

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

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Background: Menopausal hormone therapy to prevent chronic conditions is currently not recommended because of its adverse effects.

Purpose: To update evidence about the effectiveness of hormone therapy in reducing risk for chronic conditions and adverse effects, and to examine whether outcomes vary among women in different subgroups.

Data Sources: MEDLINE (January 2002 to November 2011), Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the 3rd quarter of 2011), Scopus, and reference lists.

Study Selection: Randomized, placebo-controlled trials of menopausal hormone therapy published in English since 2002 that assessed primary prevention of chronic conditions.

Data Extraction: Investigators extracted data on participants, study design, analysis, follow-up, and results; 2 investigators independently rated study quality by using established criteria.

Data Synthesis: 9 fair-quality trials met the inclusion criteria. The Women's Health Initiative reported most of the results, had 11 years of follow-up, and had data most applicable to postmenopausal women in the United States. It showed that estrogen plus progestin reduced fractures (46 fewer per 10 000 woman-years) and increased invasive breast cancer (8 more per 10 000 woman-years), stroke (9 more per 10 000 woman-years), deep venous thrombosis (12 more per 10 000 woman-years), pulmonary embolism (9 more per 10 000 woman-years), lung cancer death (5 more per 10 000 woman-years), gallbladder disease (20 more per 10 000 woman-years), dementia (22 more per 10 000 woman-years), and urinary incontinence (872 more per 10 000 woman-years). Estrogen-only therapy reduced fractures (56 fewer per 10 000 woman-years) and invasive breast cancer incidence (8 fewer per 10 000 woman-years) and death (2 fewer per 10 000 woman-years) and increased stroke (11 more per 10 000 woman-years), deep venous thrombosis (7 more per 10 000 woman-years), gallbladder disease (33 more per 10 000 woman-years), and urinary incontinence (1271 more per 10 000 woman-years). Outcomes did not consistently differ by age or comorbid conditions.

Limitation: Limitations of the trials included low adherence, high attrition, inadequate power to detect risks for some outcomes, and evaluation of few regimens.

Conclusion: Estrogen plus progestin and estrogen alone decreased risk for fractures but increased risk for stroke, thromboembolic events, gallbladder disease, and urinary incontinence. Estrogen plus progestin increased risk for breast cancer and probable dementia, whereas estrogen alone decreased risk for breast cancer.

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Menopausal hormone therapy includes various forms, doses, and regimens of estrogen, alone or combined with progestin (1). The combined regimen is used by a woman with a uterus to prevent endometrial proliferation and endometrial cancer (1). Before the WHI (Women's Health Initiative) trials (2, 3), menopausal hormone therapy was routinely used by postmenopausal women to prevent chronic conditions, such as cardiovascular disease, dementia, and osteoporosis. However, the initial results of the trials, published for estrogen plus progestin in 2002 (2, 3) and for estrogen only in 2004 (2, 3), indicated important adverse health effects. In response, the U.S. Preventive Services Task Force (USPSTF) issued recommendations against using hormone therapy to prevent chronic conditions for estrogen plus progestin in 2002 (4) and for estrogen only in 2005 (5). Several other professional groups provided similar recommendations (6–10). The current indications for use from the U.S. Food and Drug Administration include short-term treatment of menopausal symptoms, such as vasomotor hot flashes or urogenital atrophy, and prevention of osteoporosis (1).

Our systematic review for the USPSTF updates evidence about the effectiveness of hormone therapy in reducing risks for chronic conditions and its adverse effects, and examines differences in outcomes among population subgroups. Use of hormone therapy to treat menopausal symptoms or for other indications is outside its scope. This update focuses on studies published since 2002 and evidence gaps that were unresolved at the time of the previous recommendations.

METHODS

Key Questions and Analytic Framework

We developed and followed a standard protocol. A technical report (11) details the methods and includes

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Web-Only

CME quiz

search strategies and additional evidence tables. Key questions were based on evidence from the previous review (12) and developed by using the methods of the USPSTF (13) to address the benefits and harms of menopausal hormone therapy to prevent chronic conditions and differences between population subgroups. Subgroups are defined by premature menopause; surgical menopause; age; type, dose, and method of hormone delivery; and presence of comorbid conditions. Investigators created an analytic framework incorporating the key questions and outlining the patient populations, interventions, outcomes, and harms (Appendix Figure 1, available at www.annals.org).

The target population includes postmenopausal adult women eligible for hormone therapy. Women with known contraindications, such as thrombotic disorders or hormone-sensitive cancer (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 (deep venous thrombosis [DVT] and pulmonary embolism [PE]); cancer of the breast, colon, lung, endometrium, or ovaries; fractures at various sites; cognition and dementia; disease-specific and all-cause mortality; and new findings reported by the trials. This review 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.

Data Sources and Searches

In conjunction with a research librarian, we searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the 3rd quarter of 2011), MEDLINE (2002 to 30 November 2011), reference lists of papers, and Scopus for relevant English-language studies and systematic reviews.

Study Selection

We selected studies on the basis of inclusion and exclusion criteria developed for each key question. For all key questions, we included only randomized, controlled trials of postmenopausal hormone therapy versus placebo. We did not include observational studies because of the existence of published randomized trials designed to address the key questions directly and the known biases inherent in observational studies of menopausal hormone use. We included trials that matched the target population, evaluated the primary prevention of new conditions rather than treatment of existing conditions, and provided risk reduction or elevation estimates for hormone therapy compared with placebo. We included estimates for individual hormone therapy regimens and excluded estimates that pooled results from different regimens. For trials that enrolled women with preexisting conditions, such as CHD in HERS (Heart and Estrogen/progestin Replacement Study), we used data for all outcomes except preexisting conditions and related conditions.

For trials that reported outcomes at various times, we selected results appropriate to specific outcome measures. For conditions known to be related to ongoing exposure to hormone therapy, such as thromboembolic disease and osteoporotic fractures, we selected results reported at the end of the trial intervention phase. For conditions that were initiated during exposure but continued after the intervention phase, such as cancer, we used results reported at the end of the trial's postintervention phase, if available. We reviewed our selection of results from the WHI trials with the WHI investigators.

Data Extraction and Quality Assessment

From the included studies, an investigator abstracted details of the patient population, study design, analysis, follow-up, and results. Key data elements were confirmed by a second investigator. By using predefined criteria developed by the USPSTF for randomized trials (13), 2 investigators independently rated the quality of studies (good, fair, or poor) and resolved discrepancies by consensus.

Data Synthesis and Analysis

We used results from the WHI trials, including the main trials, WHIMS, and WHISCA, as the main estimates for each outcome rather than perform meta-analysis of all trials because the trials were heterogeneous, the WHI trials were most applicable to the key questions, and the results from these trials would dominate the meta-analysis because of their large enrollment. As a group, the research team used methods developed by the USPSTF to assess the overall quality of the body of evidence for each key question (good, fair, or poor) on the basis of the number, quality, and size of studies; consistency of results between studies; and directness of evidence (13).

External Review

The draft report was reviewed by content experts, USPSTF members, the Agency for Healthcare Research and Quality (AHRQ) program officers, and collaborative partners.

Role of the Funding Source

The AHRQ funded this research under a contract to support the work of the USPSTF. Researchers worked with USPSTF members and AHRQ staff to define the scope, analytic framework, and key questions; resolve issues arising during the project; and review the final report to ensure that it met basic methodological standards for systematic reviews. The AHRQ provided project oversight, reviewed the draft report, and distributed the draft for external review by outside experts. The AHRQ had no role in the selection, critical appraisal, or synthesis of evidence. The investigators were solely responsible for the content and the decision to submit the manuscript for publication.

RESULTS

Of 4524 abstracts identified from searches, 51 full-text articles from 9 trials (2, 3, 14–62) met our inclusion criteria (**Appendix Figure 2**, available at www.annals.org). We also included an article with new results from the WHI (63), which was published after our literature search.

Characteristics of Included Trials

The 9 placebo-controlled trials were the 2 main WHI trials (2, 3, 14–40, 63), WHIMS (Women's Health Initiative Memory Study) (41–45), WHISCA (Women's Health Initiative Study of Cognitive Aging) (46–48), EMS (Estrogen Memory Study) (49), HERS (50–56), ESPRIT (Oestrogen in the Prevention of Reinfarction Trial) (57), ULTRA (Ultra-Low-Dose Transdermal Estrogen Assessment) (58–61), and WISDOM (Women's International Study of Long-Duration Oestrogen After Menopause) (62) (**Appendix Table**, available at www.annals.org).

The main WHI trials compared conjugated equine estrogen (CEE), 0.625 mg/d, plus medroxyprogesterone acetate (MPA), 2.5 mg/d, with placebo (64) or CEE only with placebo (2) in women with hysterectomies. The trials recruited women aged 50 to 79 years at several sites in the United States, enrolling 16 608 in the estrogen plus progestin trial and 10 739 in the estrogen-only trial. The primary outcome was CHD, and the primary adverse event outcome was invasive breast cancer. Secondary outcomes included fracture incidence at the hip and other sites; stroke; thromboembolism; endometrial, colorectal, and other types of cancer; and mortality. A global index of risks and benefits, including the primary outcomes as well as stroke, PE, colorectal cancer, hip fracture, and death from other causes, was used to summarize overall effects.

The data and safety monitoring boards stopped both trials early because of increased adverse effects of hormone therapy. Although planned for 8.5 years, the estrogen plus progestin trial was stopped in 2002 after an average of 5.2 years because the increases in breast cancer, CHD, stroke, and PE outweighed the reductions in fractures and colon cancer (3). After participants stopped receiving medication, follow-up assessments of outcomes continued until the end of the pre-defined trial period in 2005 (28); 95% of participants were followed for a postintervention period of 2.5 years (18) and 83% for a further extension period until 2009 (18), for a cumulative follow-up of 11 years. The estrogen-only trial was terminated in 2004 because of an increased risk for stroke in the estrogen group after an average follow-up of 6.8 years. Approximately 78% of participants agreed to continue follow-up for a total of 10.7 years (18, 34).

The WHI was not a head-to-head trial of estrogen plus progestin versus estrogen only. Moreover, the characteristics of women enrolled in the 2 main WHI trials differed (**Table 1**) (2, 3). Women in the estrogen-only trial had more risk factors for cardiovascular disease, including higher body mass index (BMI); history of myocardial infarctions, stroke, and thromboembolism; higher systolic

and diastolic blood pressure; and treatment for elevated cholesterol levels, hypertension, and diabetes. Women in the estrogen-only trial had fewer risk factors for breast cancer, including previous hysterectomy and bilateral oophorectomy, lower rates of nulliparity, and a smaller proportion of women who first became pregnant at age 30 years or older. More women in the estrogen-only trial had relatives with breast cancer and higher BMI, both of which increase risk for breast cancer.

Three trials were designed for cognitive outcomes, including the WHIMS and WHISCA trials of women enrolled in the main WHI trials. WHIMS (45) evaluated the effect of hormone therapy on probable dementia in women aged 65 years or older with normal cognition by using the Modified Mini-Mental State Examination. Secondary outcomes were mild cognitive impairment and global cognitive function. WHISCA (47, 48) enrolled women from 14 of the 39 WHIMS sites to evaluate cognitive function by using a battery of tests. The EMS (49) is a small trial of a cyclic regimen of 17- β estradiol plus norethindrone versus placebo that reported measures of memory (short-delay verbal recall, immediate recall, new list recall, cued recall, and recognition memory).

Two secondary prevention trials evaluated the effect of hormone therapy on CHD events and several additional outcomes. HERS, which compared CEE plus MPA with placebo, enrolled 2763 postmenopausal women with established CHD (50, 54). Primary outcomes included nonfatal myocardial infarction or CHD death. Secondary outcomes included other CHD events, vascular disease, cancer, thromboembolism, gallbladder disease, fractures, mortality, uterine bleeding, and other adverse effects. The trial ended after 4 years; study medication was stopped, although women were instructed to continue hormone therapy under the guidance of their physicians, and follow-up (HERSII) continued for a cumulative period of 6.8 years (52, 53). ESPRIT, which compared estradiol valerate with placebo, enrolled 1017 postmenopausal women who had just survived their first myocardial infarction (57). 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 adherence to treatment.

Two other trials provided limited results. The ULTRA trial (58) compared an ultra-low dose of transdermal estradiol (0.014 mg/d) with placebo to evaluate bone mineral density, clinical fractures, endometrial hyperplasia, urinary incontinence, and cognitive function. WISDOM (62) was designed to measure long-term outcomes of CEE plus MPA, primarily major cardiovascular disease events, osteoporotic fractures, and breast cancer. The study closed during the recruitment phase, follow-up was short, the power of the study was greatly reduced, and most outcomes were not obtained.

All trials met the criteria for fair quality. High attrition or low adherence to medications was the most common

Table 1. Baseline Characteristics of WHI Trial Participants

Characteristic	Estrogen Plus Progestin Trial		Estrogen-Only Trial	
	Estrogen Plus Progestin	Placebo	Estrogen	Placebo
Participants, <i>n</i>	8506	8102	5310	5429
Mean duration of trial, y		5.2		6.8
Adherence at end of trial, %	58	62		46.2
Participants starting hormone therapy on their own during trial, %	6.2	10.7	5.7	9.1
Mean age at enrollment, y	63.2	63.3	63.6	63.6
Nonwhite race, %	16.1	16.0	24.5	24.9
Previous or current hormone use, %	26.1	25.6	47.8	48.9
Hysterectomy at age <40 y, %		NA	39.8	39.8*
Hysterectomy at age 40–49 y, %		NA	43.2	42.2*
Bilateral oophorectomy, %		NA	39.5	42.0*
Never pregnant, %	10.1	10.3†	9.3	8.5
First pregnancy at age ≥30 years, %	10.6	9.7†	4.9	5.9
Female relative had breast cancer, %	16.0	15.3	18.0	17.1‡
Current smoker, %	10.5	10.5	10.3	10.6
Mean body mass index, kg/m ²	28.5	28.5	30.1	30.1‡§
Myocardial infarction, %	1.6	1.9	3.1	3.2§
Stroke, %	0.7	1.0	1.4	1.7§
Deep venous thrombosis or pulmonary embolism, %	0.9	0.8	1.6	1.5§
Mean systolic BP, mm Hg	127.6	127.8	130.4	130.2§
Mean diastolic BP, mm Hg	75.6	75.8	76.5	76.5§
Treated for hypertension or BP >140/90 mm Hg, %	35.7	36.4	48.0	47.4§
Elevated cholesterol level requiring medication, %	12.5	12.9	14.5	15.9§
Aspirin use at baseline, %	19.1	20.1	19.4	19.7
Treatment for diabetes, %	4.4	4.4	7.7	7.6§
Fracture at age ≥55 y, %	13.5	13.6	14.0	13.2

BP = blood pressure; NA = not applicable; WHI = Women’s Health Initiative.
 * Decreased risk for breast cancer among participants in the WHI estrogen-only trial.
 † Increased risk for breast cancer among participants in the WHI estrogen plus progestin trial.
 ‡ Increased risk for breast cancer among participants in the WHI estrogen-only trial.
 § Increased risk for cardiovascular disease among participants in the WHI estrogen plus progestin trial.

deficit (WHI [14, 28, 34], HERS [50, 54], and ESPRIT [57]). In the WHI estrogen plus progestin trial, 42% of participants in the hormone group and 38% in the placebo group stopped taking study medications during the trial (14, 28), whereas 54% discontinued therapy in the estrogen-only trial (34). For both WHI trials, the drop-in and drop-out rates exceeded design projections. The WHI trials (2, 3) and WISDOM (62) were discontinued prematurely because of adverse events. Other methodological limitations included differences between groups at baseline (WHIMS [44, 45], HERS [50, 54], and ULTRA [61]), small sample size (EMS [49]), short follow-up periods (WISDOM [62]), unclear ascertainment of some outcomes (WHISCA [47, 48], EMS [49], and WHI [15, 30, 36, 55]), and unblinding of treatment groups (WHI [2, 3] and HERS [52, 53]).

Benefits of Menopausal Hormone Therapy to Prevent Chronic Conditions

The results of the trials indicated benefits for women randomly assigned to hormone therapy that varied by regimen (Table 2 provides estimates of relative and absolute benefits). Women receiving estrogen only in the WHI trial had reduced incidence of invasive breast cancer (hazard ratio [HR], 0.77 [95% CI, 0.62 to 0.95]) (34) and reduced breast cancer mortality (HR, 0.37 [CI, 0.13 to 0.91]) (63). Colorectal cancer was reduced for women who received

estrogen plus progestin (HR, 0.75 [CI, 0.57 to 1.00]) (28), although the results were of borderline statistical significance. Colorectal cancer was not reduced for women who received estrogen only in the WHI trial (34) or estrogen plus progestin in HERS (53).

The incidence of diabetes was reduced for women who received estrogen plus progestin in the WHI trial (HR, 0.79 [CI, 0.67 to 0.93]) (36) and in HERS (HR, 0.65 [CI, 0.48 to 0.89]) (55) but not in the WHI estrogen-only trial (15). Diabetes was diagnosed by self-report in the WHI trial and fasting glucose levels of 6.9 mmol/L or greater (≥124.3 mg/dL) in HERS.

Both estrogen plus progestin and estrogen reduced hip, vertebral, and total fractures in the WHI trials (28) but not in HERS (53). For estrogen plus progestin, estimates included HRs of 0.67 (CI, 0.47 to 0.95) for hip, 0.68 (CI, 0.48 to 0.96) for vertebral, and 0.76 (CI, 0.69 to 0.83) for total fractures (28). The results of the estrogen-only trial were similar (28).

Harms of Menopausal Hormone Therapy to Prevent Chronic Conditions

The results of the trials indicated several important adverse effects for women randomly assigned to receive hormone therapy (Table 2 provides estimates of relative and absolute risks for harms). Incidence of invasive breast cancer was reduced in the WHI estrogen-only trial but

Table 2. Results of the Women's Health Initiative Trials

Outcome	Estrogen Plus Progestin Versus Placebo			Estrogen-Only Versus Placebo		
	Hazard Ratio (95% CI)	Reference	Difference in events per 10 000 women-years (95% CI)*	Hazard Ratio (95% CI)	Reference	Difference in events per 10 000 women-years (95% CI)*
Cancer						
Invasive breast	1.25 (1.07–1.46)†	18	8 (3–14) more	0.77 (0.62–0.95)†	34	8 (1–14) fewer
Colorectal	0.75 (0.57–1.00)‡	28	–	1.11 (0.82–1.50)§	34	–
Lung	1.23 (0.92–1.63)	21	–	1.17 (0.81–1.69)	19	–
Endometrial	0.78 (0.52–1.16)§	28	–	Not reported	–	–
Ovarian	1.58 (0.77–3.24)	14	–	Not reported	–	–
Cervical	1.44 (0.47–4.42)	14	–	Not reported	–	–
Cardiovascular events						
Coronary heart disease	1.22 (0.99–1.51)‡	28	–	0.95 (0.78–1.15)§	34	–
Stroke	1.34 (1.05–1.71)§	28	9 (2–15) more	1.36 (1.08–1.71)§	34	11 (2–20) more
Thromboembolic events						
Deep venous thrombosis	1.88 (1.38–2.55)§	28	12 (6–17) more	1.47 (1.06–2.05)§	34	7 (1–14) more
Pulmonary embolism	1.98 (1.36–2.87)§	28	9 (4–14) more	1.37 (0.90–2.07)§	34	–
Diabetes¶	0.79 (0.67–0.93)	36	15 (4–26) fewer	0.88 (0.77–1.01)	15	–
Fractures						
Hip	0.67 (0.47–0.95)§	28	6 (1–10) fewer	0.61 (0.41–0.91)	2	7 (1–12) fewer
Vertebral	0.68 (0.48–0.96)§	28	6 (1–11) fewer	0.62 (0.42–0.93)	2	6 (1–12) fewer
Total**	0.76 (0.69–0.83)§	28	46 (29–63) fewer	0.70 (0.63–0.79)	2	56 (37–75) fewer
Mortality						
All-cause	1.04 (0.91–1.18)§	28	–	1.02 (0.91–1.15)§	34	–
Breast cancer	1.96 (1.00–4.04)	18	–	0.37 (0.13–0.91)	63	2 (1–3) fewer
Lung cancer	1.71 (1.16–2.52)	21	5 (1–8) more	Not reported	–	–
Gallbladder disease††	1.61 (1.30–2.00)	23	20 (11–29) more	1.79 (1.44–2.22)	23	33 (20–45) more
Cognitive function						
Probable dementia	2.05 (1.21–3.48)	45	22 (5–39) more	1.49 (0.83–2.66)	44	–
Mild impairment	1.07 (0.74–1.55)	45	–	1.34 (0.95–1.89)	44	–
Urinary incontinence‡‡	1.39 (1.27–1.52)	30	872 (591–1153) more	1.53 (1.37–1.71)	30	1271 (883–1660) more

* Assumes a constant rate of events across the study period, although rates actually varied by outcome (e.g., thromboembolic events occurred early during therapy whereas cases of cancer occurred later).

† Updated results are statistically significant, initial results were not.

‡ Updated results are not statistically significant, initial results were.

§ Updated results are similar to initial results.

|| Myocardial infarctions and death from coronary heart disease.

¶ Self-reported new diagnosis requiring treatment with drugs.

** Includes all reported clinical fractures except fractures of the ribs, chest or sternum, skull or face, fingers, toes, and cervical vertebrae.

†† Cholecystitis or cholelithiasis.

‡‡ Stress, urge, or mixed urinary incontinence.

increased in the estrogen plus progestin trial (HR, 1.25 [CI, 1.07 to 1.46]) (18). Hormone users also had more abnormal mammography results, larger-sized tumors, and more advanced stages of breast cancer (18, 20). Other types of cancer, including lung, endometrial, ovarian, and cervical cancer, were not increased in the estrogen plus progestin trial (14, 21, 28), and lung cancer was not increased in the estrogen-only trial (19). Invasive breast, lung, and endometrial cancer were not increased in HERSII (53).

Contrary to the cardioprotective effects initially hypothesized by the WHI investigators, women randomly assigned to receive estrogen plus progestin in the WHI trial had increased incidence of CHD, including nonfatal myo-

cardial infarction and CHD death (HR, 1.22 [CI, 0.99 to 1.51]), that was not statistically significant (28). Coronary heart disease was not increased in women randomly assigned to receive estrogen only (34).

Stroke was increased for both estrogen plus progestin (HR, 1.34 [CI, 1.05 to 1.71]) (28) and estrogen only (HR, 1.36 [CI, 1.08 to 1.71]) (34) in the WHI trials. Thromboembolic events were also increased in the WHI estrogen plus progestin (HR, 1.88 [CI, 1.38 to 2.55] for DVT and 1.98 [CI, 1.36 to 2.87] for PE [28]) and estrogen-only (HR, 1.47 [CI, 1.06 to 2.05] for DVT and 1.37 [CI, 0.90 to 2.07] for PE [34]) trials.

No statistically significant increases in all-cause mortality were observed in the WHI estrogen plus progestin

(28) or estrogen-only (34) trials, HERSII (53), or ESPRIT (57). Death from breast cancer (HR, 1.96 [CI, 1.00 to 4.04]) (18) and lung cancer (HR, 1.71 [CI, 1.16 to 2.52]) (21) were increased for women in the WHI estrogen plus progestin trial, although results for breast cancer mortality were of borderline statistical significance.

Gallbladder disease was increased in both WHI trials (HR, 1.61 [CI, 1.30 to 2.00] in the estrogen plus progestin trial and 1.79 [CI, 1.44 to 2.22] in the estrogen-only trial), as were cholecystectomy and cholecystitis (23).

Measures of impaired cognitive function were increased for probable dementia (HR, 2.05 [CI, 1.21 to 3.48]) but not for mild cognitive impairment (45) in women in the WHI estrogen plus progestin trial. These measures were not increased in the WHI estrogen-only trial (44) or the ULTRA trial (61).

The incidence of overall urinary incontinence was increased for women in the WHI estrogen plus progestin (relative risk, 1.39 [CI, 1.27 to 1.52]) (30) and estrogen-only (relative risk, 1.53 [CI, 1.37 to 1.71]) (30) trials after 1 year of treatment. Further analysis indicated increased risk for different types of urinary incontinence, including stress, urgency, and mixed. In a subsample of estrogen plus progestin users who were continent at baseline but developed incontinence, incontinence persisted during 3 years of follow-up (30). Weekly, stress, and urge incontinence were increased among estrogen plus progestin users in HERS (weekly odds ratio, 1.6 [CI, 1.3 to 1.9]) (56), but urinary incontinence was not significantly increased in the ULTRA trial (60).

Variability of Outcomes in Population Subgroups

Subgroup analyses of results based on individual characteristics were restricted to age and a few comorbid conditions.

In the WHI estrogen plus progestin trial, breast cancer incidence did not significantly differ on the basis of age, BMI, Gail risk score (18, 20), or first-degree family history (26) but increased with previous use of oral contraceptives (20) or menopausal therapy with estrogen plus progestin (18, 20) and with current smoking (20). Age also had no effect on the relationship between hormone therapy and breast cancer incidence in the WHI estrogen-only trial (2), but risks were significantly reduced in women without a previous biopsy indicating benign breast disease or a family history of breast cancer (63).

Subgroup analyses of the WHI estrogen plus progestin trial indicated no statistically significant interactions between several risk factors, hormone therapy, and CHD, except for women with elevated levels of low-density lipoprotein cholesterol at baseline (35). Overall, CHD events were increased during the first year of the trial compared with later years (35). Similar analyses for the estrogen-only trial indicated that women with elevated levels of C-reactive protein at baseline who received estrogen had a greater risk for CHD, but the results of all other analyses

were not statistically significant (33). An additional subgroup analysis of the 2 WHI trials indicated that women initiating hormone therapy within 10 years of menopause had a statistically nonsignificant reduction in CHD risk compared with an increased risk among women initiating therapy 20 or more years since menopause (38).

Risk for stroke was similar for all subgroups evaluated for the 2 WHI trials (28, 34). For thromboembolic disease, use of estrogen plus progestin increased the risks associated with older age, being overweight or obese, or having factor V Leiden (25). Analysis of subgroups in the WHI estrogen-only trial indicated no associations with venous thrombosis (24).

The protective effect of estrogen plus progestin on fractures did not differ by age, BMI, smoking status, history of falls, personal or family history of fracture, calcium intake, previous hormone therapy, bone mineral density, or fracture risk score in the WHI trial (17). No subgroup differences were found in WHIMS (42, 43). In the WHI trials, urinary incontinence was related to older age and increasing time since menopause (30). In HERS, urinary incontinence was not increased among estrogen plus progestin users younger than 60 years (56).

DISCUSSION

We found that 9 trials published since 2002 provided outcome data relevant to USPSTF recommendations for postmenopausal hormone therapy (Table 3). Trials included the 2 main WHI trials, 2 trials consisting of subsamples from the WHI trials (WHIMS and WHISCA), EMS, HERS, ESPRIT, ULTRA trial, and WISDOM. Only the WHI trials were designed and powered to evaluate the effectiveness of hormone therapy for primary prevention of several conditions that were the focus of this review. The WHI trials met criteria for fair quality, provided most of the estimates of benefits and harms, had 11 years of follow-up, and were most applicable to the target population. Although results of the other trials were consistent with the WHI trials for selected outcomes, they measured few outcomes and were often inadequately powered to detect potentially important differences among groups.

The results of the WHI trials indicated some benefits with hormone therapy. Women randomly assigned to estrogen plus progestin had fewer fractures (hip, 6 fewer per 10 000 woman-years; vertebral, 6 fewer per 10 000 woman-years; and total, 46 fewer per 10 000 woman-years) and fewer cases of diabetes (15 fewer per 10 000 woman-years) than those randomly assigned to placebo. Women randomly assigned to estrogen only had fewer fractures (hip, 7 fewer per 10 000 woman-years; vertebral, 6 fewer per 10 000 woman-years; and total, 56 fewer per 10 000 woman-years) and fewer cases of invasive breast cancer (8 fewer per 10 000 woman-years) and breast cancer deaths (2 fewer per 10 000 woman-years). Whereas frac-

Table 3. Summary of Evidence

Key Question	Studies, n	Design	Limitations	Consistency	Applicability	Overall Quality	Findings
1. What are the benefits of menopausal hormone therapy when used to prevent chronic conditions? Potential benefits include reduced fractures and colorectal cancer.	9	RCT	High attrition rates, differential loss to follow-up, and low adherence	Consistent	High	Fair	In the WHI estrogen plus progestin trial, diabetes and hip, vertebral, and total fractures were significantly reduced compared with placebo. In the WHI estrogen-only trial, invasive breast cancer incidence and death and hip, vertebral, and total fractures were reduced. Women in HERS who received estrogen plus progestin had reduced diabetes but not fractures.
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, endometrial, or ovarian cancer; and cholecystitis.	9	RCT	High attrition rates, differential loss to follow-up, and low adherence	Consistent	High	Fair	In the WHI estrogen plus progestin trial, invasive breast cancer incidence, 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 venous thrombosis, gallbladder disease, and urinary incontinence were increased. Women in HERS who received estrogen plus progestin had increased urinary incontinence.
3. Do benefits and harms differ by subgroups? Subgroups include women with premature menopause or surgical menopause and groups by age of use; type, dose, and mode of delivery of hormones; and presence of comorbid conditions.	9	RCT	Some subgroups included in this review were not evaluated in trials	Not relevant	Not relevant	Varies	Subgroup comparisons were limited and inconclusive.

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

tures were a major predefined secondary outcome and were determined by clinical and radiographic criteria, diabetes was diagnosed on the basis of a less rigorous approach by using post hoc analysis of self-reports. In comparison, women in HERS who received estrogen plus progestin also had reduced risk for diabetes on the basis of blood glucose levels, but not reduced fractures.

The WHI trials also demonstrated several harms. Women randomly assigned to estrogen plus progestin had more cases of invasive breast cancer (8 more per 10 000 woman-years), stroke (9 more per 10 000 woman-years), DVT (12 more per 10 000 woman-years), PE (9 more per 10 000 woman-years), gallbladder disease (20 more per 10 000 woman-years), probable dementia (22 more per 10 000 woman-years), and urinary incontinence (872 more per 10 000 woman-years) and more deaths from lung cancer (5 more per 10 000 woman-years) than those randomly assigned to placebo. Women randomly assigned to estrogen only had more cases of stroke (11 more per 10 000 woman-years), DVT (7 more per 10 000 woman-years), gallbladder disease (33 more per 10 000 woman-years), and urinary incontinence (1271 more per 10 000 woman-years). Women in HERS who received estrogen

plus progestin also had increased risk for urinary incontinence.

These results reflect updated estimates from the WHI trials that differ from initial results for some outcomes. For both WHI trials, initial results for invasive breast cancer were not statistically significant. After 11 years of follow-up, results indicated a statistically significant increased risk for breast cancer from estrogen plus progestin and decreased risk from estrogen only. Although the initial results for estrogen plus progestin indicated reduced risk for colorectal cancer and increased risk for CHD, the updated estimates were of only borderline statistical significance. Updated results for other outcomes did not substantially change from initial estimates. As expected, statistically significant results for outcomes related to ongoing hormone exposure, such as stroke, thromboembolism, and fractures, became nonsignificant during the postintervention period (14, 18, 28, 34). The HRs for breast cancer also decreased after estrogen plus progestin therapy was discontinued, although cases continued to accrue (22).

Subgroup analyses were not performed for women who had premature or surgical menopause or used various types, doses, and methods of hormone delivery. Subgroup

analyses based on age and comorbid conditions lacked power for many of the comparisons and indicated few statistically significant differences. These included increased breast cancer for women who received estrogen plus progestin who had previously smoked or used oral contraceptives or postmenopausal estrogen plus progestin; increased CHD for women who received estrogen plus progestin and had high low-density lipoprotein cholesterol levels or who received estrogen only and had high C-reactive protein levels; increased thromboembolic disease for women who received estrogen plus progestin and were older or obese or had factor V Leiden; and increased urinary incontinence for older women who received either regimen. Subgroup analyses of CHD outcomes suggested that women who were 20 years or more since menopause or were aged 70 years or older had the highest risks and younger women had lower risk, although these differences were not statistically significant. Other than these findings, trials provided few results applicable to clinical decisions about selecting hormone therapy based on individual patient characteristics.

Our review has limitations. Few trials met our inclusion criteria, although the number of participants was large. Few outcomes were reported in more than 2 trials and measurements varied, limiting comparisons across trials. Most trials had high attrition or low adherence to medications, including the WHI trials, in which nearly one half of the participants discontinued therapy during the trial. Post hoc analysis, small sample sizes, and differential adherence rates also limited the interpretation of results. Our review was limited to trials published in English, although no relevant trials were identified from abstracts of non-English-language journals, additional citation searches, or expert reviewers.

Trial participants were generally aged 60 to 69 years, which restricts the applicability of our findings. Research directed at women who are transitioning through menopause or immediately postmenopausal (in other words, most current hormone users) would be useful. Although the U.S. Food and Drug Administration has approved various types, doses, and delivery methods of menopausal hormones with differing physiologic effects (1), prevention trials have largely focused on oral CEE. Additional research is needed to understand the effects of other hormonal agents on health outcomes.

Continuing research is needed on such long-term outcomes as cancer and death to fully understand the implications of hormone therapy. In the WHI estrogen-only trial, a statistically significant reduction in invasive breast cancer incidence and mortality among estrogen users was only recently reported after nearly 11 years of follow-up (34, 63), whereas the results of the estrogen plus progestin trial indicated an increase in breast cancer (18). It is unclear whether this discrepancy is due to the concomitant use of progestin, the differences between women who have

had a hysterectomy and those who have not, or other reasons.

In conclusion, our update of evidence from trials published since 2002 indicates that both hormone therapy regimens decrease risk for fractures but increase risk for stroke, thromboembolic events, gallbladder disease, and urinary incontinence. Estrogen plus progestin also increases risk for breast cancer and probable dementia, whereas estrogen alone decreases risk for breast cancer.

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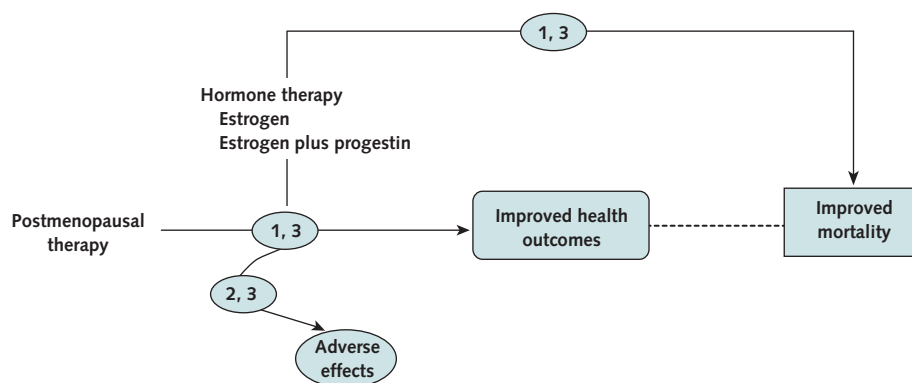
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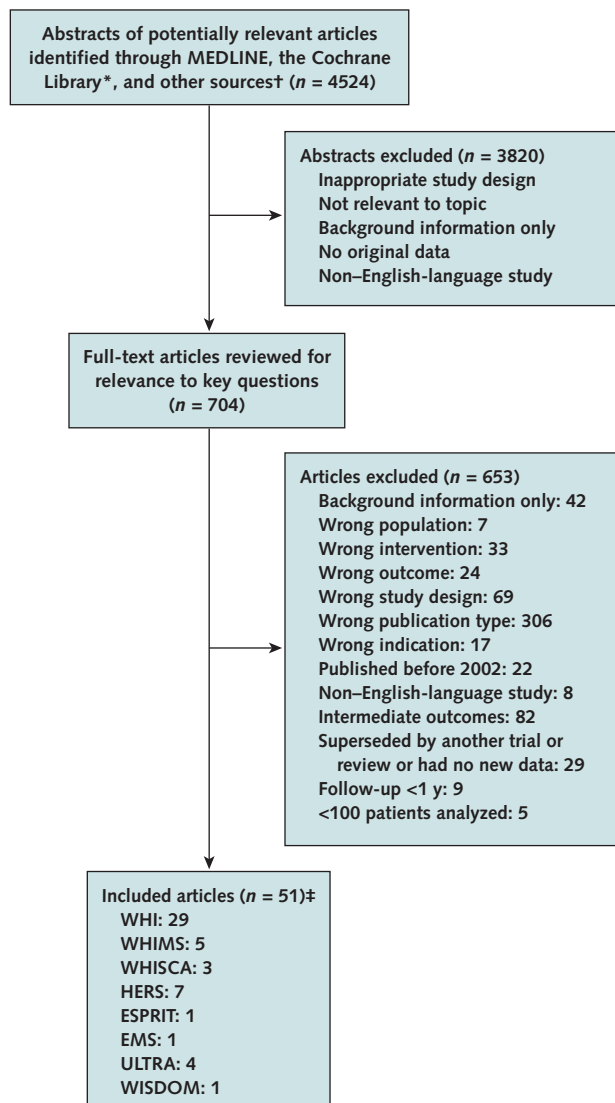
Appendix Figure 1. Analytic framework and key questions.



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, endometrial, or ovarian cancer; and cholecystitis.
3. Do benefits and harms differ by subgroup?
Subgroups include women with premature menopause or surgical menopause and groups by age of use; type, dose, and mode of delivery of hormones; and presence of comorbid conditions.

Appendix Figure 2. Summary of evidence search and selection.



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 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.

* Includes the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

† Includes reference lists, Scopus, and studies suggested by experts.

‡ Studies that met the inclusion criteria for the key questions included in this systematic review.

Appendix Table. Randomized, Controlled Trials Included in This Update

Trial (Reference)	Intervention	Participants	Outcomes
WHI estrogen plus progestin trials			
Main trial (3, 14, 17, 20, 22, 23, 25, 27, 29, 30, 32, 35, 36, 38, 39, 40)	CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, vs. placebo (8506 vs. 8102 participants) for 5.2 y	Postmenopausal women without hysterectomies, aged 50–79 y, recruited across the United States	Invasive breast, colorectal, lung, or endometrial cancer; all-cause mortality; fractures; thromboembolic events (deep venous thrombosis or pulmonary embolism); coronary heart disease events; stroke; diabetes; gallbladder disease; cognitive function; and urinary incontinence
Postintervention phase (21, 28, 26)	CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, vs. placebo for 8.6 years of cumulative use	95% of women from the main trial who provided follow-up information	Invasive breast, colorectal, lung, or endometrial cancer; all-cause mortality; fractures; thromboembolic events; coronary heart disease events; and stroke
Extension phase (18)	CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, vs. placebo for 11 y of cumulative use	83% of women from the main trial who consented for the extension phase	Invasive breast cancer
WHIMS (41, 43, 45)	CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, vs. placebo (2229 vs. 2303 participants) for 4.1 y	WHI trial participants aged >65 y and free of probable dementia	Cognitive function
WHISCA (46, 48)	CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, vs. placebo (690 vs. 726 participants) for 1.4 y	WHIMS trial participants at 1 of 14 WHIMS centers	Cognitive function
WHI estrogen-only trials			
Main trial (2, 15, 16, 19, 23, 24, 30, 31, 33, 37, 38)	CEE, 0.625 mg/d, vs. placebo (5310 vs. 5429 participants) for 6.8 y	Postmenopausal women with hysterectomies, aged 50–79 y, recruited across the United States	Invasive breast, colorectal, or lung cancer; all-cause mortality; fractures; thromboembolic events; coronary heart disease events; stroke; diabetes; gallbladder disease; cognitive function; and urinary incontinence
Extension phase (18, 34, 63)	CEE, 0.625 mg/d, vs. placebo for 10.7 y of cumulative use	78% of women from the main trial who consented for the extension phase	Invasive breast cancer or colorectal cancer, all-cause mortality, fractures, thromboembolic events, coronary heart disease events, and stroke
WHIMS (42, 44)	CEE, 0.625 mg/d, vs. placebo (1464 vs. 1483 participants) for 4.1 years	WHI trial participants aged >65 y and free of probable dementia	Cognitive function
WHISCA (46, 47)	CEE, 0.625 mg/d, vs. placebo (434 vs. 452 participants) for 1.4 years	WHIMS trial participants at 1 of 14 WHIMS centers	Cognitive function
HERS			
Main trial (50, 54–56)	CEE, 0.625 mg/d, plus MPA, 2.5 mg, vs. placebo (1380 vs. 1383 participants) for 4.1 years	Postmenopausal women with established coronary artery disease but no hysterectomies, aged ≤80 y, recruited across the United States	Invasive breast, colorectal, lung, or endometrial cancer; all-cause mortality; fractures; diabetes; cognitive function; and urinary incontinence
Follow-up (HERSII) (52, 53)	CEE, 0.625 mg/d, plus MPA, 2.5 mg, vs. placebo (1156 vs. 1165 participants) for 6.8 years cumulative use	93% of women from the HERS trial who consented for follow-up	Invasive breast, colorectal, lung, or endometrial cancer and all-cause mortality
ESPRIT (57)	Estradiol valerate, 2 mg/d, vs. placebo (513 vs. 504 participants) for 2 y	Women aged 50–60 y admitted to coronary care units or general medical wards, met diagnostic criteria for initial myocardial infarction, and were discharged from the hospital within 31 d of admission	Invasive breast cancer
EMS (49)	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 vs. placebo (70 vs. 72 participants) for 2 y	Postmenopausal women both with and without hysterectomies, age >60 y	Invasive breast cancer and cognitive function
ULTRA (58–61)	Transdermal estradiol, 0.014 mg/d, vs. placebo (208 vs. 209 participants) for 2 y	Postmenopausal women without hysterectomies who had normal bone mineral density	Fractures, cognitive function, and urinary incontinence
WISDOM (62)	CEE, 0.625 mg/d, plus MPA, 2.5–5.0 mg/d, vs. placebo (2196 vs. 2189 participants) for 11.9 mo	Postmenopausal women age 50–69 y	Invasive breast cancer

CEE = conjugated equine estrogen; EMS = Estrogen Memory Study; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HERS = Heart and Estrogen/progestin Replacement Study; MPA = medroxyprogesterone acetate; 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.