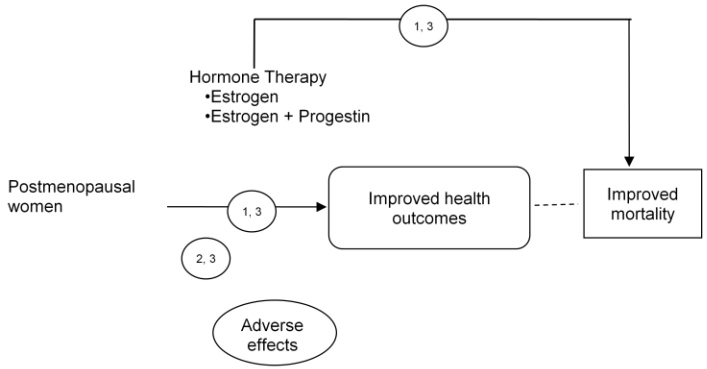
15. American College of Obstetricians and Gynecologists Women's Health Care Physicians. Executive Summary: hormone therapy. *Obstet Gynecol.* 2004;104(4 Suppl):1S-4.
16. American Academy of Family Physicians. Hormone Replacement Therapy. Leawood, KS: American Academy of Family Physicians; 2005. Accessed at http://www.aafp.org/online/en/home/clinical/exam/hormonereplacement.html on 4 May 2012.
17. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 420, November 2008: hormone therapy and heart disease. *Obstet Gynecol.* 2008;112(5):1189-92.
18. Mosca L, Benjamin E, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *Circulation.* 2011;123(11):1243-62.
19. Canadian Task Force on Preventive Health Care. Hormone Replacement Therapy for the Primary Prevention of Chronic Diseases. Ottowa, Canada: Canadian Task Force on Preventive Health Care 2004. Accessed at http://www.canadiantaskforce.ca/recommendations/2003_01_eng.html on 4 May 2012.
20. North American Menopause Society; Gass ML, Manson JE, et al. The 2012 hormone therapy position statement of the North American Menopause Society. *Menopause.* 2012;19(3):257-271.
21. American College of Physicians. ACP Clinical Practice Guidelines. Philadelphia: American College of Physicians; 2012. Accessed at http://www.acponline.org/clinical_information/guidelines/guidelines/ on 4 May 2012.
22. Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. *Am J Prev Med.* 2001;20(3S):21-35.
23. Anderson GL, Judd HL, Kaunitz AM, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA.* 2003;290(13):1739-48.
24. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA.* 2003;290(13):1729-38.
25. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA.* 2010;304(15):1684-92.
26. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA.* 2003;289(24):3243-53.
27. Chlebowski RT, Schwartz AG, Wakelee H, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. *Lancet.* 2009;374(9697):1243-51.
28. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med.* 2004;350(10):991-1004.
29. Cirillo DJ, Wallace RB, Rodabough RJ, et al. Effect of estrogen therapy on gallbladder disease. *JAMA.* 2005;293:330-9.
30. Cushman M, Kuller LH, Prentice R, et al. Estrogen plus progestin and risk of venous thrombosis. *JAMA.* 2004;292(13):1573-80.
31. Gramling R, Eaton CB, Rothman KJ, et al. Hormone replacement therapy, family history, and breast cancer risk among postmenopausal women. *Epidemiology.* 2009;20(5):752-6.

32. Hays J, Ockene JK, Brunner RL, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med.* 2003;348(19):1839-54.
33. Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA.* 2008;299(9):1036-45.
34. Hendrix SL. The Women's Health Initiative estrogen plus progestin trial: the study and how it changes our practice. *J Am Osteopath Assoc.* 2003;103(2 Suppl 2):S3-5.
35. Hendrix SL, Cochrane BB, Nygaard IE, et al. Effects of estrogen with and without progestin on urinary incontinence. *JAMA.* 2005;293(8):935-48.
36. Hsia J, Criqui MH, Rodabough RJ, et al. Estrogen plus progestin and the risk of peripheral aerterial disease. *Circulation.* 2004;109(5):620-6.
37. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med.* 2003;349(6):523-34.
38. Margolis KL, Bonds DE, Rodabough RJ, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative hormone trial. *Diabetologia.* 2004;47(7):1175-87.
39. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA.* 2007;297(13):1465-77.
40. Toh S, Hernandez-Diaz S, Logan R, et al. Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: does the increased risk ever disappear? A randomized trial. *Ann Intern Med.* 2010;152(4):211-7.
41. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA.* 2003;289(20):2673-84.
42. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA.* 2004;291(14):1701-12.
43. Bonds DE, Lasser N, Qi L, et al. The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. *Diabetologia.* 2006;49(3):459-68.
44. Brunner RL, Gass M, Aragaki A, et al. Effects of conjugated equine estrogen on health-related quality of life in postmenopausal women with hysterectomy: results from the Women's Health Initiative randomized clinical trial. *Arch Intern Med.* 2005;165(17):1976-86.
45. Chlebowski RT, Anderson GL, Manson JE, et al. Lung cancer among postmenopausal women treated with estrogen alone in the Women's Health Initiative randomized trial. *J Natl Cancer Inst.* 2010;102(18):1413-21.
46. Curb JD, Prentice RL, Bray PF, et al. Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med.* 2006;166(7):772-80.
47. Hendrix SL, Wassertheil-Smoller S, Johnson KC, et al. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation.* 2006;113(20):2425-34.
48. Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med.* 2006;166(3):357-65.
49. LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA.* 2011;305(13):1305-14.

50. Ritenbaugh C, Stanford JL, Wu L, et al. Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. *Cancer Epidemiol Biomarkers Prev.* 2008;17(10):2609-18.
51. Culhane NS. Estrogen plus progestin may increase incidence of dementia. *J Fam Pract.* 2003;52(10):754-5.
52. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA.* 2004;291(24):2959-68.
53. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA.* 2003;289(20):2663-72.
54. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA.* 2004;291(24):2947-58.
55. Shumaker SA, Legault C, Rapp SR, et al. 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. *JAMA.* 2003;289(20):2651-62.
56. Espeland MA, Brunner RL, Hogan PE, et al. 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. *J Am Geriatr Soc.* 2010;58(7):1263-71.
57. Resnick SM, Espeland MA, An Y, et al. Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. *J Clin Endocrinol Metab.* 2009;94(11):4152-61.
58. Resnick SM, Maki PM, Rapp SR, et al. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *J Clin Endocrinol Metab.* 2006;91(5):1802-10.
59. Grady D, Applegate W, Bush T, et al. Heart and Estrogen/progestin Replacement Study (HERS): design, methods, and baseline characteristics. *Control Clin Trials.* 1998;19(4):314-35.
60. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA.* 2002;288(1):49-57.
61. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA.* 2002;288(1):58-66.
62. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA.* 1998;280(7):605-13.
63. Kanaya AM, Herrington D, Vittinghoff E, et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 2003;138(1):1-9.
64. Steinauer JE, Waetjen LE, Vittinghoff E, et al. Postmenopausal hormone therapy: does it cause incontinence? *Obstet Gynecol.* 2005;106(5 Pt 1):940-5.

65. Grady D, Yaffe K, Kristof M, et al. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. *Am J Med.* 2002;113(7):543-8.
66. Vickers MR, Martin J, Meade TW; WISDOM Study Team. The Women's International Study of Long-Duration Oestrogen After Menopause (WISDOM): a randomised controlled trial. *BMC Womens Health.* 2007;7:2.
67. Cherry N, Gilmour K, Hannaford P, et al. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet.* 2002;360(9350):2001-8.
68. Tierney MC, Oh P, Moineddin R, et al. A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women. *Psychoneuroendocrinology.* 2009;34(7):1065-74.
69. Ettinger B, Ensrud KE, Wallace R, et al. Effects of ultralow-dose transdermal estradiol on bone mineral density: a randomized clinical trial. *Obstet Gynecol.* 2004;104(3):443-51.
70. Johnson SR, Ettinger B, Macer JL, et al. Uterine and vaginal effects of unopposed ultralow-dose transdermal estradiol. *Obstet Gynecol.* 2005;105(4):779-87.
71. Waetjen LE, Brown JS, Vittinghoff E, et al. The effect of ultralow-dose transdermal estradiol on urinary incontinence in postmenopausal women. *Obstet Gynecol.* 2005;106(5 Pt 1):946-52.
72. Yaffe K, Vittinghoff E, Ensrud KE, et al. Effects of ultra-low-dose transdermal estradiol on cognition and health-related quality of life. *Arch Neurol.* 2006;63(7):945-50.
73. Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol.* 2012;13:476-486.
74. Rossouw JE. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials.* 1998;19(1):61-109.
75. Cauley JA, McTiernan A, Rodabough RJ, et al. Statin use and breast cancer: prospective results from the Women's Health Initiative. *J Natl Cancer Inst.* 2006;98(10):700-7.

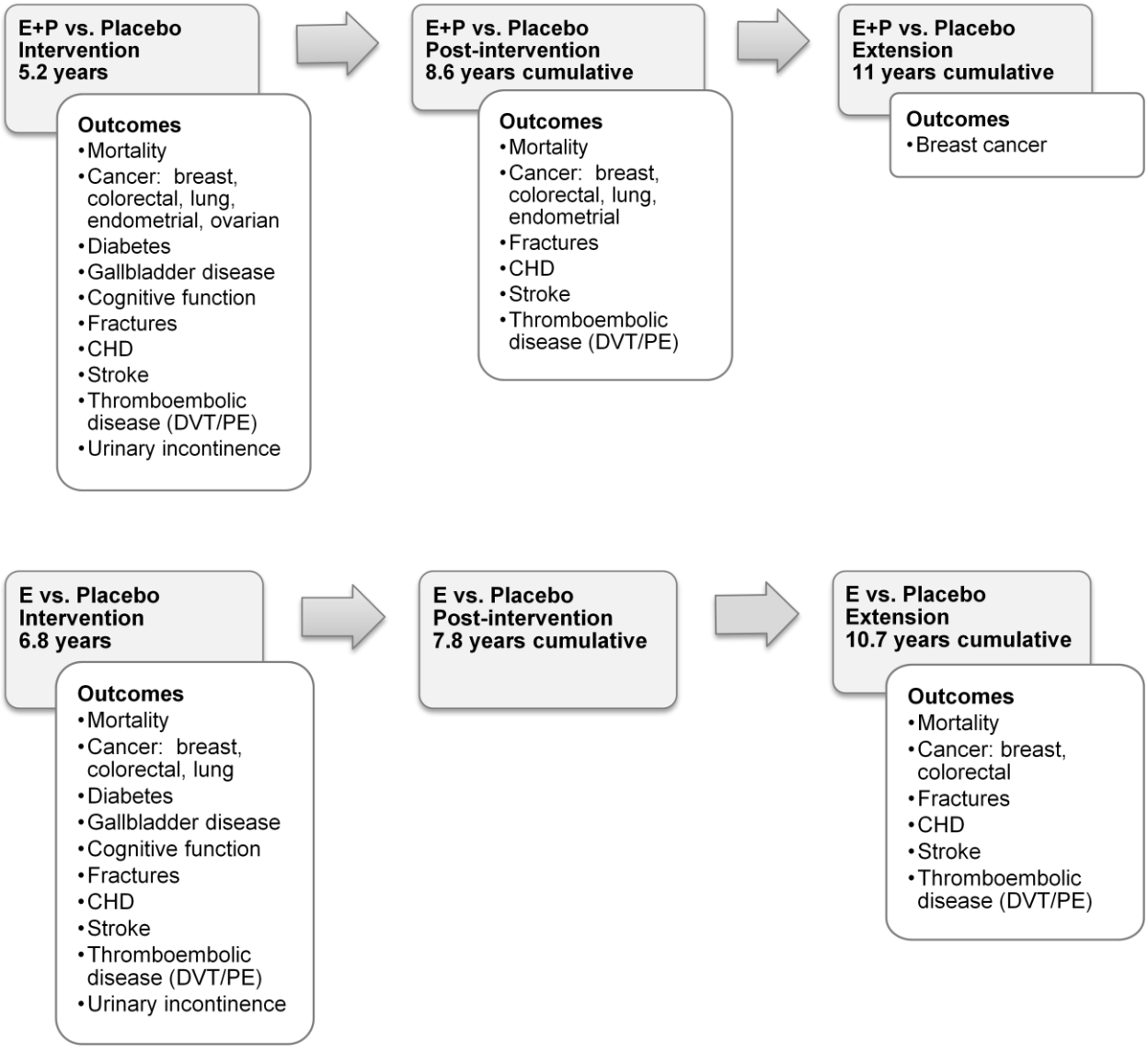
Figure 1. Analytic Framework and Key Questions



Key Questions

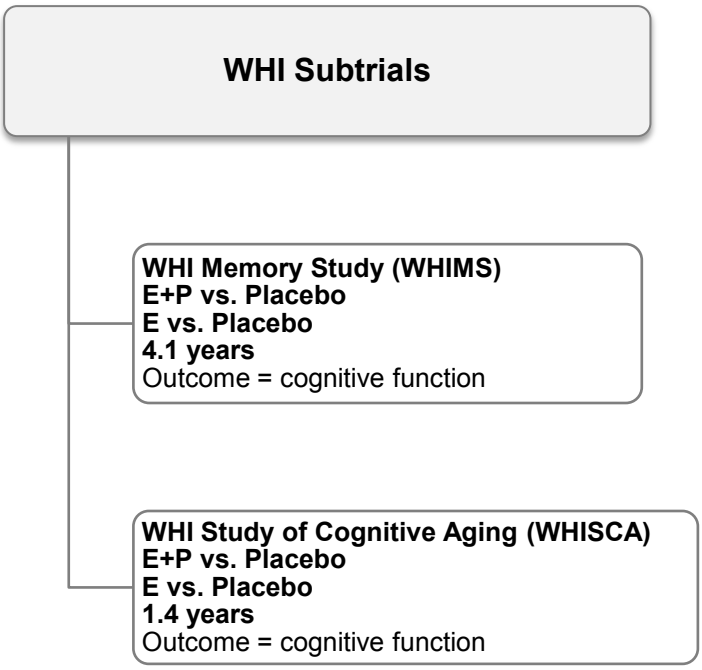
1. What are the benefits of menopausal hormone therapy when used to prevent chronic conditions? Potential benefits include reduced fractures and colorectal cancer.
2. What are the harms of menopausal hormone therapy when used to prevent chronic conditions? Potential harms include coronary heart disease 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



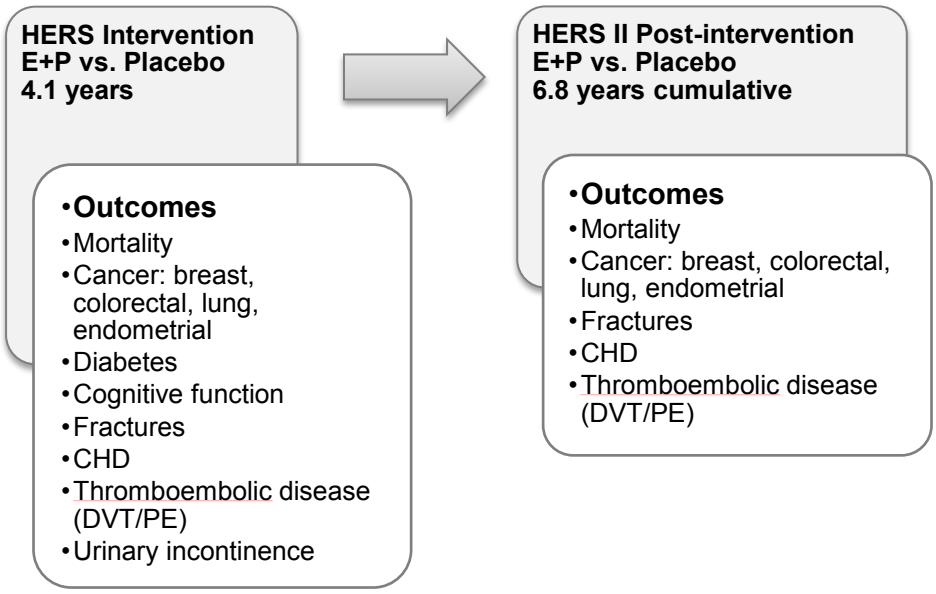
Abbreviations: CHD=coronary heart disease; DVT=deep vein thrombosis; E=estrogen; HT=hormone therapy; P=progestin; PE=pulmonary embolus.

Figure 3. Design of the Women's Health Initiative Hormone Therapy Subtrials



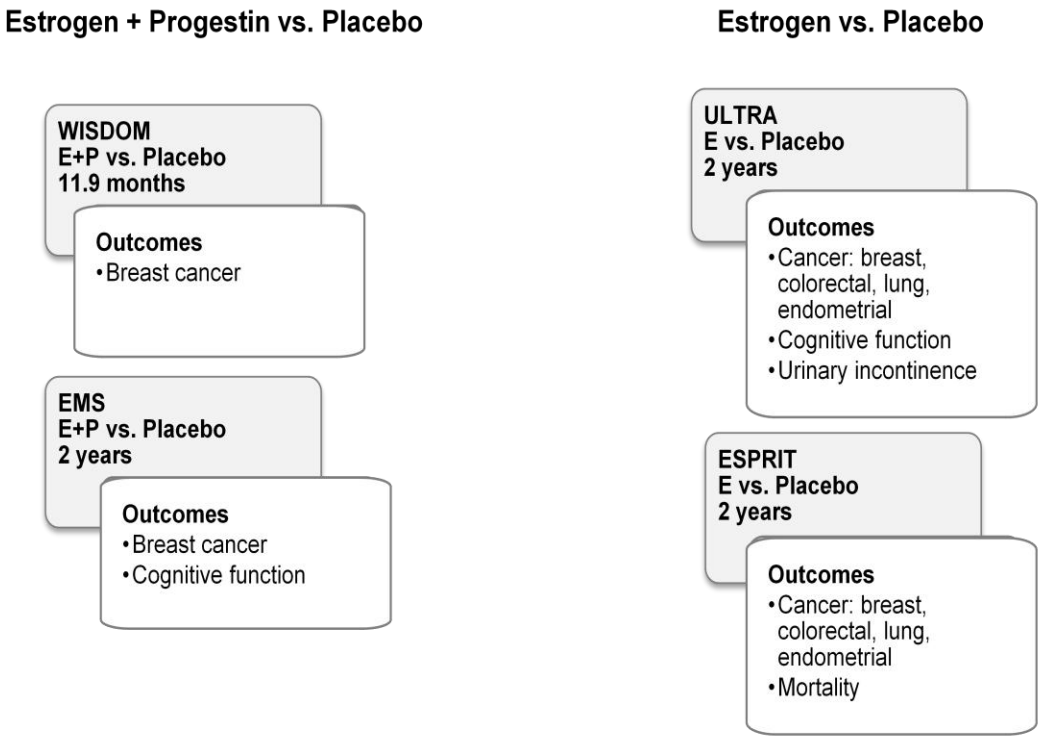
Abbreviations: E=estrogen; HT=hormone therapy; P=progestin; WHI=Women's Health Initiative.

Figure 4. Design of Heart and Estrogen/Progestin Replacement Study (HERS) and HERS II Trials



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.

Figure 5. Designs of Additional Included Trials



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

Organization, year	Recommendations
American College of Physicians[21]	Recommends the U.S. Preventive Services Task Force Web site and the Canadian Task Force on Preventive Health Care.
American Academy of Family Physicians, 2005[16]	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).
American Congress of Obstetricians and Gynecologists, 2004[17]	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.
American Heart Association, 2011[18]	Recommends against the use of hormone therapy for primary and secondary prevention of cardiovascular disease in women (Class III, Level of Evidence A).
North American Menopause Society, 2010[20]	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 Asosiacion 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.
Canadian Task Force on Preventive Health Care, 2004[19]	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).

Table 2. Randomized, Controlled Trials and Quality Ratings

Trial	Author, year	Intervention	Participants	Quality Rating/Limitations
Women's Health Initiative (WHI) E+P Trial	Anderson, 2003;[23] Cauley, 2003;[24] Chlebowski, 2003;[26] Chlebowski, 2004;[28] Cirillo, 2005;[29] Cushman, 2004;[30] Hays, 2003;[32] Hendrix, 2003;[34] Hendrix, 2005;[35] Hsia, 2004;[36] Manson, 2003;[37] Margolis, 2004;[38] Rossouw, 2002;[12] Rossouw, 2007;[39] Toh, 2010;[40] Wassertheil-Smoller, 2003[41]	CEE 0.625 mg/d, plus MPA 2.5 mg/d (N=8506) Placebo (N=8102)	• Postmenopausal • 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;[27] Gramling, 2009;[31] Heiss, 2008[33]	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[25]	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;[51] Rapp, 2003;[53] Shumaker, 2003[55]	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;[56] Resnick, 2006[58]	CEE 0.625 mg/d plus MPA 2.5 mg/d (N=690) Placebo (N=726)	• WHIMS E+P trial participants • Free of probable dementia • At 1 of 14 WHIMS centers	Fair High attrition
WHI E Trial	Anderson, 2004;[42] Bonds, 2006;[43] Brunner, 2005;[44] Chlebowski, 2010;[45] Cirillo, 2005;[29] Curb, 2006;[46] Hendrix, 2005;[35] Hendrix, 2006;[47] Hsia, 2006;[48] Ritenbaugh, 2008;[50] Rossouw, 2007[39]	CEE 0.625 mg/d (N=5310) Placebo (N=5429)	• Postmenopausal • 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 E Extension Phase	Chlebowski, 2010;[45] LaCroix, 2011[49]	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;[52] Shumaker, 2004[54]	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;[56] Resnick, 2009[57]	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;[59] Hulley, 1998;[62] Kanaya, 2003;[63] Steinauer, 2005[64]	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

Trial	Author, year	Intervention	Participants	Quality Rating/Limitations
Heart and Estrogen/ Progestin Replacement Study Phase II (HERS II)	Grady, 2002;[60,65] Hulley, 2002[61]	CEE 0.625 mg/d plus MPA 2.5 mg (N=1156) Placebo (N=1165)	Women from the original HERS who consented to followup	Fair
Oestrogen in the Prevention of Reinfarction Trial (ESPRIT)	Cherry, 2002[67]	Estradiol valerate 2 mg/d (N=513) Placebo (N=504)	• 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	Fair Unclear attrition rates, compliance differed between E and placebo groups
Estrogen Memory Study (EMS)	Tierney, 2009[68]	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)	• Age >60 years • Last menstrual cycle >12 months before screening • Fluent in English and could read normal print and hear normal speech	Good Regimen not standard (cyclical E+P and E alone for all participants regardless of intact uterus or not); small sample size
Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA)	Ettinger, 2004;[69] Johnson, 2005;[70] Waetjen, 2005;[71] Yaffe, 2006[72]	Unopposed transdermal estradiol 0.014 mg/d (N=208) Placebo (N=209)	• Aged 60-80 years • Intact uterus • At least 5 years past menopause • Bone mineral density normal for age	Fair Bone mineral density at lumbar spine differed between groups at baseline
Women's International Study of Long Duration Oestrogen After Menopause (WISDOM)	Vickers 2007[66]	CEE 0.625 mg/d plus MPA 2.5-5.0 mg/d (N=2196) Placebo (N=2189)	• Aged 50-69 years • Postmenopausal	Fair Short followup (11.9 months) due to early termination prompted by published risks of estrogen; primary outcome changed from stroke to unstable angina; extension of age at randomization from 64 to 69, unblended 38% CEE plus MPA group vs. 4% placebo

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

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

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

Trials and Hormone Regimens (E+P or E vs. Placebo)											
Characteristic (Hormone Therapy; Placebo)	**WHI E+P**	**WHI E**	**WHIMS E+P**	**WHIMS E**	**WHISCA E+P**	**WHISCA E**	**HERS E+P**	**ESPRIT E**	**EMS E+P**	**WISDOM E+P**	**ULTRA E**
N	8506;8102	5310;5429	2229;2303	1464;1483	690;726	434;452	1380;1383	513;504	70;72	2196;2189	191;185
Age (mean yrs)	63.2;63.3	63.6;63.6	63.2;63.3	63.6;63.6	73.69;73.86	74.01;74.02	67;67	62.3;62.9	75;74.5	63.3;63.3	66.8;66.7
Nonwhite race (%)	16.1;16.0	24.5;24.9	-	17.3;16.4	8.4;7.0	14.09;13.08	12;10	3;3	4.3;9.7	1;1.4	7.2;8.1
Previous or current HT (%)	26.1;25.6	47.8;48.9	21.8;22.4	45.8;44.7	21.2;22.6	49.54;46.24	1.7;1.7	12;10	31.4;23.6	55;54.3	-
Hysterectomy age <40 yr (%)	-	39.8;39.8	-	-	-	-	-	-	-	-	-
Hysterectomy age 40-49 yrs (%)	-	43.2;42.2	-	-	-	-	-	-	-	-	-
Bilateral oophorectomy (%)	-	39.5;42.0	-	-	-	-	-	-	-	-	-
Never pregnant (%)	10.1;10.3	9.3;8.5	-	-	-	-	-	-	-	-	-
First pregnancy age ≥30 yr (%)	10.6;9.7	4.9;5.9	-	-	-	-	-	-	-	-	-
Female relative with breast cancer (%)	16.0;15.3	18.0;17.1	-	-	-	-	-	-	-	8;9	-
Current smoker (%)	10.5;10.5	10.3;10.6	6.7;6.9	7.3;8.0	6.2;5.0	3.72;7.59	13;13	54;52	-	12;14	7.7;6.2
Mean BMI (kg/m^2)	28.5;28.5	30.1;30.1	-	-	28.5;28.1	29.40;29.21	57;55	26.8;26.7	27;26.6	27.9;28.0	28.3;28.0
History of MI (%)	1.6;1.9	3.1;3.2	-	-	-	-	1.2;1.2	-	5.7;4.2	2;1	-
History of stroke (%)	0.7;1.0	1.4;1.7	1;1.9	1.8;2.1	1;1	1.15;1.77	-	-	-	1;2	-
History of DVT or PE (%)	0.9;0.8	1.6;1.5	-	-	-	-	-	-	-	-	-
Mean SBP (mm Hg)	127.6;127.8	130.4;130.2	-	-	-	-	135;135	-	-	-	-
Mean DBP (mm Hg)	75.6;75.8	76.5;76.5	-	-	-	-	73;73	-	-	-	-
Treated for hypertension or BP>140/90 (%)	35.7;36.4	48.0;47.4	-	47.3;42.3	44.4;46.0	53.69;51.11		-	-	-	-
Elevated cholesterol requiring medication (%)	12.5;12.9	14.5;15.9	-	-	-	-		-	-	-	-
Prior aspirin use or use at baseline (%)	19.1;20.1	19.4;19.7	28.1;29.6	28.0;30.9	-	-	5.6;5.6	-	-	-	-
History of or treatment for diabetes (%)	4.4;4.4	7.7;7.6	7;6.5	11.3;10.6	5.4;6.2	10.14;10.84	19;18	15;15	7.1;11.1	3;4	-
Fracture age ≥55 yrs (%)	13.5;13.6	14.0;13.2	-	-	-	-	-	-	-	-	-

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=Oestrogen in the Prevention of Reinfarction Trial; HERS=Heart and Estrogen/Progestin Replacement Study; HT=hormone therapy; MI=myocardial infarction; P=progestin; PE=pulmonary embolism; 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

Outcome	E+P vs. Placebo		E vs. Placebo	
	HR (95% CI)	Differences in events per 10,000 women-years (95% CI)*	HR (95% CI)	Differences in events per 10,000 women-years (95% CI)*
Cancer				
Invasive breast	1.25 (1.07-1.46)[25]	8 (3-14) more	0.77 (0.62-0.95)[49]	8 (1-14) less
Colorectal	0.75 (0.57-1.00)[33]	Not significant	1.11 (0.82-1.50)[49]	Not significant
Lung	1.23 (0.92-1.63)[27]	Not significant	1.17 (0.81-1.69)[45]	Not significant
Endometrial	0.78 (0.52-1.16)[33]	Not significant	Not reported	Not reported
Ovarian	1.58 (0.77-3.24)[23]	Not significant	Not reported	Not reported
Cervical	1.44 (0.47-4.42)[23]	Not significant	Not reported	Not reported
Cardiovascular events				
Coronary heart disease (CHD death and total MI)	1.22 (0.99-1.51)[33]	Not significant	0.95 (0.78-1.15)[49]	Not significant
Stroke	1.34 (1.05-1.71)[33]	9 (2-15) more	1.36 (1.08-1.71)[49]	11 (2-20) more
Thromboembolic events				
Deep vein thrombosis	1.88 (1.38-2.55)[33]	12 (6-17) more	1.47 (1.06-2.05)[49]	7 (1-14) more
Pulmonary embolism	1.98 (1.36-2.87)[33]	9 (4-14) more	1.37 (0.90-2.07)[49]	Not significant
Diabetes				
Self-reported new diagnosis requiring treatment with drugs	0.79 (0.67-0.93)[38]	15 (4-26) less	0.88 (0.77-1.01)[43]	Not significant
Fractures				
Hip	0.67 (0.47-0.95)[33]	6 (1-10) less	0.61 (0.41-0.91)[42]	7 (1-12) less
Vertebral	0.68 (0.48-0.96)[33]	6 (1-11) less	0.62 (0.42-0.93)[42]	6 (1-12) less
Total fractures	0.76 (0.69-0.83)[33]	46 (29-63) less	0.70 (0.63-0.79)[42]	56 (37-75) less
Mortality				
All-cause mortality	1.04 (0.91-1.18)[33]	Not significant	1.02 (0.91-1.15)[49]	Not significant
Breast cancer mortality	1.96 (1.00-4.04)[25]	Not significant	0.37 (0.13-0.91)[73]	2 (1-3) less
Lung cancer mortality	1.71 (1.16-2.52)[27]	5 (1-8) more	Not reported	Not reported
Gallbladder				
Gallbladder disease (cholecystitis and cholelithiasis)	1.61 (1.30-2.00)[29]	20 (11-29) more	1.79 (1.44-2.22)[29]	33 (20-45) more
Cognitive function				
Probable dementia	2.05 (1.21-3.48)[55]	22 (5-39) more	1.49 (0.83-2.66)[54]	Not significant
Mild cognitive impairment	1.07 (0.74-1.55)[55]	Not significant	1.34 (0.95-1.89)[54]	Not significant
Urinary incontinence				
Overall urinary incontinence (stress, urge, or mixed)	1.39 (1.27-1.52)[35]	872 (591-1153) more	1.53 (1.37-1.71)[35]	1271 (883-1660) more

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

Number of studies	Design	Limitations	Consistency	Applicability	Overall quality	Findings
Key Question 1. What are the benefits of menopausal hormone therapy when used to prevent chronic conditions?						
9 main trials	RCT	High attrition rates; differential loss to followup; low adherence	Consistent	High	Fair	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.
Key Question 2. What are the harms of menopausal hormone therapy when used to prevent chronic conditions?						
9 main trials	RCT	High attrition rates; differential loss to followup; low adherence	Consistent	High	Fair	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.
Key Question 3. Do benefits and harms differ by subgroups?						
9 main trials	RCT	Most subgroups were not evaluated in trials	Not relevant	Not relevant	Varied	Subgroup comparisons were limited and inconclusive.

Abbreviations: HERS=Heart and Estrogen/Progestin Replacement Study; RCT=randomized, controlled trial; WHI=Women's Health Initiative.

Appendix A. List of Acronyms and Abbreviations

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

Appendix A. List of Acronyms and Abbreviations

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

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1947 to November Week 3 2011>
Search Strategy:
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1 exp Hormone Replacement Therapy/ (18014)
2 ((oestrogen$ or estrogen$ or hormon$) adj3 (replac$ or treat$ or therap$ or interven$)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (61635)
3 exp Estrogens/ad, tu, ae, to (30285)
4 exp Estradiol Congeners/ad, tu, ae, to (16224)
5 1 or 2 or 3 or 4 (83066)
6 exp climacteric/ (42184)
7 (menopaus$ or postmenopaus$ or premenopaus$ or perimenopaus$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (71436)
8 6 or 7 (73433)
9 5 and 8 (21705)
10 limit 5 to yr="2002 -Current" (30216)
11 limit 10 to randomized controlled trial (2532)
12 systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or (systematic review.ti,ab. and review.pt.) or consensus development conference.pt. or practice guideline.pt. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. (62504)
13 evidence based.ti. or exp Evidence-Based Medicine/ or best practice$.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)

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 english language (2184)
60 limit 58 to abstracts (2022)

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

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

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

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

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

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

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

	Include	Exclude
Population	Generally healthy postmenopausal women eligible for menopausal hormone therapy. Characteristics of enrolled participants are applicable to the U.S. primary care population.	Animals, men, premenopausal women, postmenopausal women with contraindications for hormone therapy use, or populations not applicable to U.S. primary care.
Interventions	Estrogen only or combined with progestin for prevention of chronic conditions. Medications are available for use in the United States.	Contraceptives, other hormones, or treatment of menopausal symptoms.
Outcomes	Health outcomes include mortality, fractures; coronary heart disease; stroke; venous thromboembolism; breast, colorectal, endometrial, and ovarian cancer; cholecystitis; cognition; urinary incontinence; and others.	Menopausal symptoms; intermediate health outcomes, such as lipid levels or bone mineral density.
Study types and designs	English-language randomized, controlled trials published in 2002 or later.	Observational studies (case-control and cohort) or case studies.
Duration	1 year of treatment.	Less than 1 year of treatment.

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: Ccomparable 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, 2001[22]

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

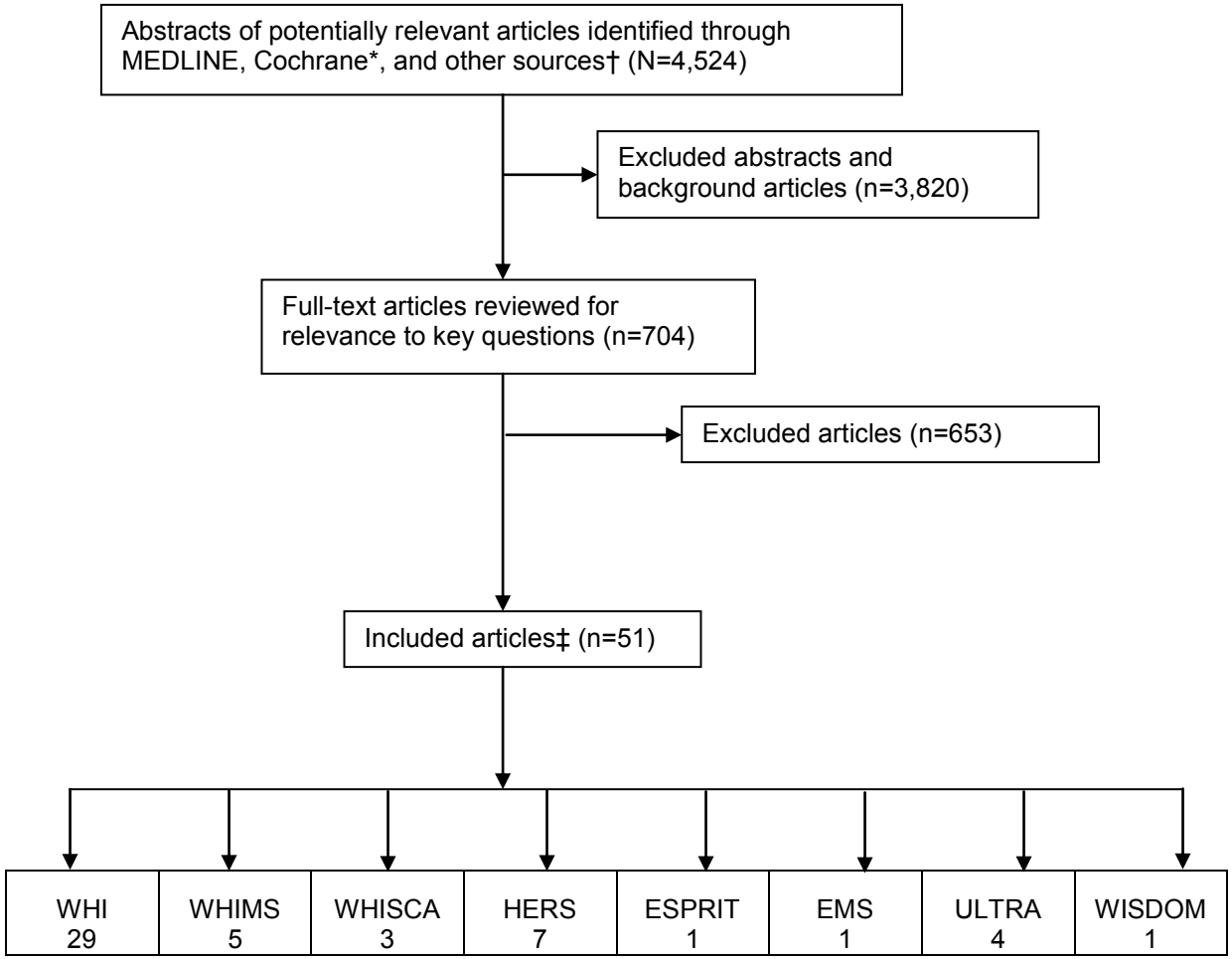
Jacques Rossouw, M.D., Chief, Women's Health Initiative Branch, National Heart, Lung and Blood Institute

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



*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

Reports from the Swedish Council on Technology Assessment In Health Care (SBU). Treatment of asthma and COPD: an evidence-based review. *Int J Technol Assess Health Care.* 2002;18(4):832-860. 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

Hormone replacement therapy. *Med Lett Drugs Ther.* 2002;44(1138):78. Exclusion code: 7

Has lower-dose HRT come of age? *Harv Womens Health Watch.* 2002;9(10):1-2. Exclusion code: 7

Stunning HRT research points providers in new directions. *Dis Manag Advis.* 2002;8(8):113-117. Exclusion code: 7

Getting to the HRT of the matter. *Johns Hopkins Med Lett Health After 50.* 2002;14(5):4-5. Exclusion code: 7

Hormones and heart disease—down, not out. *Harv Heart Lett.* 2002;12(7):3-5. Exclusion code: 7

Facts About Menopausal Hormone Therapy. *U.S. Department of Health and Human Services: National Heart, Lung, and Blood Institute.* 2002(revised 2005);05-5200:1-24. Exclusion code: 7

Canadian consensus on osteoporosis. Preventing osteoporosis among postmenopausal women. *Can Fam Physician.* 2003;49:487. Exclusion code: 7

HRT: Update on the risk of breast cancer and long-term safety. *Curr Probl Pharmacovigilance.* 2003;29:1-3. Exclusion code: 2

Post-menopausal hormone replacement therapy (cont'd): risk-benefit balance in the hot seat. *Prescrire Int.* 2004;13(71):106-109. Exclusion code: 7

Menostar: a low-dose estrogen patch for osteoporosis. *Med Lett Drugs Ther.* 2004;46(1190):69-70. Exclusion code: 7

Appendix B6. List of Excluded Full-Text Articles

NIH State-of-the-Science Conference Statement on management of menopause-related symptoms. *NIH Consens State Sci Statements.* 2005;22(1):1-38. Exclusion code: 7

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

Drugs for postmenopausal osteoporosis. *Treat Guidel Med Lett.* 2008;6(74):67-74. Exclusion code: 7

Hormone therapy: an update on risks and benefits. *Mayo Clin Womens Healthsource.* 2009;(Suppl):1-8. Exclusion code: 7

Timing of hormone therapy influences breast cancer risk. *Harv Womens Health Watch.* 2011;18(8):7. Exclusion code: 7

Abramov Y, Borik S, Yahalom C, et al. The effect of hormone therapy on the risk for age-related maculopathy in postmenopausal women. *Menopause.* 2004;11(1):62-68. Exclusion code: 6

Abramson BL. Postmenopausal hormone replacement therapy and the prevention of cardiovascular disease: a review. *J Cardiovasc Risk.* 2002;9(6):309-314. Exclusion code: 7

Abramson BL; Canadian Task Force on Preventive Health Care. Postmenopausal hormone replacement therapy for primary prevention of cardiovascular and cerebrovascular disease: recommendation statement from the Canadian Task Force on Preventive Health Care. *CMAJ.* 2004;170(9):1388-1389. Exclusion code: 2

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 Kadri H, Hassan S, Al-Fozan HM, Hajeer A. Hormone therapy for endometriosis and surgical menopause. *Cochrane Database Syst Rev.* 2009;(1):CD005997. Exclusion code: 8

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

Aldrighi JM, Alecrin IN, Caldas MA, et al. Effects of estradiol on myocardial global performance index in hypertensive postmenopausal women. *Gynecol Endocrinol.* 2004;19(5):282-292. Exclusion code: 9

Aldrighi JM, Calvoso-Junior R, Alecrin IN, et al. Estrogen replacement and exercise capacity in postmenopausal women: a randomized placebo-controlled study. *Gynecol Endocrinol.* 2005;21(6):324-329. Exclusion code: 11

Alexandersen P, Tanko LB, Bagger YZ, et al. The long-term impact of 2-3 years of hormone replacement therapy on cardiovascular mortality and atherosclerosis in healthy women. *Climacteric.* 2006;9(2):108-118. Exclusion code: 9

Appendix B6. List of Excluded Full-Text Articles

Alhola P, Tuomisto H, Saarinen R, et al. Estrogen + progestin therapy and cognition: a randomized placebo-controlled double-blind study. *J Obstet Gynaecol Res.* 2010;36(4):796-802. Exclusion code: 14

Allison MA, Manson JE, Langer RD, et al. Oophorectomy, hormone therapy, and subclinical coronary artery disease in women with hysterectomy: the Women's Health Initiative coronary artery calcium study. *Menopause.* 2008;15(4 Pt 1):639-647. Exclusion code: 11

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

Althuis MD, Fergenbaum JH, Garcia-Closas M, et al. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. *Cancer Epidemiol Biomarkers Prev.* 2004;13(10):1558-1568. Exclusion code: 7

Alving B. NIH asks participants in Women's Health Initiative estrogen-alone study to stop study pills, begin follow-up phase. *South Med J.* 2004;97(4):425-426. 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

American College of Obstetricians and Gynecologists Women's Health Care Physicians. Osteoporosis. *Obstet Gynecol.* 2004;104(4 Suppl):66S-76S. Exclusion code: 7

American College of Obstetricians and Gynecologists Women's Health Care Physicians. Venous thromboembolic disease. *Obstet Gynecol.* 2004;104(4 Suppl):118S-127S. Exclusion code: 7

American College of Obstetricians and Gynecologists Women's Health Care Physicians. Stroke. *Obstet Gynecol.* 2004;104(4 Suppl):97S-105S. Exclusion code: 7

American College of Obstetricians and Gynecologists Women's Health Care Physicians. Coronary heart disease. *Obstet Gynecol.* 2004;104(4 Suppl):41S-48S. Exclusion code: 7

American College of Obstetricians and Gynecologists Women's Health Care Physicians. Cognition and dementia. *Obstet Gynecol.* 2004;104(4 Suppl):25S-40S. Exclusion code: 7

American College of Obstetricians and Gynecologists. ACOG issues state-of-the-art guide to hormone therapy. 2004. Exclusion code: 7

American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 420, November 2008: hormone therapy and heart disease. *Obstet Gynecol.* 2008;112(5):1189-1192. Exclusion code: 2

American College of Obstetricians and Gynecologists Committee on Practice Bulletins. ACOG Practice Bulletin: clinical management guidelines for obstetrician-gynecologists. Osteoporosis. *Obstet Gynecol.* 2004;103:203-216. Exclusion code: 2

American College of Obstetricians and Gynecologists Women's Health Care Physicians. Executive summary: hormone therapy. *Obstet Gynecol.* 2004;104(4 Suppl):1S-4S. Exclusion code: 6

Appendix B6. List of Excluded Full-Text Articles

American Medical Association. Health risks outweigh benefits for combined estrogen plus progestin. Clinical trial stopped early in major study. *Ginecol Obstet Mex.* 2002;70:411-412. Exclusion code: 7

American Medical Association. Postmenopausal hormone therapy offers no protection against heart attacks. *Ginecol Obstet Mex.* 2002;70:404-405. Exclusion code: 10

Ancelin ML, Ritchie K. Lifelong endocrine fluctuations and related cognitive disorders. *Curr Pharm Des.* 2005;11(32):4229-4252. Exclusion code: 7

Ancelin ML, Berr C. Hormonal replacement therapy and Alzheimer's disease. All quiet on the western front? *Psychol.* 2003;1(4):251-257. Exclusion code: 7

Anderer P, Saletu B, Gruber D, et al. Age-related cognitive decline in the menopause: effects of hormone replacement therapy on cognitive event-related potentials. *Maturitas.* 2005;51(3):254-269. Exclusion code: 6

Anderer P, Saletu B, Saletu-Zyhlarz G, et al. Brain regions activated during an auditory discrimination task in insomniac postmenopausal patients before and after hormone replacement therapy: low-resolution brain electromagnetic tomography applied to event-related potentials. *Neuropsychobiology.* 2004;49(3):134-153. Exclusion code: 11

Anderer P, Semlitsch HV, Saletu B, et al. Effects of hormone replacement therapy on perceptual and cognitive event-related potentials in menopausal insomnia. *Psychoneuroendocrinology.* 2003;28(3):419-445. Exclusion code: 11

Anderson GL, Chlebowski RT, Rossouw JE, et al. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. *Maturitas.* 2006;55(2):103-115. Exclusion code: 12

Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. *JAMA.* 2004;291(14):1701-1712. Exclusion code: 12

Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative study design. *Ann Epidemiol.* 2003;13(9 Suppl):S5-17. Exclusion code: 2

Andresen MS, Eilertsen AL, Abildgaard U, Sandset PM. Hormone therapy and raloxifene reduce the coagulation inhibitor potential. *Blood Coagul Fibrinolysis.* 2007;18(5):455-460. Exclusion code: 5

Angerer P, Stork S, Kothny W, von Schacky C. Effect of postmenopausal hormone replacement on atherosclerosis in femoral arteries. *Maturitas.* 2002;41(1):51-60. Exclusion code: 11

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

Antoine C, Liebens F, Carly B, et al. Influence of HRT on prognostic factors for breast cancer: a systematic review after the Women's Health Initiative trial. *Human Reproduction.* 2004;19(3):741-756. Exclusion code: 11

Antonicelli R, Olivieri F, Morichi V, et al. Prevention of cardiovascular events in early

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

Apgar BS, Weismiller DG. Hormone therapy: continuing discussion and debate. *Am Fam Physician.* 2003;67(7):1444. Exclusion code: 7

Ardila E, Echevery J, Sanchez R. Phytoestrogens in the treatment of postmenopausal osteoporosis. *Cochrane Database Syst Rev.* 2009(1). Exclusion code: 7

Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke.* 2003;34(8):2060-2065. Exclusion code: 9

Arjmandi BH, Khalil DA, Smith BJ, et al. Soy protein has a greater effect on bone in postmenopausal women not on hormone replacement therapy, as evidenced by reducing bone resorption and urinary calcium excretion. *J Clin Endocrinol Metab.* 2003;88(3):1048-1054. Exclusion code: 4

Armitage M, Nooney J, Evans S. Recent concerns surrounding HRT. *Clin Endocrinol (Oxf).* 2003;59(2):145-155. Exclusion code: 7

Arora S, Jain A, Chitra R. Effects of short-term hormone replacement on atherogenic indices in Indian postmenopausal women. *Indian J Clin Biochem.* 2006;21(1):41-47. Exclusion code: 11

Ashraf MS, Vongpatanasin W. Estrogen and hypertension. *Curr Hypertens Rep.* 2006;8(5):368-376. Exclusion code: 11

Askanase AD. Estrogen therapy in systemic lupus erythematosus. *Treat.* 2004;3(1):19-26. Exclusion code: 3

Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause.* 2006;13(2):265-279. Exclusion code: 6

Bagger YZ, Tanko LB, Alexandersen P, et al. Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study. *Bone.* 2004;34(4):728-735. Exclusion code: 9

Bagger YZ, Tanko LB, Alexandersen P, et al. Early postmenopausal hormone therapy may prevent cognitive impairment later in life. *Menopause.* 2005;12(1):12-17. Exclusion code: 6

Bahl VK, Naik N. Hormone replacement therapy and coronary artery disease: buried alive? *Indian Heart J.* 2002;54(1):23-30. Exclusion code: 7

Bain CA, Walters MR, Lees KR, Lumsden MA. The effect of HRT on cerebral haemodynamics and cerebral vasomotor reactivity in post-menopausal women. *Human Reproduction.* 2004;19(10):2411-2414. Exclusion code: 11

Baker LD, Sambamurti K, Craft S, et al. 17β-estradiol reduces plasma Aβ40 for HRT-naive postmenopausal women with Alzheimer disease: a preliminary study. *Am J Geriatr Psychiatry.* 2003;11(2):239-244. Exclusion code: 11

Appendix B6. List of Excluded Full-Text Articles

Ballard VL, Edelberg JM. Harnessing hormonal signaling for cardioprotection. *Sci Aging Knowl Environ.* 2005;2005(51):6. Exclusion code: 7

Banach T, Dobrek L, Milewicz T, et al. Effect of hormonal replacement therapy on autonomic regulation of the heart. *Przegl Lek.* 2004;61(5):509-513. Exclusion code: 11

Banks E, Beral V, Reeves G. Published results on breast cancer and hormone replacement therapy in the Million Women Study are correct. *Climacteric.* 2004;7(4):415-7. Exclusion code: 7

Banks E, Beral V, Reeves G, et al. Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. *JAMA.* 2004;291(18):2212-2220. Exclusion code: 6

Banks E, Canfell K, Reeves G. HRT and breast cancer: recent findings in the context of the evidence to date. *Womens Health.* 2008;4(5):427-431. Exclusion code: 7

Banks E, Reeves G, Evans S. Disease incidence associated with long-term use of hormone replacement therapy. *Menopause and Hormone Replacement: Proceedings of the Forty Seventh Study Group of the Royal College of Obstetricians and Gynaecologists.* 2004:241-254. Exclusion code: 7

Barad D, Kooperberg C, Wactawski-Wende J, et al. Prior oral contraception and postmenopausal fracture: a Women's Health Initiative observational cohort study. *Fertil Steril.* 2005;84(2):374-383. Exclusion code: 4

Barr RJ, Stewart A, Torgerson DJ, Reid DM. Population screening for osteoporosis risk: a randomised control trial of medication use and fracture risk. *Osteoporos Int.* 2010;21(4):561-568. Exclusion code: 4

Barrett-Connor E, Grady D, Sashegyi A, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial *JAMA.* 2002;287(7):847-857. Exclusion code: 4

Barrett-Connor E, Grady D, Stefanick ML. The rise and fall of menopausal hormone therapy. *Annu Rev Public Health.* 2005;26:115-140. Exclusion code: 7

Basile JN. Estrogen replacement does not prevent recurrent stroke or death in postmenopausal women after an ischemic stroke. *J Clin Hypertens.* 2002;4(1):48-49. Exclusion code: 7

Bath PM, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ.* 2005;330(7487):342. Exclusion code: 12

Battaglia C, Cianciosi A, Mancini F, et al. Angeliq versus Activelle in normotensive postmenopausal women: a prospective, randomized pilot study. *Menopause.* 2009;16(4):803-809. Exclusion code: 11

Bauer DC, Mundy GR, Jamal SA, et al. Use of stains and fracture: results of 4 prospective studies and cumulative meta-analysis of observational studies and controlled trials. *Arch Intern Med.* 2004;164(2):146-152. Exclusion code: 4

Baum M. Breast cancer survival and the use of HRT. *Breast.* 2005;14(3):178-180. Exclusion code: 7

Appendix B6. List of Excluded Full-Text Articles

Benschop L, Farquhar C, van der Poel N, Heineman MJ. Interventions for women with endometrioma prior to assisted reproductive technology. *Cochrane Database Syst Rev.* 2010;(11):CD008571. Exclusion code: 8

Benster B, Carey A, Wadsworth F, et al. Double-blind placebo-controlled study to evaluate the effect of pro-juven progesterone cream on atherosclerosis and bone density. *Menopause Int.* 2009;15(3):100-106. Exclusion code: 4

Beral V, Banks E, Reeves G. Evidence from randomised trials on the long-term effects of hormone replacement therapy. *Lancet.* 2002;360(9337):942-944. Exclusion code: 9

Beral V, Banks E, Reeves G. Long-term effects of hormone replacement therapy. *Lancet.* 2003;361(9353):254-255. Exclusion code: 7

Beral V, Bull D, Green JB, et al. Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet.* 2007;369(9574):1703-1710. Exclusion code: 6

Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet.* 2003;362(9382):419-427. Exclusion code: 6

Beral V, Reeves G, Banks E. Current evidence about the effect of hormone replacement therapy on the incidence of major conditions in postmenopausal women. *BJOG.* 2005;112(6):692-695. Exclusion code: 7

Beral V, Reeves G, Bull D, et al. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. *J Natl Cancer Inst.* 2011;103(4):296-305. Exclusion code: 6

Berg AO; U.S. Preventive Services Task Force. Postmenopausal hormone replacement therapy for the primary prevention of chronic conditions: recommendations and rationale. *Am J Nurs.* 2003;103(6):83-91. Exclusion code: 2

Bergert FW, Conrad D, Ehrenthal K, et al. Pharmacotherapy guidelines for the aged by family doctors for the use of family doctors: part C—special pharmacology. *Int J Clin Pharmacol Ther.* 2009;47(3):141-152. Exclusion code: 7

Bernstein L. The risk of breast, endometrial and ovarian cancer in users of hormonal preparations. *Basic Clin Pharmacol Toxicol.* 2006;98(3):288-296. Exclusion code: 7

Bhattoa HP, Bettembuk P, Balogh A, et al. The effect of 1-year transdermal estrogen replacement therapy on bone mineral density and biochemical markers of bone turnover in osteopenic postmenopausal systemic lupus erythematosus patients: a randomized, double-blind, placebo-controlled trial. *Osteoporos Int.* 2004;15(5):396-404. Exclusion code: 11

Bhavnani BR, Strickler RC. Menopausal hormone therapy. *J Obstet Gynaecol Can.* 2005;27(2):137-162. Exclusion code: 7

Bibbins-Domingo K, Lin F, Vittinghoff E, et al. Predictors of heart failure among women with coronary disease. *Circulation.* 2004;110(11):1424-1430. Exclusion code: 5

Bibbins-Domingo K, Lin F, Vittinghoff E, et al. Effect of hormone therapy on mortality rates among women with heart failure and coronary artery disease. *Am J Cardiol.* 2005;95(2):289-291. Exclusion code: 4

Appendix B6. List of Excluded Full-Text Articles

Billeci AM, Paciaroni M, Caso V, Agnelli G. Hormone replacement therapy and stroke. *Curr Vasc Pharmacol.* 2008;6(2):112-123. Exclusion code: 7

Birkhauser MH, Panay N, Archer DF, et al. Updated practical recommendations for hormone replacement therapy in the peri- and postmenopause. *Climacteric.* 2008;11(2):108-123. Exclusion code: 2

Biscup P. Risks and benefits of long-term hormone replacement therapy. *Am J Health-Syst Pharm.* 2003;60(14):1419-1425. Exclusion code: 7

Bittner V. Postmenopausal hormone therapy and the risk of cardiovascular disease. *Expert Opin Pharmacother.* 2009;10(13):2041-2053. Exclusion code: 7

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

Blake J. Menopause: evidence-based practice. *Best Pract Res Clin Obstet Gynaecol.* 2006;20(6):799-839. Exclusion code: 7

Blake JM, Collins JA, Reid RL, et al. The SOGC statement on the WHI report on estrogen and progestin use in postmenopausal women. *J Obstet Gynaecol Can.* 2002;24(10):783-790. Exclusion code: 10

Bliss JM, Gray R. Breast cancer and hormone-replacement therapy: the Million Women Study. *Lancet.* 2003;362(9392):1328-1329. Exclusion code: 7

Blumel JE, Castelo-Branco C, Leal T, et al. Effects of transdermal estrogens on endothelial function in postmenopausal women with coronary disease. *Climacteric.* 2003;6(1):38-44. Exclusion code: 11

Boone RH, Cheung AM, Girlan LM, Heathcote EJ. Osteoporosis in primary biliary cirrhosis: a randomized trial of the efficacy and feasibility of estrogen/ progestin. *Dig Dis Sci.* 2006;51(6):1103-1112. Exclusion code: 8

Booth EA, Lucchesi BR. Estrogen-mediated protection in myocardial ischemia-reperfusion injury. *Cardiovasc Toxicol.* 2008;8(3):101-113. Exclusion code: 6

Botlero R, Urquhart DM, Davis SR, Bell RJ. Prevelance and incidence of urinary incontinence in women: review of the literature and investigation of methodological issues. *Int J Urol.* 2008;15:230-234. Exclusion code: 5

Bots ML, Evans GW, Riley W, et al. The effect of tibolone and continuous combined conjugated equine oestrogens plus medroxyprogesterone acetate on progression of carotid intima-media thickness: the Osteoporosis Prevention and Arterial effects of tiboLone (OPAL) study. *Eur Heart J.* 2006;27(6):746-755. Exclusion code: 11

Bots ML, Evans GW, Riley W, et al. The Osteoporosis Prevention and Arterial effects of tiboLone (OPAL) study: design and baseline characteristics. *Control Clin Trials.* 2003;24(6):752-775. Exclusion code: 7

Bozkurt B. Where do we currently stand with advice on hormone replacement therapy for women? *Methodist Debakey Cardiovasc J.* 2010;6(4):21-25. Exclusion code: 7

Appendix B6. List of Excluded Full-Text Articles

Braendle W. The Million Women Study, an additional observational study with the implications and limits of an observational study. *Maturitas.* 2003;46(2):101-102. Exclusion code: 7

Brandao CM, Lima MG, Silva AL, et al. Treatment of postmenopausal osteoporosis in women: a systematic review. *Cad Saude Publica.* 2008;24(Suppl 4):s592-606. Exclusion code: 8

Brandin LM, Gustafsson H, Ghanoum B, et al. Effects of estrogen plus progesterone on hemodynamic and vascular reactivity in hypertensive postmenopausal women. *Blood Press.* 2010;19(3):156-163. Exclusion code: 11

Brass LM. Hormone replacement therapy and stroke: clinical trials review. *Stroke.* 2004;35(11 Suppl 1):2644-2647. Exclusion code: 7

Bray PF, Howard TD, Vittinghoff E, et al. Effect of genetic variations in platelet glycoproteins Ibα and VI on the risk for coronary heart disease events in postmenopausal women taking hormone therapy. *Blood.* 2007;109(5):1862-1869. Exclusion code: 5

Brinton EA, Hodis HN, Merriam GR, et al. Can menopausal hormone therapy prevent coronary heart disease? *Trends Endocrinol Metab.* 2008;19(6):206-212. Exclusion code: 7

Bromley SE, de Vries CS, Thomas D, Farmer RD. Hormone replacement therapy and risk of acute myocardial infarction: a review of the literature. *Drug Saf.* 2005;28(6):473-493. Exclusion code: 7

Brosnan JF, Sheppard BL, Norris LA. Haemostatic activation in post-menopausal women taking low-dose hormone therapy: less effect with transdermal administration? *Thromb Haemostas.* 2007;97(4):558-565. Exclusion code: 11

Brown CM, Suzuki S, Jelks KA, Wise PM. Estradiol is a potent protective, restorative, and trophic factor after brain injury. *Semin Reprod Med.* 2009;27(3):240-249. Exclusion code: 11

Brown JS. Epidemiology and changing demographics of overactive bladder: a focus on the postmenopausal woman. *Geriatrics.* 2002;57(Suppl 1):6-12. Exclusion code: 7

Brown NJ, Abbas A, Byrne D, et al. Comparative effects of estrogen and angiotensin-converting enzyme inhibition on plasminogen activator inhibitor-1 in healthy postmenopausal women. *Circulation.* 2002;105(3):304-309. Exclusion code: 4

Brown S. WHI Memory Study fails to find oestrogen benefit in dementia. *J Br Menopause Soc.* 2004;10(3):93. Exclusion code: 7

Brown S. Transdermal hormone replacement therapy not associated with an increased risk of stroke. *Menopause Int.* 2010;16(2):48-49. Exclusion code: 7

Brownley KA, Hinderliter AL, West SG, et al. Cardiovascular effects of 6 months of hormone replacement therapy versus placebo: differences associated with years since menopause. *Am J Obstet Gynecol.* 2004;190(4):1052-1058. Exclusion code: 11

Bruce D, Frick A, Rymer J, et al. A comparison of hormone therapies on the urinary excretion of prostacyclin and thromboxane A2. *Climacteric.* 2008;11(6):447-453. Exclusion code: 4

Appendix B6. List of Excluded Full-Text Articles

Bruyere O, Reginster JY. Fracture prevention in postmenopausal women. *Clin Evid.* 2002(7):979-982. Exclusion code: 9

Buchholz S, Horn F, Ortmann O. Hormone replacement therapy in peri- and postmenopausal women and breast cancer risk. *Ther Umsch.* 2008;65(4):231-234. Exclusion code: 10

Burger H. Hormone replacement therapy in the post-Women's Health Initiative era: report at a meeting held in Funchal, Madeira, February 24-25, 2003. *Climacteric.* 2003;6(Suppl 1):11-36. Exclusion code: 7

Burger HG. WHI risks: any relevance to menopause management? *Maturitas.* 2007;57(1):6-10. Exclusion code: 7

Burkhardt MS, Foster JK, Laws SM, et al. Oestrogen replacement therapy may improve memory functioning in the absence of APOE ε4. *J Alzheimers Dis.* 2004;6(3):221-228. Exclusion code: 6

Bushnell CD. The Women's Health Initiative trial and stroke risk. *Lancet Neurol.* 2002;1(5):277. Exclusion code: 7

Bushnell CD. Oestrogen and stroke in women: assessment of risk. *Lancet Neurol.* 2005;4(11):743-751. Exclusion code: 7

Bushnell CD. Hormone replacement therapy and stroke: the current state of knowledge and directions for future research. *Semin Neurol.* 2006;26(1):123-130. Exclusion code: 7

Bushnell CD, Newby LK, Goldstein LB, et al. Statin use and stroke outcomes in the Heart and Estrogen-Progestin Replacement Study (HERS). *Neurology.* 2004;62(6):968-970. Exclusion code: 4

Byington RP, Furberg CD, Herrington DM, et al. Effect of estrogen plus progestin on progression of carotid atherosclerosis in postmenopausal women with heart disease: HERS B-mode substudy. *Arterioscler Thromb Vasc Biol.* 2002;22(10):1692-1697. Exclusion code: 5

Byrjalsen I, Leeming DJ, Qvist P, et al. Bone turnover and bone collagen maturation in osteoporosis: effects of antiresorptive therapies. *Osteoporos Int.* 2008;19(3):339-348. Exclusion code: 11

Cagnacci A, Tarquini R, Perfetto F, et al. Endothelin-1 and nitric oxide levels are related to cardiovascular risk factors but are not modified by estradiol replacement in healthy postmenopausal women. A cross-sectional and a randomized cross-over study. *Maturitas.* 2003;44(2):117-124. Exclusion code: 6

Campagnoli C, Colombo P, De Aloysio D, et al. Positive effects on cardiovascular and breast metabolic markers of oral estradiol and dydrogesterone in comparison with transdermal estradiol and norethisterone acetate. *Maturitas.* 2002;41(4):299-311. Exclusion code: 11

Campbell IA, Douglas JG, Francis RM, et al. Hormone replacement therapy (HRT) or etidronate for osteoporosis in postmenopausal asthmatics on glucocorticoids: a randomised factorial trial. *Scott Med J.* 2009;54(1):21-25. Exclusion code: 8

Campisi R, Nathan L, Pampaloni MH, et al. Noninvasive assessment of coronary microcirculatory function in postmenopausal women and effects of short-term and long-term estrogen administration. *Circulation.* 2002;105(4):425-430. Exclusion code: 11

Appendix B6. List of Excluded Full-Text Articles

Campos-Outcalt D. Clarifying the US Preventive Services Task Force's 2005 recommendations. *J Fam Pract.* 2006;55(5):425-428. Exclusion code: 7

Canderelli R, Leccesse LA, Miller NL, Unruh Davidson J. Benefits of hormone replacement therapy in postmenopausal women. *J Am Acad Nurse Pract.* 2007;19(12):635-641. Exclusion code: 7

Canonico M, Oger E, Conrad J, et al. Obesity and risk of venous thromboembolism among postmenopausal women: differential impact of hormone therapy by route of estrogen administration. *J Thromb Haemost.* 2006;4(6):1259-1265. Exclusion code: 6

Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: Impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation.* 2007;115(7):840-845. Exclusion code: 6

Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ.* 2008;336(7655):1227-1231. Exclusion code: 12

Cardozo L, Lose G, McClish D, Versi E. A systematic review of the effects of estrogens for symptoms suggestive of overactive bladder *Acta Obstet Gynecol Scand.* 2004;83:892-897. Exclusion code: 9

Carwile E, Wagner AK, Crago E, Alexander SA. Estrogen and stroke: a review of the current literature. *J Neurosci Nurs.* 2009;41(1):18-25. Exclusion code: 7

Castiglione-Gertsch M. Hormone replacement and breast cancer. *Ann Oncol.* 2004;15(Suppl 4):iv275-277. Exclusion code: 7

Cauley JA, LaCroix AZ, Robbins JA, et al. Baseline serum estradiol and fracture reduction during treatment with hormone therapy: the Women's Health Initiative randomized trial. *Osteoporos Int.* 2010;21(1):167-177. Exclusion code: 5

Cauley JA, Song J, Dowsett SA, et al. Risk factors for breast cancer in older women: the relative contribution of bone mineral density and other established risk factors. *Breast Cancer Res Treat.* 2007;102(2):181-188. Exclusion code: 4

Centre for Reviews and Dissemination. Preventing fractures in postmenopausal women with osteoporosis: a review of recent controlled trials of antiresorptive agents [abstract]. *Database Abstr Rev Effects.* 2011(2). Exclusion code: 7

Centre for Reviews and Dissemination. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis [abstract]. *Database Abstr Rev Effects.* 2011(2). Exclusion code: 7

Centre for Reviews and Dissemination. Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis [abstract]. *Database Abstr Rev Effects.* 2011(2). Exclusion code: 7

Centre for Reviews and Dissemination. Hormone replacement therapy and cognitive performance in postmenopausal women: a review by cognitive domain [abstract]. *Database Abstr Rev Effects.* 2011(2). Exclusion code: 6

Appendix B6. List of Excluded Full-Text Articles

Centre for Reviews and Dissemination. Hormone replacement therapy and cognition [abstract]. *Database Abstr Rev Effects.* 2011(2). Exclusion code: 7

Centre for Reviews and Dissemination. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia [abstract]. *Database Abstr Rev Effects.* 2011(2). Exclusion code: 7

Centre for Reviews and Dissemination. The effect of estrogen replacement therapy on cognitive function in women: a critical review of the literature [abstract]. *Database Abstr Rev Effects.* 2011(2). Exclusion code: 7

Centre for Reviews and Dissemination. Combined continuous hormone replacement therapy: a critical review [abstract]. *Database Abstr Rev Effects.* 2011(2). Exclusion code: 7

Centre for Reviews and Dissemination. Brief report: coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis [abstract]. *Database Abstr Rev Effects.* 2011(2). Exclusion code: 7

Centre for Reviews and Dissemination. Association between hormone replacement therapy and subsequent stroke: a meta-analysis [abstract]. *Database Abstr Rev Effects.* 2011(2). Exclusion code: 7

Cerquetani E, Vitale C, Mercuro G, et al. Comparative vascular effects of hormone replacement therapy and raloxifene in women at increased cardiovascular risk. *Gynecol Endocrinol.* 2004;18(6):291-298. Exclusion code: 11

Chan WS, Ray J, Wai EK, et al. Risk of stroke in women exposed to low-dose oral contraceptives: a critical evaluation of the evidence. *Arch Intern Med.* 2004;164(7):741-747. Exclusion code: 4

Chang C, Lin CH. Hormone replacement therapy and menopause: a review of randomized, double-blind, placebo-controlled trials. *Kaohsiung J Med Sci.* 2003;19(6):257-270. Exclusion code: 7

Chao HT, Kuo CD, Su YJ, et al. Short-term effect of transdermal estrogen on autonomic nervous modulation in postmenopausal women. *Fertil Steril.* 2005;84(5):1477-1483. Exclusion code: 11

Chen CL, Weiss NS, Newcomb P, et al. Hormone replacement therapy in relation to breast cancer. *JAMA.* 2002;287(6):734-741. Exclusion code: 6

Chen WY, Colditz GA, Rosner B, et al. Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. *Ann Intern Med.* 2002;137(10):798-804. Exclusion code: 9

Chen WY, Manson JE , Hankinson SE, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med.* 2006;166:1027-1032. Exclusion code: 6

Cheung AM, Feig DS, Kapral M, et al. Prevention of osteoporosis and osteoporotic fractures in postmenopausal women: recommendation statement from the Canadian Task Force on Preventive Health Care. *CMAJ.* 2004;170(11):1665-1667. Exclusion code: 2

Chlebowski RT. Menopausal hormone therapy, hormone receptor status, and lung cancer in women. *Semin Oncol.* 2009;36(6):566-571. Exclusion code: 7

Appendix B6. List of Excluded Full-Text Articles

Chlebowski RT, Anderson G, Manson JE, et al. Estrogen alone in postmenopausal women and breast cancer detection by means of mammography and breast biopsy. *J Clin Oncol.* 2010;28(16):2690-2697. Exclusion code: 12

Chlebowski RT, Anderson GL, Lane DS, et al. Predicting risk of breast cancer in postmenopausal women by hormone receptor status. *J Natl Cancer Inst.* 2007;99(22):1695-1705. Exclusion code: 5

Chlebowski RT, Schwartz AG, Wakelee H, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. *Lancet.* 2009;374(9697):1243-1251. Exclusion code: 12

Cho L, Mukherjee D. Hormone replacement therapy and secondary cardiovascular prevention: a meta-analysis of randomized trials. *Cardiology.* 2005;104(3):143-147. Exclusion code: 8

Chou ET, Schulman SP, Thiemann DR, et al. Effect of short-term estrogen with and without progesterone therapy on circulating markers of endothelial activation and injury in postmenopausal women with unstable angina pectoris. *Am J Cardiol.* 2003;91(10):1240-1242. Exclusion code: 11

Christodoulakos G, Panoulis C, Kouskouni E, et al. Effects of estrogen-progestin and raloxifene therapy on nitric oxide, prostacyclin and endothelin-1 synthesis. *Gynecol Endocrinol.* 2002;16(1):9-17. Exclusion code: 11

Cirillo DJ, Wallace RB, Wu L, Yood RA. Effect of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative. *Arthritis Rheum.* 2006;54(10):3194-3204. Exclusion code: 11

Clarke SC, Kelleher J, Lloyd-Jones H, et al. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT atherosclerosis study. *BJOG.* 2002;109(9):1056-1062. Exclusion code: 8

Close P, Neuprez A, Reginster JY. Developments in the pharmacotherapeutic management of osteoporosis. *Expert Opin Pharmacother.* 2006;7(12):1603-1615. Exclusion code: 4

Cody JD, Richardson K, Moehrer B, et al. Oestrogen therapy for urinary incontinence in post-menopausal women. *Cochrane Database Syst Rev.* 2009(4):CD001405. Exclusion code: 8

Coker LH, Espeland MA, Rapp SR, et al. Postmenopausal hormone therapy and cognitive outcomes: the Women's Health Initiative Memory Study (WHIMS). *J Steroid Biochem Mol Biol.* 2010;118(4-5):304-310. Exclusion code: 12

Coker LH, Hogan PE, Bryan NR, et al. Postmenopausal hormone therapy and subclinical cerebrovascular disease: the WHIMS-MRI Study. *Neurology.* 2009;72(2):125-134. Exclusion code: 11

Col NF, Bowlby LA, McGarry K. The role of menopausal hormone therapy in preventing osteoporotic fractures: a critical review of the clinical evidence. *Minerva Med.* 2005;96(5):331-342. Exclusion code: 7

Col NF, Pauker SG. The discrepancy between observational studies and randomized trials of menopausal hormone therapy: did expectations shape experience? *Ann Intern Med.* 2003;139(11):923-929.

Appendix B6. List of Excluded Full-Text Articles

Exclusion code: 7

Colenda CC, Legault C, Rapp SR, et al. Psychiatric disorders and cognitive dysfunction among older, postmenopausal women: results from the Women's Health Initiative Memory Study. *Am J Geriatr Psychiatry.* 2010;18(2):177-186. Exclusion code: 6

Collins JA, Blake JM, Crosignani PG. Breast cancer risk with postmenopausal hormonal treatment. *Hum Reprod Update.* 2005;11(6):545-560. Exclusion code: 5

Collins P. Risk factors for cardiovascular disease and hormone therapy in women. *Heart.* 2006;92(Suppl III):iii24-28. Exclusion code: 7

Committee on Safety of Medicines. Further advice on safety of HRT: risk:benefit unfavourable for first-line use in prevention of osteoporosis. *Medicines and Healthcare Products Regulatory Agency.* 2003. Exclusion code: 7

Compston J. How to manage osteoporosis after the menopause. *Baillieres Best Pract Res Clin Rheumatol.* 2005;19(6):1007-1019. Exclusion code: 7

Compston JE, Watts NB. Combination therapy for postmenopausal osteoporosis. *Clin Endocrinol.* 2002;56(5):565-569. Exclusion code: 9

Conner P, Soderqvist G, Skoog L, et al. Breast cell proliferation in postmenopausal women during HRT evaluated through fine needle aspiration cytology. *Breast Cancer Res Treat.* 2003;78(2):159-165. Exclusion code: 11

Corson SL. HRT: forever or never? *Int J Fertil Womens Med.* 2002;47(4):150-151. Exclusion code: 7

Cosman F, Baz-Hecht M, Cushman M, et al. Short-term effects of estrogen, tamoxifen and raloxifene on hemostasis: a randomized-controlled study and review of the literature. *Thromb Res.* 2005;116(1):1-13. Exclusion code: 11

Couzin J. Estrogen research. The great estrogen conundrum. *Science.* 2003;302(5648):1136-1138. Exclusion code: 7

Cowley G, Springen K. Reconsidering HRT. *Newsweek.* 2002;139(17):71. Exclusion code: 7

Craig MC, Maki PM, Murphy DG. The Women's Health Initiative Memory Study: findings and implications for treatment. *Lancet Neurol.* 2005;4(3):190-194. Exclusion code: 12

Crandall C. Combination treatment of osteoporosis: a clinical review. *J Womens Health Gend Based Med.* 2002;11(3):211-224. Exclusion code: 7

Crandall C. Low-dose estrogen therapy for menopausal women: a review of efficacy and safety. *J Womens Health.* 2003;12(8):723-747. Exclusion code: 7

Crandall CJ, Aragaki AK, Chlebowski RT, et al. New-onset breast tenderness after initiation of estrogen plus progestin therapy and breast cancer risk. *Arch Intern Med.* 2009;169(18):1684-1691. Exclusion code: 11

Cranney A, Guyatt G, Griffith L, et al. Meta-analyses of therapies for postmenopausal osteoporosis, IX: summary of meta-analyses of therapies for

postmenopausal osteoporosis. *Endocr Rev.* 2002;23(4):570-578. Exclusion code: 7

Creasman WT. Breast cancer: the role of hormone therapy. *Semin Reprod Med.* 2005;23(2):167-171. Exclusion code: 7

Csizmadi I, Collet JP, Benedetti JF, Hanley JA. The effect of transdermal and oral oestrogen replacement therapy on colorectal cancer risk in postmenopausal women. *Br J Cancer.* 2004;90:76-81. Exclusion code: 6

Cummings SR, Karpf DB, Harris F, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. *Am J Med.* 2002;112(4):281-289. Exclusion code: 9

Cutolo M, Sulli A, Seriolo B. Estrogens, autoimmunity and the heart. *Lupus.* 2005;14(9):675-678. Exclusion code: 11

Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast-cancer prevention trials. *Lancet.* 2003;361(9354):296-300. Exclusion code: 4

Czlonkowska A, Ciesielska A, Joniec I. Influence of estrogens on neurodegenerative processes. *Med Sci Monit.* 2003;9(10):RA247-256. Exclusion code: 7

Dalal D, Robbins JA. Management of hyperlipidemia in the elderly population: an evidence-based approach. *South Med J.* 2002;95(11):1255-1261. Exclusion code: 7

Davey DA. Menopause and HRT—keeping perspective. *S Afr Med J*. 2004;94(1):23-25. Exclusion code: 7

Davis SR, Stuckey BG, Norman RJ, et al. Effects of the route of estrogen administration on insulinlike growth factor-I, IGF binding protein-3, and insulin resistance in healthy postmenopausal women: results from a randomized, controlled study. *Menopause.* 2008;15(6):1065-1069. Exclusion code: 11

Day A. Lessons from the Women's Health Initiative: primary prevention and gender health. *CMAJ.* 2002;167(4):361-362. Exclusion code: 7

de Klerk BM, Schiphof D, Groeneveld FP, et al. Limited evidence for a protective effect of unopposed oestrogen therapy for osteoarthritis of the hip: a systematic review. *Rheumatology (Oxford).* 2009;48:104-112. Exclusion code: 7

de Kraker AT, Kenemans P, Smolders RG, et al. Short-term effects of two continuous combined oestrogen-progestogen therapies on several cardiovascular risk markers in healthy postmenopausal women: a randomised controlled trial. *Eur J Obstet Gynecol Reprod Biol.* 2009;142(2):139-144. Exclusion code: 11

de Villiers T. The role of menopausal hormone therapy in osteoporosis. *Climacteric.* 2007;10(Suppl 2):71-73. Exclusion code: 7

de Villiers TJ. Bone health and osteoporosis in postmenopausal women. *Best Pract Res Clin Obstet Gynaecol.* 2009;23(1):73-85. Exclusion code: 7

Decensi A, Bonanni B, Baglietto L, et al. A two-by-two factorial trial comparing oral with transdermal estrogen therapy and fenretinide with placebo on breast cancer biomarkers. *Clin Cancer Res.* 2004;10(13):4389-4397. Exclusion code: 11

Decensi A, Omodei U, Robertson C, et al. Effect of transdermal estradiol and oral

conjugated estrogen on C-reactive protein in retinoid-placebo trial in healthy women. *Circulation.* 2002;106(10):1224-1228. Exclusion code: 11

Dehn B. Care of the menopausal patient: a nurse practitioner's view. *J Am Acad Nurse Pract.* 2007;19(8):427-437. Exclusion code: 7

Denes P, Larson JC, Lloyd-Jones DM, et al. Major and minor ECG abnormalities in asymptomatic women and risk of cardiovascular events and mortality. *JAMA.* 2007;297(9):978-985. Exclusion code: 11

Deo R, Lin F, Vittinghoff E, et al. Kidney dysfunction and sudden cardiac death among women with coronary heart disease. *Hypertension.* 2008;51(6):1578-1582. Exclusion code: 11

Derman RJ. Estrogens and bone. *Int J Fertil Womens Med.* 2003;48(3):102-105. Exclusion code: 7

Derry PS. Time trends in the HERS secondary prevention trial: much ado about nothing? *J Am Med Womens Assoc.* 2002;57(4):215-216. Exclusion code: 7

Dezarnaulds G, Fraser IS. Vaginal ring delivery of hormone replacement therapy: a review. *Expert Opin Pharmacother.* 2003;4:201-212. Exclusion code: 7

Di Carlo C, Tommaselli GA, Sammartino A, et al. Serum leptin levels and body composition in postmenopausal women: effects of hormone therapy. *Menopause.* 2004;11(4):466-473. Exclusion code: 11

Diamanti-Kandarakis E. Hormone replacement therapy and risk of malignancy. *Curr Opin Obstet Gynecol.* 2004;16(1):73-78. Exclusion code: 7

Dick SE, DeWitt DE, Anawalt BD. Postmenopausal hormone replacement therapy and major clinical outcomes: a focus on cardiovascular disease, osteoporosis, dementia, and breast and endometrial neoplasia. *Am J Manag Care.* 2002;8(1):95-104; quiz 105-106. Exclusion code: 6

Dimai HP, Pietschmann P, Resch H, et al. Guidelines for drug therapy of postmenopausal osteoporosis. *Wien Med Wochenschr.* 2002;152(23-24):596-612. Exclusion code: 10

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

Doherty JA, Cushing-Haugen KL, Saltzman BS, et al. Long-term use of postmenopausal estrogen and progestin hormone therapies and the risk of endometrial cancer. *Am J Obstet Gynecol.* 2007;197:139.e131-7. Exclusion code: 6

Doren M. Estrogen therapy for prevention and treatment of osteoporosis. *Maturitas.* 2002;43(Suppl 1):S53-56. Exclusion code: 7

Doty TJ. Postmenopausal hormone replacement therapy after the Women's Health Initiative. *JAAPA.* 2005;18(1):30-37. Exclusion code: 7

Duan DH. Different dose hormone-replacement therapy in treatment of postmenopausal osteoporosis. *Acta Acad Med Shanghai.* 2003;30(5):477-479. Exclusion code: 11

Dubey RK, Imthurn B, Barton M, Jackson EK. Vascular consequences of menopause

and hormone therapy: importance of timing of treatment and type of estrogen. *Cardiovasc Res.* 2005;66(2):295-306. Exclusion code: 11

Dubey RK, Tofovic SP, Jackson EK. Cardiovascular pharmacology of estradiol metabolites. *J Pharmacol Exp Ther.* 2004;308(2):403-409. Exclusion code: 11

Dull P. Hormone replacement therapy. *Prim Care.* 2006;33(4):953-963. Exclusion code: 7

Dumas J, Hancur-Bucci C, Naylor M, et al. Estrogen treatment effects on anticholinergic-induced cognitive dysfunction in normal postmenopausal women. *Neuropsychopharmacology.* 2006;31(9):2065-2078. Exclusion code: 13

Dumas J, Hancur-Bucci C, Naylor M, et al. Estradiol interacts with the cholinergic system to affect verbal memory in postmenopausal women: evidence for the critical period hypothesis. *Horm Behav.* 2008;53(1):159-169. Exclusion code: 14

Dumas JA, Kutz AM, Naylor MR, et al. Increased memory load-related frontal activation after estradiol treatment in postmenopausal women. *Horm Behav.* 2010;58(5):929-935. Exclusion code: 11

Dunkin J, Rasgon N, Zeller M, et al. Estrogen replacement and cognition in postmenopausal women: effect of years since menopause on response to treatment. *Drug Dev Res.* 2005;66(2):150-159. Exclusion code: 13

Duvernoy C, Martin J, Briesmiester K, et al. Myocardial blood flow and flow reserve in response to hormone therapy in postmenopausal women with risk factors for coronary disease. *J Clin Endocrinol Metab.* 2004;89(6):2783-2788. Exclusion code: 11

Duvernoy CS, Rose PA, Kim HM, et al. Combined continuous ethinyl estradiol/ norethindrone acetate does not improve forearm blood flow in postmenopausal women at risk for cardiovascular events: a pilot study. *J Womens Health.* 2007;16(7):963-970. Exclusion code: 11

Edinburgh RCoPo. Consensus Conference on Hormone Replacement Therapy. 2003. Exclusion code: 7

Edmonds MJ, Crichton TJ, Runciman WB, Pradhan M. Evidence-based risk factors for postoperative deep vein thrombosis. *ANZ J Surg.* 2004;74(12):1082-1097. Exclusion code: 5

Eichner SF, Lloyd KB, Timpe EM. Comparing therapies for postmenopausal osteoporosis prevention and treatment. *Ann Pharmacother.* 2003;37(5):711-724. Exclusion code: 7

Eilertsen AL, Qvigstad E, Andersen TO, et al. Conventional-dose hormone therapy (HT) and tibolone, but not low-dose HT and raloxifene, increase markers of activated coagulation. *Maturitas.* 2006;55(3):278-287. Exclusion code: 11

Enserink M. Women's health. The vanishing promises of hormone replacement. *Science.* 2002;297(5580):325-326. Exclusion code: 7

Espeland MA, Tindle HA, Bushnell CA, et al. Brain volumes, cognitive impairment, and conjugated equine estrogens. *J Gerontol A Biol Sci Med Sci.* 2009;64(12):1243-1250. Exclusion code: 11

Espie M, Daures JP, Chevallier T, et al. Breast cancer incidence and hormone

replacement therapy: results from the MISSION study, prospective phase. *Gynecol Endocrinol.* 2007;23(7):391-397. Exclusion code: 6

Evio S, Pekkarinen T, Sintonen H, et al. The effect of hormone therapy on the health-related quality of life in elderly women. *Maturitas.* 2007;56(2):122-128. Exclusion code: 5

Fait T, Vrablik M, Zizka Z, Kostirova M. Changes in hemostatic variables induced by estrogen replacement therapy: comparison of transdermal and oral administration in a crossover-designed study. *Gynecol Obstet Invest.* 2008;65(1):47-51. Exclusion code: 11

Farag NH, Mahata M, Ziegler MG, et al. Hormone replacement therapy increases renal kallikrein excretion in healthy postmenopausal women. *Life Sci.* 2003;72(11):1279-1288. Exclusion code: 11

Farag NH, Nelesen RA, Parry BL, et al. Autonomic and cardiovascular function in postmenopausal women: the effects of estrogen versus combination therapy. *Am J Obstet Gynecol.* 2002;186(5):954-961. Exclusion code: 11

Farquhar C, Marjoribanks J, Lethaby A, et al. Long term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev.* 2009(2):CD004143. Exclusion code: 12

Feigin VL, Rinkel GJ, Lawes CM, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke.* 2005;36(12):2773-2780. Exclusion code: 7

Fenkci V, Yilmazer M, Alpaslan M, et al. The short-term effects of different regimens of hormone replacement therapy on left ventricular structure and performance in healthy postmenopausal women: a prospective, controlled echocardiographic study. *Gynecol Obstet Invest.* 2003;55(3):139-144. Exclusion code: 9

Fenton A, Panay N. Communication: do we have a problem? *Climacteric.* 2008;11(4):265-266. Exclusion code: 7

Fenton A, Panay N. Hormone therapy and colorectal cancer. *Climacteric.* 2009;12(2):89-90. Exclusion code: 7

Fernandez H, Lucas C, Hedon B, et al. One year comparison between two add-back therapies in patients treated with a GnRH agonist for symptomatic endometriosis: a randomized double-blind trial. *Human Reproduction.* 2004;19(6):1465-1471. Exclusion code: 8

File SE, Heard JE, Rymer J. Trough oestradiol levels associated with cognitive impairment in post-menopausal women after 10 years of oestradiol implants. *Psychopharmacology (Berl).* 2002;161(1):107-112. Exclusion code: 6

Fillit HM. The role of hormone replacement therapy in the prevention of Alzheimer disease. *Arch Intern Med.* 2002;162:1934-1942. Exclusion code: 7

Fink K, Clark B. Screening for osteoporosis in postmenopausal women. *Am Fam Physician.* 2004;69(1):139-140. Exclusion code: 7

Fletcher SW, Colditz GA. Failure of estrogen plus progestin therapy for prevention. *JAMA.* 2002;288:366-368. Exclusion code: 7

Appendix B6. List of Excluded Full-Text Articles

Folsom AR, Anderson JP, Ross JA. Estrogen replacement therapy and ovarian cancer. *Epidemiology.* 2004;15(1):100-104. Exclusion code: 6

Freda MC. What a surprise. *MCN Am J Matern Child Nurs.* 2007;32(3):137. Exclusion code: 7

Freeman EE, Munoz B, Bressler SB, West SK. Hormone replacement therapy, reproductive factors, and age-related macular degeneration: the Salisbury eye evaluation project. *Ophthalmic Epidemiol.* 2005;12:37-45. Exclusion code: 6

Frye CA. Steroids, reproductive endocrine function, and cognition: a review. *Minerva Ginecol.* 2009;61(6):563-585. Exclusion code: 7

Fuchs FD. Hormonal replacement and cardiovascular disease: a guideline against the evidence. *Arq Bras Cardiol.* 2009;93(1):e11-13. Exclusion code: 10

Fugh-Berman A, Scialli AR. Gynecologists and estrogen: an affair of the heart. *Perspect Biol Med.* 2006;49(1):115-130. Exclusion code: 7

Furberg CD, Vittinghoff E, Davidson M, et al. Subgroup interactions in the Heart and Estrogen/Progestin Replacement Study: lessons learned. *Circulation.* 2002;105(8):917-922. Exclusion code: 6

Furness S, Roberts H, Marjoribanks J, et al. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *Cochrane Database Syst Rev.* 2009(2):CD000402. Exclusion code: 11

Fylstra DL. Postmenopausal hormone replacement therapy: does the progestin make a difference? *J S C Med Assoc.* 2002;98(1):12-19. Exclusion code: 4

Gabriel SR, Carmona L, Roque M, et al. Hormone replacement therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev.* 2005(2):CD002229. Exclusion code: 12

Gabriel-Cox K. Hormone replacement therapy and primary prevention: alas, again. *Prev Cardiol.* 2003;6(1):61-62. Exclusion code: 7

Gallus S, Negri E, Chatenoud L, et al. Post-menopausal hormonal therapy and gallbladder cancer risk. *Int J Cancer.* 2002;99:762-763. Exclusion code: 6

Gambacciani M, Genazzani AR. The missing R. *Gynecol Endocrinol.* 2003;17(2):91-94. Exclusion code: 7

Gambacciani M, Monteleone P, Sacco A, Genazzani AR. Hormone replacement therapy and endometrial, ovarian and colorectal cancer. *Baillieres Best Pract Res Clin Endocrinol Metab.* 2003;17:139-147. Exclusion code: 7

Gambone JC. How we got to the Women's Health Initiative hormone replacement trial. *J Am Osteopath Assoc.* 2003;103(2 Suppl 2):S1-2. Exclusion code: 7

Gami AS, Wright S, Ballman KV, et al. Hormone replacement therapy and risk of acute myocardial infarction in postmenopausal women with diabetes mellitus. *Am J Cardiol.* 2003;91:1275-1277. Exclusion code: 6

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

regression analysis. *Maturitas.* 2004;47(3):175-183. Exclusion code: 7

Garbe E, Suissa S. Hormone replacement therapy and acute coronary outcomes: methodological issues between randomized and observational studies. *Human Reproduction.* 2004;19(1):8-13. Exclusion code: 7

Garnero P, Jamin C, Benhamou CL, et al. Effects of tibolone and combined 17β-estradiol and norethisterone acetate on serum C-reactive protein in healthy post-menopausal women: a randomized trial. *Human Reproduction.* 2002;17(10):2748-2753. Exclusion code: 4

Gatto NM, Hodis HN, Liu CR, et al. Brachial artery vasoreactivity is associated with cross-sectional and longitudinal anatomical measures of atherosclerosis in postmenopausal women with coronary artery disease. *Atherosclerosis.* 2008;196(2):674-681. Exclusion code: 11

Genazzani AR, Gambacciani M. A personal initiative for women's health: to challenge the Women's Health Initiative. *Gynecol Endocrinol.* 2002;16(4):255-257. Exclusion code: 7

Genazzani AR, Gambacciani M, Schneider HP, et al. Postmenopausal osteoporosis: therapeutic options. *Climacteric.* 2005;8(2):99-109. Exclusion code: 7

Giangregorio L, Papaioannou A, Cranney A, et al. Fragility fractures and the osteoporosis care gap: an international phenomenon. *Semin Arthritis Rheum.* 2006;35(5):293-305. Exclusion code: 5

Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation.* 2003;107(1):149-158. Exclusion code: 7

Gibson CL, Gray LJ, Murphy SP, Bath PM. Estrogens and experimental ischemic stroke: a systematic review. *J Cereb Blood Flow Metab.* 2006;26(9):1103-1113. Exclusion code: 3

Giersig C. Progestin and breast cancer. The missing pieces of a puzzle. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz.* 2008;51(7):782-786. Exclusion code: 7

Girdler SS, Hinderliter AL, Wells EC, et al. Transdermal versus oral estrogen therapy in postmenopausal smokers: hemodynamic and endothelial effects. *Obstet Gynecol.* 2004;103(1):169-180. Exclusion code: 11

Glud E, Kjaer SK, Thomsen BL, et al. Hormone therapy and the impact of estrogen intake on the risk of ovarian cancer. *Arch Intern Med.* 2004;164:2253-2259. Exclusion code: 6

Goderie-Plomp HW, van der Klift M, de Ronde W, et al. Endogenous sex hormones, sex-hormone binding globulin, and the risk of incident vertebral fractures in elderly men and women: the Rotterdam study. *J Clin Endocrinol Metab.* 2004;89(7):3261-3269. Exclusion code: 6

Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease

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

Goldzieher JW. Hormone replacement therapy and the Women's Health Initiative: the emperor has no clothes. *Endocr Pract.* 2004;10(5):448-449. Exclusion code: 7

Gomberg-Maitland M, Wenger NK, Feyzi J, et al. Anticoagulation in women with non-valvular atrial fibrillation in the stroke prevention using an oral thrombin inhibitor (SPORTIF) trials. *Eur Heart J.* 2006;27(16):1947-1953. Exclusion code: 4

Gompel A, Plu-Bureau G. Is the decrease in breast cancer incidence related to a decrease in postmenopausal hormone therapy? *Ann N Y Acad Sci.* 2010;1205:268-276. Exclusion code: 7

Gorins A. Progestins and risk of breast cancer. Much ado about nothing? *Eur J Gynaecol Oncol.* 2003;24(5):345-350. Exclusion code: 7

Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA.* 2002;288(1):49-57. Exclusion code: 2

Graff-Iversen S, Hammar N, Thelle DS, Tonstad S. Hormone therapy and mortality during a 14-year follow-up of 14,324 Norwegian women. *J Intern Med.* 2004;256(5):437-445. Exclusion code: 6

Greenspan SL, Resnick NM, Parker RA. Early changes in biochemical markers of bone turnover are associated with long-term changes in bone mineral density in elderly women on alendronate, hormone replacement therapy, or combination therapy: a three-year, double-blind, placebo-controlled, randomized clinical trial. *J Clin Endocrinol Metab.* 2005;90(5):2762-2767. Exclusion code: 11

Greenspan SL, Resnick NM, Parker RA. The effect of hormone replacement on physical performance in community-dwelling elderly women. *Am J Med.* 2005;118(11):1232-1239. Exclusion code: 9

Greiser CM, Greiser EM, Doren M. Menopausal hormone therapy and risk of breast cancer: a meta-analysis of epidemiological studies and randomized controlled trials. *Hum Reprod Update.* 2005;11(6):561-573. Exclusion code: 7

Greiser CM, Greiser EM, Doren M. Menopausal hormone therapy and risk of ovarian cancer: systematic review and meta-analysis. *Hum Reprod Update.* 2007;13(5):453-463. Exclusion code: 6

Grodstein F, Manson J, Stampfer M, Rexrode KM. Postmenopausal hormone therapy and stroke: role of time since menopause and age at intiation of hormone therapy. *Arch Intern Med.* 2008;168:861-866. Exclusion code: 6

Grodstein F, Manson JE, Stampfer M. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. *J Womens Health.* 2006;15:35-44. Exclusion code: 9

Guaschino S, Grimaldi E, Sartore A, et al. Visual function in menopause: the role of

hormone replacement therapy. *Menopause.* 2003;10(1):53-57. Exclusion code: 11

Guay MP, Dragomir A, Pilon D, et al. Changes in pattern of use, clinical characteristics and persistence rate of hormone replacement therapy among postmenopausal women after the WHI publication. *Pharmacoepidemiol Drug Saf.* 2007;16(1):17-27. Exclusion code: 6

Guvenal T, Durna A, Erden O, et al. Effects of different postmenopausal hormone therapy regimens on cerebral blood flow and cognitive functions. *Adv Ther.* 2009;26(8):805-811. Exclusion code: 14

Hachul H, Bittencourt LR, Andersen ML, et al. Effects of hormone therapy with estrogen and/or progesterone on sleep pattern in postmenopausal women. *Int J Gynaecol Obstet.* 2008;103(3):207-212. Exclusion code: 5

Hale G, Paul-Labrador M, Dwyer JH, Merz CN. Isoflavone supplementation and endothelial function in menopausal women. *Clin Endocrinol (Oxf).* 2002;56(6):693-701. Exclusion code: 4

Hamada AL, Maruo T, Samoto T, et al. Estradiol/progesterone-releasing vaginal rings for hormone replacement therapy in postmenopausal women. *Gynecol Endocrinol.* 2003;17:247-254. Exclusion code: 5

Harman SM, Vittinghoff E, Brinton EA, et al. Timing and duration of menopausal hormone treatment may affect cardiovascular outcomes. *Am J Med.* 2011;124(3):199-205. Exclusion code: 7

Heinrich AB, Wolf OT. Investigating the effects of estradiol or estradiol/progesterone treatment on mood, depressive symptoms, menopausal symptoms and subjective sleep quality in older healthy hysterectomized women: a questionnaire study. *Neuropsychobiology.* 2005;52(1):17-23. Exclusion code: 5

Hellgren M, Conard J, Norris L, Kluft C. Cardiovascular risk markers during treatment with estradiol and trimegestone or dydrogesterone. *Maturitas.* 2009;62(3):287-293. Exclusion code: 11

Henderson VW. Aging, estrogens, and episodic memory in women. *Cogn Behav Neurol.* 2009;22(4):205-214. Exclusion code: 7

Henderson VW. Action of estrogens in the aging brain: dementia and cognitive aging. *Biochim Biophys Acta.* 2010;1800(10):1077-1083. Exclusion code: 7

Hernandez-Avila M, Liang MH, Willett WC, et al. Exogenous sex hormones and the risk of rheumatoid arthritis. *Arthritis Rheum.* 1990;33(947-953). Exclusion code: 6

Hirai K, Tsuda H. Estrogen and urinary incontinence. *Int J Urol.* 2009;16(1):45-48. Exclusion code: 7

Hogervorst E, Bandelow S. Sex steroids to maintain cognitive function in women after the menopause: a meta-analyses of treatment trials. *Maturitas.* 2010;66(1):56-71. Exclusion code: 8

Hogervorst E, Yaffe K, Richards M, Huppert F. Hormone replacement therapy to maintain cognitive function in women with dementia. *Cochrane Database Syst Rev.* 2002(3):CD003799. Exclusion code: 12

Hoibraaten E, Qvigstad E, Arnesen H, et al. Increased risk of recurrent venous thromboembolism during hormone

replacement therapy: results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). *Thromb Haemost.* 2000;84(6):961-967. Exclusion code: 8

Howell A, Evans GD. Hormone replacement therapy and breast cancer. *Recent Results Cancer Res.* 2011;188:115-124. Exclusion code: 7

Hsia J, Alderman EL, Verter JI, et al. Women's angiographic vitamin and estrogen trial: design and methods. *Control Clin Trials.* 2002;23(6):708-727. Exclusion code: 7

Hsia J, Criqui MH, Herrington DM, et al. Conjugated equine estrogens and peripheral arterial disease risk: the Women's Health Initiative. *Am Heart J.* 2006;152(1):170-176. Exclusion code: 12

Huang AJ, Ettinger B, Vittinghoff E, et al. Endogenous estrogen levels and the effects of ultra-low-dose transdermal estradiol therapy on bone turnover and BMD in postmenopausal women. *J Bone Miner Res.* 2007;22(11):1791-1797. Exclusion code: 11

Humphrey LL. Hormone Replacement Therapy and Breast Cancer. *Agency for Healthcare Research and Quality.* 2002. Exclusion code: 2

Humphrey LL, Chan BK, Sox HC. Postmenopausal hormone replacement therapy and the primary prevention of cardiovascular disease. *Ann Intern Med.* 2002;137(4):273-284. Exclusion code: 12

Humphrey LL, Takano LM, Chan BK. Postmenopausal Hormone Replacement Therapy and Cardiovascular Disease. *U.S. Preventive Services Task Force.* 2002. Exclusion code: 2

Hundrup YA, Hoidrup S, Ekholm O, et al. Risk of low-energy hip, wrist, and upper arm fractures among current and previous users of hormone replacement therapy: the Danish nurse cohort study. *Eur J Epidemiol.* 2004;19(12):1089-1095. Exclusion code: 6

Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, bisphosphonates, calcitonin, vitamin D and vitamin K in postmenopausal women with osteoporosis. *J Bone Min Res.* 2002;18(Suppl 2):S158. Exclusion code: 4

Ishida Y, Kawai S. A two-year randomized controlled trial of hormone replacement therapy, etidronate, calcitonin, vitamin D, or vitamin K, in women with postmenopausal osteoporosis. *J Bone Min Res.* 2002;17(Suppl 1):S478. Exclusion code: 11

Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, vitamin D and vitamin K in postmenopausal osteoporosis. *Bone.* 2003;33(5 Suppl 1):S220. Exclusion code: 7

Ishida Y, Soh H, Tsuchida S, et al. Effectiveness of hormone replacement therapy, etidronate, calcitonin, vitamin D, and vitamin K in postmenopausal women with osteoporosis. *Bone.* 2002;3(Suppl):S50. Exclusion code: 7

Janicka K. The influence of hormone therapy upon cognitive style and depression in menopausal women. *Przegl Menopauz.* 2008;7(2):61-68. Exclusion code: 5

Joffe H. The impact of estrogen therapy on cognition in perimenopausal and postmenopausal women. 2001. Exclusion code: 7

Joffe H, Hall JE, Gruber S, et al. Estrogen therapy selectively enhances prefrontal

cognitive processes: a randomized, double-blind, placebo-controlled study with functional magnetic resonance imaging in perimenopausal and recently postmenopausal women. *Menopause.* 2006;13(3):411-422. Exclusion code: 13

John SC, Malcolm W. Oral versus non-oral hormone replacement therapy: how important is the route of administration? *Ginekol Pol.* 2007;78(7):514-520. Exclusion code: 7

Johnson JR, Lacey JV Jr, Lazovich D, et al. Menopausal hormone therapy and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev.* 2009;18(1):196-203. Exclusion code: 6

Kang JH, Weuve J, Grodstein F. Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. *Neurology.* 2004;63(1):101-107. Exclusion code: 6

Karakorpi M, Alhola P, Urrila AS, et al. Hormone treatment gives no benefit against cognitive changes caused by acute sleep deprivation in postmenopausal women. *Neuropsychopharmacology.* 2006;31(9):2079-2088. Exclusion code: 8

Katzman R, Brown R, Fuld P, et al. Validation of a short Orientation-Memory Concentration Test of cognitive impairment. *Am J Psychiatry.* 1983;140:734-739. Exclusion code: 7

Kesslak JP. Can estrogen play a significant role in the prevention of Alzheimer's disease? *J Neural Transm Suppl.* 2002;Supplementum.(62):227-239. Exclusion code: 7

Khan MA, Hlatky MA, Liu MW, et al. Effect of postmenopausal hormone therapy on coronary heart disease events after percutaneous transluminal coronary angioplasty. *Am J Cardiol.* 2003;91(8):989-991. Exclusion code: 8

Kirsh V, Kreiger N. Estrogen and estrogen-progestrin replacement therapy and risk of postmenopausal breast cancer in Canada. *Cancer Causes Control.* 2002;13:583-590. Exclusion code: 6

Klein KP, Rapp SR. Women's cognitive health: postmenopausal dementia and the Women's Health Initiative memory study. *Womens Health Issues.* 2004;14(3):71-74. Exclusion code: 7

Kloosterboer HJ, Ederveen AG. Pros and cons of existing treatment modalities in osteoporosis: a comparison between tibolone, SERMs and estrogen (+/- progestogen) treatments. *J Steroid Biochem Mol Biol.* 2003;83:157-165. Exclusion code: 7

Kocoska-Maras L, Zethraeus N, Radestad AF, et al. A randomized trial of the effect of testosterone and estrogen on verbal fluency, verbal memory, and spatial ability in healthy postmenopausal women. *Fertil Steril.* 2011;95(1):152-157. Exclusion code: 4

Koh KK. Effects of estrogen on the vascular wall: vasomotor function and inflammation. *Cardiovasc Res.* 2002;55(4):714-726. Exclusion code: 7

Krikorian R, Welge J, Shidler M, et al. Estrogen therapy does not improve cognitive function in early menopause. *Fertil Steril.* 2003;80(3):S16-S17. Exclusion code: 7

Kurt M, Bekci B, Karakas S. Hormone replacement therapy and cognitive function in postmenopausal women. *Maturitas.* 2006;53(1):39-48. Exclusion code: 6

Appendix B6. List of Excluded Full-Text Articles

La Vecchia C. Menopause, hormone therapy and breast cancer risk. *Eur J Cancer Prev.* 2003;12(5):437-438. Exclusion code: 7

La Vecchia C, Gallus S, Fernandez E. Hormone replacement therapy and colorectal cancer: an update. *J Br Menopause Soc.* 2005;11(4):166-172. Exclusion code: 7

Lacey JV Jr, Kreimer AR, Buys SS, et al. Breast cancer epidemiology according to recognized breast cancer risk factors in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial cohort. *BMC Cancer.* 2009;9:84. Exclusion code: 6

Lacey JV Jr, Mink PJ, Lubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA.* 2002;288(3):334-341. Exclusion code: 6

LaCroix AZ. Estrogen with and without progestin: benefits and risks of short-term use. *Am J Med.* 2005;118(Suppl 12B):79-87. Exclusion code: 7

Lamon-Fava S, Herrington DM, Horvath KV, et al. Effect of hormone replacement therapy on plasma lipoprotein levels and coronary atherosclerosis progression in postmenopausal women according to type 2 diabetes mellitus status. *Metabolism.* 2010;59(12):1794-1800. Exclusion code: 11

Landa MC. Role of hormone replacement therapy in the prevention and treatment of menopausal osteoporosis. *An Sist Sanit Navar.* 2003;26(Suppl 3):99-105. Exclusion code: 10

Langer RD. Hormone replacement and the prevention of cardiovascular disease. *Am J Cardiol.* 2002;89(12A):36E-46E. Exclusion code: 7

Lawlor DA, Smith GD. Cardiovascular risk and hormone replacement therapy. *Curr Opin Obstet Gynecol.* 2006;18(6):658-665. Exclusion code: 7

LeBlanc ES. Hormone therapy with oestrogen or oestrogen plus progesterone decreases cognitive function in older postmenopausal women. *Evid Based Healthcare Pub Health.* 2004;8(6):398-401. Exclusion code: 7

LeBlanc ES, Chan BK, Nelson HD. Hormone Replacement Therapy and Cognition. *Agency for Healthcare Research and Quality.* 2002. Exclusion code: 2

LeBlanc ES, Janowsky J, Chan BK, Nelson HD. Hormone replacement therapy and cognition: systematic review and meta-analysis *JAMA.* 2001;285(11):1489-1499. Exclusion code: 2

Lee S, Kolonel L, Wilkens L, et al. Postmenopausal hormone therapy and breast cancer risk: the mulitethnic cohort. *Int J Cancer.* 2006;118(5):1285-1291. Exclusion code: 6

Lemaitre RN, Heckbert SR, Psaty BM, et al. Hormone replacement therapy and associated risk of stroke in postmenopausal women. *Arch Intern Med.* 2002;162(17):1954-1960. Exclusion code: 6

Lemaitre RN, Weiss NS, Smith NL, et al. Esterified estrogen and conjugated equine estrogen and the risk of incident myocardial infarction and stroke. *Arch Intern Med.* 2006;166(4):399-404. Exclusion code: 6

Lethaby A, Hogervorst E, Richards M, et al. Hormone replacement therapy for cognitive function in postmenopausal women. *Cochrane Database Syst Rev.* 2008(1). Exclusion code: 12

Appendix B6. List of Excluded Full-Text Articles

Li CL, Malone KE, Porter PL, et al. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. *JAMA.* 2003;289(24):3254-3263. Exclusion code: 6

Li WJ, Xu LZ, Liu HW, et al. Effects of Kuntai capsule and hormone replacement therapy on cognitive function and mental symptoms of early postmenopausal women: a randomized controlled trial. *Chin J Integr Med.* 2010;8(4):321-327. Exclusion code: 4

Lindsay R. Hormone therapy and osteoporosis. *Menopaus Med.* 2003;11(2):1-4. Exclusion code: 7

Lobo RA. Evaluation of cardiovascular event rates with hormone therapy in healthy, early postmenopausal women: results from 2 large clinical trials. *Arch Intern Med.* 2004;164(5):482-484. Exclusion code: 7

Lokkegard E, Jovanovic Z, Heitmann BL, et al. Increased risk of stroke in hypertensive women using hormone therapy. *Arch Neurol.* 2003;60:1379-1384. Exclusion code: 6

Low LF, Anstey KJ. Hormone replacement therapy and cognitive performance in postmenopausal women—a review by cognitive domain. *Neurosci Biobehav Rev.* 2006;30(1):66-84. Exclusion code: 7

Lyytinen H, Pukkula E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstet Gynecol.* 2006;108(6):1354-1360. Exclusion code: 6

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

Magee SR, Taylor JS. Hormone therapy in postmenopausal and perimenopausal women. *Am Fam Physician.* 2006;74(9):1501-1503. Exclusion code: 7

Magliano DJ, Rogers SL, Abramson MJ, Tonkin AM. Hormone therapy and cardiovascular disease: a systematic review and meta-analysis. *BJOG.* 2006;113(1):5-14. Exclusion code: 12

Maki PM. A systematic review of clinical trials of hormone therapy on cognitive function: effects of age at initiation and progestin use. *Ann N Y Acad Sci.* 2005;1052:182-197. Exclusion code: 12

Maki PM. Hormone therapy and cognitive function: is there a critical period for benefit? *Neuroscience.* 2006;138(3):1027-1030. Exclusion code: 7

Maki PM, Sundermann E. Hormone therapy and cognitive function. *Hum Reprod Update.* 2009;15(6):667-681. Exclusion code: 2

Manwaring P, Phoon S, Diamond T, Howes LG. Effects of hormone replacement therapy on cardiovascular responses in postmenopausal women with and without type 2 diabetes. *Maturitas.* 2002;43(3):157-164. Exclusion code: 11

Marinho RM, Soares JM Jr, Santiago RC, et al. Effects of estradiol on the cognitive function of postmenopausal women. *Maturitas.* 2008;60(3-4):230-234. Exclusion code: 9

Marsden J, A'Hern R, Whitehead M. More breast cancer findings from the Women's Health Initiative. *J Br Menopause Soc.* 2003;9(3):97-99. Exclusion code: 7

Merz CN, Olson MB, McClure C, et al. A randomized controlled trial of low-dose

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

Miller J, Chan BK, Nelson HD. Hormone Replacement Therapy and Risk of Venous Thromboembolism. *Agency for Healthcare Research and Quality.* 2002. Exclusion code: 2

Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002;136(9):680-690. Exclusion code: 12

Miller KJ, Conney JC, Rasgon NL, et al. Mood symptoms and cognitive performance in women estrogen users and nonusers and men. *J Am Geriatr Soc.* 2002;50(11):1826-1830. Exclusion code: 6

Million Women Study Collaborators. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet.* 2005;365:1543-1551. Exclusion code: 9

Montgomery Rice V. Hormone replacement therapy: optimising the dose and route of administration. *Drugs Aging.* 2002;19(11):807-818. Exclusion code: 7

Moorman PG, Schildkraut JM, Calingaert B, et al. Menopausal hormones and risk of ovarian cancer. *Am J Obstet Gynecol.* 2005;193:76-82. Exclusion code: 6

Morch LS, Lokkegaard E, Andreasen AH, et al. Hormone therapy and ovarian cancer. *JAMA.* 2009;302:298-305. Exclusion code: 6

Murkes D, Conner P, Leifland K, et al. Effects of percutaneous estradiol-oral progesterone versus oral conjugated equine estrogens-medroxyprogesterone acetate on breast cell proliferation and bcl-2 protein in healthy women. *Fertil Steril.* 2011;95(3):1188-1191. Exclusion code: 11

Naftolin F, Schneider HP, Sturdee DW, et al. Guidelines for hormone treatment of women in the menopausal transition and beyond. *Climacteric.* 2004;7(4):333-337. Exclusion code: 7

Nair GV, Chaput LA, Vittinghoff E, et al. Pulse pressure and cardiovascular events in postmenopausal women with coronary heart disease. *Chest.* 2005;127(5):1498-1506. Exclusion code: 5

Nash HA, Alvarez-Sanchez F, Mishell DR, et a;. Estradiol-delivering vaginal rings for hormone replacement therapy. *Am J Obstet Gynecol.* 1999;181:1400-1406. Exclusion code: 5

Nelson HD. Assessing benefits and harms of hormone replacement therapy: clinical applications. *JAMA.* 2002;288(7):882-884. Exclusion code: 2

Nelson HD. Hormone Replacement Therapy and Osteoporosis. *Agency for Healthcare Research and Quality.* 2002. Exclusion code: 2

Nelson HD, Helfand M, Woolf SH, Allan JD. Screening for postmenopausal osteoporosis: a review of the evidence for the U.S. Preventive Services Task Force.

Appendix B6. List of Excluded Full-Text Articles

Ann Intern Med. 2002;137:529-541. Exclusion code: 2

Nelson HD, Humphrey LL, Nygren P, et al. Postmenopausal hormone replacement therapy: scientific review. *JAMA.* 2002;288(7):872-881. Exclusion code: 2

Nelson HD, Rizzo J, Harris E, et al. Osteoporosis and fractures in postmenopausal women using estrogen *Arch Intern Med.* 2002;162:2278-2284. Exclusion code: 6

Newcomb P, Titus-Ernstoff L, Egan K, et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2002;11(7):593-600. Exclusion code: 6

Noller KL. Estrogen replacement therapy and risk of ovarian cancer. *JAMA.* 2002;288(3):368-369. Exclusion code: 7

Norbury R, Cutter WJ, Compton J, et al. The neuroprotective effects of estrogen on the aging brain. *Exp Gerontol.* 2003;38:109-117. Exclusion code: 7

North American Menopause Society. Amended report from the NAMS Advisory Panel on Postmenopausal Hormone Therapy. *Menopause.* 2003;10(1):6-12. Exclusion code: 12

North American Menopause Society. Role of progestogen in hormone therapy for postmenopausal women: position statement of the North American Menopause Society. *Menopause.* 2003;10(2):113-132. Exclusion code: 12

North American Menopause Society. The role of testosterone therapy in postmenopausal women: position statement of the North American Menopause Society. *Menopause.* 2005;12(5):496-511. Exclusion code: 4

North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of the North American Menopause Society. *Menopause.* 2010;17(2):242-255. Exclusion code: 2

North American Menopause Society. Estrogen and progestogen use in peri- and postmenopausal women: September 2003 position statement of the North American Menopause Society. *Menopause.* 2003;10(6):497-506 Exclusion code: 12

North American Menopause Society. Recommendations for estrogen and progestogen use in peri- and postmenopausal women: October 2004 position statement of the North American Menopause Society. *Menopause.* 2004;11(6):589-600. Exclusion code: 12

North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of the North American Menopause Society. *Menopause.* 2010;17(2):242-255. Exclusion code: 2

Oh JY, Barrett-Connor E, Wedick NM, Wingard DL. Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo Study. *Diabetes Care.* 2002;25(1):55-60. Exclusion code: 6

Olsson H, Ingvar C, Bladstrom A. Hormone replacement therapy containing progestins and given continuously increases breast carcinoma risk in Sweden. *Cancer.* 2003;97(6):1387-1392. Exclusion code: 6

Appendix B6. List of Excluded Full-Text Articles

Pace DT. Menopause: studying the research. *Nurse Pract.* 2006;31(8):17-23. Exclusion code: 7

Palacios S. Advances in hormone replacement therapy: making the menopause manageable. *BMC Womens Health.* 2008;8:22. Exclusion code: 7

Pan HA, Wang ST, Pai MC, et al. Cognitive function variations in postmenopausal women treated with continuous, combined HRT or tibolone: a comparison. *J Reprod Med.* 2003;48(5):375-380. Exclusion code: 4

Panay N. Hormone replacement therapy: the way forward. *J Fam Plann Reprod Health Care.* 2004;30(1):21-24. Exclusion code: 7

Panay N. New products and regimens (since 2003). *Climacteric.* 2007;10(Suppl 2):109-114. Exclusion code: 7

Panay N. Estrogen dose: the cardiovascular impact. *Climacteric.* 2009;12(Suppl 1):91-95. Exclusion code: 7

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

Park BD, Lookinland S, Beckstrand RL, Chasson S. Factor V Leiden and venous thromboembolism: risk associated with hormone replacement therapy. *J Am Acad Nurse Pract.* 2003;15(10):458-466. Exclusion code: 7

Parry BL, Meliska CJ, Martinez LF, et al. Menopause: neuroendocrine changes and hormone replacement therapy. *J Am Med Womens Assoc.* 2004;59(2):135-145. Exclusion code: 4

Parsons E, Newby LK, Bhapkar MV, et al. Postmenopausal hormone use in women with acute coronary syndromes. *J Womens Health.* 2004;13(8):863-871. Exclusion code: 8

Paschalis EP, Boskey AL, Kassem M, Eriksen EF. Effect of hormone replacement therapy on bone quality in early postmenopausal women. *J Bone Miner Res.* 2003;18(6):955-959. Exclusion code: 11

Pedersen AT, Ottesen B. Issues to debate on the Women's Health Initiative (WHI) study: epidemiology or randomized clinical trials—time out for hormone replacement therapy studies? *Human Reproduction.* 2003;18(11):2241-2244. Exclusion code: 7

Peeyananjarassri K, Baber R. Effects of low-dose hormone therapy on menopausal symptoms, bone mineral density, endometrium, and the cardiovascular system: a review of randomized clinical trials. *Climacteric.* 2005;8(1):13-23. Exclusion code: 11

Pefanco MA, Kenny AM, Kaplan RF, et al. The effect of 3-year treatment with 0.25 mg/day of micronized 17β-estradiol on cognitive function in older postmenopausal women. *J Am Geriatr Soc.* 2007;55(3):426-431. Exclusion code: 14

Peiris A, Iskandar S. Hormone replacement therapy and lipids: time to reconsider our options? *South Med J.* 2002;95(9):961-963. Exclusion code: 7

Penckofer SM, Hackbarth D, Schwertz DW. Estrogen plus progestin therapy: the cardiovascular risks exceed the benefits. *J Cardiovasc Nurs.* 2003;18(5):347-355. 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-

Appendix B6. List of Excluded Full-Text Articles

Women's Health Initiative era. *Fertil Steril.* 2009;92(4):1171-1186. Exclusion code: 7

Perrotta C, Aznar M, Mejia R, et al. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. *Cochrane Database Syst Rev.* 2009(1). Exclusion code: 8

Persad CC, Zubieta JK, Love T, et al. Enhanced neuroactivation during verbal memory processing in postmenopausal women receiving short-term hormone therapy. *Fertil Sterility.* 2009;92(1):197-204. Exclusion code: 11

Petitti D, Buckwalter JG, Crooks VC, Chiu V. Prevelance of dementia in users of hormone replacement therapy as defined by prescription data. *J Gerontol.* 2002;57A(8):M532-M538. Exclusion code: 6

Peverill RE. Hormone therapy and venous thromboembolism. *Baillieres Best Pract Res Clin Endocrinol Metab.* 2003;17:149-164. Exclusion code: 7

Phillips LS, Langer RD. Postmenopausal hormone therapy: critical reappraisal and a unified hypothesis. *Fertil Steril.* 2005;83(3):558-566. Exclusion code: 7

Pickar JH, Yeh I, Wheeler JE, et al. Endometrial effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril.* 2001;76(1):25-31. Exclusion code: 11

Pickar JH, Yeh IT, Wheeler JE, et al. Endometrial effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate: two-year substudy results. *Fertil Steril.* 2003;80(5):1234-1240. Exclusion code: 9

Pines A. WHI and aftermath: looking beyond the figures. *Maturitas.* 2005;51(1):48-50. Exclusion code: 7

Pines A, Sturdee DW, Birkhaeuser MH, et al. IMS updated recommendations on postmenopausal hormone therapy. *Climacteric.* 2007;10:181-194. Exclusion code: 2

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

Pines A, Sturdee DW, Birkhauser MH, et al. HRT in the early menopause: scientific evidence and common perceptions. *Climacteric.* 2008;11(4):267-272. Exclusion code: 7

Pines A, Sturdee DW, Birkhauser MH; International Menopause Society. Hormone therapy and cardiovascular disease in the early postmenopause: the WHI data revisited. *Climacteric.* 2007;10(3):195-196. Exclusion code: 7

Pinkerton JV, Henderson VW. Estrogen and cognition, with a focus on Alzheimer's disease. *Semin Reprod Med.* 2005;23(2):172-179. Exclusion code: 7

Pinkerton JV, Santen R. Use of alternatives to estrogen for treatment of menopause. *Minerva Endocrinol.* 2002;27(1):21-41. Exclusion code: 7

Pitkin J, Rees MC, Gray S, et al. Managing the menopause: BMS Council Consensus statement on HRT. *J Br Menopause Soc.* 2004;10(1):33-36. Exclusion code: 7

Appendix B6. List of Excluded Full-Text Articles

Pitkin J, Rees MC, Gray S, et al. Managing the menopause: British Menopause Society Council consensus statement on hormone replacement therapy. *J Br Menopause Soc.* 2005;11(4):152-156. Exclusion code: 7

Pitkin J, Rees MC, Gray S, et al. Management of premature menopause. *Menopause Int.* 2007;13(1):44-45. Exclusion code: 7

Pitkin J, Rees MC, Gray S, et al. Managing the menopause: British Menopause Society Council consensus statement on hormone replacement therapy. *J Br Menopause Soc.* 2003;9(3):129-131. Exclusion code: 7

Plonczynski DJ, Plonczynski KJ. Hormone therapy in perimenopausal and postmenopausal women: examining the evidence on cardiovascular disease risks. *J Gerontol Nurs.* 2007;33(5):48-55. Exclusion code: 7

Poirier-Solomon L. HRT: findings from the Women's Health Initiative. *Diabetes Forecast.* 2002;55(12):34-36. Exclusion code: 7

Ponzone R, Sismondi P. Selected highlights from the 27th San Antonio Breast Cancer Symposium. San Antonio, TX, USA, 8-11 December 2004. *Expert Opin Pharmacother.* 2005;6(7):1257-1267. Exclusion code: 7

Popp AW, Bodmer C, Senn C, et al. Prevention of postmenopausal bone loss with long-cycle hormone replacement therapy. *Maturitas.* 2006;53(2):191-200. Exclusion code: 11

Porch JV, Lee IM, Cook NR, et al. Estrogen-progestin replacement therapy and breast cancer risk: the Women's Health Study (United States). *Cancer Causes Control.* 2002;13(9):847-854. Exclusion code: 6

Practice Committee of the American Society for Reproductive Medicine. Estrogen and progestogen therapy in postmenopausal women. *Fertil Steril.* 2006;86(5 Suppl 1):S75-88. Exclusion code: 7

Prelevic GM, Kocjan T, Markou A. Hormone replacement therapy in postmenopausal women. *Minerva Endocrinol.* 2005;30(1):27-36. Exclusion code: 7

Prentice LL, Abramson MJ, Cicuttini FF, Wluka AA. Hormone replacement therapy for osteoarthritis in peri-menopausal and post-menopausal women. *Cochrane Database Syst Rev.* 2009(1). Exclusion code: 7

Prentice RL, Anderson GL. The Women's Health Initiative: lessons learned. *Annu Rev Public Health.* 2008;29:131-150. Exclusion code: 7

Prentice RL, Chlebowski RT, Stefanick ML, et al. Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative clinical trial and observational study. *Am J Epidemiol.* 2008;167(12):1407-1415. Exclusion code: 2

Prentice RL, Chlebowski RT, Stefanick ML, et al. Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. *Am J Epidemiol.* 2008;167(10):1207-1216. Exclusion code: 2

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

clinical trial. *Am J Epidemiol.* 2005;162(5):404-414. Exclusion code: 2

Prentice RL, Langer RD, Stefanick ML, et al. Combined analysis of Women's Health Initiative observational and clinical trial data on postmenopausal hormone treatment and cardiovascular disease. *Am J Epidemiol.* 2006;163(7):589-599. Exclusion code: 2

Prentice RL, Manson JE, Langer RD, et al. Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. *Am J Epidemiol.* 2009;170(1):12-23. Exclusion code: 2

Prentice RL, Pettinger M, Anderson GL. Statistical issues arising in the Women's Health Initiative. *Biometrics.* 2005;61(4):899-911. Exclusion code: 7

Prentice RL, Pettinger M, Beresford SA, et al. Colorectal cancer in relation to postmenopausal estrogen and estrogen plus progestin in the Women's Health Initiative clinical trial and observational study. *Cancer Epidemiol Biomarkers Prev.* 2009;18(5):1531-1537. Exclusion code: 2

Prestwood KM, Kenny AM, Kleppinger A, Kulldorff M. Ultralow-dose micronized 17β-estradiol and bone density and bone metabolism in older women: a randomized controlled trial. *JAMA.* 2003;290(8):1042-1048. Exclusion code: 11

Prisant LM. Preventing type II diabetes mellitus. *J Clin Pharmacol.* 2004;44(4):406-413. Exclusion code: 7

Rabadi MH, Blass J. Randomized clinical stroke trials in 2003. *Curr Atheroscler Rep.* 2004;6(4):257-260. Exclusion code: 7

Rabadi MH, Blass J. Randomized clinical stroke trials in 2004. *Curr Atheroscler Rep.* 2005;7(4):319-325. Exclusion code: 7

Rachon D, Teede H. Postmenopausal hormone therapy and the risk of venous thromboembolism. *Climacteric.* 2008;11(4):273-279. Exclusion code: 7

Randolph JF Jr; Women's Health Initiative Estrogen/Progestin and HERS II Trials. Be careful of what you wish for: putting the WHI estrogen/progestin and HERS II trials in perspective. *Medscape Womens Health.* 2002;7(4):7. Exclusion code: 7

Rasgon Natalie L, Dunkin J, Altshuler Lori L, Rapkin A. Estrogen-replacement therapy: cognition and depression in postmenopausal women. *155th Annual Meeting of the American Psychiatric Association.* 2002. Exclusion code: 7

Rasgon NL, Dunkin J, Altshuler LL, Rapkin A. Estrogen-replacement therapy: cognition and depression in postmenopausal women. *153rd Annual Meeting of the American Psychiatric Association.* 2000. Exclusion code: 7

Reed SD, Newton KM, Lacroix AZ. Indications for hormone therapy: the post-Women's Health Initiative era. *Endocrinol Metab Clin North Am.* 2004;33(4):691-715. Exclusion code: 7

Rees M, Stevenson J; British Menopause Society Council. Primary prevention of coronary heart disease in women. *Menopause Int.* 2008;14(1):40-45. Exclusion code: 7

Reid RL. Hormone therapy: the Women's Health Initiative has caused confusion and concern. *Fertil Steril.* 2003;80(3):491-493. Exclusion code: 7

Appendix B6. List of Excluded Full-Text Articles

Resnick SM, Coker LH, Maki PM, et al. The Women's Health Initiative Study of Cognitive Aging (WHISCA): a randomized clinical trial of the effects of hormone therapy on age-associated cognitive decline. *Clinical Trials.* 2004;1(5):440-450. Exclusion code: 7

Resnick SM, Espeland MA, Jaramillo SA, et al. Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI Study. *Neurology.* 2009;72(2):135-142. Exclusion code: 11

Resnick SM, Henderson VW. Hormone therapy and risk of Alzheimer disease. *JAMA.* 2002;288:2170-2172. Exclusion code: 7

Resnick SM, Pham DL, Kraut MA, et al. Longitudinal magnetic resonance imaging studies of older aldults: a shrinking brain. *J Neuroscience.* 2003;23(8):3295-3301. Exclusion code: 11

Richman S, Edusa V, Fadiel A, Naftolin F. Low-dose estrogen therapy for prevention of osteoporosis: working our way back to monotherapy. *Menopause.* 2006;13(1):148-155. Exclusion code: 7

Riman T, Dickman PW, Nilsson S, et al. Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in swedish women. *J Natl Cancer Inst.* 2002;94(7):497-504. Exclusion code: 6

Rivera R, Gousse A. Does postmenopausal hormone therapy cause urinary incontinence? *Nat Clin Pract Urol.* 2006;3(6):304-305. Exclusion code: 7

Rizzoli R. Osteoporosis: non-hormonal treatment. *Climacteric.* 2007;10(Suppl 2):74-78. Exclusion code: 7

Roberts H, Lethaby A. Revised key messages for hormone replacement therapy from the New Zealand Guidelines Group. *Aust N Z J Obstet Gynaecol.* 2003;43(4):273-279. Exclusion code: 2

Roberts SS. What your doctor is reading: hormone replacement therapy. *Diabetes Self Manag.* 2002;19(6):78-81. Exclusion code: 7

Romero A, Alonso C, Rincon M, et al. Risk of venous thromboembolic disease in women: a qualitative systematic review. *Eur J Obstet Gynecol Reprod Biol.* 2005;121(1):8-17. Exclusion code: 7

Rosano G, Fini M. Postmenopausal women and cardiovascular risk: impact of hormone replacement therapy. *Cardiol Rev.* 2002;10:51-60. Exclusion code: 9

Rosano GM, Maffei S, Andreassi MG, et al. Hormone replacement therapy and cardioprotection: a new dawn? A statement of the Study Group on Cardiovascular Disease in Women of the Italian Society of Cardiology on hormone replacement therapy in postmenopausal women. *J Cardiovasc Med.* 2009;10(1):85-92. Exclusion code: 7

Rosano GM, Vitale C, Fini M. Hormone replacement therapy and cardioprotection: what is good and what is bad for the cardiovascular system? *Ann N Y Acad Sci.* 2006;1092:341-348. Exclusion code: 7

Rosano GM, Vitale C, Lello S. Postmenopausal hormone therapy: lessons from observational and randomized studies. *Endocrine.* 2004;24(3):251-254. Exclusion code: 7

Rosano GM, Vitale C, Silvestri A, Fini M. Hormone replacement therapy and cardioprotection: the end of the tale? *Ann N*

Appendix B6. List of Excluded Full-Text Articles

Y Acad Sci. 2003;997:351-357. Exclusion code: 7

Rosenberg L, Hoffman M. Hormone replacement therapy—finally, good data. *S Afr Med J*. 2004;94(1):26-27. Exclusion code: 7

Rossing MA, Cushing-Haugen KL, Wicklund KG, et al. Menopausal hormone therapy and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 2007;16:2548-2556. Exclusion code: 6

Rossouw JE. Effect of postmenopausal hormone therapy on cardiovascular risk. *J Hypertension.* 2002;20(Suppl 2):62-65. Exclusion code: 7

Rossouw JE. Coronary heart disease in menopausal women: implications of primary and secondary prevention trials of hormones. *Maturitas.* 2005;51(1):51-63. Exclusion code: 7

Rossouw JE. Implications of recent clinical trials of postmenopausal hormone therapy for management of cardiovascular disease. *Ann N Y Acad Sci.* 2006;1089:444-453. Exclusion code: 7

Rousseau ME. Hormone replacement therapy: short-term versus long-term use. *J Midwifery Womens Health.* 2002;47(6):461-470. Exclusion code: 7

Ryan J, Scali J, Carriere I, et al. Hormonal treatment, mild cognitive impairment and Alzheimer's disease. *Int Psychogeriatr.* 2008;20(1):47-56. Exclusion code: 7

Sakuma I, Kitabatake A. Menopause and cardiovascular diseases in women. *Intern Med.* 2004;43(2):151-154. Exclusion code: 7

Saletu B. Sleep, vigilance and cognition in postmenopausal women: placebo-controlled studies with 2 mg estradiol valerate, with and without 3 mg dienogest. *Climacteric.* 2003;6(Suppl 2):37-45. Exclusion code: 13

Salpeter SR, Walsh JM, Greyber E, et al. Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. *J Gen Intern Med.* 2004;19(7):791-804. Exclusion code: 9

Salpeter SR, Walsh JM, Greyber E, Salpeter EE. Brief report: coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. *J Gen Intern Med.* 2006;21(4):363-366. Exclusion code: 12

Sammartino A, Cirillo D, Mandato VD, et al. Osteoporosis and cardiovascular disease: benefit-risk of hormone replacement therapy. *J Endocrinol Invest.* 2005;28(10 Suppl):80-84. Exclusion code: 7

Samsioe G. HRT and cardiovascular disease. *Ann N Y Acad Sci.* 2003;997:358-372. Exclusion code: 7

Sano M, Jacobs D, Andrews H, et al. A multi-center, randomized, double blind placebo-controlled trial of estrogens to prevent Alzheimer's disease and loss of memory in women: design and baseline characteristics. *Clinical Trials.* 2008;5(5):523-533. Exclusion code: 7

Santen RJ. Risk of breast cancer with progestins: critical assessment of current data. *Steroids.* 2003;68(10-13):953-964. Exclusion code: 4

Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J*

Appendix B6. List of Excluded Full-Text Articles

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

Sare GM, Gray LJ, Bath PM. Association between hormone replacement therapy and subsequent arterial and venous vascular events: a meta-analysis. *Eur Heart J.* 2008;29(16):2031-2041. Exclusion code: 12

Scalco MZ, van Reekum R. Prevention of Alzheimer disease: encouraging evidence. *Can Fam Physician.* 2006;52:200-207. Exclusion code: 7

Scarabin PY, Oger E, Plu-Bureau G. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet.* 2003;362(9382):428-432. Exclusion code: 6

Schenck-Gustafsson K, Brincat M, Erel CT, et al. EMAS position statement: managing the menopause in the context of coronary heart disease. *Maturitas.* 2011;68(1):94-97. Exclusion code: 7

Schiff R, Bulpitt CJ, Wesnes KA, Rajkumar C. Short-term transdermal estradiol therapy, cognition and depressive symptoms in healthy older women: a randomised placebo controlled pilot cross-over study. *Psychoneuroendocrinology.* 2005;30(4):309-315. Exclusion code: 13

Schnatz PF. Hormonal therapy: does it increase or decrease cardiovascular risk? *Obstet Gynecol Surv.* 2006;61(10):673-681. Exclusion code: 7

Seeger H, Mueck AO. Are the progestins responsible for breast cancer risk during hormone therapy in the postmenopause? Experimental vs. clinical data. *J Steroid Biochem Mol Biol.* 2008;109(1-2):11-15. Exclusion code: 4

Seifert-Klauss V, Kingwell E, Hitchcock CL, et al. Estrogen and progestogen use in peri- and postmenopausal women: March 2007 position statement of the North American Menopause Society. *Menopause.* 2008;15(1):203-205. Exclusion code: 7

Seitzman RL, Mangione C, Ensrud KE, et al. Postmenopausal hormone therapy and age-related maculopathy in older women. *Ophthalmic Epidemiology* 2008;15:308-316. Exclusion code: 6

Selby P. Postmenopausal osteoporosis. *Curr.* 2004;2(3):101-106. Exclusion code: 7

Serock MR, Wells AK, Khalil RA. Modulators of vascular sex hormone receptors and their effects in estrogen-deficiency states associated with menopause. *Recent Patents Cardiovasc Drug Discov.* 2008;3(3):165-186. Exclusion code: 7

Shah NR, Borenstein J, Dubois RW. Postmenopausal hormone therapy and breast cancer: a systematic review and meta-analysis. *Menopause.* 2005;12(6):668-678. Exclusion code: 9

Shapiro S. Risks of estrogen plus progestin therapy: a sensitivity analysis of findings in the Women's Health Initiative randomized controlled trial. *Climacteric*. 2003;6(4):302-310. Exclusion code: 2

Shapiro S. The Million Women Study: potential biases do not allow uncritical acceptance of the data. *Climacteric.* 2004;7(1):3-7. Exclusion code: 7

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

Climacteric. 2006;9(6):416-420. Exclusion code: 7

Shapiro S. Recent epidemiological evidence relevant to the clinical management of the menopause. *Climacteric.* 2007;10(Suppl 2):2-15. Exclusion code: 7

Shapiro S. Oral contraceptives, hormone therapy and cardiovascular risk. *Climacteric.* 2008;11(5):355-363. Exclusion code: 7

Sharma S. Hormone replacement therapy in menopause: current concerns and considerations. *Kathmandu Univ.* 2003;1(4):288-293. Exclusion code: 7

Shaywitz SE, Naftolin F, Zelterman D, et al. Better oral reading and short-term memory in midlife, postmenopausal women taking estrogen. *Menopause.* 2003;10(5):420-426. Exclusion code: 13

Sherman AM, Shumaker SA, Sharp P, et al. No effect of HRT on health-related quality of life in postmenopausal women with heart disease. *Minerva Ginecol.* 2003;55(6):511-517. Exclusion code: 3

Sherwin BB. Estrogen and cognitive functioning in women. *Endocr Rev.* 2003;24:133-151. Exclusion code: 7

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

Sherwin BB. Surgical menopause, estrogen, and cognitive function in women: what do the findings tell us? *Ann N Y Acad Sci.* 2005;1052:3-10. Exclusion code: 7

Sherwin BB. Estrogen and cognitive aging in women. *Neuroscience.* 2006;138(3):1021-1026. Exclusion code: 7

Sherwin BB. The critical period hypothesis: can it explain discrepancies in the oestrogen-cognition literature? *J Neuroendocrinol.* 2007;19(2):77-81. Exclusion code: 7

Sherwin BB. Estrogen therapy: is time of initiation critical for neuroprotection? *Nat Rev Endocrinol.* 2009;5(11):620-627. Exclusion code: 7

Sherwin BB, Henry JF. Brain aging modulates the neuroprotective effects of estrogen on selective aspects of cognition in women: a critical review. *Front Neuroendocrinol.* 2008;29(1):88-113. Exclusion code: 7

Shulman LP. The menopausal transition: how does route of delivery affect the risk/benefit ratio of hormone therapy? *J Fam Pract.* 2004;Suppl:S13-17. Exclusion code: 7

Shulman LP. Transdermal hormone therapy and bone health. *Clin Interv Aging.* 2008;3(1):51-54. Exclusion code: 7

Shumaker S, Reboussin BA, Espeland MA, et al. The Women's Health Initiative Memory Study (WHIMS): a trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. *Control Clin Trials.* 1998;19:604-621. Exclusion code: 2

Siddiqui NI, Rahman S, Mia AR, Shamsuzzaman AK. Evaluation of hormone replacement therapy. *Mymensingh Med J.* 2005;14(2):212-218. Exclusion code: 7

Simon JA. Postmenopausal hormone therapy: risks versus benefits reassessed. *Nat Rev Endocrinol.* 2010;6(12):661-663. Exclusion code: 7

Appendix B6. List of Excluded Full-Text Articles

Simon JA, Nahum GG, Stanislaw H, Gaines T. The breast cancer "plunge" after initial publication of the WHI results: an alternative explanation. *Maturitas.* 2010;66(3):277-284. Exclusion code: 7

Simon JA, Snabes MC. Menopausal hormone therapy for vasomotor symptoms: balancing the risks and benefits with ultra-low doses of estrogen. *Expert Opin Investig Drugs.* 2007;16(12):2005-2020. Exclusion code: 7

Simon JA, Wehren LE, Ascott-Evans BH, et al. Skeletal consequences of hormone therapy discontinuance: a systematic review. *Obstet Gynecol Surv.* 2006;61(2):115-124. Exclusion code: 11

Sitruk-Ware R. New hormonal therapies and regimens in the postmenopause: routes of administration and timing of initiation. *Climacteric.* 2007;10(5):358-370. Exclusion code: 7

Skouby SO, Al-Azzawi F, Barlow D, et al. Climacteric medicine: European Menopause and Andropause Society (EMAS) 2004/2005 position statements on peri- and postmenopausal hormone replacement therapy. *Maturitas.* 2005;51(1):8-14. Exclusion code: 2

Skouby SO, Barlow D, Samsioe G, et al. Climacteric medicine: European Menopause and Andropause Society (EMAS) statements on postmenopausal hormonal therapy. *Maturitas.* 2004;48(1):19-25. Exclusion code: 12

Skouby SO, Jespersen J. Progestins in HRT: sufferance or desire? *Maturitas.* 2009;62(4):371-375. Exclusion code: 4

Skouby SO, Jespersen J, Kluft C, et al. On the route to combined evidence from OC and HRT/ERT. *Eur J Contracept Reprod Health Care.* 2002;7(4):185-198. Exclusion code: 7

Smith JD, Chakrabarti E, Levin-Allerhand JA. Drug discovery: estrogen-related compounds in mouse models of Alzheimer's disease. *J Mol Neurosci.* 2004;24(1):145-147. Exclusion code: 7

Smith NL, Heckbert SR, Lemaitre RN, et al. Esterified estrogens and conjugated equine estrogens and the risk of venous thrombosis. *JAMA.* 2004;292(13):1581-1587. Exclusion code: 6

Smith YR, Love T, Persad CC, et al. Impact of combined estradiol and norethindrone therapy on visuospatial working memory assessed by functional magnetic resonance imaging. *J Clin Endocrinol Metab.* 2006;91(11):4476-4481. Exclusion code: 11

Snow KK, Cote J, Yang W, et al. Association between reproductive and hormonal factors and age-related maculopathy in postmenopausal women. *Am J Ophthalmol.* 2002;134:842-848. Exclusion code: 6

Sohrabji F. Estrogen: a neuroprotective or proinflammatory hormone? Emerging evidence from reproductive aging models. *Ann N Y Acad Sci.* 2005;1052:75-90. Exclusion code: 3

Speroff L. The Million Women Study and breast cancer. *Maturitas.* 2003;46(1):1-6. Exclusion code: 7

Speroff L. Postmenopausal hormone therapy and breast cancer: a clinician's message for patients. *Endocrine.* 2004;24(3):211-216. Exclusion code: 7

Appendix B6. List of Excluded Full-Text Articles

Speroff L. A clinician's review of the WHI-related literature. *Int J Fertil Womens Med.* 2004;49(6):252-267. Exclusion code: 7

Speroff L. Postmenopausal hormone therapy and the risk of breast cancer: a clinician's view. *Maturitas.* 2004;49(1):51-57. Exclusion code: 7

Speroff L. The future of postmenopausal hormone therapy: it's time to move forward. *Maturitas.* 2007;57(1):103-106. Exclusion code: 7

Speroff L. Transdermal hormone therapy and the risk of stroke and venous thrombosis. *Climacteric.* 2010;13(5):429-432. Exclusion code: 7

Srinivasan KN, Satyamurthy I. Coronary artery disease in women. *J Assoc Physicians India.* 2002;50:259-264. Exclusion code: 7

Standridge JB. Pharmacotherapeutic approaches to the prevention of Alzheimer's disease. *Am J Geriatr Pharmacother.* 2004;2(2):119-132. Exclusion code: 7

Staren ED, Omer S. Hormone replacement therapy in postmenopausal women. *Am J Surg.* 2004;188(2):136-149. Exclusion code: 7

Stefanick ML. Estrogens and progestins: background and history, trends in use, and guidelines and regimes approved by the US Food and Drug Administration. *Am J Med.* 2005;118(12B):64S-73S. Exclusion code: 2

Stefanick ML. Postmenopausal hormone therapy and cardiovascular disease in women. *Nutr Metab Cardiovasc Dis.* 2010;20(6):451-458. Exclusion code: 7

Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA.* 2006;295(14):1647-1657. Exclusion code: 12

Stefanick ML, Cochrane B, Hsia J, et al. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. *Ann Epidemiol.* 2003;13(9 Suppl 1):S78-86. Exclusion code: 2

Stevens MC, Clark VP, Prestwood KM. Low-dose estradiol alters brain activity. *Psychiatry Res.* 2005;139(3):199-217. Exclusion code: 14

Stevenson J. Long term effects of hormone replacement therapy. *Lancet.* 2003;361(9353):253-254. Exclusion code: 7

Stevenson JC. The metabolic basis for the effects of HRT on coronary heart disease. *Endocrine.* 2004;24(3):239-244. Exclusion code: 7

Stevenson JC. Hormone replacement therapy: review, update, and remaining questions after the Women's Health Initiative Study. *Curr.* 2004;2(1):12-16. Exclusion code: 7

Stevenson JC. HRT and the primary prevention of cardiovascular disease. *Maturitas.* 2007;57(1):31-34. Exclusion code: 7

Stevenson JC. HRT and cardiovascular disease. *Best Pract Res Clin Obstet Gynaecol.* 2009;23(1):109-120. Exclusion code: 7

Stevenson JC, Hodis HN, Pickar JH, Lobo RA. Coronary heart disease and menopause management: the swinging pendulum of

Appendix B6. List of Excluded Full-Text Articles

HRT. *Atherosclerosis.* 2009;207(2):336-340. Exclusion code: 7

Stevenson M, Jones ML, De Nigris E, et al. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. *Health Technol Assess.* 2005;9(22):1-160. Exclusion code: 4

Stovall DW, Pinkerton JV. Estrogen agonists/antagonists in combination with estrogen for prevention and treatment of menopause-associated signs and symptoms. *Womens Health.* 2008;4(3):257-268. Exclusion code: 4

Stramba-Badiale M. Postmenopausal hormone therapy and the risk of cardiovascular disease. *J Cardiovasc Med.* 2009;10(4):303-309. Exclusion code: 7

Strandberg TE, Ylikorkala O, Tikkanen MJ. Differing effects of oral and transdermal hormone replacement therapy on cardiovascular risk factors in healthy postmenopausal women. *Am J Cardiol.* 2003;92(2):212-214. Exclusion code: 11

Strickler RC. Women's Health Initiative results: a glass more empty than full. *Fertil Steril.* 2003;80(3):488-490. Exclusion code: 7

Tan O, Harman SM, Naftolin F. What can we learn from design faults in the Women's Health Initiative randomized clinical trial? *Bull NYU Hosp Jt Dis.* 2009;67(2):226-229. Exclusion code: 7

Tannen RL, Weiner MG, Xie D, Barnhart K. A simulation using data from a primary care practice database closely replicated the Women's Health Initiative trial. *J Clin Epidemiol.* 2007;60(7):686-695. Exclusion code: 6

Tannen RL, Weiner MG, Xie D, Barnhart K. Perspectives on hormone replacement therapy: the Women's Health Initiative and new observational studies sampling the overall population. *Fertil Steril.* 2008;90(2):258-264. Exclusion code: 7

Tansavatdi K, McClain B, Herrington DM. The effects of smoking on estradiol metabolism. *Minerva Ginecol.* 2004;56(1):105-114. Exclusion code: 7

Taylor HS, Manson JE. Update in hormone therapy use in menopause. *J Clin Endocrinol Metab.* 2011;96(2):255-264. Exclusion code: 7

Teede H. Hormone replacement therapy and the prevention of cardiovascular disease. *Hum Reprod Update.* 2002;8:201-215. Exclusion code: 6

Teede HJ. Controversies in HRT. *Aust Fam Physician.* 2002;31(5):413-418. Exclusion code: 7

Teede HJ. The menopause and HRT: hormone replacement therapy, cardiovascular and cerebrovascular disease. *Baillieres Best Pract Res Clin Endocrinol Metab.* 2003;17(1):73-90. Exclusion code: 7

Theroux R. Postmenopausal hormone use: what does the latest evidence show? *Nurs Womens Health.* 2008;12(1):56-61. Exclusion code: 7

Thomas LH, Barrett J, Cross S, et al. Prevention and treatment of urinary incontinence after stroke in adults. *Cochrane Database Syst Rev.* 2005(3):CD004462. Exclusion code: 12

Appendix B6. List of Excluded Full-Text Articles

Thomas LH, Cross S, Barrett J, et al. Treatment of urinary incontinence after stroke in adults. *Cochrane Database Syst Rev.* 2009(1). Exclusion code: 4

Thorneycroft IH, Goldzieher JW. Venous thromboembolism: a review. *J Reprod Med.* 2003;48(Suppl 11):911-920. Exclusion code: 7

Timins JK. Current issues in hormone replacement therapy. *N J Med.* 2004;101(3):21-27. Exclusion code: 7

Tinelli FG, Tinelli A, Sena T. Clinical effects of hormone replacement therapy with estradiol valerate and cyproterone acetate in perimenopausal women. *Minerva Ginecol.* 2002;54(1):67-73. Exclusion code: 10

Toles CA. The incidence of cardiovascular disease in menopausal women on hormone replacement therapy: a clinical evidence-based medicine review. *J Natl Black Nurses Assoc.* 2007;18(2):75-80. Exclusion code: 7

Toth S, Blanchard E, Herman L, et al. Weighing the risks and benefits of hormone therapy. *JAAPA.* 2003;16(6):45-47. Exclusion code: 7

Tsolaki M, Grammaticos P, Karanasou C, et al. Serum estradiol, progesterone, testosterone, FSH and LH levels in postmenopausal women with Alzheimer's dementia. *Hell J Nucl Med.* 2005;8(1):39-42. Exclusion code: 6

Turgeon JL, Carr MC, Maki PM, et al. Complex actions of sex steroids in adipose tissue, the cardiovascular system, and brain: insights from basic science and clinical studies. *Endocr Rev.* 2006;27(6):575-605. Exclusion code: 3

U.S. Preventive Services Task Force. Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: recommendations and rationale. *Ann Intern Med.* 2002;137(10):834-839. Exclusion code: 12

U.S. Preventive Services Task Force. Postmenopausal hormone replacement therapy for the primary prevention of chronic conditions: recommendations and rationale. *Am Fam Physician.* 2003;67(2):358-364. Exclusion code: 2

U.S. Preventive Services Task Force. Hormone therapy for the prevention of chronic conditions in postmenopausal women: recommendations from the U.S. Preventive Services Task Force. *Ann Intern Med.* 2005;142(10):855-860. Exclusion code: 12

Uebelhart B, Frey D, Uebelhart D. Hormone replacement therapy: what is the evidence today? *Z Rheumatol.* 2003;62(6):508-511. Exclusion code: 7

Utian WH, Archer DF, Bachmann GA, et al. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of the North American Menopause Society. *Menopause.* 2008;15(4 Pt 1):584-602. Exclusion code: 2

Utian WH, Gass ML, Pickar JH. Body mass index does not influence response to treatment, nor does body weight change with lower doses of conjugated estrogens and medroxyprogesterone acetate in early postmenopausal women. *Menopause.* 2004;11(3):306-314. Exclusion code: 11

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

van der Mooren MJ, Kenemans P. The Million Women Study: a licence to kill other investigations? *Eur J Obstet Gynecol Reprod Biol.* 2004;113(1):3-5. Exclusion code: 7

van der Schouw YT, Grobbee DE. Menopausal complaints, oestrogens, and heart disease risk: an explanation for discrepant findings on the benefits of post-menopausal hormone therapy. *Eur Heart J.* 2005;26(14):1358-1361. Exclusion code: 7

Vandenbroucke JP. The HRT controversy: observational studies and RCTs fall in line. *Lancet.* 2009;373(9671):1233-1235. Exclusion code: 7

Varner RE. Menopausal hormone replacement therapy. *Curr Womens Health Rep.* 2003;3(5):410-417. Exclusion code: 7

Veerus P, Hovi SL, Fischer K, et al. Results from the Estonian postmenopausal hormone therapy trial [ISRCTN35338757]. *Maturitas.* 2006;55(2):162-173. Exclusion code: 9

Vercambre MN, Fournier A, Boutron-Ruault MC, et al. Differential dietary nutrient intake according to hormone replacement therapy use: an underestimated confounding factor in epidemiologic studies? *Am J Epidemiol.* 2007;166(12):1451-1460. Exclusion code: 4

Verkooijen HM, Bouchardy C, Vinh-Hung V, et al. The incidence of breast cancer and changes in the use of hormone replacement therapy: a review of the evidence. *Maturitas.* 2009;64(2):80-85. Exclusion code: 7

Vestergaard P, Hermann AP, Stilgren L, et al. Effects of 5 years of hormonal replacement therapy on menopausal symptoms and blood pressure: a randomised controlled study. *Maturitas.* 2003;46(2):123-132. Exclusion code: 11

Vickers M, Collins N. Progress on the WISDOM trial: Women's International Study of the Long Duration Oestrogen After Menpause. *Climacteric.* 2002;5(Suppl):133-134. Exclusion code: 7

Vickers M, Meade T, Darbyshire J. WISDOM: history and early demise—was it inevitable? *Climacteric.* 2002;5(4):317-325. Exclusion code: 2

Vickers MR, Martin J, Meade TW, et al. The Women's International Study of Long-Duration Oestrogen After Menopause (WISDOM): a randomised controlled trial. *BMC Womens Health.* 2007;7(2). Exclusion code: 2

Viscoli CM, Brass LM, Kernan WN, et al. A clinical trial of estrogen-replacement therapy after ischemic stroke. *New Engl J Med.* 2001;345(17):1243-1249. Exclusion code: 8

Viscoli CM, Brass LM, Kernan WN, et al. Estrogen therapy and risk of cognitive decline: results from the Women's Estrogen for Stroke Trial (WEST). *Am J Obstet Gynecol.* 2005;192(2):387-393. Exclusion code: 9

Vogelvang TE, Mijatovic V, Kamp O, et al. Neither long-term treatment with raloxifene nor hormone replacement therapy modulate cardiac function in healthy postmenopausal women: two randomized, placebo-controlled, 2-year studies. *Am J Obstet Gynecol.* 2002;186(4):729-736. Exclusion code: 11

Vogelvang TE, van der Mooren MJ, Mijatovic V. Hormone replacement therapy, selective estrogen receptor modulators, and tissue-specific compounds: cardiovascular

effects and clinical implications. *Treat.* 2004;3(2):105-115. Exclusion code: 11

Vukovic V, Lovrencic-Huzjan A, Solter VV, et al. Hormone replacement therapy—is there a place for its use in neurology? *Coll Antropol.* 2003;27(1):413-424. Exclusion code: 7

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

Walitt B, Pettinger M, Weinstein A, et al. Effects of postmenopausal hormone therapy on rheumatoid arthritis: the Women's Health Initiative randomized controlled trials. *Arthritis Rheum.* 2008;59(3):302-310. Exclusion code: 5

Warner J, Butler R. Dementia. *Clin Evid.* 2002(7):846-866. Exclusion code: 9

Warren MP. A comparative review of the risks and benefits of hormone replacement therapy regimens. *Am J Obstet Gynecol.* 2004;190(4):1141-1167. Exclusion code: 7

Warren MP. Historical perspectives in postmenopausal hormone therapy: defining the right dose and duration. *Mayo Clin Proc.* 2007;82(2):219-226. Exclusion code: 7

Wasnich RD, Bagger YZ, Hosking DJ, et al. Changes in bone density and turnover after alendronate or estrogen withdrawal. *Menopause.* 2004;11(6 Pt 1):622-630. Exclusion code: 11

Wathen CN, Feig DS, Feightner JW, et al. Hormone replacement therapy for the primary prevention of chronic diseases: recommendation statement from the Canadian Task Force on Preventive Health Care. *CMAJ.* 2004;170(10):1535-1537. Exclusion code: 2

Weiner MG, Barnhart K, Xie D, Tannen RL. Hormone therapy and coronary heart disease in young women. *Menopause.* 2008;15(1):86-93. Exclusion code: 6

Welty FK. Alternative hormone replacement regimens: is there a need for further clinical trials? *Curr Opin Lipidol.* 2003;14(6):585-591. Exclusion code: 7

Wenger NK. Menopausal hormone therapy: is there evidence for cardiac protection? *Int Urol Nephrol.* 2004;36(4):617-623. Exclusion code: 7

Whitehead M. Hormone replacement therapy with estradiol and drospirenone: an overview of the clinical data. *J Br Menopause Soc.* 2006;12(Suppl 1):4-7. Exclusion code: 7

Wildemeersch D, Dhont M, Weyers S, Temmerman M. Miniature, low-dose, intrauterine drug-delivery systems. *Ann N Y Acad Sci.* 2003;997:174-184. Exclusion code: 4

Wildemeersch D, Pylyser K, De Wever N, et al. Endometrial safety after 5 years of continuous combined transdermal estrogen and intrauterine levonorgestrel delivery for postmenopausal hormone substitution. *Maturitas.* 2007;57(2):205-209. Exclusion code: 11

Williams JK, Suparto I. Hormone replacement therapy and cardiovascular disease: lessons from a monkey model of postmenopausal women. *Ilar J.* 2004;45(2):139-146. Exclusion code: 3

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

Wise PM. Estrogens and neuroprotection. *Trends Endocrinol Metab.* 2002;13(6):229-230. Exclusion code: 7

Wise PM. Estrogens and cerebrovascular stroke: what do animal models teach us? *Ann N Y Acad Sci.* 2005;1052:225-232. Exclusion code: 3

Wise PM, Dubal DB, Rau SW, et al. Are estrogens protective or risk factors in brain injury and neurodegeneration? Reevaluation after the Women's Health Initiative. *Endocr Rev.* 2005;26(3):308-312. Exclusion code: 7

Wolf OT, Heinrich AB, Hanstein B, Kirschbaum C. Estradiol or estradiol/progesterone treatment in older women: no strong effects on cognition. *Neurobiol Aging.* 2005;26(7):1029-1033. Exclusion code: 13

Woo J, Lau E, Ho SC, et al. Comparison of Pueraria lobata with hormone replacement therapy in treating the adverse health consequences of menopause. *Menopause.* 2003;10(4):352-361. Exclusion code: 13

Writing Group for the 3rd European Conference on Sex Steroids and Cardiovascular Diseases. The European Consensus Development Conference 2002: sex steroids and cardiovascular diseases. On the route to combined evidence from OC and HRT/ERT. *Maturitas.* 2003;44(1):69-82. Exclusion code: 7

Wu O. Postmenopausal hormone replacement therapy and venous thromboembolism. *Gend Med.* 2005;2(Suppl A):S18-27. Exclusion code: 7

Wu ZL, Zhao YC, Yu CS, et al. Comparative study with three agents of hormone replacement therapy in postmenopausal women. *J Pract Obstet Gynecol.* 2002;18(4):225-227. Exclusion code: 11

Wysowski DK, Governale LA. Use of menopausal hormones in the United States, 1992 through June 2003. *Pharmacoepidemiol Drug Saf.* 2005;14(3):171-176. Exclusion code: 5

Yaffe K, Sawaya GF, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA.* 1998;279:688-695. Exclusion code: 13

Yasmeen S, Romano PS, Pettinger M, et al. Incidence of cervical cytological abnormalities with aging in the Women's Health Initiative: a randomized controlled trial. *Obstet Gynecol.* 2006;108(2):410-419. Exclusion code: 5

Yasui T, Uemura H, Takikawa M, Irahara M. Hormone replacement therapy in postmenopausal women. *J Med Invest.* 2003;50(3-4):136-145. Exclusion code: 7

Ylikangas S, Backstrom T, Heikkinen J. Cost-effectiveness of continuous combined hormone replacement therapy in long-term use: economic evaluation based on a 9-year study in Finland. *Curr Med Res Opin.* 2007;23(1):57-64. Exclusion code: 5

Yoo JW, Lee CH. Drug delivery systems for hormone therapy. *J Controlled Release.* 2006;112(1):1-14. Exclusion code: 7

Zandi PP, Carlson MC, Plassman BL, et al. Hormone replacement therapy and incidence of Alzheimer disease in older women: the

Appendix B6. List of Excluded Full-Text Articles

Cache County Study. *JAMA.* 2002;288(17):2123-2129. Exclusion code: 6

Zec RF, Trivedi MA. The effects of estrogen replacement therapy on neuropsychological functioning in postmenopausal women with and without dementia: a critical and theoretical review. *Neuropsychol Rev.* 2002;12(2):65-109. Exclusion code: 7

Zethraeus N, Borgstrom F, Jonsson B, Kanis J. Reassessment of the cost-effectiveness of hormone replacement therapy in Sweden: results based on the Women's Health Initiative randomized controlled trial. *Int J Technol Assess Health Care.* 2005;21(4):433-441. Exclusion code: 5

Zhou B, Sun Q, Cong R, et al. Hormone replacement therapy and ovarian cancer risk: a meta-analysis. *Gynecologic Oncology* 2008;108:641-651. Exclusion code: 7

Zizic TM. Pharmacologic prevention of osteoporotic fractures. *Am Fam Physician.* 2004;70(7):1293-1300. Exclusion code: 7

Appendix C1. Quality Assessment of Randomized, Controlled Trials

Author, Year Trial	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Maintain comparable groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Anderson, 2004[42] WHI	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Anderson, 2003[23] WHI	Yes	Yes	Yes	Compliance rates similar	Yes	Yes	Yes	Yes
Cherry, 2002[67] ESPRIT	Yes	Yes	Yes	Greater noncompliance in treatment group	Yes	Yes	Yes	Yes
Ettinger, 2004[69] ULTRA	Yes	Yes	Mostly: 2% lower lumbar spine BMD in treatment group compared with placebo group	Unclear	Yes	Yes	Yes	Yes
Heiss, 2008[33] WHI extension	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hulley, 2002[61] HERS II	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
LaCroix, 2011[49] WHI extension	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Resnick, 2006[58] WHISCA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Author, Year Trial	Reporting of attrition, crossovers, adherence, and contamination?	Loss to followup differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Outcomes prespecified?	Funding source	External validity	Quality rating
Anderson, 2004[42] WHI	Yes	No	Yes	No	Yes	National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services	Good	Fair
Anderson, 2003[23] WHI	Yes	No	Yes	NR	Yes	National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services	Good	Fair
Cherry, 2002[66] ESPRIT	Unclear	Unclear	Yes	NR	Yes	Schering AG	Fair	Fair
Ettinger, 2004[68] ULTRA	Yes: attrition and adherence No: crossovers and contamination	No	Yes	No	Yes	Berlex Laboratories, Inc	Fair	Fair
Heiss, 2008[33] WHI extension	Yes	No	Yes	No	Yes	National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services	Good	Fair
Hulley, 2002[61] HERS II	Yes	No	Yes	Yes	Yes	Wyeth-Ayerst Research	Good/Fair	Fair
LaCroix, 2011[49] WHI extension	Yes	No	Yes	No	Yes	National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services	Good	Fair
Resnick, 2006[58] WHISCA	Yes	Completion rates at year 3: 42.2% E+P vs. 44.1% placebo	Yes	No	Yes	National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services	Good	Fair

Appendix C1. Quality Assessment of Randomized, Controlled Trials

Author, Year Trial	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Maintain comparable groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Resnick, 2009[57] WHISCA	Yes	Yes	Mostly, except for smoking status	Yes	Yes	Yes	Yes	Yes
Rossouw, 2002[12] WHI	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Shumaker, 2003[55] WHIMS	Yes	Yes	Mostly, except for history of stroke and prior statins use	NR	Yes	Yes	Yes	Yes
Shumaker, 2004[54] WHIMS	Yes	Yes	Mostly, except for hypertension	NR	Yes	Yes	Yes	Yes
Tierney, 2009[68] EMS	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Vickers, 2007[66] WISDOM	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes

Author, Year Trial	Reporting of attrition, crossovers, adherence, and contamination?	Loss to followup differential/high?	Intention-to-treat analysis?	Post-randomization exclusions?	Outcomes prespecified?	Funding source	External validity	Quality rating
Resnick, 2009[57] WHISCA	Yes	Completion rates at year 4: 75.1% estrogen vs. 71.9% placebo	Yes	No	Yes	National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services	Good	Fair
Rossouw, 2002[12] WHI	Yes	No	Yes	No	Yes	National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services	Good	Fair
Shumaker, 2003[55] WHIMS	Yes: attrition and adherence No: crossovers and contamination	Year 6 3MSE scores obtained for 31 (1.45%) E+P and 44 (1.98%) placebo participants	Yes	No	Yes	National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services	Good	Fair
Shumaker, 2004[54] WHIMS	Yes: attrition and adherence No: crossovers and contamination	Drop out rate for year 7: 59.4% for estrogen vs. 54.2% for placebo	Yes	No	Yes	National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services	Good	Fair
Tierney, 2009[67] EMS	Yes: attrition and adherence No: crossovers and contamination	No	Yes	No	Yes	Not reported	Fair	Fair
Vickers, 2007[74] WISDOM	Yes	Unclear; prematurely closed trial	Yes	Unclear	Unclear: primary outcome changed	Not reported	Fair	Fair

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

Author, year; title	Population	Results (Treatment vs. Placebo) Breast cancer incidence
Chlebowski, 2010;[25] Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. **WHI Estrogen plus progestin trial**	Women enrolled in WHI trial: **Estrogen plus progestin** 8,506 Intervention phase 8,056 Post-intervention phase 8,506 Extension phase **Placebo** 8,102 Intervention phase 7,682 Post-intervention phase 8,102 Extension phase	**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 **Overall mortality per year** 25 vs. 12; HR, 1.96 (95% CI, 1.00 to 4.04); p=0.049 **Rates when analyses limited to 80% adherence** 14 vs.5; HR, 2.96 (95% CI, 1.00 to 8.77); p=0.053
Chlebowski, 2003;[26] 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** 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 nonadeherent women are excluded (HR, 1.49; p<0.001) **Without prior menopausal hormone use** 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) **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)
Rossouw, 2002;[12] 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	**Invasive breast cancer** 166 (0.38 annualized %) vs. 124 (0.30 annualized %); HR, 1.26 (95% CI, 1.00 to 1.59) **Breast cancer mortality** 3 (0.01 annualized %) vs. 2 (<0.01 annualized %)
Gramling, 2009;[31] Hormone replacement therapy, family history, and breast cancer risk among postmenopausal women (longitudinal follow-up). **WHI Estrogen plus progestin trial**	Women enrolled in WHI trial: 16,608 Enrolled 8,506 Estrogen plus progestin 8,102 Placebo	**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 **Those without a first-degree family history of breast cancer** Total: 7,497 vs. 7,202 Invasive breast cancer: 164 vs. 125 Woman-years: 41,998 vs. 37,798
Heiss, 2008;[33] Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. **WHI Estrogen plus progestin trial**	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)	**Intervention phase** 206 (0.43 annualized %) vs. 153 (0.34 annualized %); HR, 1.26 (95% CI, 1.02 to 1.55) **Postintervention phase** 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 **Overall combined phase data** 285 (0.43 annualized %) vs. 213 (0.34 annualized %); HR, 1.27 (95% CI, 1.06 to 1.51)

Appendix C2. Evidence Table of Trials Reporting Incidence of Breast Cancer

Author, year; title	Population	Results (Treatment vs. Placebo) Breast cancer incidence
LaCroix, 2011;[49] Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy post-intervention. **WHI Estrogen only trial**	Women enrolled in WHI trial: 10,739 Enrolled 5,310 Estrogen 5,429 Placebo	**Intervention stage** 104 vs. 135; HR, 0.79 (95% CI, 0.61 to 1.02); p=0.76 **Postintervention** 47 vs. 64; HR, 0.75 (95% CI, 0.51 to 1.09); p=0.76 **Overall** 151 vs. 199; HR, 0.77 (95% CI, 0.62 to 0.95); p=0.76
Anderson, 2004;[42] Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. **WHI Estrogen only trial**	Women enrolled in WHI trial: 10,739 Enrolled 5,310 Estrogen 5,429 Placebo	**Number of patients (annualized %)** 94 (0.26) vs. 124 (0.33); HR, 0.77 (95% CI, 0.59 to 1.01)
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 from original HERS trial who consented to followup: 2,321 (93% of surviving participants from HERS)	**Total** 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 **HERS** 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 **HERS II** 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 2.24); p=0.83 **Unadjusted ITT vs. adjusted ITT vs. adjusted as-treated** 1.27 (95% CI, 0.84 to 1.94) vs. 1.27 (95% CI, 0.84 to 1.94) vs. 1.11 (95% CI, 0.61 to 2.03)
Cherry (ESPRIT Team), 2002;[67] Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomized placebo controlled trial. **ESPRIT Estrogen only trial**	Postmenopausal women aged 50-69 years who had survived a first myocardial infarction: 1,017 Enrolled 513 Estrogen 504 Placebo	**Cases by 24 months** 4 (1%) vs. 4 (1%); HR, 0.98 (95% CI, 0.25 to 3.91); p=1.00
Vickers, 2007;[66] Main morbidities recorded in the Women's International Study of Long Duration Oestrogen After Menopause (WISDOM): a randomized controlled trial of hormone replacement therapy in postmenopausal women. **WISDOM Estrogen plus progestin trial**	4,385 Enrolled (estrogen plus progestin vs. placebo trial only) 2,196 Estrogen plus progestin 2,189 Placebo	**Breast cancer incidence** 5 vs. 7; HR, not reported **Mortality from breast cancer** 0 vs. 0; HR, not reported

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

Author, year; title	Population	Results (Treatment vs. Placebo) Incidence of colorectal cancer
Heiss 2008;[33] Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. **WHI Estrogen plus progestin trial**	Women in the post-intervention phase of WHI: 16,608 Enrolled 8,506 Estrogen plus progestin 8,102 Placebo	**Clinical Trial Phase** 50 vs.75; HR, 0.62 (95% CI, 0.43 to 0.89) **Post-intervention phase** 34 vs.30; HR, 1.08 (95% CI, 0.66 to 1.77); p=0.007 **Overall combined phase data** 84 vs.105; HR, 0.75 (95% CI, 0.57 to 1.00)
Chlebowski, 2004;[28] Estrogen plus progestin and colorectal cancer in postmenopausal women. **WHI Estrogen plus progestin trial**	Women enrolled in WHI trial: 16,608 Enrolled 8,506 Estrogen + progestin 8,102 Placebo	**Annualized rate of colorectal cancer** Colorectal cancer: 48 vs.74; HR, 0.61 (95% CI, 0.42 to 0.87); p=0.007 Invasive colorectal cancer: 43 vs. 72; HR, 0.56 (95% CI, 0.38 to 0.81); p= 0.003 **Within invasive colorectal cancer** Colon cancer: 35 vs. 61; HR, 0.54 (95% CI, 0.36 to 0.82); p= 0.004 Rectal cancer: 8 vs.11; HR, 0.66 (95% CI, 0.26 to 0.65); p=0.37
Rossouw, 2002;[12] Risks and benefits of estrogen plus progestin in healthy postmenopausal women. **WHI Estrogen plus progestin trial**	Women enrolled in WHI trial: 16,608 Enrolled 8,506 Estrogen plus progestin 8,102 Placebo	**Colorectal cancer** 45 vs. 67; HR, 0.63 (nominal 95% CI, 0.43 to 0.92) (adjusted 95% CI, 0.32 to -1.24) **Colorectal cancer by followup year** Year 1: 10 vs.15; HR, 0.64 Year 2: 11 vs. 9; HR, 1.17 Year 3: 6 vs. 8; HR, 0.72 Year 4: 9 vs. 20; HR, 0.43 Year 5: 4 vs. 8; HR, 0.47 Year 6 and later: 5 vs. 7; HR, 0.59
LaCroix, 2011;[49] Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy post-intervention. **WHI Estrogen only trial**	Women enrolled in WHI trial: 10,739 Enrolled 5,310 Estrogen 5,429 Placebo	**Colorectal cancer** Intervention stage: 65 vs. 58; HR, 1.15 (95% CI, 0.81 to1.64); p= 0.71 Postintervention: 24 vs. 24; HR, 1.01 (95% CI, 0.58 to 1.79); p=0.71 Overall: 89 vs. 82; HR, 1.11 (95% CI, 0.82 to 1.50); p=0.71
Ritenbaugh, 2008;[50] Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. **WHI Estrogen only trial**	Women enrolled in WHI trial: 10,739 Enrolled 5,310 Estrogen 5,429 Placebo	**Incidence of invasive colorectal cancer** 58 vs. 53; HR, 1.12 (95% CI, 0.77 to 1.63); p=0.55 **Within invasive colorectal cancer** Colon cancer: 53 vs. 43; HR, 1.26 (95% CI, 0.84 to1.88); p=0.26 Rectal cancer: 5 vs.10; HR, 0.53 (95% CI, 0.18 to 1.56); p=0.25
Anderson, 2004;[42] Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. **WHI Estrogen only trial**	Women enrolled in WHI trial: 10,739 Enrolled 5,310 Estrogen 5,429 Placebo	**Colorectal cancer** 61 vs. 58; HR, 1.08 (nominal 95% CI, 0.75 to 1.55); (adjusted 95% CI, 0.63 to 1.86)
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 from original HERS trial who consented to followup: 2,321 (93% of surviving patients from HERS)	**Colon cancer (events per 1,000 person-years)** HERS: 2.0 vs. 2.9; HR, 0.69 (95% CI, 0.32 to 1.49); p=0.35 HERS II: 10/3.4 vs. 10/3.4; HR, 1.01 (95% CI, 0.42 to 2.43); p=0.98 Total: 21/2.5 vs. 26/3.1; HR, 0.81 (95% CI, 0.46 to 1.45); p=0.48 p-value for treatment-time interaction = 0.52 **Unadjusted ITT vs. adjusted ITT vs. adjusted as-treated** 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)

Appendix C3. Evidence Table of Trials Reporting Incidence of Colorectal Cancer

Author, year; title	Population	Results (Treatment vs. Placebo) Incidence of colorectal cancer
Tierney, 2009;[68] A randomized double-blind trial of the effects of hormone therpay on delayed verbal recall in older women. **EMS Estrogen plus progestin trial**	Within the greater Toronto area; enrolled between April 2000 and January 2004; aged >60 years; last menstrual cycle >12 months before screening; fluent in English and could read normal print and hear normal speech. 142 Enrolled 70 Estrogen + progestin 72 Placebo	**Colorectal cancer** 0 vs. 0
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**	4,385 Enrolled 2,196 Estrogen plus progestin 2,189 Placebo	**Colorectal Cancer** 2 vs. 2; HR, not reported **Mortality** 1 vs. 0; HR, not reported

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

Author, year; title	Population	Results (Treatment vs. Placebo) Diabetes incidence
Margolis, 2004;[38] Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. **WHI Estrogen plus progestin trial**	Excluded women with self-reported diabetes at baseline: 15,641 Enrolled 8,014 Estrogen plus progestin 7,627 Placebo	**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
Bonds, 2006;[43] The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. **WHI Estrogen only trial**	Excluded women with self-reported diabetes at baseline: 9,712 Enrolled 4,806 Estrogen 4,906 Placebo	**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)
Kanaya, 2003;[63] Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/Progestin Replacement Study. **HERS Estrogen plus progestin trial**	Excluded women with self-reported diabetes at baseline: 2,763 Enrolled 1,380 Estrogen plus progestin 1,383 Placebo	**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)

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

Author, year; title	Population	Results (Treatment vs. Placebo) Cardiovascular disease incidence during intervention
Heiss, 2008;[33] Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin (WHI, post-treatment). **WHI Estrogen plus progestin trial**	Women enrolled in WHI E+P trial: 8,052 Estrogen plus progestin 7,678 Placebo	**Overall CHD** 196 vs. 154; HR, 1.22 (95% CI, 0.99 to 1.51) **CHD death** 40 vs. 36; HR, 1.04 (95% CI, 0.67 to 1.64) **Total MI** 168 vs. 127; HR, 1.26 (95% CI, 1.00 to 1.59) **Stroke** 159 vs. 110; HR, 1.34 (95% CI, 1.05 to 1.71) **DVT** 122 vs. 61; HR, 1.88 (95% CI, 1.38 to 2.55) **PE** 87 vs. 41; HR, 1.98 (95% CI, 1.36 to 2.87) **All CVD events** 785 vs. 660; HR, 1.13 (95% CI, 1.02 to 1.25)
Manson, 2003;[37] Estrogen plus progestin and the risk of coronary heart disease. **WHI Estrogen plus progestin trial**	Women enrolled in WHI E+P trial: 8,052 Estrogen plus progestin 7,678 Placebo	**Overall CHD** 188 vs. 147; HR, 1.24 (95% CI, 1.00 to 1.54) **Nonfatal MI** 151 vs. 114; HR, 1.28 (95% CI, 1.00 to 1.63) **CHD death** 39 vs. 34; HR, 1.10 (95% CI, 0.70 to 1.75) **CHF** 113 vs. 109; HR, 0.99 (95% CI, 0.76 to 1.29) **Subgroups not associated with HT and outcomes** 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. **Subgroups associated with HT and outcomes** LDL cholesterol level; also risk highest and most significant during the first year of the trial.
Wassertheil-Smoller, 2003;[41] Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. **WHI Estrogen plus progestin trial**	Women enrolled in WHI E+P trial: 8,052 Estrogen plus progestin 7,678 Placebo	**All stroke** 151 vs. 107; HR, 1.31 (95% CI, 1.02 to 1.68) **Ischemic stroke** 125 vs. 81; HR, 1.44 (95% CI, 1.09 to 1.90) **Hemorrhagic stroke** 18 vs. 20; HR, 0.82 (95% CI, 0.43 to 1.56) **Subgroups not associated with HT and outcomes** Prior oral contraceptive use. **Subgroups associated with HT and outcomes** 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.

Appendix C5. Evidence Table of Trials Reporting Incidence of Cardiovascular Disease

Author, year; title	Population	Results (Treatment vs. Placebo) Cardiovascular disease incidence during intervention
Cushman, 2004;[30] Estrogen plus progestin and risk of venous thrombosis. **WHI Estrogen plus progestin trial**	Women enrolled in WHI trial: 8,052 Estrogen plus progestin 7,678 Placebo	**VT** 167 vs. 76; HR, 2.06 (95% CI, 1.57 to 2.70) **DVT** 123 vs. 59; HR, 1.95 (95% CI, 1.43 to 2.67) **PE** 86 vs. 38; HR, 2.13 (95% CI, 1.45 to 3.11) **Subgroups not associated with HT and outcomes** Genetic variants except Factor V Leiden. **Subgroups associated with HT and outcomes** Age, BMI, Factor V Leiden.
Rossouw, 2007;[39] Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. **WHI Estrogen plus progestin and estrogen only trials**	Women enrolled in WHI trial: 8,052 Estrogen plus progestin 7,678 Placebo 5,310 Estrogen 5,429 Placebo	**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) **Subgroups not associated with HT and outcomes** Age, years since menopause for stroke. **Subgroups associated with HT and outcomes** Years since menopause for CHD. Interaction with CHD and vasomotor symptoms at baseline
LaCroix, 2011;[49] 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	**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) **All CVD events** 874 vs. 811; HR, 1.11 (95% CI, 1.01 to 1.23)
Hsia, 2006;[48] Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. **WHI Estrogen only trial**	Women enrolled in WHI trial: 5,310 Estrogen 5,429 Placebo	**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. **Subgroups not associated with CEE and CHD outcomes** 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. **Significant association** High C-reactive protein levels.

Appendix C5. Evidence Table of Trials Reporting Incidence of Cardiovascular Disease

Author, year; title	Population	Results (Treatment vs. Placebo) Cardiovascular disease incidence during intervention
Hendrix, 2006;[47] 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;[46] 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

Author, year; title	Population	Results (Treatment vs. Placebo) Fracture incidence
Cauley, 2003;[24] 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;[12] 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;[49] 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;[42] 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;[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 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

Author, year; title	Population	Results (Treatment vs. Placebo) Lung cancer incidence
Chlebowski, 2009;[27] Ostrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. **WHI Estrogen plus progestin trial**	Women enrolled in WHI trial: 16,608 Enrolled 8,506 Estrogen plus progestin 8,102 Placebo	**Lung cancer incidence** 109 vs. 85; HR, 0.23 (95% CI, 0.92 to 1.63); p=0.16 **Lung cancer mortality** Mortality from lung cancer: 73 vs. 40; HR, 1.71 (95% CI, 1.6 to 2.52); p=0.01 Non-small cell: 62 vs. 31; HR, 1.87 (95% CI, 1.22 to 2.88); p=0.004 Small cell: 11 vs. 9; HR, 1.16 (95% CI, 0.48 to 2.79); p=0.75 Mortality after diagnosis: 78 vs. 49; HR, 1.50 (95% CI, 1.05 to 2.14); p=0.03 Non-small cell: 67 vs. 39; HR, 1.61; (95% CI, 1.09 to 2.39); p=0.02 Small cell: 11 vs. 10; HR, 1.04 (95% CI, 0.44 to 2.46); p=0.92
Chlebowski, 2010;[45] Lung cancer among postmeopausal women treated with estrogen alone in the Women's Health Initiative randomized trial. **WHI Estrogen only trial**	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
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 ITT vs. adjusted as-treated** 1.39 vs. 1.43 vs. 1.73
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**	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

Author, year; title	Population	Results (Treatment vs. Placebo)	
		Gynecological cancer incidence	Other outcomes
Heiss, 2008;[33] Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. **WHI Estrogen plus progestin trial**	Women enrolled in WHI trial: 15,730 Analyzed 8,052 Estrogen plus progestin 7,678 Placebo	**Endometrial cancer (postintervention phase only)** 17 (0.09 annualized %) vs. 21 (0.11 annualized %); HR, 0.75 (95% CI, 0.40 to 1.43); p=0.83 **Endometrial cancer (intervention and postintervention phases combined)** 44 (0.07 annualized %) vs. 52 (0.08 annualized %); HR, 0.78 (95% CI, 0.52 to 1.16)	Not reported
Anderson, 2004;[42] Effects of estrogen plus progestin on gynecological cancers and associated diagnostic procedures: 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	**Ovarian cancer** 20 (0.04 annualized %) vs. 12 (0.03 annualized %); HR, 1.58 (95% CI, 0.77 to 3.24) Mortality: 9 vs. 3; HR, 2.70 (95% CI, 0.73 to 10.0) Observed annual incidence rate: 34 per 100,000 person-years Rate of diagnosis: 42 per 100,000 person-years vs. 27 per 100,000 person-years **Endometrial cancer** 27 (0.06 annualized %) vs. 31 (0.07 annualized %); HR, 0.81 (95% CI, 0.48 to 1.36) Observed incidence rate: 62 per 100,000 person-years Rate of diagnosis: 56 per 100,000 person-years vs. 69 per 100,000 person-years **Cervical cancer** 8 (0.02 annualized %) vs. 5 (0.01 annualized %); HR, 1.44 (95% CI, 0.47 to 4.42) **Other gynecological cancer (including fallopian, primary peritoneum cancers)** 6 (<0.01%) vs.1 (<0.01%); HR, not reported	**Followup endometrial biopsy** Routine biopsy subgroup and endometrial cancer: 0 vs. 0 Usual care subgroup and endometrial cancer: 7 (0.3%) vs. 7 (1.6%)
Hulley, 2002;[61] Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study Follow-up **HERS II Estrogen plus progestin trial**	Women reconsenting to followup period of HERS study: 2,485 Eligible from HERS 1,156 Estrogen plus progestin 1,165 Placebo	**Endometrial cancer** HERS: 2 (0.4 events per 1,000 person-years) vs. 5 (0.9 events per 1,000 person-years); HR, 0.39 (95% CI, 0.08 to 2.02); p=0.26 HERS II: 0 vs. 3 (1.0 events per 1,000 person-years) Interaction between HR in HERS and HERS II: p=0.99 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	Not reported
Cherry, 2002;[67] Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. **ESPRIT Estrogen alone**	Women enrolled in ESPRIT trial: 1,017 Enrolled 513 Estrogen 504 Placebo	**Endometrial cancer** 0 vs.0	208/373 women without hysterectomy had vaginal bleeding with treatment; 189 had biopsy; 8/189 had atypical hyperplasia, 12 complex hyperplasia, 57 simple hyperplasia, and 112 negative biopsy. Endometrium of all women with abnormal biopsy reverted to normal after treatment with medroxyprogesterone or cessation of estrogen. No women required hysterectomies because of bleeding or abnormal histology.
Johnson, 2005;[70] Uterine and vaginal effects of unopposed ultralow-dose transdermal estradiol. **ULTRA Estrogen alone**	Women enrolled in ULTRA trial: 417 Enrolled 208 Estrogen 209 Placebo Analysis focused on women with endometrial biopsy results: 188 Estrogen 177 Placebo	**Endometrial cancer** 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	Benign or atrophic endometrium: 83.5% vs. 86.4%; p=0.5 Proliferative endometrium: 8.5% vs. 1.1%; p=0.06 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

Appendix C8. Evidence Table of Trials Reporting Incidence of Gynecological Cancers

Author, year; title	Population	Results (Treatment vs. Placebo)	
		Gynecological cancer incidence	Other outcomes
			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).

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.

Appendix C9. Evidence Table of Trials Reporting Incidence of Mortality

Author, year; title	Population	Results (Treatment vs. Placebo) Mortality incidence
Heiss, 2008;[33] Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. **WHI Estrogen plus progestin trial**	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] Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy. **WHI Estrogen only trial**	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] Noncardiovascular disease outcomes during 6.8 years of hormone therapy. **HERS II Estrogen plus progestin trial**	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] Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. **ESPRIT Estrogen only trial**	All women enrolled in ESPRIT trial followed through trial completetion	**All-cause mortality** 32 (6.2%) vs. 39 (7.7%); 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

Author, year; title	Population	Results (Treatment vs. Placebo)	
		Gallbladder event incidence	Other outcomes
Cirillo, 2005;[29] 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

Author, year; title	Population	Results (Treatment vs. Placebo)				
		PD incidence	MCI incidence	Other dementia diagnosis outcomes	3MSE Scores	Other measures
Shumaker, 2003;[55] 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. **WHIMS Estrogen plus progestin trial**	Women enrolled in WHI trial aged ≥65 years without probable dementia: 4,532 Enrolled 2,229 Estrogen plus progestin 2,303 Placebo	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	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	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 to1.89); p=NR No differences between groups in type of dementia diagnosed, with majority being diagnosed AD: 20 (50%) vs. 12 (57.1%)	NR	NR
Rapp, 2003;[53] Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. **WHIMS Estrogen plus progestin trial**	Women enrolled in WHI trial aged ≥65 years without probable dementia and with >1 postrandomization 3MSE score: 4,381 Enrolled 2,145 Estrogen plus progestin 2,236 Placebo	NR	NR	NR	**Mean change from baseline in 3MSE** Overall: 0.149 (SE, 0.021) vs. 0.213 (SE, 0.020); difference: -0.063 (95% CI, -1.20 to -0.006); p=0.03	NR
Espeland, 2004;[52] Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. **WHIMS Estrogen plus progestin and estrogen only trial**	Women enrolled in WHI trial aged ≥65 years without probable dementia, enrolled in WHIMS >6 months after initiation of assigned WHI therapy and with >1 post-randomization 3MSE score: 4,344 Enrolled 2,131 Estrogen plus progestin 2,213 Placebo 1,387 Estrogen 1,421 Placebo	NR	NR	NR	**Mean difference in change from baseline in 3MSE** E+P: No differences E: Overall: -0.26 (95% CI, -0.52 to 0.00); p=0.04 No difference between groups on means	NR
Resnick, 2006;[58] Effects of combination estrogen plus progestin hormone treatment on cognition and affect. **WHISCA Estrogen plus progestin trial**	Women enrolled in WHIMS trial, limited to 14 of 39 WHIMS locations: 1,416 Enrolled 690 Estrogen plus progestin 726 Placebo	5 (0.7%) vs. 6 (0.8%)	6 (0.9%) vs. 13 (1.8%)	NR	NR	**Differences** BVRT errors: -0.27 (SE, 0.11); p=0.012 CVLT total list A: -0.52 (SE, 0.20); p=0.0009 CVLT short-delay free: -0.24 (SE, 0.10); p=0.016 CVLT long-delay free: -0.23 (SE, 0.10); p=0.015

Appendix C11. Evidence Table of Trials Reporting Incidence of Cognitive Functioning

Author, year; title	Population	Results (Treatment vs. Placebo)				
		PD incidence	MCI incidence	Other dementia diagnosis outcomes	3MSE Scores	Other measures
Espeland, 2010;[56] 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. **WHISCA Estrogen plus progestin trial**	Women enrolled in WHISCA and participated in extension after termination of trial	NR	NR	NR	NR	**On trial** Global cognitive function: -0.080 (SE, 0.034); p=0.02 **Posttrial** No differences between groups
Shumaker, 2004;[54] Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. **WHIMS Estrogen only trial**	Women enrolled in WHI trial aged ≥65 years without probable dementia: 2947 Enrolled 1464 Estrogen 1483 Placebo	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	7.6 vs. 5.8 per 1,000 person-years HR, 1.34 (95% CI, 0.95 to 1.89); p=NS	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%)	NR	NR
Resnick, 2009;[57] Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. **WHISCA Estrogen only trial**	Women enrolled in WHIMS trial, limited to 14 of 39 WHIMS locations: 866 Enrolled 434 Estrogen 452 Placebo	4 (0.9%) vs. 2 (0.4%)	18 (4.1%) vs. 15 (3.3%)	NR	NR	**Differences in change** Card rotations: 1.26 (SE, 0.48); p=0.008 No other differences on any measures
Espeland, 2010;[56] 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. **WHISCA Estrogen only trial**	Women enrolled in WHISCA and participated in extension after termination of trial	NR	NR	NR	NR	**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

Appendix C11. Evidence Table of Trials Reporting Incidence of Cognitive Functioning

Author, year; title	Population	Results (Treatment vs. Placebo)				
		PD incidence	MCI incidence	Other dementia diagnosis outcomes	3MSE Scores	Other measures
Grady, 2002;[65] Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/Progestin Replacement Study. **HERS Estrogen plus progestin trial**	Completed HERS trial at any 1 of 10 out of 20 centers: 1,063 Enrolled 662 Estrogen plus progestin 666 Placebo	NR	NR	NR	No differences between groups	**Verbal fluency** 15.9 (SD, 4.8) vs. 16.6 (SD, 4.8); difference= -0.7 (95% CI, -1.3 to -0.1); p=0.02 No other differences betweeen groups
Tierney, 2009;[68] A randomized duoble-blind trial of the effects of hormone therapy on delayed verbal recall in older women. **EMS Estrogen plus progestin trial**	Women aged ≥60 years with last menstrual period ≥12 months before, with normal to just below normal scores on cogntive battery tests, but free of dementia: 142 Enrolled 70 Estrogen plus progestin 72 Placebo	NR	NR	NR	No differences between groups	**Of those at or above average scores at baseline (N=37 vs. 36)** Mean adjusted CVLT short-delay recall year 1: 10.37 vs. 8.67; p=0.007 Mean adjusted CVLT short-delay recall year 2: 10.61 vs. 9.02; p=0.01
Yaffe, 2006;[72] Effects of ultra-low-dose transdermal estradiol on cognition and health-related quality of life. **ULTRA Estrogen only trial**	Women aged 60-80 years with an intact uterus and ≥5 years beyond menopause with normal BMD: 417 Enrolled 208 Estrogen 209 Placebo	NR	NR	NR	**Mean difference between groups (estradiol tertile 1 vs. 2 vs. 3)** 3MSE: -2.01 (p<0.001) vs. 0.01 (p=0.99) vs. -0.22 (p=0.73); overall p=0.05 No other differences	No differences between groups on any tests

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

Author, year; title	Population	Results (Treatment vs. Placebo) Urinary incontinence incidence
Hendrix, 2005;[35] Effects of estrogen with and without progestin on urinary incontinence. **WHI Estrogen plus progestin and estrogen only trials**	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) 4,476 Estrogen (1,526 continent at baseline) 4,517 Placebo (1,547 continent at baseline)	**Results at 1 year** 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=0.001 **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)
Steinauer, 2005;[64] Postmenopausal hormone therapy: does it cause incontinence? **HERS Estrogen plus progestin trial**	Analysis focused on women reporting no episodes of incontinence in the past week at baseline: 1,208 Enrolled 597 Estrogen plus progestin 611 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)
Waetjen, 2005;[71] The effect of ultra-low dose transdermal estradiol on urinary incontinence in postmenopausal women. **ULTRA Estrogen only trial**	Women enrolled in ULTRA trial who were continent at baseline: 605 Eligible 208 Estrogen 209 Placebo	39.0% vs. 36.8%; OR, 1.2 (95% CI, 0.7 to 2.2); p=0.74

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

Author, year; title	Population	Results (Treatment vs. Placebo)
Colorectal cancer		
Ritenbaugh, 2008;[50] 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, 2.12 (95% CI, 1.074 to 4.19) 158.7-163.9: 18 (0.15%) vs. 15 (0.12%); HR, 1.27 (95% CI, 0.64 to 2.52) 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;[49] 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) 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;[42] 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 Plaecbo	**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)
Breast cancer		
Chlebowski, 2010;[25] 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). **Estrogen plus progestin** Intervention phase: 8,506 Postintervention phase: 8,056 Extension phase analyzed: 8,506 **Placebo** Intervention phase: 8,102 Postintervention phase: 7,682 Extension phase analyzed: 8,102	**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

Author, year; title	Population	Results (Treatment vs. Placebo)
Chlebowski, 2003;[28] 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** <u>Without prior menopausal hormone therapy use</u> 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 to1.82) 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 <u>With prior menopausal hormone therapy use</u> Treatment (2,225) 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 <u>Overall</u> 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;[49] 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 completetion of trial (postintervention phase): 10,739 Enrolled 5,310 Estrogen 5,429 Placebo	**Cumulative annualized rates for invasive breast cancer** <u>Age at screening (years)</u> 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;[12] 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 %)** <u>By followup year</u> 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

Author, year; title	Population	Results (Treatment vs. Placebo)
Anderson, 2004;[42] 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 Plaecbo	**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)
Gramling, 2009;[31] Hormone replacement therapy, family history, and breast cancer risk among postmenopausal women. **WHI Estrogen plus progestin trial**	Women enrolled in WHI trial (longitudinal followup): 16,608 Enrolled 8,506 Estrogen plus progestin 8,102 Placebo	**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%)
Urinary incontinence		
Hendrix, 2005;[35] Effects of estrogen with and without progestin on urinary incontinence. **WHI Estrogen plus progestin trial**	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)	**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<0.001 60-69: RR, 2.11 (95% CI, 1.70 to 2.62); p<0.001 70-79: RR, 2.59 (95% CI, 1.77 to 3.81); p<0.001 Duration since menopause (years) <5: RR, 1.21 (95% CI, 0.83 to 1.77) 5 to <10: RR, 1.70 (95% CI, 1.19 to 2.44); p=0.005 10 to <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 Menopaual 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) <5: RR, 1.25 (95% CI, 0.80 to 1.93) 5 to <10: RR, 1.17 (95% CI, 0.80 to 1.70) 10 to <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, 0.65 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)

Appendix C13. Evidence Table of Trials Reporting Outcomes by Subgroups

Author, year; title	Population	Results (Treatment vs. Placebo)
		Mixed urinary incontinence Age at screening (years) 50-54: RR, 2.11 (95% CI, 0.55 to 8.06) 55-59: RR, 1.05 (95% CI, 0.58 to 1.91) 60-69: RR, 1.46 (95% CI, 0.94 to 2.26) 70-79: RR, 2.24 (95% CI, 1.17 to 4.30); p=0.26 Duration since menopause (years) <5: RR,1.32 (95% CI, 0.59 to 2.96) 5 to <10: RR, 1.53 (95% CI, 0.71 to 3.29) 10 to <15: RR, 1.31 (95% CI, 0.67 to 2.56) ≥15: RR, 1.58 (95% CI, 0.99 to 2.50); p=0.73 Menopausal hormone therapy use Never: RR, 1.43 (95% CI, 1.01 to 2.02); p=0.49 Past: RR, 1.39 (0.69 to 2.79) Current: RR, 3.64 (0.79 to 16.79)
Hendrix, 2005;[35] Effects of estrogen with and without progestin on urinary incontinence. **WHI Estrogen only trial**	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)	**Stress urinary incontinence** Age at screening (years) 50-54: RR, 1.13 (95% CI, 0.69 to 1.86) 55-59: RR, 2.32 (95% CI, 1.42 to 3.77); p=0.002 60-69: RR, 2.10 (95% CI, 1.60 to 2.74); p=0.002 70-79: RR, 3.91 (95% CI, 2.31 to 6.60); p=0.002 Duration since menopause (years) <5: RR, 0.95 (95% CI, 0.47 to 1.90) 5 to <10: RR, 2.18 (95% CI, 1.04 to 4.57); p=0.02 10 to <15: RR, 2.01 (95% CI, 1.17 to 3.44); p=0.02 ≥15: RR, 2.56 (95% CI, 1.93 to 3.39); p=0.02 Menopausal hormone therapy use Never: RR, 2.25 (95% CI, 1.72 to 2.95); p=0.55 Past: RR, 2.24 (95% CI, 1.62 to 3.10); p=0.55 Current: RR, 1.60 (95% CI, 0.93 to 2.75) **Urge urinary incontinence** Age at screening (years) 50-54: RR, 0.85 (95% CI, 0.44 to 1.66) 55-59: RR, 0.94 (95% CI, 0.56 to 1.57) 60-69: RR, 1.49 (95% CI, 1.14 to 1.95); p=0.05 70-79: RR, 1.45 (95% CI, 1.07 to 1.98); p=0.05 Duration since menopause (years) <5: RR, 1.37 (95% CI, 0.60 to 3.12) 5 to <10: RR, 1.26 (95% CI, 0.62 to 2.58) 10 to <15: RR, 0.74 (95% CI, 0.43 to 1.26) ≥15: RR, 1.46 (95% CI, 1.16 to 1.84); p=0.35 Menopausal hormone therapy use Never: RR, 1.33 (95% CI, 1.03 to 1.70); p=0.58 Past: RR, 1.23 (95% CI, 0.92 to 1.64) Current: RR, 1.81 (95% CI, 0.94 to 3.49) **Mixed urinary incontinence** Age at screening (years) 50-54: RR, 1.07 (95% CI, 0.38 to 2.99) 55-59: RR, 0.69 (95% CI, 0.23 to 2.06)

Appendix C13. Evidence Table of Trials Reporting Outcomes by Subgroups

Author, year; title	Population	Results (Treatment vs. Placebo)
		60-69: RR, 2.05 (95% CI, 1.25 to 3.35); p=0.04 70-79: RR, 2.63 (95% CI, 1.32 to 5.25); p=0.04 Duration since menopause (years) <5: RR, 2.62 (95% CI, 0.94 to 7.30) 5 to <10: RR, 0.36 (95% CI, 0.7 to 1.74) 10 to <15: RR, 0.89 (95% CI, 0.36 to 2.20) ≥15: RR, 2.11 (95% CI, 1.35 to 3.30); p=0.46 Menopausal hormone therapy use Never: RR, 1.36 (95% CI, 0.85 to 2.18) Past: RR, 2.65 (95% CI, 1.47 to 4.79); p=0.15 Current: RR, 1.75 (95% CI, 0.57 to 5.35) Smoking status Never: RR, 2.57 (95% CI, 1.55 to 4.27); p=0.05 Past: RR, 1.51 (95% CI, 0.89 to 2.58) Current: RR, 0.38 (0.08 to 1.86)
Diabetes		
Margolis, 2004;[38] 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**	Excluded women with self-reported diabetes at baseline: 15,641 Eligible from WHI 8,014 Estrogen plus progestin 7,627 Placebo	**Incidence of new diabetes diagnosis** BMI <25: 32 vs. 34; HR, 1.00 BMI 25-29: 57 vs. 75; HR, 1.77 (95% CI, 1.32 to 2.38); p=0.0002 BMI ≥30: 123 vs. 143; HR, 4.06 (95% CI, 3.09 to 5.35); p<0.0001 Waist circumference >88 cm: 138 vs. 189; HR, 3.57 (95% CI, 2.90 to 4.39); p<0.0001 Change in waist circumference from baseline to year 1 of >2.0 cm: 59 vs. 78; HR, 1.31 (95% CI, 1.04 to 1.65); p=0.020
Bonds, 2006;[43] The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. **Estrogen only trial**	Excluded women with self-reported diabetes at baseline: 9,712 Eligible from WHI 4,806 Estrogen 4,906 Placebo	**Incidence of new diabetes diagnosis** Current smoker: 31 (0.6%) vs. 59 (1.2%); HR, 0.54 (95% CI, 0.35 to 0.84); p=0.02

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.