JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women

Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Postmenopausal status coincides with increased risks for chronic conditions such as heart disease, osteoporosis, cognitive impairment, or some types of cancers. Previously, hormone therapy was used for the primary prevention of these chronic conditions.

OBJECTIVE To update evidence for the US Preventive Services Task Force on the benefits and harms of hormone therapy in reducing risks for chronic conditions.

DATA SOURCES MEDLINE, Cochrane Library, EMBASE, and trial registries from June 1, 2011, through August 1, 2016. Surveillance for new evidence in targeted publications was conducted through July 1, 2017.

STUDY SELECTION English-language randomized clinical trials reporting health outcomes.

DATA EXTRACTION AND SYNTHESIS Dual review of abstracts, full-text articles, and study quality; meta-analyses when at least 3 similar studies were available.

MAIN OUTCOMES AND MEASURES Beneficial or harmful changes in risks for various chronic conditions.

RESULTS Eighteen trials (n = 40 058; range, 142-16 608; mean age, 53-79 years) were included. Women using estrogen-only therapy compared with placebo had significantly lower risks, per 10 000 person-years, for diabetes (−19 cases [95% CI, −34 to −3]) and fractures (−53 cases [95% CI, −69 to −39]). Risks were statistically significantly increased, per 10 000 person-years, for gallbladder disease (30 more cases [95% CI, 16 to 48]), stroke (11 more cases [95% CI, 2 to 23]), venous thromboembolism (11 more cases [95% CI, 3 to 22]), and urinary incontinence (1261 more cases [95% CI, 880 to 1689]). Women using estrogen plus progestin compared with placebo experienced significantly lower risks, per 10 000 person-years, for colorectal cancer (−6 cases [95% CI, −9 to −1]), diabetes (−14 cases [95% CI, −24 to −3), and fractures (−44 cases [95% CI, −71 to −13). Risks, per 10 000 person-years, were significantly increased for invasive breast cancer (9 more cases [95% CI, 1 to 19]), probable dementia (22 more cases [95% CI, 4 to 53]), gallbladder disease (21 more cases [95% CI, 10 to 34]), stroke (9 more cases [95% CI, 2 to 19]), urinary incontinence (876 more cases [95% CI, 606 to 1168]), and venous thromboembolism (21 more cases [95% CI, 12 to 33]).

CONCLUSIONS AND RELEVANCE Hormone therapy for the primary prevention of chronic conditions in menopausal women is associated with some beneficial effects but also with a substantial increase of risks for harms. The available evidence regarding benefits and harms of early initiation of hormone therapy is inconclusive.

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The onset of menopause coincides with an increased risk for common, preventable diseases such as cardiovascular disease, osteoporosis (and subsequent fractures), cognitive impairment, and some types of cancers. Before publication of the Women's Health Initiative (WHI) in 2002,[1] hormone therapy was commonly prescribed for primary prevention of these conditions in women with and without menopausal symptoms. Hormone therapy has various forms, doses, and regimens of estrogen with or without progestin.[2] Women who have not had hysterectomies use a combination therapy of estrogen plus progestin to prevent endometrial proliferation and endometrial cancer; women who have had hysterectomies use only estrogen.

Natural menopause occurs at a median age of 51.3 years, and questions persist whether the initiation of hormone therapy at a younger age than in the WHI trials (mean age, 63 years) could reduce the risk of cardiovascular disease,[3,4] dementia,[5] and mortality[6] (a concept often referred to as the timing hypothesis).

This review updates evidence on benefits and harms of hormone therapy for the primary prevention of chronic conditions to inform a recommendation by the US Preventive Services Task Force (USPSTF). In 2013, the USPSTF recommended against the use of hormone therapy for the primary prevention of chronic conditions (grade D recommendation).

Methods

Scope of Review

This review updates a previous review for the USPSTF on this topic.[7] Detailed methods are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/final-evidence-review/menopausal-hormone-therapy-preventive-medication1. **Figure 1** presents the analytic framework and key questions (KQs) that guided the review.

Data Sources and Searches

MEDLINE (via PubMed), the Cochrane Library, EMBASE, and International Pharmaceutical Abstracts were searched for English-language articles published from June 1, 2011, through August 1, 2016. Targeted searches were conducted for unpublished literature (ClinicalTrials.gov, the Health Services Research Projects in Process, the World Health Organization International Clinical Trials Registry Platform, NIH Reporter, and Drugs@FDA.gov). This search included relevant citations from the previous review,[7] reference lists of other pertinent review articles, and literature suggested by peer reviewers or public comment respondents. The eMethods in the Supplement present detailed search strategies for electronic databases.

Between August 2016 and July 2017, ongoing surveillance through article alerts and targeted searches of journals with high impact factors helped ensure inclusion of major studies affecting the conclusions or understanding of the evidence and the related USPSTF recommendation.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles to determine eligibility using prespecified criteria for each KQ (eTable 1 in the Supplement). Conflicts were resolved by discussion and consensus.

The review included studies of generally healthy perimenopausal and postmenopausal women who were eligible for hormone therapy. Women with and without menopausal symptoms were included if the focus of the analysis was on either the primary prevention of chronic conditions or harms of hormone therapy. In some cases the review included populations for which use of hormone therapy was intended for secondary prevention if there was an additional focus of the analysis on primary prevention or harms.

The review examined use of systemic therapy (ie, pill, patch, or injection) with estrogen-only formulations or combination preparations of estrogen plus progestin of 1 year or more for the primary prevention of chronic conditions. Medications had to have been approved by the US Food and Drug Administration for this purpose and had to be available for use in the United States (**Table 1**).

For all KQs, the review included trials enrolling women from primary care settings but not inpatient or institutional settings such as nursing homes or similar facilities.

With respect to geography, the review included studies conducted in the United States or in countries designated by the United Nations Development Programme as having a very high Human Development Index.[11]

Data Extraction and Quality Assessment

For each included study, 1 investigator abstracted information about design, population, intervention, comparator, outcome, timing, and setting. A second investigator reviewed for completeness and accuracy. Differences were resolved by consensus or adjudication by a third senior investigator. Two investigators independently assessed the quality of each study as good, fair, or poor using USPSTF predefined criteria.[12] Individual study quality ratings are provided in eTable 2 in the Supplement.

Data Synthesis and Analysis

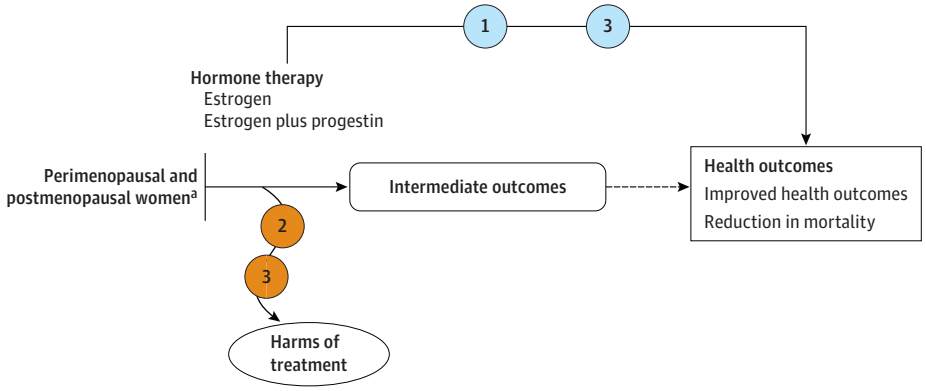
The review includes qualitative synthesis for each KQ. Assessing the number of trials available and their clinical and methodological heterogeneity (following established guidance[13]) helped determine whether meta-analyses were appropriate. When at least 3 similar trials were available, quantitative synthesis of studies with random-effects models was conducted, using the inverse-variance–weighted method (DerSimonian and Laird). For all quantitative syntheses, the χ^2 statistic and the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity rather than chance) were calculated to assess statistical heterogeneity in effects between studies.[14]

The outcome measure for all quantitative analyses was the relative risk of a beneficial or harmful change in risks (eg, increase or reduction of cardiovascular events). Absent meta-analytic estimates, relative risks of outcomes of interest were based primarily on a recent publication summarizing results of the WHI trials.[15] Therefore, effect estimates might differ slightly from hazard ratios reported in earlier WHI publications.

All quantitative analyses were based on Comprehensive Meta-Analysis Version 3 (Biostat Inc). Statistical significance was assumed when 95% CIs of pooled results did not cross the null (ie, 1). All testing was 2-sided.

The strength of evidence was rated for each major outcome using the domains set out in guidance from the Agency for Healthcare Research and Quality.[16] Two reviewers assessed each strength-of-evidence domain for each key outcome and developed the overall

Figure 1. Analytic Framework and Key Questions



Key questions

1 What are the benefits of menopausal hormone therapy when used for the primary prevention of chronic conditions?

2 What are the harms of menopausal hormone therapy when used for the primary prevention of chronic conditions?

3 Do the benefits and harms of menopausal hormone therapy differ by subgroup (race or ethnicity; women with premature menopause; women with surgical menopause; age during hormone therapy use; duration of use; type, dose, and mode of delivery of hormone therapy; and comorbid condition) or by timing of intervention (initiation of hormone therapy during perimenopause vs postmenopause)?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions (KQs) that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. A dashed line indicates a relationship between an intermediate outcome and a health outcome that is presumed to describe the natural progression of the disease. Further details are available in the USPSTF procedure manual.[8]

[a] Definitions of perimenopausal and postmenopausal women are based on STRAW+ 10 criteria.[9]

strength-of-evidence grades. Strength-of-evidence grades reflect the confidence that the reviewers have that various estimates of effect are close to true effects with respect to the KQs in a systematic review.

Results

The searches identified 2241 citations (**Figure 2**). Overall, 68 articles from the previous review[7] and this update represented a total of 18 good- or fair-quality trials. Included articles provided data on 40 058 perimenopausal and postmenopausal women comparing the effects of estrogen, either alone or in combination with progestin, with placebo for the primary prevention of chronic conditions. Of the 18 included trials, 13 were conducted in the United States. The remaining trials came from Australia, Canada, Estonia, New Zealand, and the United Kingdom. The duration of follow-up in the trials averaged 3.5 years. The mean age of women participating in trials ranged from 53[17] to 79[18] years. The majority of participants were white; proportions of women of other races/ethnicities ranged from 1%[19] to 41%.[20]

Table 2 summarizes the main characteristics and quality ratings of eligible trials. Of these trials, 5 were rated as of good quality and 13 as of fair quality. Three trials (described in Table 2) met eligibility criteria[24,30,35]; however, they did not stratify results by regimen (ie, estrogen only or estrogen plus progestin), so their findings could not be used for our analyses.

The WHI trials were the only studies powered to assess the effectiveness of hormone therapy for the primary prevention of various chronic conditions.[15] They enrolled generally healthy postmenopausal women aged 50 to 79 years and compared oral conjugated equine estrogen (0.625 mg/d), with or without medroxyprogesterone (2.5 mg/d), with placebo. The WHI trials had the longest follow-up among included trials (median of 7.2 years for the estrogen-only trial; 5.6 years for the estrogen plus progestin trial). Outcome-specific evidence from the WHI and other trials are available in eTables 3 through 18 in the Supplement.

Benefits of Menopausal Hormone Therapy

Key Question 1. What are the benefits of menopausal hormone therapy when used for the primary prevention of chronic conditions?

Estrogen Only

For women using estrogen only, the risks for osteoporotic fractures and diabetes, and the long-term risk for breast cancer, were statistically significantly reduced. Long-term observational follow-up studies of the WHI showed that, except for a reduced risk of invasive breast cancer, beneficial effects did not persist after stopping hormone therapy. Outcomes with no statistically significant reductions in risk included colorectal cancer, lung cancer, coronary heart disease, probable dementia, quality of life, and all-cause mortality. Some of these nonsignificant outcomes, however, had wide confidence intervals encompassing both clinically relevant benefits and harms, leading to inconclusive results. **Table 3** presents the estimated increases or reductions of events for various outcomes per 10 000 person-years for women who received estrogen-only therapy compared with those who received placebo. Estimates are based on meta-analyses of included trials or, if meta-analyses were not feasible, on results from the largest and most reliable trial (usually the WHI). **Figure 3** depicts the corresponding absolute risk differences with 95% CIs. **Table 4** summarizes the underlying strength of evidence.

Table 1. Systemic Hormone Therapies Approved by the US Food and Drug Administration[2,10]

Hormone Therapy Category and Generic Name	Brand Name	Product Type	Dosage[a]
Estrogen-Only Formulations			
Estradiol[b]	Alora	Patch	0.025 mg to 0.1 mg, worn for 24 h twice weekly
	Climara	Patch	0.025 mg to 0.1 mg, worn for 24 h once weekly
	Estrace	Pill	0.5 mg/d to 2 mg/d
	Estraderm	Patch	0.05 mg to 0.1 mg, continuously or cyclically[c]
	Menostar	Patch	0.014 mg, worn for 24 h once weekly
	Minivelle	Patch	0.025 mg/24 h to 0.1 mg/24 h, worn for 24 h twice weekly
	Vivelle	Patch	0.0375 mg to 0.1 mg daily
	Vivelle-Dot	Patch	0.025 mg to 0.1 mg, worn for 24 h twice weekly
Estradiol acetate[b]	Femtrace	Pill	0.45 mg/d to 1.8 mg/d, daily
Esterified estrogen[b]	Menest	Pill	0.3 mg/d to 1.25 mg/d, cyclically[c]
Estropipate[d]	Ogen	Pill	0.75 mg/d to 3 mg/d
Conjugated estrogens[e]	Premarin	Pill, injection	0.3 mg/d cyclically, single 25-mg injection[c]
Synthetic conjugated estrogens[f]	Enjuvia	Pill	0.3 mg/d
Combination Estrogen + Progestin Formulations			
Estradiol + drospirenone[b,g]	Angeliq	Pill	Drospirenone (0.25 mg/d to 0.5 mg/d) + estradiol (0.5 mg/d to 1 mg/d)
Estradiol + norethindrone acetate[b,f]	Activella	Pill	Estradiol (0.5 mg/d to 1 mg/d) + norethindrone (0.1 mg/d)
	Combipatch	Patch	Estradiol (0.05 mg) + norethindrone (0.14 mg to 0.25 mg), worn for 24 h once weekly
Estradiol + norgestimate[b,g]	Prefest	Pill	Repeat estradiol (1 mg/d) for 3 d, followed by estradiol (1 mg/d) + norgestimate (0.09 mg/d) for 3 d
Estradiol + levonorgestrel[b,g]	Climara Pro	Patch	Estradiol (0.045 mg) + levonorgestrel (0.015 mg), worn for 24 h once weekly
Conjugated estrogen + MPA[g]	Prempro	Pill	Conjugated estrogen (0.625 mg/d) + MPA (5 mg/d)
Ethinyl estradiol + norethindrone acetate[b,f]	Femhrt	Pill	Ethinyl estradiol (0.0025 mg/d) + norethindrone acetate (0.5 mg/d)

Abbreviation: MPA, medroxyprogesterone acetate.

[a] Dosages are based on the package inserts for the brand-name formulations.

[b] Estradiol can be from natural sources or prepared synthetically.

[c] Cyclically indicates "within a cycle," eg, repeat 3 weeks of treatment and 1 week off.

[d] Natural estrogenic substance prepared from purified crystalline estrone.

[e] Conjugated estrogens, such as conjugated equine estrogens, are derived wholly or partially from the urine of pregnant mares or from synthetic estrone and equilin.

[f] Synthetic conjugated estrogens are prepared using plant sources, such yams and soy, and use only synthetic resources.

[g] Synthetic progestin.

The WHI (n = 10 739)[15] reported statistically significant reductions in risk for osteoporotic fractures among women taking estrogen-only therapy compared with women taking placebo (−53 fractures per 10 000 patient-years [95% CI, −69 to −39]). Likewise, based on WHI data (n = 9917), the incidence of diabetes was significantly reduced in women taking estrogen-only therapy (−19 cases per 10 000 patient-years [95% CI, −34 to −3]).[15,37]

Five randomized clinical trials[15,21-23,29,36,48,49,61,77,79] with data on more than 13 000 women reported breast cancer incidence. Trial results were not pooled, primarily because of heterogeneity in study duration and outcome measures. In the WHI (n = 10 739), estrogen alone produced a nonsignificant decrease in invasive breast cancer risk compared with placebo during the 7.2-year (median) intervention phase (−7 cases per 10 000 patient-years [95% CI, −14 +0.4]).[15,48] Between-group differences became statistically significant during cumulative (trial and postintervention phase; median, 13 years) follow-up (hazard ratio [HR], 0.79 [95% CI, 0.65-0.97]).[15]

Estrogen plus Progestin

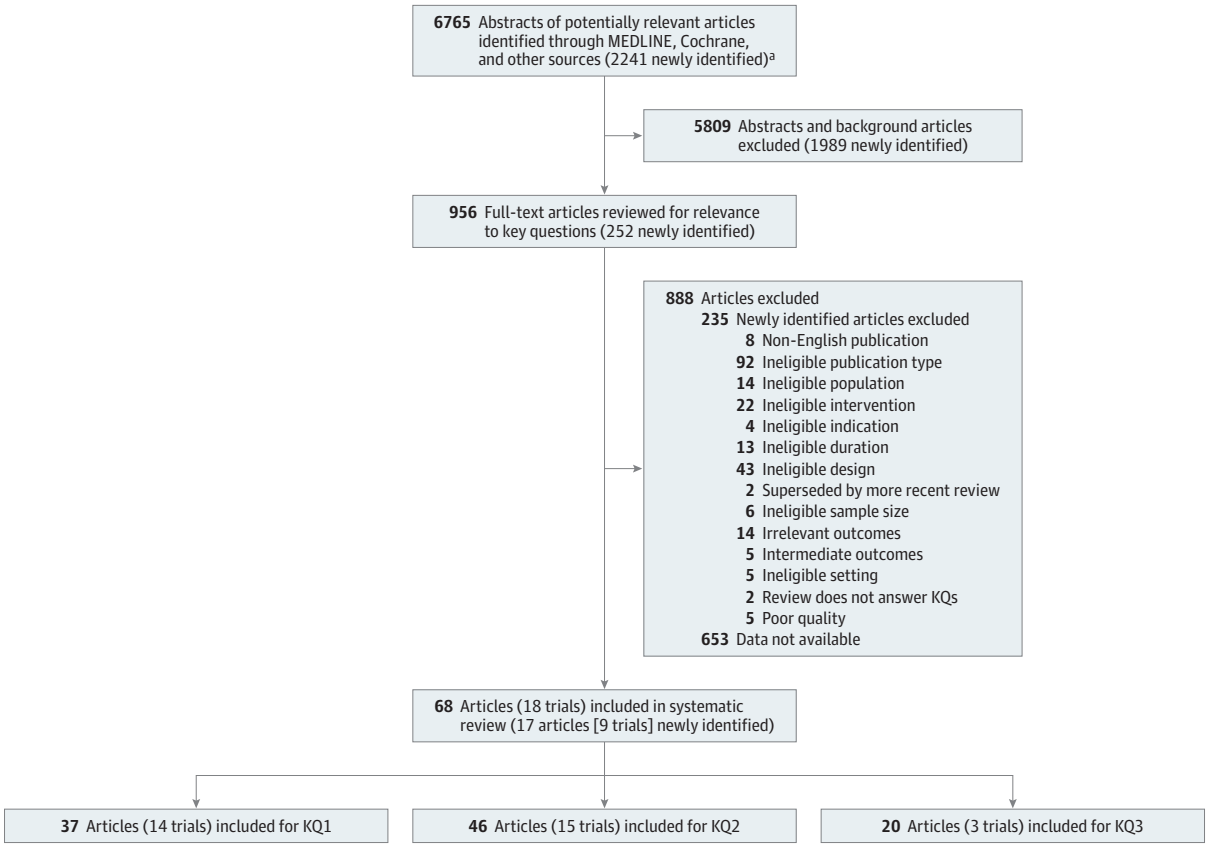
Women taking combination therapy experienced statistically significant reductions in risk for colorectal cancer, osteoporotic fractures, and diabetes compared with women in the placebo groups (Figure 3). Except for a lower risk of colorectal cancer, beneficial associations did not persist after stopping hormone therapy. No statistically significant differences for cervical cancer, endometrial cancer, lung cancer, ovarian cancer, quality of life, and all-cause mortality were found. Some of these nonsignificant outcomes, however, had wide confidence intervals encompassing both clinically relevant benefits and harms, leading to inconclusive results (Table 3 and Figure 3). **Table 5** summarizes the underlying strength of evidence.

Four trials (the WHI [n = 16 608],[1,15,54,61,67] the Estrogen Memory Study [EMS; n = 142],[18] the Heart and Estrogen Replacement Study [HERS; n = 2763],[80] and the Women's International Study of Long Duration Estrogen After Menopause [WISDOM; n = 4385][19]) with data on more than 20 000 women reported on the incidence of colorectal cancer. During the WHI intervention phase, women receiving combination therapy experienced a statistically significant reduction in risk for colorectal cancer (−6 cases per 10 000 patient-years [95% CI, −9 to −1]). The HERS trial reported a numeric decrease in the risk of colorectal cancer with use of estrogen plus progestin during 4.1 years of follow-up (HR, 0.69 [95% CI, 0.32-1.49]); EMS (n = 142) and WISDOM (n = 4385) had too small sample sizes and were of too short duration to have adequate power to detect differences in rates of colorectal cancer (<2 years; zero events in EMS and 4 events in WISDOM).

Estrogen plus progestin therapy protected against incident diabetes among women in HERS (n = 2029)[27] and the WHI (n = 15 874).[60] In the WHI, the larger of the 2 trials, new diabetes diagnoses were significantly reduced in women receiving hormone therapy compared with women receiving placebo (−14 cases per 10 000 patient-years [95% CI, −24 to −3]).[15,60]

Five trials (n = 20 499) reported on fractures: EMS (n = 142),[18] the Estonian Postmenopausal Hormone Therapy Trial (EPHT; n = 777),[20] the Estrogen Replacement and Atherosclerosis Study (ERA; n = 209),[22] HERS (n = 2763),[80] and the WHI (n = 16 608).[1,15,52,67] In our

Figure 2. Summary of Evidence Search and Selection



Six articles from the Women's Health Initiative reported results of unblinded, long-term postintervention follow-up. These articles were used in addressing key questions (KQs) 1 and 2 only.

[a] Searches were conducted of MEDLINE, the Cochrane Library, EMBASE, International Pharmaceutical Abstracts, ClinicalTrials.gov, Drugs@FDA.gov, the Health Services Research Projects in Process, NIH Reporter, and the World Health Organization International Clinical Trials Registry Platform.

random-effects meta-analysis (eFigure 1 in the Supplement), combination therapy was associated with a statistically significant risk reduction for fractures (−44 cases per 10 000 patient-years [95% CI, −71 to −13]).

Harms of Menopausal Hormone Therapy

Key Question 2. What are the harms of menopausal hormone therapy when used for the primary prevention of chronic conditions?

Estrogen Only

Women receiving estrogen-only therapy had statistically significant increases in risk for gallbladder disease, stroke, urinary incontinence, and venous thromboembolism (Table 3 and Figure 3; Table 4 summarizes the strength of evidence). Increased risks did not persist after stopping hormone therapy.

The Postmenopausal Estrogen/Progestin Interventions Trial (PEPI; n = 349)[29] and the WHI (n = 8376)[40] reported increased risks for gallbladder disease in women receiving estrogen-only therapy. In the WHI, the increased risk was statistically significant (30 more cases per 10 000 patient-years [95% CI, 16 to 48]).

Of 3 trials assessing the risk of stroke (Estrogen in the Prevention of Atherosclerosis Trial [EPAT; n = 222],[21] ERA [n = 205], and the WHI [n = 10 739][15,48]), only the WHI provided statistically significant results. Estrogen-only therapy led to a statistically significant increase in risk for stroke (11 more cases per 10 000 patient-years [95% CI, 2 to 23]).

Two trials (the Ultra-Low-Dose Transdermal Estrogen Assessment [ULTRA; n = 239][33] and the WHI [n = 3073][42]) with data on more than 3200 continent women found higher risks of urinary incontinence (self-reported) in the treatment groups for all time points (1261 more cases per 10 000 patient-years [95% CI, 880 to 1689]).

Based on the WHI (n = 10 739) results,[15] women randomized to estrogen-only therapy had a statistically significant increase in risk of venous thromboembolism compared with those randomized to placebo (11 more cases per 10 000 patient-years [95% CI, 3 to 22]).

To balance benefits and harms, the WHI used a global index based on beneficial and harmful events. For estrogen-only therapy, the global index did not show a statistically significant difference in overall beneficial or harmful events (HR, 1.03 [95% CI, 0.93-1.13]).

Estrogen plus Progestin

Women receiving combination therapy had statistically significant increases in risk for invasive breast cancer, probable dementia, gallbladder disease, stroke, urinary incontinence, and venous thromboembolism compared with women receiving placebo (Table 3 and Figure 3; Table 5 summarizes the strength of evidence).

Table 2. Characteristics of Randomized Clinical Trials of Use of Hormone Therapy

Trial Name, Source	Country and Participant Information	Intervention and Duration[a]	Quality Rating[b]
Estrogen Memory Study (EMS) Tierney et al, 2009[18]	Canada Ages 61-87 y Last menstrual cycle >12 mo before screening Fluent in English and could read normal print and hear normal speech	17β-estradiol (1 mg/d for 4 d) then 17β-estradiol (1 mg) + norethindrone (0.35 mg/d) for 3 d, repeated every week (n = 70) Placebo (n = 72) Duration, 2 y	Fair
Estrogen in the Prevention of Atherosclerosis (EPAT) Hodis et al, 2011[21]	United States Ages 46-80 y Postmenopausal women with low-density lipoprotein cholesterol level ≥130 mg/dL	Micronized 17β-estradiol (1 mg/d) (n = 111) Placebo (n = 111) Duration, 2 y	Fair
Estonian Postmenopausal Hormone Therapy Trial (EPHT) Veerus et al, 2003[20]	Estonia Ages 50-64 y An elapsed 12 mo or more since the last period at the randomization stage	CEE (0.625 mg/d) + MPA (2.5 mg/d) (n = 404) Placebo (n = 373) Mean duration, 3.4 y	Fair
Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis (ERA) Herrington et al, 2000[22]	United States Ages 41-79 y Postmenopausal women not currently receiving estrogen replacement therapy and with >1 epicardial coronary stenosis of ≥30% of the luminal diameter	CEE (0.625 mg/d) (n = 100) CEE (0.625 mg/d) + MPA (2.5 mg/d) (n = 104) Placebo (n = 105) Duration, 3 y	Fair
Estrogen in the Prevention of Reinfarction Trial (ESPRIT) Cherry et al, 2002[23]	United Kingdom Ages 50-69 y Admitted to coronary care units or general medical wards in participating hospitals Met diagnostic criteria for initial myocardial infarction Discharged from hospital within 31 d of admission	Estradiol valerate (2 mg/d) (n = 513) Placebo (n = 504) Duration, 2 y	Fair
Greenspan et al, 2005[24]	United States Ages 65-90 y Community-dwelling women	CEE (0.625 mg/d) + MPA (2.5 mg/d) (n = 187) Placebo (n = 186) Duration, 3 y	Good
Heart and Estrogen/Progestin Replacement Study (HERS) Grady et al, 1998[25] Hulley et al, 1998[26] Kanaya et al, 2003[27] Steinauer et al, 2005[28]	United States Ages ≤80 y (mean, 66.7) Intact uterus Postmenopausal Established coronary artery disease	CEE (0.625 mg/d) + MPA (2.5 mg/d) (n = 1380) Placebo (n = 1383) Mean duration, 4.1 y	Good
Kronos Early Estrogen Prevention Study-Cognitive and Affective Study (KEEPS-Cog) Gleason et al, 2015[17]	United States Ages 42-58 y Intact uterus Recently postmenopausal At risk for cardiovascular disease	CEE (0.45 mg/d) + MP (200 mg/d, 12 d/mo) (n = 220) Transdermal estradiol (50 μg/d) + MP (200 mg/d, 12 d/mo) (n = 211) Placebo (n = 262) Duration, 4 y	Fair
Postmenopausal Estrogen and Progestin Interventions Trial (PEPI) PEPI, 1995[29]	United States Ages 45-64 y With or without a uterus Naturally or surgically menopausal	CEE (0.625 mg/d) (n = 175) CEE (0.625 mg/d) + MPA (10 mg/d, 12 d/mo) (n = 174) CEE (0.625 mg/d) + MP (200 mg/d, 12 d/mo) (n = 178) Placebo (n = 174) Duration, 3 y	Fair
STOP-IT Gallagher et al, 2001[30]	United States Ages 65-77 y Femoral neck density within normal range for age	CEE (0.625 mg/d) + MPA (2.5 mg/d) (n = 121) CEE (0.625 mg/d) + MPA (2.5 mg/d) + calcitriol (0.25 μg twice daily) (n = 122) Calcitriol (0.25 μg twice daily) (n = 123) Placebo (n = 123) Duration, 3 y	Fair
Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA) Ettinger et al, 2004[31] Johnson et al, 2005[32] Waetjen et al, 2005[33] Yaffe et al, 2006[34]	United States Ages 60-80 y Intact uterus At least 5 y past menopause Bone mineral density normal for age	Unopposed transdermal estradiol (0.014 mg/d) (n = 208) Placebo (n = 209) Duration, 2 y	Good
Women's Angiographic Vitamin and Estrogen Trial (WAVE) Waters et al, 2002[35]	United States, Canada Postmenopausal Mean age of 65 y Coronary angiogram performed within 4 mo of study entry	CEE (0.625 mg/d) + MPA (2.5 mg/d) (n = 210) Placebo (n = 213) Mean duration, 2.8 y	Fair
Women's Health Initiative (WHI) Estrogen Trial Anderson et al, 2004[36] Bonds et al, 2006[37] Brunner et al, 2005[38] Chlebowski et al, 2010[39] Cirillo et al, 2005[40] Curb et al, 2006[41] Hendrix et al, 2005[42] Hendrix et al, 2006[43] Hsia et al, 2006[44] Manson et al, 2013[15] Ritenbaugh et al, 2008[45] Rossouw et al, 2007[46]	United States Postmenopausal Ages 50-79 y Prior hysterectomy 3-mo washout required for women using hormone therapy at baseline	CEE (0.625 mg/d) (n = 5310) Placebo (n = 5429) Median duration, 7.2 y	Fair

(continued)

Table 2. Characteristics of Randomized Clinical Trials of Use of Hormone Therapy (continued)

Trial Name, Source	Country and Participant Information	Intervention and Duration[a]	Quality Rating[b]
WHI Estrogen Trial postintervention and postintervention extension phases Chlebowski et al, 2010[47] LaCroix et al, 2011[48] Manson et al, 2013[15]	9666 participants from WHI (90%) had any postintervention follow up and 7645 (71%) consented to participate in the extension phase	CEE (0.625 mg/d) (n = 5310) Placebo (n = 5429) Mean duration, 6.6 y	Fair
WHI Estrogen + Progestin Trial Anderson et al, 2012[49] Anderson et al, 2003[50] Canonico et al, 2014[51] Cauley et al, 2003[52] Chlebowski et al, 2003[53] Chlebowski et al, 2004[54] Cirillo et al, 2005[40] Cushman et al, 2004[55] Hays et al, 2003[56] Hendrix et al, 2003[57] Hendrix et al, 2005[42] Hsia et al, 2004[58] Manson et al, 2003[59] Manson et al, 2013[15] Margolis et al, 2004[60] Prentice et al, 2009[61] Rossouw et al, 2002[1] Rossouw et al, 2007[46] Tang et al, 2011[62] Toh et al, 2010[63] Wassertheil-Smoller et al, 2003[64]	United States Postmenopausal Ages 50-79 y 3-mo washout period for women using hormone therapy at baseline	CEE (0.625 mg/d) + MPA (2.5 mg/d) (n = 8506) Placebo (n = 8102) Median duration, 5.6 y	Fair
WHI Estrogen + Progestin postintervention and postintervention extension phases Chlebowski et al, 2009[65] Chlebowski et al, 2010[47] Gramling et al, 2009[66] Heiss et al, 2008[67] Manson et al, 2013[15]	15 747 participants from WHI (95%) had any postintervention follow-up and 12 788 (77%) consented to participate in the extension phase	CEE (0.625 mg/d) + MPA (2.5 mg/d) (n = 8506) Placebo (n = 8102) Median duration, 8.2 y	Fair
Women's Health Initiative Memory Study (WHIMS)—Estrogen Espeland et al, 2004[68] Shumaker et al, 2004[69]	United States WHI participants enrolled in estrogen-only trial Ages 65-79 y Free of probable dementia Able and willing to undergo annual cognitive assessment	CEE (0.625 mg/d) (n = 1464) Placebo (n = 1483) Duration, 5.2 y	Good
WHIMS—Estrogen + Progestin Culhane, 2003[70] Rapp et al, 2003[71] Shumaker et al, 2003[72]	United States WHI participants enrolled in estrogen + progestin trial Age >65 y Free of probable dementia Able and willing to undergo annual cognitive assessment	CEE (0.625 mg/d) + MPA (2.5 mg/d) (n = 2229) Placebo (n = 2303) Duration, 5.4 y	Good
Women's Health Initiative Memory Study of Younger Women (WHIMSY) Espeland et al, 2013[73]	United States Postmenopausal Ages 50-55 y 3-mo washout period for women using hormone therapy at baseline	CEE (0.625 mg/d) + MPA (2.5 mg/d) (n = 696) Placebo (n = 630) Duration, 7.2 y	Fair
Women's Health Initiative Study of Cognitive Aging (WHISCA)—Estrogen Espeland et al, 2010[74] Resnick et al, 2009[75]	United States WHIMS estrogen-only trial participants Free of probable dementia At 1 of 14 WHIMS centers	CEE (0.625 mg/d) + MPA (2.5 mg/d) (n = 434) Placebo (n = 452) Duration, 2.7 y	Good
WHISCA—Estrogen + Progestin Espeland et al, 2010[74] Resnick et al, 2006[76]	United States WHIMS estrogen + progestin trial participants Free of probable dementia At 1 of 14 WHIMS centers	CEE (0.625 mg/d) + MPA (2.5 mg/d) (n = 690) Placebo (n = 726) Duration, 3 y	Good
Women's International Study of Long Duration Estrogen After Menopause (WISDOM) Vickers et al, 2007[19]	United Kingdom Postmenopausal Ages 50-69 y	CEE (0.625 mg/d) + MPA (2.5-5.0 mg/d) (n = 2196) Placebo (n = 2189) Duration, 1 y	Fair

Abbreviations: CEE, conjugated equine estrogen; MP, cyclic micronized progesterone; MPA, medroxyprogesterone acetate; USPSTF, US Preventive Services Task Force.

[a] Duration of follow-up and duration of active treatment (except for the Women's Health Initiative follow-up study, for which "duration" indicates follow-up only).

[b] The quality of each study was assessed as good, fair, or poor using USPSTF predefined criteria.[12] Individual study quality ratings by domain are reported in eTable 2 in the Supplement.

Six trials (the WHI [n = 16 608],[1,15,47,53,61,66,67,79] HERS [n = 2763],[80] PEPI [n = 700],[29] EPHT [n = 777],[20] ERA [n = 209],[22] and WISDOM [n = 4385][19]) reported on breast cancer incidence based on data from more than 25 000 women. Trial results were not

pooled because of heterogeneity in study duration and outcome measures. During the intervention phase of the WHI, women assigned to estrogen plus progestin had a statistically significant increase in risk of invasive breast cancer (9 more cases per 10 000 person-years [95% CI, 1 to 19]).[15] The risk of invasive breast cancer remained significantly increased during a median postintervention follow-up of 8.2 years (HR, 1.32 [95% CI, 1.08-1.61]). The HERS trial also reported that more women randomized to estrogen plus progestin developed breast cancer during the 4.1-year (mean) intervention phase than did the women receiving placebo, but the results were not statistically significant (HR, 1.38 [95% CI, 0.82-2.31]).[80] The other trials reported inconclusive findings.

A meta-analysis of 3 trials (EPHT,[20] PEPI,[29] and the WHI[1]) with data on 18 081 women yielded a numerically higher risk of coronary events in women treated with combination therapy than in those receiving placebo (8 more cases per 10 000 patient-years [95% CI, 0 to 18]) (eFigure 2 in the Supplement).

One WHI trial (WHI Memory Study [WHIMS][72]) evaluated the risk of probable dementia or mild cognitive impairment among 4532 women taking estrogen plus progestin during 5.4 years of follow-up. WHIMS was limited to women aged 65 to 79 years at baseline who were free of probable dementia. Women using estrogen plus progestin had a higher risk of probable dementia than those receiving placebo (22 more cases per 10 000 patient-years [95% CI, 4 to 53]). WHIMS did not find an elevated risk of mild cognitive impairment.[72]

Based on the WHI data, risks for gallbladder disease (21 more cases per 10 000 patient-years [95% CI, 10 to 34]), stroke (9 more cases per 10 000 patient-years [95% CI, 2 to 19]), urinary incontinence (876 more cases per 10 000 patient-years [95% CI, 606 to 1168]), and venous thromboembolism (21 more cases per 10 000 patient-years [95% CI, 12 to 33]) were also statistically significantly increased among women taking estrogen plus progestin compared with women taking placebo (Figure 3). Because of small sample sizes, other trials produced inconclusive results with wide confidence intervals encompassing beneficial and harmful effects on these outcomes.

The WHI global index balancing benefits and harms was associated with 20 additional adverse events per 10 000 person-years for estrogen plus progestin therapy (HR, 1.12 [95% CI, 1.02-1.24]).[15]

Table 3. Estimated Event Rate Increase (Harm) or Decrease (Benefit) per 10 000 Person-Years Associated With the Use of Hormone Therapy

	Event Rate Difference, per 10 000 Person-Years (95% CI)	
Outcome	Estrogen Only	Estrogen + Progestin
Breast cancer (invasive)	−7 (−14 to 0.4)	9 (1 to 19)
Cervical cancer	NA[a]	1 (−1 to 4)
Colorectal cancer	2 (−3 to 10)	−6 (−9 to −1)
Endometrial cancer	NA[a]	−1 (−3 to 3)
Lung cancer	1 (−4 to 8)	1 (−4 to 7)
Ovarian cancer	No data	2 (−1 to 6)[b]
Coronary heart disease	−3 (−12 to 8)	8 (0 to 18)
Dementia (probable)	12 (−4 to 41)	22 (4 to 53)
Diabetes	−19 (−34 to −3)[b]	−14 (−24 to −3)[b]
Fractures (osteoporotic)	−53 (−69 to −39)[b]	−44 (−71 to −13)
Gallbladder disease	30 (16 to 48)[b]	21 (10 to 34)[b]
Stroke	11 (2 to 23)	9 (2 to 19)
Urinary incontinence	1261 (880 to 1689)	876 (606 to 1168)
Venous thromboembolism (DVT or PE)	11 (3 to 22)	21 (12 to 33)
All-cause mortality	1 (−10 to 14)	1 (−9 to 12)

Abbreviations: DVT, deep vein thrombosis; NA, not applicable; PE, pulmonary embolism.

[a] Not applicable to women after hysterectomy.

[b] Point estimate is slightly different from estimate reported in Manson et al[15] because of the use of relative risks instead of hazard ratios.

Difference in Benefits and Harms by Subgroup

Key Question 3. Do the benefits and harms of menopausal hormone therapy differ by subgroup (race or ethnicity; women with premature menopause; women with surgical menopause; age during hormone therapy use; duration of use; type, dose, and mode of delivery of hormone therapy; and comborbid condition) or by timing of intervention (initiation of hormone therapy during perimenopause vs postmenopause)?

Subgroups

Trials did not report results for most of the subgroups. Subgroup analyses were restricted to age, race/ethnicity, and a limited number of comorbidities or risk factors. In general, tests of interactions did not detect any statistically significant subgroup effects for most outcomes of interest. An exception is the interaction with age. Analyses that compared younger (50 to 59 years) with older (70 to 79 years) women using estrogen-only therapy yielded statistically significant trends for increasing risks by age for myocardial infarction (HR, 0.55 [95% CI, 0.31-1.00] vs HR, 1.24 [95% CI, 0.88-1.75]; $P = .02$ for trend),[15] colorectal cancer (HR, 0.71 [95% CI, 0.30-1.67] vs HR, 2.24 [95% CI, 1.16-4.30]; $P = .02$ for trend),[15] and all-cause mortality (HR, 0.70 [95% CI, 0.46-1.09] vs HR, 1.21 [95% CI, 0.95-1.56]; $P = .04$ for trend).[15] Such subgroup differences, however, are based on relatively few events and should be interpreted cautiously. For example, only 48 women in the 50- to 59-year-old age group experienced a myocardial infarction. eTable 19 in the Supplement presents the strength of evidence for subgroup results.

Timing of Intervention

Post hoc subgroup analyses of WHI data regarding the association of timing of hormone therapy (ie, initiation during early or late postmenopause) with benefits and risks found that time since menopause did not have a statistically significant association with the risk of coronary heart disease in women using estrogen-only therapy.[61]

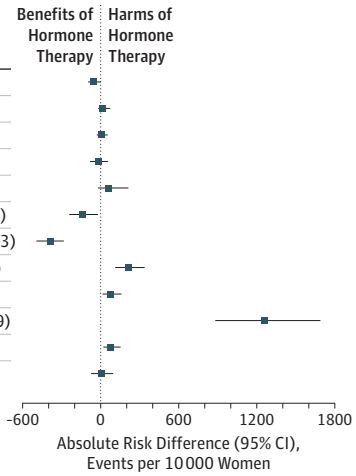
For combination therapy, one post hoc subgroup analysis found that women who began therapy within 10 years of menopause did not have the elevated risk for myocardial infarction, unlike women who started therapy more than 20 years after menopause (HR, 0.91 [95% CI, 0.54-1.52] vs HR, 1.99 [95% CI, 1.32-3.02]; $P = .01$).[15] However, another post hoc subgroup analysis took hormone therapy use of women before enrollment into the WHI into consideration and reported that coronary risks did not differ between early and late initiation of hormone therapy.[61]

For several outcomes, no statistically significant differences were found between women using hormone therapy and women receiving placebo. For estrogen-only therapy, no statistically significant differences were found for probable dementia, breast

Figure 3. Absolute Risk Reductions or Increases for Women Treated With Estrogen Alone and With Estrogen Plus Progestin

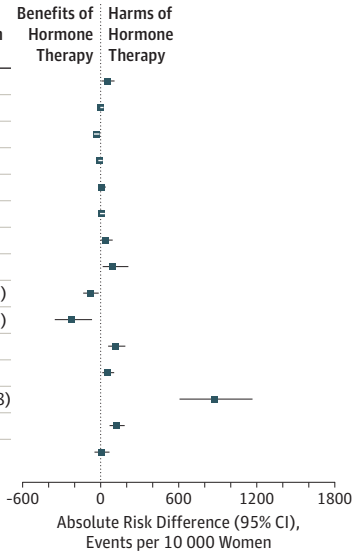
A Estrogen alone

Outcome	No. of Trials	Strength of Evidence	No. of Events/Total No.		RR (95% CI)	Absolute Risk Difference, Events per 10 000 Women (95% CI)
			Treatment	Placebo		
Breast cancer (invasive)	1[13]	Moderate	104/5310	135/5429	0.79 (0.61-1.01)	-52 (-97 to 3)
Colorectal cancer	1[13]	Low	65/5310	58/5429	1.15 (0.81-1.63)	16 (-20 to 73)
Lung cancer	1[13]	Low	62/5310	61/5429	1.04 (0.73-1.48)	5 (-30 to 54)
Coronary heart disease	3[23,29,31]	High	203/5596	224/5714	0.95 (0.79-1.14)	-20 (-82 to 55)
Dementia (probable)	1[77]	Low	28/1464	19/1483	1.49 (0.84-2.66)	63 (-21 to 213)
Diabetes	1[13]	Moderate	449/4900	527/5017	0.87 (0.77-0.98)	-137 (-242 to -21)
Fractures (osteoporotic)	1[13]	High	544/5310	767/5429	0.73 (0.65-0.80)	-382 (-495 to -283)
Gallbladder disease	1[39]	Moderate	228/4141	143/4235	1.63 (1.33-2.00)	213 (111 to 338)
Stroke	1[13]	Moderate	169/5310	129/5429	1.33 (1.06-1.67)	79 (14 to 160)
Urinary incontinence	1[41]	Moderate	557/1526	368/1547	1.53 (1.37-1.71)	1261 (880 to 1689)
Venous thromboembolism	1[13]	Moderate	137/5310	98/5429	1.43 (1.11-1.85)	78 (20 to 153)
All-cause mortality	3[23,29,31]	High	340/5923	342/6038	1.01 (0.88-1.17)	6 (-74 to 96)



B Estrogen + progestin

Outcome	No. of Trials	Strength of Evidence	No. of Events/Total No.		RR (95% CI)	Absolute Risk Difference, Events per 10 000 Women (95% CI)
			Treatment	Placebo		
Breast cancer (invasive)	1[13]	High	206/8506	155/8102	1.27 (1.03-1.56)	52 (6 to 107)
Cervical cancer	1[65]	Low	8/8506	5/8102	1.52 (0.50-4.66)	3 (-3 to 23)
Colorectal cancer	1[13]	Moderate	50/8506	75/8102	0.64 (0.44-0.91)	-33 (-52 to -8)
Endometrial cancer	1[13]	Low	27/8506	30/8102	0.86 (0.51-1.44)	-5 (-18 to 6)
Lung cancer	1[13]	Moderate	78/8506	70/8102	1.06 (0.77-1.46)	5 (-20 to 40)
Ovarian cancer	1[13]	Low	24/8506	16/8102	1.43 (0.76-2.69)	9 (-5 to 33)
Coronary heart disease	3[18,32,71]	High	205/9506	155/8712	1.23 (1.00-1.52)	41 (7 to 93)
Dementia (probable)	1[45]	Moderate	40/2229	21/2303	1.97 (1.16-3.33)	88 (15 to 213)
Diabetes	1[37]	Moderate	328/8132	373/7742	0.84 (0.72-0.97)	-77 (-135 to -15)
Fractures (osteoporotic)	5[16,18,31,34,35]	High	903/10 464	1092/10 035	0.80 (0.68-0.94)	-221 (-353 to -66)
Gallbladder disease	1[39]	Moderate	228/7308	135/6895	1.59 (1.29-1.97)	116 (57 to 190)
Stroke	1[13]	High	159/8506	109/8102	1.39 (1.09-1.77)	53 (12 to 104)
Urinary incontinence	1[41]	Moderate	834/2675	563/2507	1.39 (1.27-1.52)	876 (606 to 1168)
Venous thromboembolism	1[13]	Moderate	209/8506	102/8102	1.95 (1.54-2.47)	120 (68 to 185)
All-cause mortality	3[31, 34, 35]	Moderate	384/9990	368/9590	1.01 (0.88-1.17)	4 (-48 to 68)



A, Follow-up periods for all outcomes are 7.1 years except for fractures (7.2 years), probable dementia (5.2 years), and urinary incontinence (1 year). B, Follow-up periods for all outcomes are 5.6 years except for fractures (5.0 years), coronary heart disease (5.1 years), probable dementia (4 years), and urinary incontinence (1 year). Relative risks (RRs) were calculated to determine absolute risk reductions and increases presented in this Figure because it is unclear whether the proportional hazards assumption is always met in trials of long-term hormone therapy. Estimates of RRs might differ from hazard ratios of trials presented in the text. Estimates using 1 trial are based on the best available single study. The quality of each study was assessed as good, fair, or poor using USPSTF predefined criteria.[12] Individual study quality ratings by domain are provided in eTable 2 in the Supplement.

cancer, colorectal cancer, lung cancer, coronary heart disease, quality of life, and all-cause mortality. For estrogen plus progestin therapy, no statistically significant differences were found for cervical cancer, endometrial cancer, lung cancer, ovarian cancer, quality of life, and all-cause mortality. eTable 19 in the Supplement presents the strength of evidence of these findings.

Discussion

Table 4 and Table 5 present summaries of the evidence for this review. Women taking hormone therapy to prevent chronic conditions may experience some benefits (eg, reduced risks for fractures and diabetes) but also several important harms (eg, higher risks for stroke, thromboembolic events, gallbladder disease, and urinary incontinence). The WHI global index that balanced benefits and harms of hormone therapy found no significant difference for estrogen-only therapy but found significantly more harmful events for combination therapy. These results pertain to asymptomatic women who use hormone therapy for the purpose of preventing chronic conditions. A recently published long-term follow-up study of the WHI trials, however, showed that the exposure to hormone therapy during the WHI intervention phases (5.6 years for estrogen-only therapy and 7.2 years for estrogen plus progestin)

Table 4. Summary of Evidence: Estrogen-Only Trials (Key Questions 1 and 2)[a]

No. of Studies and Observations	Summary of Findings by Outcome	Consistency and Precision	Reporting Bias	Body of Evidence Limitations	EPC Assessment of Strength of Evidence
Menopausal Women Posthysterectomy					
5 RCTs[15,21-23,36,48,49,61,77]; 239 events in 10 739 women contribute to effect estimate (based on 1 RCT[15])	Invasive breast cancer (follow-up, 7.2 y): nonsignificant lower risk with HT (HR, 0.79; 95% CI, 0.61-1.02)	Consistent Imprecise	Undetected	Three studies followed up participants for a relatively short duration (2-3 y)	Moderate
4 RCTs[21,22,29,44]; 422 events in 11 310 women contribute to effect estimate (based on 3 RCTs[21,29,44])	Coronary heart disease (follow-up, 6.8 y in meta-analysis): no significant risk reduction or increase with HT (RR, 0.95; 95% CI, 0.79-1.14)	Consistent Precise	Undetected	None	High
1 RCT[68,69,78]; 47 events in 2947 women contribute to effect estimate	Probable dementia (follow-up, 5.2 y): no significant risk increase or reduction with HT (HR, 1.49; 95% CI, 0.83-2.66)	NA Imprecise	Undetected	None	Low
1 RCT[15,37]; 976 events in 9917 women contribute to effect estimate	Diabetes (follow-up, 7.1 y): risk reduction with HT (HR, 0.86; 95% CI, 0.76-0.98)	NA Reasonably precise	Undetected	Diabetes is self-reported	Moderate
2 RCTs[15,22,48,50]; 1227 events in 10 739 women contribute to effect estimate (based on 1 RCT[15])	Fractures (follow-up, 6.8 y): significant risk decrease with HT (HR, 0. 70; 95% CI, 0.63-0.79)	Consistent Precise	Undetected	None	High
2 RCTs[29,40]; 371 events in 8376 women contribute to effect estimate (based on 1 RCT[40])	Gallbladder events (follow-up, 7.2 y): significant risk increase with HT (HR, 1.67; 95% CI, 1.35-2.06	Consistent Reasonably precise	Undetected	Gallbladder disease is self-reported	Moderate
3 RCTs[21,22,48]; 298 events in 10 739 women contribute to effect estimate (based on 1 RCT[15])	Stroke (follow-up, 7.2 y): significant increase with HT (HR, 1.35; 95% CI, 1.07-1.70)	Consistent Reasonably precise	Undetected	Three studies followed participants for a relatively short duration (2-3 y)	Moderate
2 RCTs[33,42]; 925 events in 3073 women contribute to effect size (based on 1 RCT[42])	Urinary incontinence (follow-up, 1 y): significant risk increase with HT (RR, 1.53; 95% CI, 1.37-1.71)	Consistent Precise	Undetected	Urinary incontinence is self-reported	Moderate
2 RCTs[21,48]; 144 (DVT) and 91 (PE) events in 10 739 women contribute to effect estimates (based on 1 RCT[15])	Venous thromboembolism (follow-up, 7.1 y): nonsignificant increased risk of PE (HR, 1.35; 95% CI, 0.89-2.05) and significant increased risk of DVT (HR, 1.48; 95% CI, 1.06-2.07) in the WHI	Consistent Reasonably precise	Undetected	None	Moderate
1 RCT[15]	Quality of life (follow-up, 7.1 y): similar scores on most items of the RAND-36	NA Precise	Undetected	None	Moderate
3 RCTs[22,23,48]; 682 events in 11 961 women contribute to effect estimate	All-cause mortality (follow-up, 6.8 y in meta-analysis): no significant risk increase/reduction with HT (RR, 1.01; 95% CI, 0.88-1.17)	Consistent Precise	Undetected	None	High

(continued)

Table 4. Summary of Evidence: Estrogen-Only Trials (Key Questions 1 and 2)[a] (continued)

No. of Studies and Observations	Summary of Findings by Outcome	Consistency and Precision	Reporting Bias	Body of Evidence Limitations	EPC Assessment of Strength of Evidence
Menopausal Women With Intact Uterus					
1 RCT[15,45]; 123 events in 10 739 women contribute to effect estimate	Colorectal cancer (follow-up, 7.2 y): no significant risk increase or reduction with HT (HR, 1.15; 95% CI, 0.81-1.64)	NA Imprecise	Undetected	None	Low
1 RCT[15,39]; 123 events in 10 739 women contribute to effect estimate	Lung cancer (follow-up, 7.2 y): no significant risk increase or reduction with HT (HR, 1.05; 95% CI, 0.74-1.49)	NA Imprecise	Undetected	None	Low
Menopausal Women Without Intact Uterus					
1 RCT[77]; 1 event in 1017 women contribute to effect estimate	Cervical cancer (follow-up, 12.6 y): relative risk not estimated because of low number of events	NA Imprecise	Suspected	One small study followed up participants to evaluate a rare cancer outcome over a period that included the intervention and an open-label observational period	Insufficient
1 RCT[23,77]; 5 events in 1017 women contribute to effect estimate	Ovarian cancer (follow-up, 12.6 y): no significant risk increase or reduction with HT (P = .37); RR not reported	NA Imprecise	Suspected	One small study followed up participants to evaluate a rare cancer outcome over a period that included the intervention and an open-label observational period	Insufficient

Abbreviations: DVT, deep vein thrombosis; EPC, evidence-based practice center; HR, hazard ratio; HT, hormone therapy; NA, not applicable; PE, pulmonary embolism; RAND-36, 36-Item Short Form Health Survey; RCT, randomized clinical trial; RR, relative risk; WHI, Women's Health Initiative.

[a] All studies in this table were of fair quality and were applicable to generally healthy postmenopausal women 50 years or older.

was not associated with increased or decreased risks of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.[81]

A major point of discussion in recent years has been whether the overall net benefit of hormone therapy use may be increased if therapy is started early during menopause transition or early postmenopause. This approach is often referred to as the timing hypothesis (ie, a critical window for favorable outcomes of hormone therapy treatment).[3] The hypothesis proposes that hormone therapy given at or soon after menopause reduces the risks of cardiovascular disease,[4] mortality,[6] and dementia,[5] but the potential beneficial effects will be attenuated or not experienced when hormone therapy is initiated several years after menopause. Current evidence on the effect of timing of initiation, however, is inconclusive.

A recent Cochrane review assessed the timing hypothesis by stratifying trials in a meta-analysis according to when any hormone therapy was started (the review did not stratify between estrogen-only and combination therapy).[82] If this information was not available, the authors used the mean age of participants at baseline as surrogates, which is a substantial limitation of that review. Results provided some support of the timing hypothesis. All-cause mortality was lower in the subgroup of studies in which treatment was started within 10 years of menopause compared with studies in which more than 10 years had elapsed (P = .01). Likewise, the risk of coronary heart disease was lower in women who began hormone therapy early (P = .02). Nevertheless, because of issues of potential ecological fallacy, findings of such study-level analyses have to be viewed cautiously.

Another study sometimes viewed as supporting the timing hypothesis is the Danish Osteoporosis Prevention Study (DOPS).[83] That study was not considered in the main synthesis because of poor quality attributable to lack of blinding of outcomes assessors. In addition, its findings are limited by the small number of events and the imprecision of the estimates. For example, during 10 years of treatment, only 49 cardiovascular events took place.

Limitations

This review and the underlying evidence base have several limitations. First, the trials were restricted to those published in English. Because of the large number of included trials, however, we believe that inclusion of studies not published in English would not affect our conclusions.

Second, most included trials had high attrition or low adherence to medications; this was true even for the WHI, in which 40% to 50% of participants discontinued their medications during the trial. Nevertheless, secondary analyses of the WHI limited to adherent women (ie, censoring women within 6 months of their reporting less than 80% adherence to study pills) were generally similar to intention-to-treat results[15] but with stronger findings.

Third, low event rates also limited conclusions for some outcomes. For example, in the WHI Estrogen plus Progestin Trial, only 40 women developed ovarian cancer. Likewise, event rates for cervical and endometrial cancers were low, rendering wide confidence intervals that encompassed clinically meaningful differences in risks. Thus, confidence in conclusions about benefits and risks of hormone therapy for some outcomes (cervical, endometrial, and ovarian cancer) is low.

Table 5. Summary of Evidence: Estrogen Plus Progestin Trials (Key Questions 1 and 2)[a]

No. of Studies and Observations	Summary of Findings by Outcome	Consistency and Precision	Reporting Bias	Body of Evidence Limitations	EPC Assessment of Strength of Evidence
Menopausal Women Posthysterectomy					
1 RCT[15]	Quality of life (follow-up, 5.2 y): similar scores on most items of the RAND-36	NA Precise	Undetected	None	Moderate
Menopausal Women With Intact Uterus					
5 RCTs[1,15,19,20,29,47,53,61,66,67,80]; 420 events in 19 371 women contribute to effect estimates (based on 2 RCTs[15,80])	Invasive breast cancer (follow-up, 4.1-5.6 y): significant risk increase with HT (HR, 1.24; 95% CI, 1.01-1.53) in WHI and nonsignificant increase with HT in HERS I (HR, 1.38; 95% CI, 0.82-2.31)	Consistent Reasonably precise	Undetected	None	High
1 RCT[50]; 13 events in 16 608 women contribute to effect estimate	Cervical cancer (follow-up, 5.6 y): no significant risk increase or reduction with HT (HR, 1.44; 95% CI, 0.47-4.42)	NA (single study) Imprecise	Undetected	One study followed up participants for a relatively short duration (5.6 y) to evaluate a rare cancer outcome	Low
4 RCTs[1,15,22,29,39,50,61,67,80]; 64 events in 19 371 women contribute to effect estimates (based on 2 RCTs[1,15,39,50,61,67,80])	Endometrial cancer (follow-up, 4.1 to 5.6 y): no significant risk increase or reduction with HT (HR, 0.83; 95% CI, 0.49-1.40) in the WHI and (HR, 0.39; 95% CI: 0.08-2.02) in HERS	Reasonably consistent Reasonably precise	Undetected	Studies followed up participants for a relatively short duration (up to 5.6 y) to evaluate a rare cancer outcome	Low
1 RCT[15,50]; 40 events in 16 608 women contribute to effect estimate	Ovarian cancer (follow-up, 5.6 y): no significant risk increase or reduction with HT (HR, 1.41; 95% CI, 0.75-2.66)	NA Imprecise	Undetected	Study followed up participants for a relatively short duration (5.6 y) to evaluate a rare cancer outcome	Low
6 RCTs[1,18-20,22,29]; 341 events in 18 081 women contribute to effect estimate (based on 3 RCTs[1,18,20,29])	Coronary heart disease (follow-up, 5.2 y in meta-analysis): risk increase with HT (RR, 1.23; 95% CI, 1.00-1.52)	Consistent Precise	Undetected	None	High
1 RCT[72]; 61 events in 4532 women contribute to effect estimate	Probable dementia: (follow-up, 4 y): significant risk increase with HT (HR, 2.05; 95% CI, 1.21-3.48)	NA Imprecise	Undetected	None	Moderate
2 RCTs[15,27,60]; 701 events in 15 874 women contribute to effect estimate (based on 1 RCT[15])	Diabetes (follow-up, 5.6 y): significant risk reduction with HT (HR, 0.81; 95% CI, 0.70-0.94)	Consistent Precise	Undetected	Diabetes self-reported	Moderate
5 RCTs[1,15,18,20,22,52,67,80]; 1995 events in 20 499 women contribute to effect estimate	Fractures (follow-up, 2-5.2 y): significant risk reduction with HT (RR, 0.80; 95% CI, 0.68-0.94)	Consistent Precise	Undetected	None	High

(continued)

Table 5. Summary of Evidence: Estrogen Plus Progestin Trials (Key Questions 1 and 2)[a] (continued)

No. of Studies and Observations	Summary of Findings by Outcome	Consistency and Precision	Reporting Bias	Body of Evidence Limitations	EPC Assessment of Strength of Evidence
2 RCTs[29,40]; 363 events in 14 203 women contribute to effect estimate (based on 1 RCT[40])	Gallbladder events (follow-up, 5.6 y): significant risk increase with HT (HR, 1.59; 95% CI, 1.28-1.97)	Consistent Precise	Undetected	None	Moderate
3 RCTs[15,18,20,64]; 330 events in 17 385 women contribute to effect estimates (based on 2 RCTs[15,20,64])	Stroke (follow-up, 3.4-5.6 y): significant increase with HT in WHI (HR, 1.37; 95% CI, 1.07-1.76) Risk of any cerebrovascular event: significant increase with HT in EPHT (HR, 1.06; 95% CI, 0.07-17.2)	Consistent Reasonably precise	Undetected	Outcome measures heterogeneous; 1 trial reported on stroke incidence and another reported on composite risk of various cerebrovascular events (eg, stroke, TIA)	High
2 RCTs[28,42]; 1397 events in 5182 women contribute to effect size (based on 1 RCT[42])	Urinary incontinence (follow-up, 1 y): significant risk increase with HT (RR, 1.39; 95% CI, 1.27-1.52)	Consistent Precise	Undetected	Urinary incontinence is self-reported	Moderate
4 RCTs[18,20,22,55]; 182 (DVT) and 124 (PE) events in 16 602 women contribute to effect estimates (based on 1 RCT[15])	Venous thromboembolism (follow-up, 5.6 y): significant risk increase of PE (HR, 1.98; 95% CI, 1.36-2.87) and DVT (HR, 1.87; 95% CI, 1.37-2.54) with HT in WHI at follow-up	Consistent Reasonably precise	Undetected	Three studies followed up participants for a relatively short duration (2-3 y)	Moderate
3 RCTs[22,67,80]; 752 events in 19 580 women contribute to effect estimate	All-cause mortality (follow-up, 5.2 y in meta-analysis): no significant risk increase or reduction with HT (RR, 1.01; 95% CI, 0.88-1.17)	Consistent Reasonably precise	Undetected	None	Moderate
Menopausal Women With and Without Intact Uterus					
4 RCTs[1,15,18,19,54,61,67,80]; 152 events in 19 371 women contribute to effect estimates (based on 2 RCTs[15,80])	Colorectal cancer (follow-up, 4.1 to 5.6 y): significant risk reduction with HT (HR, 0.62; 95% CI, 0.43-0.89) in the WHI and nonsignificant risk reduction with HT (HR, 0.69; 95% CI, 0.32-1.49) in HERS	Reasonably consistent Reasonably precise	Undetected	Studies followed up participants for a relatively short duration (up to 5.6 y) to evaluate a cancer outcome	Moderate
3 RCTs[15,18,65,80]; 191 events in 19 371 women contribute to effect estimates (based on 2 RCTs[15,65,80])	Lung cancer (follow-up, 4.1 to 5.6 y): no significant risk increase or reduction with HT (HR, 1.05; 95% CI, 0.76-1.45 in the WHI and HR, 1.28; 95% CI, 0.70-2.33 in HERS)	Reasonably consistent Reasonably precise	Undetected	Studies followed up participants for a relatively short duration (up to 5.6 y) to evaluate a cancer outcome	Moderate

Abbreviations: DVT, deep vein thrombosis; EPC, evidence-based practice center; EPHT, Estonian Postmenopausal Hormone Therapy Trial; HERS, Heart and Estrogen/Progestin Replacement Study; HR, hazard ratio; HT, hormone therapy; NA, not applicable; PE, pulmonary embolism; RAND-36, 36-Item Short Form Health Survey; RCT, randomized clinical trial; RR, relative risk; TIA, transient ischemic attack; WHI, Women's Health Initiative.

[a] All studies in this table were of fair quality and were applicable to generally healthy postmenopausal women 50 years or older.

Fourth, the majority of women (around 80%) were white. Subgroup analyses did not did identify differences in beneficial or harmful effects among ethnic groups, but such analyses were likely underpowered. Moreover, the majority of findings came from the WHI, which tested only 1 dose, formulation, and route of administration of hormone therapy in each trial (oral conjugated equine estrogen [0.625 mg/d] with or without medroxyprogesterone [2.5 mg/d]). Whether different formulations have different risk-benefit profiles remains unclear.

Conclusions

Hormone therapy for the primary prevention of chronic conditions in menopausal women is associated with some beneficial effects but also with a substantial increase of risks for harms. The available evidence regarding benefits and harms of early initiation of hormone therapy is inconclusive.

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Author Contributions: Dr Gartlehner had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Gartlehner, Feltner, Viswanathan.
Acquisition, analysis, or interpretation of data: Gartlehner, Patel, Feltner, Weber, Long, Mullican, Boland, Lux, Viswanathan.
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