JAMA | US Preventive Services Task Force | EVIDENCE REPORT

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

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

Gerald Gartlehner, MD, MPH; Sheila V. Patel, PhD; Shivani Reddy, MD, MS; Caroline Rains, MPH; Manny Schwimmer, MPH; Leila Kahwati, MD, MPH

IMPORTANCE It is uncertain whether hormone therapy should be used for the primary prevention of chronic conditions such as heart disease, osteoporosis, or some types of cancers.

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 PubMed/MEDLINE, Cochrane Library, EMBASE, and trial registries from January 1, 2016, through October 12, 2021; surveillance through July 2022.

STUDY SELECTION English-language randomized clinical trials and prospective cohort studies of fair or good quality.

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 Morbidity and mortality related to chronic conditions; health-related quality of life.

RESULTS Twenty trials (N = 39 145) and 3 cohort studies (N = 1 155 410) were included. Participants using estrogen only compared with placebo had significantly lower risks for diabetes over 7.1 years (1050 vs 903 cases; 134 fewer [95% CI, 18-237]) and fractures over 7.2 years (1024 vs 1413 cases; 388 fewer [95% CI, 277-489]) per 10 000 persons. Risks per 10 000 persons were statistically significantly increased for gallbladder disease over 7.1 years (1113 vs 737 cases; 377 more [95% CI, 234-540]), stroke over 7.2 years (318 vs 239 cases; 79 more [95% CI, 15-159]), venous thromboembolism over 7.2 years (258 vs 181 cases; 77 more [95% CI, 19-153]), and urinary incontinence over 1 year (2331 vs 1446 cases; 885 more [95% CI, 659-1135]). Participants using estrogen plus progestin compared with placebo experienced significantly lower risks, per 10 000 persons, for colorectal cancer over 5.6 years (59 vs 93 cases; 34 fewer [95% CI, 9-51]), diabetes over 5.6 years (403 vs 482 cases; 78 fewer [95% CI, 15-133]), and fractures over 5 years (864 vs 1094 cases; 230 fewer [95% CI, 66-372]). Risks, per 10 000 persons, were significantly increased for invasive breast cancer (242 vs 191 cases; 51 more [95% CI, 6-106]), gallbladder disease (723 vs 463 cases; 260 more [95% CI, 169-364]), stroke (187 vs 135 cases; 52 more [95% CI, 12-104]), and venous thromboembolism (246 vs 126 cases; 120 more [95% CI, 68-185]) over 5.6 years; probable dementia (179 vs 91 cases; 88 more [95% CI, 15-212]) over 4.0 years; and urinary incontinence (1707 vs 1145 cases; 562 more [95% CI, 412-726]) over 1 year.

CONCLUSIONS AND RELEVANCE Use of hormone therapy in postmenopausal persons for the primary prevention of chronic conditions was associated with some benefits but also with an increased risk of harms.

Editorial page 1712

Multimedia

Related article page 1740 and JAMA Patient Page page 1780

Supplemental content

Author Affiliations: RTI International-University of North Carolina at Chapel Hill Evidence-based Practice Center (Gartlehner, Patel, Reddy, Rains, Kahwati); Department for Evidence-based Medicine and Evaluation, Danube University Krems, Austria (Gartlehner); The Ohio State University Wexner Medical Center, Columbus (Schwimmer).

Corresponding Author: Gerald Gartlehner, MD, MPH, RTI International, 3040 E Cornwallis Rd, Research Triangle Park, NC 27709 (ggartlehner@rti.org).

JAMA. 2022;328(17):1747-1767. doi:10.1001/jama.2022.18324

The use of hormone therapy is recommended by clinical practice guidelines to manage menopause-associated symptoms.[1-3] In the past, hormone therapy also has been prescribed for the prevention of common chronic diseases such as cardiovascular disease, osteoporosis (and subsequent fractures), cognitive impairment, and some types of cancers in persons with and without menopausal symptoms. Since the publication of the Women's Health Initiative (WHI) trials in 2002,[4,5] the use of hormone therapy for the primary prevention of chronic diseases has declined. However, questions persist regarding whether the overall net benefit of hormone therapy use may be increased for persons who initiate treatment closer to the time of menopause than those enrolled in the WHI trials, a concept referred to as the timing hypothesis.[1,3]

Hormone therapy includes the use of various forms, doses, and regimens of estrogen with or without progestogen (progestin or progesterone).[6] Persons who have not had a hysterectomy use a combination therapy of estrogen plus progestogen to prevent endometrial proliferation and endometrial cancer; persons who have had a hysterectomy use only estrogen.

In 2017, the US Preventive Services Task Force (USPSTF) recommended against the use of hormone therapy for the primary prevention of chronic conditions (D recommendation).[7] This review updates a prior review on the benefits and harms of hormone therapy for the primary prevention of chronic conditions to inform an updated recommendation by the USPSTF.[8]

Methods

Scope of Review

Figure 1 presents the analytic framework and key questions (KQs) that guided the review. Detailed methods are available in the full evidence report.[11]

Data Sources and Searches

MEDLINE (via PubMed), the Cochrane Library, and EMBASE were searched for English-language articles published from January 1, 2016, through October 12, 2021 (eMethods in the Supplement). Targeted searches were conducted for unpublished literature (ClinicalTrials.gov, HSRProj, the World Health Organization's International Clinical Trials Registry Platform, NIH RePORTER, and Drugs@FDA.gov). Additional citations were identified through review of pertinent review articles and of literature suggested by peer reviewers or public comment respondents.

Between October 2021 and July 2022, ongoing surveillance through article alerts and targeted searches of selected journals was conducted to identify major studies possibly affecting the USPSTF recommendation.

Study Selection

Two investigators independently screened 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 randomized clinical trials (RCTs) and cohort studies of generally healthy perimenopausal and postmenopausal persons from primary care settings 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 the harms of hormone therapy.

The review examined the use of systemic therapy (ie, pill, patch, or injection) for 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 US (eTable 2 in the Supplement).

Studies from countries designated by the United Nations Development Programme as having a rating of "very high" on the Human Development Index were included in the review.[12]

Data Extraction and Quality Assessment

One investigator abstracted relevant information from each included study. A second investigator reviewed the information for completeness and accuracy. Differences were resolved by consensus or adjudication by a third (senior) investigator. Two investigators independently assessed the methodologic quality of each study as "good," "fair," or "poor" using the USPSTF's predefined criteria (eTables 3 and 4 in the Supplement).[13]

Data Synthesis and Analysis

The review synthesizes the evidence narratively for each KQ. When at least 3 similar trials of low clinical and methodological heterogeneity (following established guidance[14]) were available, quantitative synthesis of studies with random-effects models was conducted using a restricted maximum likelihood heterogeneity variance estimator. For all quantitative syntheses, the χ^2 statistic and the I^2 statistic were calculated to assess the statistical heterogeneity in effects between studies.[15]

The outcome measure for all quantitative analyses was the relative risk (RR) of a beneficial or harmful change in risks. When a meta-analytic estimate was absent, RRs of outcomes of interest were based primarily on publications of the WHI trials.[16] Therefore, effect estimates might differ slightly from hazard ratios (HRs) reported in earlier WHI publications.

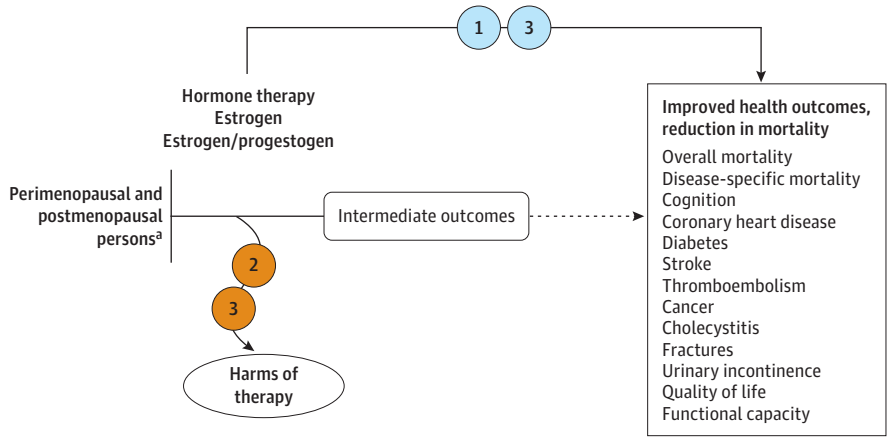
All quantitative analyses were conducted with Stata version 16.1 (StataCorp). Statistical significance was assumed when 95% confidence intervals of pooled results did not cross the null (ie, 1). All testing was 2 sided.

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.[17] Two reviewers assessed each strength-of-evidence domain for each key outcome and developed the overall strength of evidence grades.

Results

The update searches identified 2208 citations (**Figure 2**), of which 20 new articles were retained,[18-37] reporting on the following: 2 new trials,[23,31] 2 ancillary studies of the WHI,[24] previously included trials,[18-22,25-30,32,36,37] and 3 observational studies.[33-35] Combined with articles that were carried forward from the previous review,[4,5,16,38-99] 85 articles representing 20 unique fair- or good-quality trials (N = 39 145) and 3 large controlled cohort studies (N = 1 155 410) were included. Because sufficient evidence from RCTs for most outcomes was available, observational studies were used only to address outcomes for which there was no or very little evidence from RCTs.

Figure 1. Analytic Framework and Key Questions: Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons



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

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions 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 health outcome that immediately follows an intermediate outcome. For additional information on interpretation of the analytic framework, see the USPSTF Procedure Manual.[9]

[a] Definitions of perimenopausal and postmenopausal persons are based on Stages of Reproductive Aging Workshop + 10 criteria.[10]

Of the 20 included trials, 17 were conducted in the US. The remaining trials came from Australia, Canada, Estonia, New Zealand, and the UK. The mean duration of follow-up in the trials was 4.3 years.

Included articles provided data on 39 145 perimenopausal and postmenopausal persons with mean ages in trials ranging from 53 to 75 years. Most participants were White; the proportions of persons of other race and ethnicity ranged from 1% to 43%. eTable 5 in the Supplement provides a summary of participant characteristics for each included study.

Table 1 summarizes the main characteristics and quality ratings of included trials. Of these, 7 were rated as good quality and 13 as fair quality. Three trials[44,46,47] did not stratify results by treatment regimen, so their findings could not be used for the analyses.

Only the WHI trials were powered to assess the effectiveness of hormone therapy for the primary prevention of some chronic conditions.[16] The WHI trials enrolled generally healthy postmenopausal persons 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 also had the longest intervention periods (median of 7.2 years for the estrogen-only trial; 5.6 years for the estrogen plus progestin trial) and postintervention follow-up (up to 20.7 years) of included trials. Outcome-specific evidence from included trials is available in eTables 6 through 26 in the Supplement.

Benefits of Hormone Therapy

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

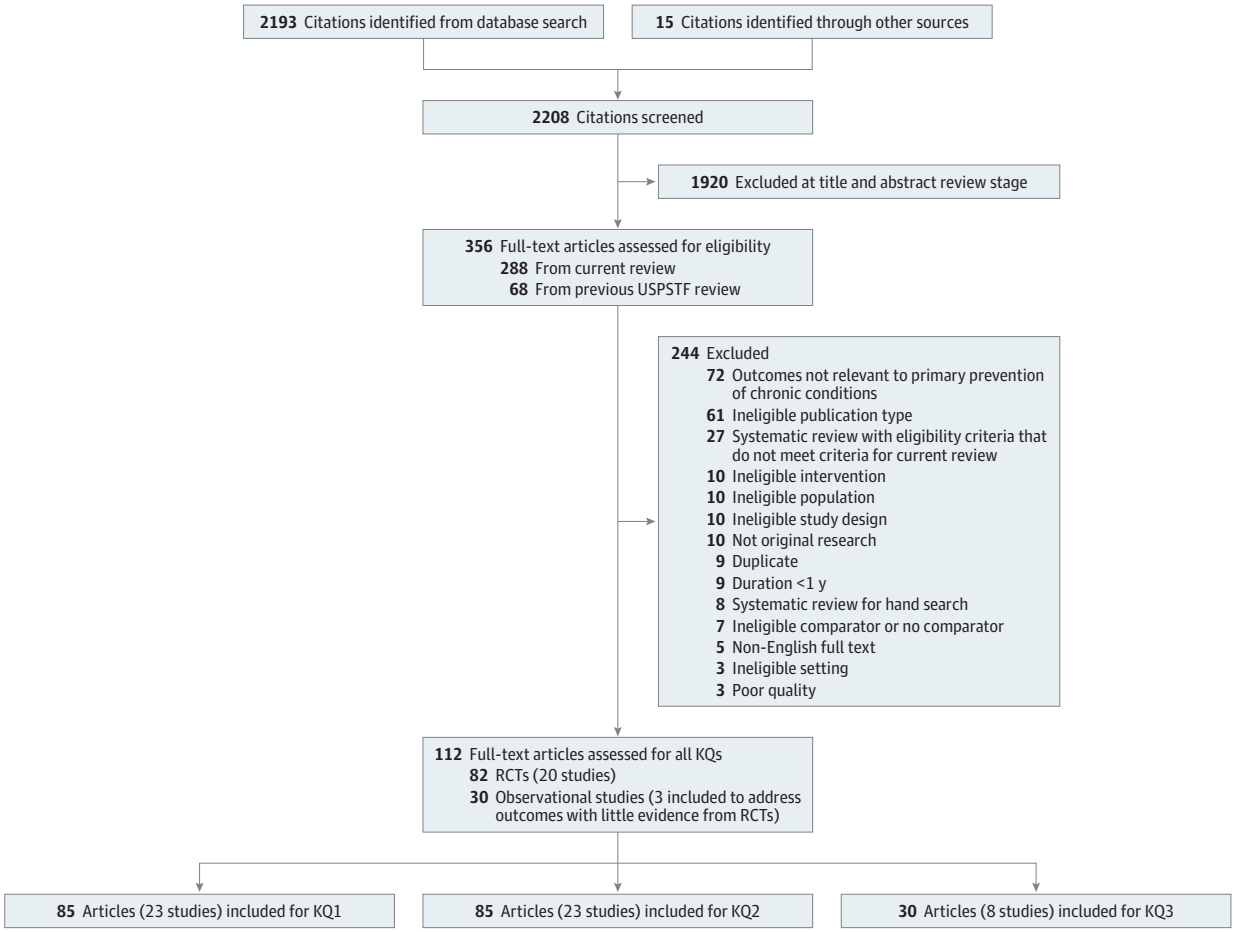
Estrogen Only

For persons using estrogen only, risk of fractures and diabetes were statistically significantly reduced compared with persons taking placebo. Beneficial associations lost statistical significance after stopping hormone therapy. The WHI (n = 10 739)[16] reported a statistically significantly reduced risk of fractures (388 fewer per 10 000 persons over 7.2 years [95% CI, 277-489 fewer]). The WHI also reported a statistically significantly reduced incidence of diabetes (134 fewer cases per 10 000 persons over 7.1 years [95% CI, 18-237 fewer]) compared with persons taking placebo.

Five RCTs[5,16,40,41,48,50,51,94,98,100,101] with data on more than 13 000 participants reported on breast cancer incidence. Trial results were not pooled primarily because of heterogeneity in study duration and definition of breast cancer. In the WHI (n = 10 739), estrogen-only therapy did not result in a significant decrease in invasive breast cancer risk compared with placebo during the 7.2-year (median) intervention phase (52 fewer cases per 10 000 patient-years [95% CI, 97 fewer to 4 more]).[16,94] The risk reduction was statistically significant during cumulative (trial and postintervention phase) follow-up at 13 years (HR, 0.79 [95% CI, 0.65-0.97])[16] and 20.7 years (HR, 0.78 [95% CI, 0.65-0.93]).[18]

Outcomes without statistically significant findings included colorectal cancer, lung cancer, coronary heart disease, peripheral arterial disease, probable dementia, quality of life, and total cancer mortality. Some of these nonsignificant outcomes, however, had wide confidence intervals encompassing both clinically relevant benefits and harms, leading to inconclusive results. **Figure 3** shows the corresponding absolute risk differences as natural frequencies with

Figure 2. Literature Search Flow Diagram: Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons



KQ indicates key question; RCT, randomized clinical trial; USPSTF, US Preventive Services Task Force.

95% CIs (strength of evidence reported in **Table 2**). Estimates are based on meta-analyses of included trials or, if meta-analyses were not feasible, based on results from the largest and most reliable trial (usually the WHI).

Estrogen Plus Progestin

Participants using combination therapy experienced statistically significantly reduced risks for colorectal cancer, fractures, and diabetes, compared with persons in the placebo groups (**Figure 4** and **Table 3**). Beneficial associations lost statistical significance after stopping hormone therapy. Four trials[16,42,50,89,96] with data on more than 20 000 persons reported on the incidence of colorectal cancer. During the WHI intervention phase, persons using combination therapy had statistically significantly reduced risks for colorectal cancer (34 fewer cases per 10 000 persons over 5.6 years [95% CI, 9-51 fewer]). The Heart and Estrogen/Progestin Replacement Study (HERS) reported a numeric decrease in the risk of colorectal cancer with estrogen plus progestin use during 4.1 years of follow-up (HR, 0.69 [95% CI, 0.32-1.49]). The other trials were too small and of too short duration to have adequate power to detect differences in colorectal cancer rates (<2 years; zero events in the Estrogen Memory Study [EMS][42] and 4 events in the Women's International Study of Long Duration Estrogen After Menopause [WISDOM][96]). A prospective cohort study with data on 85 734 postmenopausal participants confirmed the WHI findings.[34] Risk of colorectal cancer among ever and current users of estrogen plus progestin therapy in this study was statistically significantly lower compared with never users (HR, 0.76 [95% CI, 0.68-0.86] and HR, 0.72 [95% CI, 0.62-0.84], respectively).[34]

Estrogen plus progestin therapy was associated with a lower risk of diabetes among participants in the HERS (n = 2029)[88] and the WHI (n = 15 874).[86] In the WHI, the larger trial of the 2, new diabetes diagnoses were statistically significantly reduced in persons on hormone therapy compared with persons in the placebo group (78 fewer cases per 10 000 persons over 5.6 years [95% CI, 15-133 fewer]).[16,86]

Five trials with data on 20 499 participants reported on fractures[4,16,41,42,49,55,89,90] The random-effects meta-analysis (eFigure 1 in the Supplement) yielded a statistically significant association with a lower risk for persons using combination therapy (230 fewer cases per 10 000 persons over 5.0 years [95% CI, 66-372]).

Although no statistically significant reduction of endometrial cancer was observed during the trial phases, an 8.2-years postintervention follow-up of the WHI reported that statistically significantly fewer persons who had been randomized to hormone therapy during the trial phase had developed endometrial cancer (HR, 0.59

Table 1. Characteristics of Randomized Clinical Trials of Use of Hormone Therapy

Trial, source(s)	Country; participants and characteristics	Intervention; duration	Quality rating
Early vs Late Intervention Trial with Estradiol, Cognitive Endpoints (ELITE-Cog) Henderson et al,[23] 2016	US Aged 41-84 y Within 6 y of natural or surgical menopause (early postmenopause group) or ≥10 y beyond natural or surgical menopause (late menopause group); serum estradiol level <25 pg/mL	17β-estradiol (1 mg/d) (n = 323) Placebo (n = 320) Women with a uterus: cyclic micronized progesterone (45 mg as a 4% vaginal gel) Mean, 4.8 y	Fair
Estrogen Memory Study (EMS) Tierney et al,[42] 2009	Canada Aged 61-87 y Last menstrual cycle >12 mo before screening; fluent in English and able to 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 wk (n = 70) Placebo (n = 72) 2 y	Fair
Estrogen in the Prevention of Atherosclerosis (EPAT) Hodis et al,[48] 2001	US Postmenopausal women aged 46-80 y LDL-C level ≥130 mg/dL (3.37 mmol/L)	Micronized 17β-estradiol (1 mg/d) (n = 111) Placebo (n = 111) 2 y	Fair
Estonian Postmenopausal Hormone Therapy (EPHT) Veerus et al,[49] 2006	Estonia Aged 50-64 y ≥12 mo since last period at randomization stage	CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 404) Placebo (n = 373) Mean, 3.4 y	Fair
Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis (ERA)			
Herrington et al,[41] 2000	US Postmenopausal women aged 41-79 y Not receiving E replacement therapy; >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) 3.2 y	Fair
Greenspan et al,[47] 2005	US Community-dwelling women aged 65-90 y	CEE (0.625 mg/d +M PA [2.5 mg/d]) (n = 121) CEE (0.625 mg/d) (n = 66) Placebo (n = 186) 3 y	Good
Heart and Estrogen/Progestin Replacement Study (HERS) Grady et al,[81] 1998 Hulley et al,[82] 1998 Kanaya et al,[88] 2003 Steinauer et al,[69,89] 2005	US Postmenopausal, aged ≤80 y (mean, 66.7 y) Intact uterus; established coronary artery disease	CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 1380) Placebo (n = 1383) Mean, 4.1 y CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 1156) Placebo (n = 1165) Mean, 6.8 y	Good
Kronos Early Estrogen Prevention Study-Cognitive and Affective Study (KEEPS-Cog) Gleason et al,[97] 2015	US Recently postmenopausal, aged 42-58 y Intact uterus; at risk for cardiovascular disease	CEE (0.45 mg/d + MP [200 mg/d]) for 12 d/mo (n = 220) Transdermal estradiol (50 µg/d + MP [200 mg/d]) for 12 d/mo (n = 211) Placebo (n = 262) 4 y	Fair
Kronos Early Estrogen Prevention Study-MRI (KEEPS-MRI) Kantarci et al,[31] 2016	US Aged 42-59 y In good cardiovascular health; 5-36 mo past menopause; no MRI contraindication for safety and neurological disorders	CEE (0.45 mg/d + MP [200 mg/d]) for 12 d/mo (n = 31) Transdermal 17β-estradiol (50 µg/d + MP [200 mg/d]) for 12 d/mo (n = 31) Placebo (n = 39) 4 y	Fair
Postmenopausal Estrogen/Progestin Interventions (PEPI) trial Writing Group for the PEPI trial,[40] 1995	US Aged 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]) for 12 d/mo (n = 174) CEE (0.625 mg/d + MP [200 mg/d]) for 12 d/mo (n = 178) Placebo (n = 174) 3 y	Fair
STOP IT Gallagher et al,[46] 2001	US Aged 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] plus calcitriol [0.25 µg twice daily]) (n = 122) Calcitriol (0.25 µg twice daily) (n = 123) Placebo (n = 123) 3 y	Fair

(continued)

Table 1. Characteristics of Randomized Clinical Trials of Use of Hormone Therapy (continued)

Trial, source(s)	Country; participants and characteristics	Intervention; duration	Quality rating
Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA) Ettinger et al,[66] 2004 Johnson et al,[92] 2005 Waetjen et al,[72] 2005 Yaffe et al,[43] 2006	US Aged 60-80 y Intact uterus; ≥5 y past menopause; bone mineral density normal for age	Unopposed transdermal estradiol (0.014 mg/d) (n = 208) Placebo (n = 209) 2 y	Good
Women's Angiographic Vitamin and Estrogen (WAVE) Waters et al,[44] 2002	US, Canada Postmenopausal; mean age, 65 y Coronary angiogram performed within 4 mo of study entry	CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 86) CEE (0.625 mg/d) (n = 124) Placebo (n = 213) Mean, 2.8 y	Fair
Women's Health Initiative (WHI) E-only Anderson et al,[52] 2003 Bonds et al,[53] 2006 Brunner et al,[54] 2005 Chlebowski et al,[57] 2010 Cirillo et al,[93] 2005 Curb et al,[62] 2006 Hendrix et al,[85] 2005 Hendrix et al,[83] 2006 Hsia et al,[45] 2006 Hsia et al,[36] 2006 Manson et al,[16] 2013 Ritenbaugh et al,[77] 2008 Rossouw et al,[76] 2007	US Postmenopausal, aged 50-79 y Prior hysterectomy 3-mo washout period required for women using HT at baseline	CEE (0.625 mg/d) (n = 5310) Placebo (n = 5429) Median, 7.2 y	Fair
WHI E-only postintervention and postintervention extension phases Chlebowski et al,[56] 2010 LaCroix et al,[94] 2011 Manson et al,[16] 2013 Manson,[19] 2017 Prentice,[22] 2020 Prentice,[32] 2020	US 9666 WHI participants (90%) had any postintervention follow-up; 7645 (71%) consented to participate in the extension phase	Postintervention follow-up: CEE (0.625 mg/d) (n = 4794) Placebo (n = 4872) Mean, 6.6 y Postintervention extension follow-up: CEE (0.625 mg/d) (n = 3778) Placebo (n = 3867)	Fair
WHI E + P trial Anderson et al,[51] 2012 Anderson et al,[52] 2003 Canonico et al,[99] 2014 Cauley et al,[55] 2003 Chlebowski et al,[58] 2003 Chlebowski et al,[60] 2004 Cirillo et al,[93] 2005 Cushman et al,[63] 2004 Hays et al,[91] 2003 Hendrix et al,[84] 2003 Hendrix et al,[85] 2005 Hsia et al,[37] 2004 Manson et al,[87] 2003 Manson et al,[16] 2013 Margolis et al,[86] 2004 Prentice et al,[50] 2009 Rossouw et al,[4] 2002 Rossouw et al,[76] 2007 Tang et al,[38] 2011 Toh et al,[73] 2010 Wassertheil-Smoller et al,[71] 2003	US Postmenopausal, aged 50-79 y 3-mo washout period for women using HT at baseline	CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 8506) Placebo (n = 8102) Median, 5.6 y	Fair

(continued)

Table 1. Characteristics of Randomized Clinical Trials of Use of Hormone Therapy (continued)

Trial, source(s)	Country; participants and characteristics	Intervention; duration	Quality rating
WHI E + P postintervention and postintervention extension phases Chlebowski et al,[59] 2009 Chlebowski et al,[56] 2010 Gramling et al,[68] 2009 Heiss et al,[90] 2008 Manson et al,[16] 2013 Manson et al,[19] 2017 Prentice et al,[22] 2020 Prentice et al,[32] 2020	US 15 747 WHI participants (95%) had any postintervention follow-up; 12 788 (77%) consented to participate in the extension phase	Postintervention follow-up: CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 8060) Placebo (n = 7687) Median, 8.2 y Postintervention extension follow-up: CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 6545) Placebo (n = 6243)	Fair
Women's Health Initiative Memory Study (WHIMS) E only Espeland et al,[65] 2004 Shumaker et al,[75] 2004	US WHI participants aged 65-79 y enrolled in the E-only trial Free of probable dementia; able and willing to undergo annual cognitive assessment	CEE (0.625 mg/d) (n = 1464) Placebo (n = 1483) 5.2 y	Good
WHIMS E + P Culhane,[61] 2003 Rapp et al,[80] 2003 Shumaker et al,[74] 2003	US WHI participants aged >65 y enrolled in the E + P trial 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) 5.4 y	Good
Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO) Espeland et al,[24] 2017	US Postmenopausal, aged 65-79 y 3-mo washout period for women using HT at baseline; received clinic-based cognitive testing as part of WHIMS	CEE (0.625 mg/d + MPA [2.5 mg/d]) or CEE (0.625 mg/d) only (n = 1402)[a] Placebo (n = 1478) 6.4 y for overall group 7.1 y for those with prior hysterectomy 5.4 y for those without prior hysterectomy	Fair
Women's Health Initiative Memory Study of Younger Women (WHIMSY) Espeland et al,[24,39] 2013	US Postmenopausal, aged 50-55 y 3-mo washout period for women using HT at baseline	CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 696) Placebo (n = 630) 7.2 y	Fair
Women's Health Initiative Study of Cognitive Aging (WHISCA) E only Espeland et al,[64] 2010 Resnick et al,[79] 2009	US WHIMS E-only trial participants Free of probable dementia Conducted at 1 of 14 WHIMS centers; began 3 y after enrollment in WHI	CEE (0.625 mg/d) (n = 434) Placebo (n = 452) 3.6 y	Good
WHISCA E-only postintervention phase Espeland et al,[64] 2010	US WHIMS E-only trial participants Free of probable dementia Conducted at 1 of 14 WHIMS centers; began 3 y after enrollment in WHI	CEE (0.625 mg/d) (n = 434) Placebo (n = 452) 2.4 y	Good
WHISCA E + P Espeland et al,[64] 2010 Resnick et al,[78] 2006	US WHIMS E + P trial participants Free of probable dementia Conducted at 1 of 14 WHIMS centers; began 3 y after enrollment in WHI	CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 690) Placebo (n = 726) 2 y	Good
WHISCA E + P postintervention phase Espeland et al,[64] 2010	US WHIMS E + P trial participants Free of probable dementia Conducted at 1 of 14 WHIMS centers; began 3 y after enrollment in WHI	CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 690) Placebo (n = 726) 4 y	Good
Women's International Study of Long Duration Estrogen After Menopause (WISDOM) Vickers et al,[96] 2007	UK, Australia, New Zealand Postmenopausal, aged 50-69 y	CEE (0.625 mg/d + MPA [2.5-5.0 mg/d]) (n = 2196) CEE (0.625 mg/d) (n = 826) Placebo (n = 2189) 1 y	Fair

Abbreviations: CEE, conjugated equine estrogen; E, estrogen; E + P, estrogen plus progestin; HT, hormone therapy; MP, micronized progesterone; MPA, medroxyprogesterone acetate; MRI, magnetic resonance imaging; WHI, Women's Health Initiative.

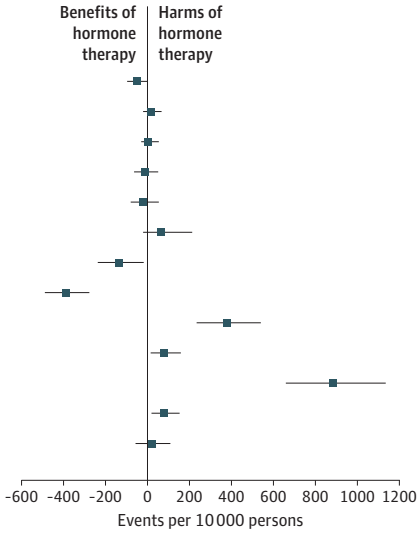
[a] Analysis did not stratify by treatment regimen.

[95% CI, 0.40-0.88]) compared with persons who had received placebo.[25] This finding is consistent with a large, retrospective Danish cohort study based on more than 900 000 participants during a mean follow-up of 9.8 years.[33]

No statistically significant difference for cervical cancer, coronary heart disease, endometrial cancer, lung cancer, ovarian cancer, peripheral arterial disease, or quality of life was found during the intervention phases. Some of the nonsignificant outcomes, however,

Figure 3. Absolute Risk Reductions or Increases for Women Treated With Estrogen Only

Outcome	No. of trials	No. of cases/total		Events per 10 000 persons (95% CI)	Strength of evidence
		Treatment	Placebo		
Breast cancer (invasive)	1	104/5310	135/5429	-52 (-97 to 4)	Moderate
Colorectal cancer	1	65/5310	58/5429	16 (-21 to 67)	Low
Lung cancer	1	62/5310	61/5429	4 (-30 to 54)	Low
Total cancer mortality	1	126/5310	136/5429	-13 (-64 to 51)	Low
Coronary heart disease	3	203/5596	219/5714	-19 (-80 to 54)	High
Dementia (probable)	1	28/1464	19/1483	63 (-21 to 213)	Low
Diabetes	1	449/4900	527/5017	-134 (-237 to -18)	Moderate
Fractures (osteoporotic)	1	544/5310	767/5429	-388 (-489 to -277)	High
Gallbladder disease	1	461/4141	312/4235	377 (234 to 540)	Moderate
Stroke	1	169/5310	130/5429	79 (15 to 159)	Moderate
Urinary incontinence	1	773/3316	499/3451	885 (659 to 1135)	Moderate
Venous thromboembolism	1	137/5310	98/5429	77 (19 to 153)	Moderate
All-cause mortality	3	309/5733	304/5854	21 (-57 to 109)	High



Findings are based on meta-analyses of included trials or, if meta-analyses were not feasible, based on results from the largest and most reliable trial (usually the Women's Health Initiative). Follow-up periods for all outcomes were 7.1 years except all-cause mortality, 2 to 7.2 years; fractures, 7.2 years; dementia, 5.2 years; and urinary incontinence, 1 year.

had wide confidence intervals, leading to inconclusive results (Figure 4; strength of evidence reported in Table 3).

Harms of Hormone Therapy

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

Estrogen Only

Persons using estrogen-only therapy had statistically significantly increased risks for gallbladder disease, stroke, urinary incontinence, and venous thromboembolism (Figure 3; strength of evidence reported in Table 2). Most increased risks were not statistically different anymore after stopping hormone therapy.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial (n = 349)[40] and the WHI (n = 8376)[93] reported increased risks for gallbladder disease in participants using estrogen-only therapy. In the WHI, the increased risk was statistically significant (377 more cases per 10 000 persons over 7.1 years [95% CI, 234-540 more]).

Of 3 trials assessing the risk of stroke (ie, Estrogen in the Prevention of Atherosclerosis Trial [EPAT] [n = 222],[48] the Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis [ERA] trial [n = 205],[41] and the WHI [n = 10 739][16,19,32,94]), only the WHI provided significant results. Estrogen-only therapy led to a statistically significantly increased risk of stroke (79 more cases per 10 000 persons over 7.2 years [95% CI, 15-159 more]).

The WHI (n = 3073)[85] found higher risks of incident urinary incontinence (self-reported), as follows: 885 more cases per 10 000 persons over 1 year (95% CI, 659-1135 more) and at 6.6 years after stopping treatment (28.6% vs 23.1%; HR, 1.24 [95% CI, 1.13-1.35]).[16] The smaller Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA) trial (n = 239) did not find a statistically significant difference between groups at 2 years.[72]

Based on the WHI (n = 10 739) results,[16] persons randomized to estrogen only had a statistically significantly increased risk of venous thromboembolism compared with those who received placebo (77 more cases per 10 000 persons over 7.2 years [95% CI, 19-153 more]).

A random-effects meta-analysis of 3 trials[16,19,23,32,41,94] with data on 11 587 persons—which was limited by the domination of WHI, which contributed 97% of events—rendered no statistically significant association with all-cause mortality between persons receiving estrogen-only therapy and those receiving placebo (eFigure 2 in the Supplement; RR, 1.04 [95% CI, 0.89-1.21]) during a mean follow-up of 7.1 years.

Estrogen Plus Progestin

For persons using combination therapy, risks for invasive breast cancer, coronary heart disease, probable dementia, gallbladder disease, stroke, urinary incontinence, and venous thromboembolism were statistically significantly increased compared with persons taking placebo (Figure 4; strength of evidence reported in Table 3).

Six trials[4,16,40,41,49,50,56,58,68,89,90,96,98] reported on breast cancer incidence based on data from more than 25 000 participants. Trial results were not pooled because of heterogeneity in study duration and outcome measures. During the intervention phase of the WHI, participants assigned to estrogen plus progestin had a statistically significantly increased risk of invasive breast cancer (51 more cases per 10 000 persons over 5.6 years [95% CI, 6-106 more]).[16] The risk of invasive breast cancer remained statistically significantly increased during 19.4 years of cumulative (trial and postintervention phase) follow-up (HR, 1.28 [95% CI, 1.13-1.45])[32]; the risk of breast cancer mortality was numerically higher (median, 20.3 years; HR, 1.35 [95% CI, 0.94-1.95]).[18] The HERS also reported that more participants randomized to estrogen plus progestin developed breast cancer during the 4.1-year (mean) intervention phase than did the participants receiving placebo, but the difference was not statistically significant (HR, 1.38 [95% CI, 0.82-2.31]).[89] The other trials reported inconclusive findings.

Table 2. Summary of Evidence by Outcome: Estrogen-Only Trials Enrolling Generally Healthy Postmenopausal Persons 50 Years or Older

Outcome	No. of studies/study designs; No. of participants	Summary of findings	Consistency and precision	Limitations	Strength of evidence[a]
Invasive breast cancer	4 RCTs[5,16,18,19,40,41,48,50,51,94]; during intervention period, 239 events in 10 739 persons contributed to effect estimate (based on 1 RCT[16]) During cumulative follow-up, number of events that contributed to effect estimate NR (based on 1 RCT[19])	Intervention follow-up of 7.2 y Nonsignificant lower risk with HT (HR, 0.79 [95% CI, 0.61-1.02]) During cumulative follow-up of 20.7 y, statistically significantly lower risk with HT (HR, 0.78 [95% CI, 0.65-0.93])	Consistent; imprecise	Fair quality; 3 studies followed up participants for a relatively short duration (2-3 y)	Moderate for benefit
Breast cancer mortality	1 RCT[19]; during intervention period, 13 events in 10 739 persons contributed to effect estimate During cumulative follow-up, 63 events in 10 739 persons contributed to effect estimate	Intervention follow-up of 7.2 y, similar risk (HR, 0.45 [95% CI, 0.14-1.46]) Significantly lower risk with HT during cumulative follow-up of at 17.7 y (HR, 0.55 [95% CI, 0.33-0.92]) and 20.7 y (HR, 0.60 [95% CI, 0.37-0.97])	NA; imprecise	Fair quality; evidence is limited to a single study	Low for benefit
Colorectal cancer	1 RCT[16,22,77]; during intervention period, 123 events in 10 739 persons contributed to effect estimate During cumulative follow-up, 123 events in 9786 persons contributed to effect estimate	Intervention follow-up of 7.2 y, no significant risk increase/reduction with HT (HR, 1.15 [95% CI, 0.81-1.64]) During cumulative follow-up of 13.0 y, similarly no significant risk increase/reduction with HT (HR, 1.13 [95% CI, 0.85-1.51])	NA; imprecise	Fair quality; none	Low for similar risks
Colorectal cancer mortality	1 RCT[19]; during intervention period, 33 events in 10 739 persons contributed to effect estimate During cumulative follow-up, 87 events in 10 739 persons contributed to effect estimate	No significant risk increase or reduction after 7.2 y of the intervention (HR, 0.98 [95% CI, 0.50-1.95]) or during cumulative follow-up of 17.7 y (HR, 1.21 [95% CI, 0.79-1.84])	NA; imprecise	Fair quality; estimates based on a single study	Low for similar risks
Lung cancer	1 RCT[16,57]; during intervention phase, 123 events in 10 739 persons contributed to effect estimate During cumulative follow-up, 223 events in 9786 persons contributed to effect estimate	Intervention follow-up of 7.2 y, no significant risk increase/reduction with HT (HR, 1.05 [95% CI, 0.74-1.49]) During cumulative follow-up of 13.0 y, no significant risk increase/reduction with HT (HR, 0.98 [95% CI, 0.75-1.27])	NA; imprecise	Fair quality; none	Low for similar risks
Lung cancer mortality	1 RCT[57]; 67 events in 10 379 persons contributed to effect estimate	Intervention follow-up of 7.9 y, no significant risk increase with HT (HR, 1.07 [95% CI, 0.66-1.72])	NA; imprecise	Fair quality; estimates based on a single study; short duration follow-up for a mortality outcome	Insufficient
Non-Hodgkin lymphoma	1 RCT[27]; 160 events in 10 685 persons contributed to effect estimate	Cumulative follow-up of 12.9 y, no significant risk increase/reduction with HT (HR, 1.02 [95% CI, 0.74-1.39])	NA; imprecise	Fair quality; none	Low for similar risks
Total cancer mortality	1 RCT[19]; during intervention period, 262 events in 10 739 persons contributed to effect estimate During cumulative follow-up, 863 events in 10 739 persons contributed to effect estimate	Intervention follow-up of 7.2 y, no significant risk reduction/increase with HT (HR, 0.96 [95% CI, 0.75-1.22]) Cumulative follow-up of 17.7 y, no significant risk reduction/increase with HT (HR, 0.99 [95% CI, 0.86-1.13])	NA; imprecise	Fair quality; evidence is limited to a single study	Low for similar risks
Coronary heart disease	4 RCTs[40,41,45,48]; during intervention period, 422 events in 11 310 persons contributed to meta-analysis (based on 3 RCTs[40,45,48]) During cumulative follow-up, 1071 events in 7645 persons contributed to effect estimate (based on 1 RCT[32])	Intervention follow-up of 2-7.2 y in meta-analysis, no significant risk reduction/increase with HT (RR, 0.95 [95% CI, 0.79-1.14]) Cumulative follow-up of 19.4 y, no significant risk reduction/increase with HT (HR, 0.97 [95% CI, 0.86-1.09])	Consistent; precise	Fair quality; none	High for similar risks

(continued)

Table 2. Summary of Evidence by Outcome: Estrogen-Only Trials Enrolling Generally Healthy Postmenopausal Persons 50 Years or Older (continued)

Outcome	No. of studies/study designs; No. of participants	Summary of findings	Consistency and precision	Limitations	Strength of evidence[a]
Coronary heart disease mortality	1 RCT[19]; during intervention period, 517 events in 10 739 persons contributed to effect estimate During cumulative follow-up, 517 events in 7645 persons contributed to effect estimate	Intervention follow-up of 7.2 y, no significant risk reduction/increase with HT (HR, 1.02 [95% CI, 0.72-1.43]) Cumulative follow-up of 17.7 y, no significant risk reduction/increase with HT (HR, 0.89 [95% CI, 0.75-1.05])	NA; precise	Fair quality; evidence is limited to a single study	Low for similar risks
Peripheral arterial disease	1 RCT[36]; 144 events in 10 739 persons contributed to effect estimate	Intervention follow-up of 7.1 y, no significant risk reduction/increase with HT (HR, 1.35 [95% CI, 0.97 to 1.88])	NA; imprecise	Fair quality; evidence is limited to a single study	Low for similar risks
Probable dementia	1 RCT[65,75]; 47 events in 2947 persons contributed to effect estimate	Intervention follow-up of 5.2 y, no significant risk increase/reduction with HT (HR, 1.49 [95% CI, 0.83-2.66])	NA; imprecise	Fair quality; none	Low for similar risks
Alzheimer disease or other dementia mortality	1 RCT[19]; during intervention period, 11 events in 10 739 persons contributed to effect estimate During cumulative follow-up, 302 events in 10 739 persons contributed to effect estimate	Intervention follow-up 7.2 y, no significant risk increase/reduction with HT (HR, 0.90 [95% CI, 0.27-2.95]) Cumulative follow-up of 17.7 y, significantly lower risk with HT (HR, 0.74 [95% CI, 0.59-0.94])	NA; imprecise for intervention phase, precise for cumulative phase	Fair quality; few events and short-term follow-up for mortality outcome (intervention phase only)	Low for benefit
Diabetes	1 RCT[16,53]; during intervention period, 976 events in 9917 persons contributed to effect estimate During cumulative follow-up, 1605 events in 9917 persons contributed to effect estimate	Intervention follow-up of 7.1 y, risk reduction with HT (HR, 0.86 [95% CI, 0.76-0.98]) Cumulative follow-up of 13.0 y, no significant risk increase/reduction with HT (HR, 0.94 [95% CI, 0.85-1.04])	NA; precise	Fair quality; diabetes is self-reported	Moderate for benefit
Fractures	2 RCTs[16,28,41,52,94]; during intervention period, 1311 events in 10 739 persons contributed to effect estimate (based on 1 RCT[16]) During postintervention follow-up, 699 events in 5 053 persons contributed to effect estimate (based on 1 RCT[28])	Intervention follow-up of 7.2 y, significant risk reduction with HT (HR, 0.72 [95% CI, 0.64-0.80]) Postintervention follow-up of 4.3 y, significant risk reduction with HT (HR, 0.85 [95% CI, 0.73-0.98])	Consistent; precise	Fair quality; none	High for benefit
Gallbladder disease	2 RCTs[16,40]; 773 events in 8376 persons contributed to effect estimate (based on 1 RCT[16])	Intervention follow-up of 7.1 y, significant risk increase with HT (HR, 1.55 [95% CI, 1.34-1.79])	Consistent; precise	Fair quality; gallbladder disease is self-reported	Moderate for harm
Stroke	3 RCTs[41,48,94]; during intervention period, 298 events in 10 739 persons contributed to effect estimate (based on 1 RCT[16]) During cumulative follow-up 791 events in 10 739 persons contributed to effect estimate (based on 1 RCT[32])	Intervention follow-up of 7.2 y, significant increase with HT (HR, 1.35 [95% CI, 1.07-1.70]) Cumulative follow-up of 19.4 y, no significant risk reduction/increase with HT (HR, 1.06 [95% CI, 0.92-1.22])	Consistent; precise	Fair quality; 3 studies followed participants for a relatively short duration (2-3 y)	Moderate for harm
Stroke mortality	1 RCT[19]; during intervention period, 47 events in 10 739 persons contributed to effect estimate During cumulative follow-up, 258 events in 10 739 persons contributed to effect estimate	Intervention follow-up of 7.2 y, no significant risk reduction/increase with HT (HR, 1.00 [95% CI, 0.57-1.78]) Cumulative follow-up of 17.7 y, no significant risk reduction/increase with HT (HR, 0.98 [95% CI, 0.77-1.26])	NA; imprecise	Fair quality; evidence is limited to a single study	Low for similar risks
Urinary incontinence	2 RCTs[16,72]; during intervention period, 1272 events in 6767 persons contributed to effect estimate (based on 1 RCT[16]) During postintervention follow-up, 1456 events in 5644 persons contributed to effect estimate (based on 1 RCT[16])	Intervention follow-up of 1 y, significant risk increase with HT (HR, 1.61 [95% CI, 1.46-1.79]) Postintervention follow-up of 6.6 y, significant risk increase with HT (HR, 1.24 [95% CI, 1.13-1.35])	Consistent; precise	Fair quality; urinary incontinence is self-reported	Moderate for harm

(continued)

Table 2. Summary of Evidence by Outcome: Estrogen-Only Trials Enrolling Generally Healthy Postmenopausal Persons 50 Years or Older (continued)

Outcome	No. of studies/study designs; No. of participants	Summary of findings	Consistency and precision	Limitations	Strength of evidence[a]
Venous thromboembolism	2 RCTs[48,94]; during intervention period, 144 (DVT) and 91 (PE) events in 10 739 persons contributed to effect estimates (based on 1 RCT[16]) During cumulative follow-up, 471 events in 9939 persons contributed to effect estimates (based on 1 RCT[16])	Intervention follow-up of 7.1 y, significant increased risk of DVT with HT (HR, 1.48 [95% CI, 1.06-2.07]) and no significant risk reduction/increase with HT in PE (HR, 1.35 [95% CI, 0.89-2.05]) Cumulative follow-up of 13.0 y, no significant risk reduction/increase with HT in DVT (HR, 1.05 [95% CI, 0.82-1.33]) or PE (HR, 1.15 [95% CI, 0.87-1.51])	Consistent; imprecise	Fair quality; none	Moderate for harm
Quality of life	1 RCT[16]; observed in 10 739 persons	Intervention follow-up of 7.1 y, similar scores on most items of the SF-36	Inconsistent regarding subscales; precise	Fair quality; none	Moderate for similar risks
All-cause mortality	3 RCTs[23,41,94]; 613 events in 11 587 persons contributed to meta-analysis	Intervention follow-up of 2-7.2 y in meta-analysis, no significant risk increase/reduction with HT (RR, 1.04 [95% CI, 0.89-1.21])	Consistent; precise	Fair quality; none	High for similar risks
	1 RCT[32]; 613 events in 10 739 persons contributed to effect estimate	Cumulative follow-up of 19.4 y, no significant risk reduction/increase with HT (HR, 0.97 [95% CI, 0.91-1.03])	NA; precise	Fair quality; evidence is limited to a single study	

Abbreviations: DVT, deep vein thrombosis; HR, hazard ratio; HT, hormone therapy; NA, not applicable; NR, not reported; PE, pulmonary embolism; RCT, randomized clinical trial; RR, relative risk; SF-36, 36-Item Short Form Health Survey.

[a] Strength of evidence ratings refer to the intervention phase except for mortality, for which they refer to cumulative follow-up.

Based on the WHI data, probable dementia (88 more cases per 10 000 persons over 4 years [95% CI, 15-212]), gallbladder disease (260 more cases per 10 000 persons over 5.6 years [95% CI, 169-364]), stroke (52 more cases per 10 000 persons over 5.6 years [95% CI, 12-104]), urinary incontinence (562 more cases per 10 000 persons over 1 year [95% CI, 412-726]), and venous thromboembolism (120 more cases per 10 000 persons over 5.6 years [95% CI, 68-185]) were also statistically significantly increased in persons taking estrogen plus progestin compared with persons taking placebo (Figure 4). Because of small sample sizes, other trials produced inconclusive results with wide confidence intervals that encompassed beneficial and harmful effects on these outcomes.

A random-effects meta-analysis of 3 trials[41,89,90] with data on 19 540 participants rendered no statistically significant association with all-cause mortality between persons receiving combination therapy and those receiving placebo (RR, 1.01 [95% CI, 0.88-1.16]) (eFigure 3 in the Supplement) during 3.2 to 5.6 years of follow-up. The risk of death among persons who received estrogen plus progestin and those who had received placebo remained similar at various postintervention and cumulative follow-ups of the WHI.[16,19,32,90]

Benefits and Harms of Hormone Therapy by Subgroup and Timing of Intervention

Key Question 3. Do the benefits and harms of menopausal hormone therapy when used for the primary prevention of chronic conditions differ by subgroup or by timing of intervention?

Subgroups

Subgroup analyses were restricted to age, race and ethnicity, oophorectomy status, and a limited number of coexisting conditions or risk factors in the WHI. 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, which was a prespecified subgroup analysis in the WHI.

Analyses that compared younger (50-59 years) and older (70-79 years) persons using estrogen-only therapy yielded statistically significant trends for increasing risks by age for myocardial infarction (P = .02 for trend), colorectal cancer (P = .02 for trend), and all-cause mortality (P = .04 for trend).[16] The significant interaction of colorectal cancer and all-cause mortality with age was no longer present with extended follow-up of 13 to 18 years.

Subgroup differences, however, are based on relatively few events and should be interpreted cautiously. For example, only 48 persons in the 50- to 59-year-old age group experienced a myocardial infarction.

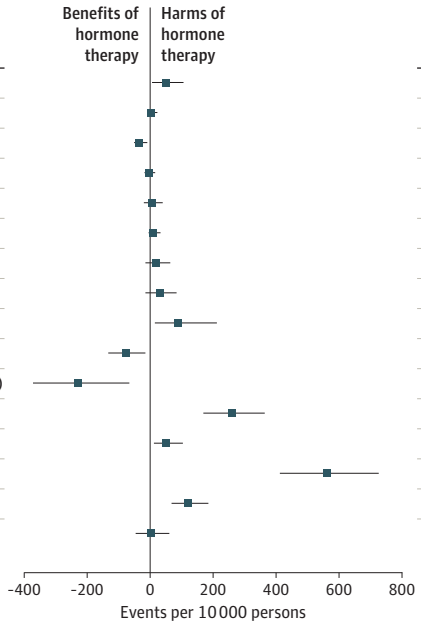
Timing of Intervention

In persons using estrogen-only therapy, post hoc subgroup analyses of the WHI data did not find a statistically significant association between timing of hormone therapy (ie, initiation during early or late postmenopause) and the risk of invasive breast cancer, colorectal cancer, coronary heart disease, stroke, or venous thromboembolism.[18,50] Likewise, the Early vs Late Intervention Trial with Estradiol, Cognitive Endpoints (ELITE-Cog) found no association of timing of hormone therapy with cognitive functioning.[23]

For combination therapy, timing of hormone therapy also had no effect on most outcomes. One post hoc subgroup analysis found that participants who began therapy within 10 years of menopause

Figure 4. Absolute Risk Reductions or Increases for Women Treated With Estrogen Plus Progestin

Outcome	No. of trials	No. of cases/total		Events per 10 000 persons (95% CI)	Strength of evidence
		Treatment	Placebo		
Breast cancer (invasive)	1	206/8506	155/8102	51 (6 to 106)	High
Cervical cancer	1	8/8506	5/8102	3 (-3 to 23)	Low
Colorectal cancer	1	50/8506	75/8102	-34 (-51 to -9)	Moderate
Endometrial cancer	1	27/8506	30/8102	-5 (-18 to 16)	Low
Lung cancer	1	78/8506	70/8102	5 (-20 to 40)	Moderate
Ovarian cancer	1	24/8506	16/8102	8 (-5 to 33)	Low
Total cancer mortality	1	133/8506	111/8102	19 (-15 to 64)	Low
Coronary heart disease	3	266/9506	221/8649	31 (-15 to 84)	High
Dementia (probable)	1	40/2229	21/2303	88 (15 to 212)	Low
Diabetes	1	328/8132	373/7742	-78 (-133 to -15)	Moderate
Fractures (osteoporotic)	5	906/10 464	1098/10 035	-230 (-372 to -66)	High
Gallbladder disease	1	528/7308	319/6895	260 (169 to 364)	Moderate
Stroke	1	159/8506	109/8102	52 (12 to 104)	Moderate
Urinary incontinence	1	1021/5981	641/5597	562 (412 to 726)	Moderate
Venous thromboembolism	1	209/8506	102/8102	120 (68 to 185)	Moderate
All-cause mortality	3	383/9990	368/9590	4 (-46 to 61)	High



Findings are based on meta-analyses of included trials or, if meta-analyses were not feasible, based on results from the largest and most reliable trial (usually the Women's Health Initiative). Follow-up periods for all outcomes were 5.6 years except fractures, 2 to 5.6 years; coronary heart disease, 2 to 5.6 years; dementia, 4 years; and urinary incontinence, 1 year.

did not have the elevated risk for myocardial infarction, unlike participants who started therapy more than 20 years after menopause (HR, 0.91 [95% CI, 0.54-1.52] vs RR, 1.99 [95% CI, 1.32-3.02]; $P = .01$).[16] However, when use of hormone therapy by persons before enrollment into the WHI was taken into consideration, coronary risks did not differ between early and late initiation of hormone therapy.[50]

Discussion

This updated evidence review showed that persons taking hormone therapy to prevent chronic conditions may experience some benefits (eg, reduced risks of fractures and diabetes) but also several important harms (eg, higher risks of stroke or thromboembolic events). The findings are summarized in Table 2 and Table 3. Exposure to hormone therapy during the intervention phases of the WHI, however, was not associated with increased risks of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.[19]

These results pertain to persons who use hormone therapy for the purpose of preventing chronic conditions. They do not pertain to persons who use hormone therapy for the management of menopausal symptoms, which requires different consideration and weighing of benefits and harms.

A major point of discussion in recent years has been whether the overall net benefit of hormone therapy use may be increased if it is started early during menopause (ie, the "timing hypothesis").[104] This hypothesis proposes that hormone therapy given at or soon after menopause reduces the risks of cardiovascular disease,[105] mortality,[106] and dementia[107] but that the potential beneficial effects will be attenuated or not experienced when hormone therapy is initiated several years after menopause. Current evidence, however, does not confirm beneficial effects of timing of initiation. A study that is sometimes viewed as supporting the timing hypothesis is the Danish Osteoporosis Prevention Study (DOPS).[108] This study was not considered in the main synthesis because of its 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.

Limitations

This review has several limitations. First, the trials were restricted to those published in English. Because of the large number of included trials, however, it is believed that any potential studies not published in English would not affect the conclusions.

Second, most included trials had high attrition or low adherence to medications; this was true for the WHI, in which 40% to 50% of participants discontinued use of their medications during the trial. Nevertheless, secondary analyses of the WHI that were limited to adherent participants (ie, censoring persons within 6 months of their reporting if they had <80% adherence with study pills) were generally similar to intention-to-treat results[16] but rendered larger effect sizes.

Third, the mean age of participants in the included studies ranged from 50 to 79 years, which is older than the mean age of persons experiencing menopause (ie, 51 years), potentially limiting the applicability of the findings. For example, in the WHI only 12.5% were aged 50 to 54 years, an age range in which most persons are likely to consider hormone therapy for the treatment of menopausal symptoms.

Table 3. Summary of Evidence by Outcome: Estrogen Plus Progestin Trials Enrolling Generally Healthy Postmenopausal Persons 50 Years or Older

Outcome	No. of studies/study designs; No. of participants	Summary of findings	Consistency and precision	Limitations	Strength of evidence[a]
Invasive breast cancer	6 RCTs[4,16,18,19,40,41,49,50,56,58,68,74,89,90,96]; during intervention phase, 420 events in 25 442 persons contributed to effect estimates (based on 2 RCTs[16,89]) During cumulative follow-up, 1006 events in 16 608 persons contributed to effect estimate (based on 1 RCT[32])	Intervention follow-up of 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]) During cumulative follow-up, the risk remained significantly increased at 19.4 y (HR, 1.28 [95% CI, 1.13-1.45])	Consistent; precise	Fair; none	High for harm
Breast cancer mortality	1 RCT[18]; during intervention period, 9 events in 16 608 persons contributed to effect estimate During cumulative follow-up, 124 events in 16 608 persons contributed to effect estimate	Intervention follow-up of 5.6 y, similar risk (HR, 1.08 [95% CI, 0.29-4.03]), no significant risk increase/reduction with HT during cumulative follow-up at 20.3 y (HR, 1.35 [95% CI, 0.94-1.95])	NA; imprecise	Fair; none	Low for similar risks
Cervical cancer	1 RCT[52]; 13 events in 16 608 persons contributed to effect estimate	Intervention follow-up of 5.6 y, no significant risk increase/reduction with HT (HR, 1.44 [95% CI, 0.47-4.42])	NA; imprecise	Fair; 1 study followed participants for a relatively short duration (5.6 y) to evaluate a rare cancer outcome	Low for similar risks
Colorectal cancer	4 RCTs[4,16,22,42,50,60,89,90,96]; during intervention period, 152 events in 19 371 persons contributed to effect estimates (based on 2 RCTs[16,89]) During cumulative follow-up, number of events that contributed to effect estimate NR; based on 2 RCTs[16,89]	Intervention follow-up of 4.1-5.6 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 During cumulative follow-up, nonsignificant risk increase in the WHI (13.0 y follow-up; HR, 1.13 [95% CI, 0.85-1.51]) and nonsignificant decreased risk in HERS (6.8 y follow-up; HR, 0.82 [95% CI, 0.46-1.47])	Consistent; precise	Fair; long-term evidence is limited to the WHI	Moderate for benefit
Colorectal cancer mortality	1 RCT[19]; during intervention period, 22 events in 16 608 persons contributed to effect estimate During cumulative follow-up, 103 events in 16 608 persons contributed to effect estimate	Intervention follow-up of 5.6 y, no significant difference (HR, 0.87 [95% CI, 0.38-1.98]) or cumulative follow-up of 17.7 y (HR, 1.01 [95% CI, 0.69-1.49])	NA; imprecise	Fair; estimates based on a single study	Low for similar risks
Endometrial cancer	4 RCTs[4,16,40,41,50,52,57,89,90]; during intervention period, 64 events in 19 371 persons contributed to effect estimates (based on 2 RCTs[4,16,50,52,57,89,90]) 1 retrospective cohort study[102] with 4379 events in ≥900 000 persons	Intervention follow-up of 4.1-5.6 y, no significant risk increase/reduction with HT in the WHI (HR, 0.83 [95% CI, 0.49-1.40]) and in HERS (HR, 0.39 [95% CI, 0.08-2.02]) Statistically significant risk reduction with HT after 13.2 y of follow-up of in the WHI (HR, 0.65 [95% CI, 0.48-0.89])	Consistent; imprecise	Fair; long-term evidence is limited to the WHI and a retrospective cohort study; because endometrial cancer is rare, overall few events in RCTs (n = 161 after 13.2 y follow-up)	Low for similar risks
Lung cancer	3 RCTs[16,29,42,59,89] during intervention period, 191 events in 19 371 persons contributed to effect estimates (based on 2 RCTs[16,59,89]) During cumulative follow-up, 433 events in 15 327 persons contributed to effect estimates (based on 2 RCTs[16,89])	Intervention follow-up of 4.1-5.6 y, no significant risk increase/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 During cumulative follow-up, no significant risk increase with HT in the WHI (13.2 y follow-up; HR, 1.10 [95% CI, 0.89-1.35]) and HERS (6.8 y follow-up; HR, 1.43 [95% CI, 0.87-2.37])	Consistent; precise	Fair; long-term evidence is limited to the WHI	Moderate for similar risks
Lung cancer mortality	1 RCT[103]; 285 events in 16 608 persons contributed to effect estimate	During cumulative follow-up of 14.0 y, no significant risk increase with HT in the WHI (HR, 1.09 ([95% CI, 0.87-1.38])	NA; imprecise	Fair; estimates based on a single study	Low for similar risks
Non-Hodgkin lymphoma	1 RCT[27]; 223 events in 16 544 persons contributed to effect estimate	Cumulative follow-up of 13.5 y, no significant risk increase/reduction with HT (HR, 0.98 [95% CI, 0.76-1.28])	NA; imprecise	Fair; none	Low for similar risks
Ovarian cancer	1 RCT[16,52]; 40 events in 16 608 persons contributed to effect estimate	Intervention follow-up of 5.6 y, no significant risk increase/reduction with HT (HR, 1.41 [95% CI, 0.75-2.66])	NA; imprecise	Fair; study followed participants for a relatively short duration (5.6 y) to evaluate a rare cancer outcome	Low for similar risks

(continued)

Table 3. Summary of Evidence by Outcome: Estrogen Plus Progestin Trials Enrolling Generally Healthy Postmenopausal Persons 50 Years or Older (continued)

Outcome	No. of studies/study designs; No. of participants	Summary of findings	Consistency and precision	Limitations	Strength of evidence[a]
Total cancer mortality	1 RCT[19]; during intervention follow-up, 244 events in 16 608 persons contributed to effect estimate During cumulative follow-up, 1344 events in 16 608 persons contributed to effect estimate	Intervention follow-up of 5.6 y, no significant risk reduction/increase with HT (HR, 1.10 [95% CI, 0.86-1.42]) Cumulative follow-up of 17.7 y, no significant risk reduction/increase with HT (HR, 1.06 [95% CI, 0.95-1.18])	NA; precise	Fair; evidence is limited to a single study	Low for similar risks
Coronary heart disease	6 RCTs[16,40-42,49,96]; during intervention period, 487 events in 18 085 persons contributed to meta-analysis (based on 3 RCTs[16,29,40,49]) During cumulative follow-up, 1362 events in 15 730 persons contributed to effect estimate (based on 1 RCT[32])	Intervention follow-up of 2-5.6 y in meta-analysis, no significant risk reduction/increase with HT (RR, 1.12 [95% CI, 0.94-1.33]) Cumulative follow-up of 19.4 y No significant risk reduction/increase with HT (HR, 1.05 [95% CI, 0.95-1.17])	Consistent; precise	Fair; none	High for similar risks
Coronary heart disease mortality	1 RCT[19]; during intervention period, 80 events in 16 608 persons contributed to effect estimate During cumulative follow-up, 595 events in 16 608 persons contributed to effect estimate	Intervention follow-up of 5.6 y, no significant risk reduction/increase with HT (HR, 0.94 [95% CI, 0.60-1.45]) Cumulative follow-up of 17.7 y No significant risk reduction/increase with HT (HR, 1.05 [95% CI, 0.89-1.23])	NA; precise	Fair; evidence is limited to a single study	Low for similar risks
Peripheral arterial disease	1 RCT[37]; 98 events in 16 608 persons contributed to effect estimate	Intervention follow-up of 5.6 y, no significant risk reduction/increase with HT (HR, 0.89 [95% CI, 0.60 to 1.32])	NA; imprecise	Fair quality; evidence is limited to a single study	Low for similar risks
Probable dementia	1 RCT[74]; 61 events in 4532 persons contributed to effect estimate	Intervention follow-up of 4 y, significant risk increase with HT (HR, 2.05 [95% CI, 1.21-3.48])	NA; imprecise	Fair; none	Low for harm
Alzheimer disease or other dementia mortality	1 RCT[19]; during intervention period, there were 0 events in 16 608 persons During cumulative follow-up, 456 events in 16 608 persons contributed to effect estimate	No events during intervention follow-up of 5.6 y Cumulative follow-up of 17.7 y, no significant risk increase/reduction with HT (HR, 0.93 [95% CI, 0.77-1.11])	NA; imprecise	Fair; evidence based on a single study	Low for similar risks
Diabetes	2 RCTs[16,86,88]; during intervention follow-up, 861 events in 17 903 persons contributed to effect estimates During cumulative follow-up, 1786 events in 15 874 persons contributed to effect estimate (based on 1 RCT[16])	Intervention follow-up of 4.1-5.6 y, significant risk reduction with HT in the WHI (HR, 0.81 [95% CI, 0.70-0.94]) and HERS (HR, 0.65 [95% CI, 0.48-0.89]) Cumulative follow-up of 13.2 y, no significant risk increase/reduction with HT in the WHI (HR, 1.02 [95% CI, 0.93-1.12])	Consistent; precise	Fair; diabetes is self-reported	Moderate for benefit
Fractures	5 RCTs[4,16,41,42,49,55,89,90]; during intervention period, 2004 events in 20 499 persons contributed to meta-analysis During postintervention follow-up, 1184 events in 10 134 persons contributed to effect estimate (based on 1 RCT[28])	Intervention follow-up of 2-5.6 y, significant risk reduction with HT (RR, 0.79 [95% CI, 0.66-0.94]) Postintervention follow-up of 4.2 y, no significant risk increase/reduction with HT (HR, 0.97 [95% CI, 0.87-1.09])	Consistent; precise	Fair; none	High for benefit
Gallbladder disease	2 RCTs[16,40]; 847 events in 14 203 persons contributed to effect estimate (based on 1 RCT[16])	Intervention follow-up of 5.6 y, significant risk increase with HT (HR, 1.57 [95% CI, 1.36-1.80])	Consistent; precise	Fair; gallbladder disease is self-reported	Moderate for harm
Stroke	3 RCTs[16,42,49]; during intervention period, 270 events in 17 385 persons contributed to effect estimates (based on 2 RCTs[16,49]) During cumulative follow-up, 1071 events in 16 608 persons contributed to effect estimate (based on 1 RCT[32])	Intervention follow-up, significant increase with HT after 5.6 y in the WHI (HR, 1.37 [95% CI, 1.07-1.76]) and no significant risk reduction/increase with HT after 3.4 y in EPHT (HR, 1.06 [95% CI, 0.07-17.2]) Cumulative follow-up of 19.4 y, increased risk with HT (HR, 1.13 [95% CI, 1.00-1.27])	Consistent; precise	Fair; outcome measures heterogeneous (stroke incidence vs composite risk of various cerebrovascular events)	Moderate for harm

(continued)

Table 3. Summary of Evidence by Outcome: Estrogen Plus Progestin Trials Enrolling Generally Healthy Postmenopausal Persons 50 Years or Older (continued)

Outcome	No. of studies/study designs; No. of participants	Summary of findings	Consistency and precision	Limitations	Strength of evidence[a]
Stroke mortality	1 RCT[19]; during intervention period, 43 events in 16 608 persons contributed to effect estimate During cumulative follow-up, 349 events in 16 608 persons contributed to effect estimate (based on 1 RCT[32])	Intervention follow-up of 5.6 y, no significant risk reduction/increase with HT (HR, 1.58 [95% CI, 0.85-2.94]) Cumulative follow-up of 17.7 y, no significant risk reduction/increase with HT (HR, 1.12 [95% CI, 0.91-1.38])	NA; imprecise	Fair; evidence is limited to a single study	Low for similar risks
Urinary incontinence	2 RCTs[16,69]; during intervention period, 2346 events in 12 786 persons contributed to effect estimates During postintervention follow-up, 2211 events in 10 073 persons contributed to effect estimate (based on 1 RCT[16])	Intervention follow-up of 1-4.2 y, significant risk increase with HT in the WHI (HR, 1.49 [95% CI, 1.36-1.63]) and HERS (OR, 1.60 [95% CI, 1.30-1.90]) Postintervention follow-up of 8.2 y, significant risk increase with HT in the WHI (HR, 1.16 [95% CI, 1.08-1.25])	Consistent; precise	Fair; urinary incontinence is self-reported	Moderate for harm
Venous thromboembolism	5 RCTs[41,42,49,63,89]; during intervention period, 216 DVT events and 143 PE events in 19 371 persons contributed to effect estimates (based on 2 RCTs[16]) During cumulative follow-up, 674 events in 15 730 persons contributed to effect estimate (based on 1 RCT[16])	Intervention follow-up of 4.1-5.6 y, significant increased risk with HT in DVT in the WHI (HR, 1.87 [95% CI, 1.37-2.54]) and in HERS (HR, 2.82 [95% CI, 1.32-6.04]); significant increased risk with HT in PE in the WHI (HR, 1.98 [95% CI, 1.36-2.87]) but not in HERS (HR, 2.78 [95% CI, 0.89-8.74]) Cumulative follow-up of 13.2 y, significant increase with HT in DVT (HR, 1.24 [95% CI, 1.01-1.53]) or PE (HR, 1.26 [95% CI, 1.00-1.59]) in the WHI	Consistent; precise	Fair; 3 studies followed participants for a relatively short duration (2-3 y)	Moderate for harm
Quality of life	1 RCT[16]; observed in 16 608 persons	Intervention follow-up of 5.6 y, similar scores on most items of the SF-36	Inconsistent regarding subscales; precise	Fair; none	Moderate for similar risks
All-cause mortality	3 RCTs[41,89,90]; 751 events in 19 580 persons contributed to meta-analysis	Intervention follow-up of 3.2-5.6 y in meta-analysis, no significant risk increase/reduction with HT (RR, 1.01 [95% CI, 0.88-1.16])	Consistent; precise	Fair; none	High for similar risks
	1 RCT[32]; 5440 events in 16 608 persons contributed to effect estimate	Cumulative follow-up of 19.4 y, no significant risk reduction/increase with HT (HR, 1.02 [95% CI, 0.97-1.08])	NA; precise	Fair; evidence is limited to a single study	

Abbreviations: DVT, deep vein thrombosis; EPHT, Estonian Postmenopausal Hormone Therapy; HERS, Heart and Estrogen/Progestin Replacement Study; HR, hazard ratio; HT, hormone therapy; NA, not applicable; NR, not reported; OR, odds ratio; PE, pulmonary embolism; RCT, randomized clinical trial; RR, relative risk; SF-36, 36-Item Short Form Health Survey; WHI, Women's Health Initiative.

[a] Strength of evidence ratings refer to the intervention phase except for mortality, for which they refer to cumulative follow-up.

Fourth, approximately 80% of the participants were categorized as of White race. Subgroup analyses did not reveal differences in beneficial or harmful effects among racial and ethnic groups, but such analyses might have been underpowered.

Fifth, most findings came from the WHI, which tested only 1 dose, formulation, and route of administration of hormone therapy in each trial (0.625 mg/d of oral conjugated equine estrogen, with or without 2.5 mg/d of medroxyprogesterone). The PEPI trial was the only study that directly compared different formulations of estrogen and progestin combinations. Whether different formulations have different risk-benefit profiles, however, remains unclear.

Conclusions

Use of hormone therapy in persons for the primary prevention of chronic conditions was significantly associated with some benefits but also with an increased risk of harms.

ARTICLE INFORMATION

Accepted for Publication: September 19, 2022.

Author Contributions: Dr Gartlehner had full access to all of 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, Patel, Kahwati.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Gartlehner, Rains.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Gartlehner, Patel.
Obtained funding: Kahwati.
Administrative, technical, or material support: Rains.
Supervision: Gartlehner, Kahwati.

Conflict of Interest Disclosures: Dr Reddy reported receiving personal fees from Boston VA Healthcare for part-time clinical work. No other disclosures were reported.

Funding/Support: This project was funded under contract HHSA-75Q80120D00007, Task Order 01, from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, under a contract to support the US Preventive Services Task Force (USPSTF).

Role of the Funder/Sponsor: Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript findings. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

Additional Contributions: We gratefully acknowledge the following individuals for their contributions to this project and deeply appreciate their considerable support for and commitment to this work, including AHRQ staff (Howard Tracer, MD; and Tracy Wolff, MD, MPH), RTI International–University of North Carolina Evidence-based Practice Center staff (Carol Woodell, BSPH; Loraine Monroe; Teyonna Downing; Michelle Bogus; Staci Rachman, BA; Sharon Barrell, MA); and Megan Van Noord, MLIS, for literature searches. We also acknowledge the contributions of members of the USPSTF. USPSTF members, peer reviewers, and federal partner reviewers did not receive financial compensation for their contributions.

Additional Information: A draft version of the full evidence report underwent external peer review from 4 content experts (Cynthia Farquhar, MD, MPH, The University of Auckland; JoAnn Manson, MD, MPH, Brigham and Women's Hospital; Susan Reed, MD, MPH, University of Washington School of Medicine; and Raja Sayegh, MD, Boston University School of Medicine) and 6 federal partner reviewers from the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases. Comments from reviewers were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF recommendation statement. It did not undergo additional review after submission to *JAMA*.

REFERENCES

1. American College of Obstetricians and Gynecologists. ACOG committee opinion No. 565: hormone therapy and heart disease. *Obstet Gynecol*. 2013;121(6):1407-1410. doi:10.1097/01.AOG.0000431053.33593.2d

2. Cobin RH, Goodman NF; AACE Reproductive Endocrinology Scientific Committee. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on menopause—2017 update. *Endocr Pract*. 2017;23(7):869-880. doi:10.4158/EP171828.PS

3. Shifren JL, Gass ML; NAMS Recommendations for Clinical Care of Midlife Women Working Group. The North American Menopause Society recommendations for clinical care of midlife women. *Menopause*. 2014;21(10):1038-1062. doi:10.1097/GME.0000000000000319

4. Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333. doi:10.1001/jama.288.3.321

5. Anderson GL, Limacher M, Assaf AR, et al; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701-1712. doi:10.1001/jama.291.14.1701

6. US Food and Drug Administration. Menopause: medicines to help you. Published 2019. Accessed August 30, 2021. https://www.fda.gov/consumers/free-publications-women/menopause-medicines-help-you

7. Grossman DC, Curry SJ, Owens DK, et al; US Preventive Services Task Force. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US Preventive Services Task Force recommendation statement. *JAMA*. 2017;318(22):2224-2233. doi:10.1001/jama.2017.18261

8. Gartlehner G, Patel SV, Feltner C, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2017;318(22):2234-2249. doi:10.1001/jama.2017.16952

9. US Preventive Services Task Force. US Preventive Services Task Force Procedure Manual. Published 2021. Accessed September 10, 2022. https://uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual

10. Harlow SD, Gass M, Hall JE, et al; STRAW 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Menopause*. 2012;19(4):387-395. doi:10.1097/gme.0b013e31824d8f40

11. Gartlehner G, Patel SV, Reddy S, Rains C, Coker-Schwimmer M, Kahwati L. *Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: An Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 222*. Agency for Healthcare Research and Quality; 2022. AHRQ publication 22-05294-EF-1.

12. United Nations Development Programme. Human Development Index (HDI) ranking. In: Human Development Report 2020: The Next Frontier: Human Development and the Anthropocene. Published 2020. Accessed July 9, 2021. http://hdr.undp.org/content/latest-human-development-index-ranking

13. Harris RP, Helfand M, Woolf SH, et al; Methods Work Group, Third US Preventive Services Task Force. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med*. 2001;20(3S):21-35. doi:10.1016/S0749-3797(01)00261-6

14. West SL, Gartlehner G, Mansfield AJ, et al. Comparative effectiveness review methods: clinical heterogeneity. AHRQ publication 10-EHC070-EF. Agency for Healthcare Research and Quality. Published 2010. Accessed September 23, 2022. https://effectivehealthcare.ahrq.gov/

15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186

16. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended

poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310(13):1353-1368. doi:10.1001/jama.2013.278040

17. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. *J Clin Epidemiol*. 2015;68(11):1312-1324. doi:10.1016/j.jclinepi.2014.11.023

18. Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative randomized clinical trials. *JAMA*. 2020;324(4):369-380. doi:10.1001/jama.2020.9482

19. Manson JE, Aragaki AK, Rossouw JE, et al; WHI Investigators. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women's Health Initiative randomized trials. *JAMA*. 2017;318(10):927-938. doi:10.1001/jama.2017.11217

20. Manson JE, Aragaki AK, Bassuk SS, et al; WHI Investigators. Menopausal estrogen-alone therapy and health outcomes in women with and without bilateral oophorectomy: a randomized trial. *Ann Intern Med*. 2019;171(6):406-414. doi:10.7326/M19-0274

21. Chlebowski RT, Anderson GL, Aragaki AK, Prentice R. Breast cancer and menopausal hormone therapy by race/ethnicity and body mass index. *J Natl Cancer Inst*. 2015;108(2):djv327. doi:10.1093/jnci/djv327

22. Prentice RL, Aragaki AK, Chlebowski RT, et al. Randomized trial evaluation of the benefits and risks of menopausal hormone therapy among women 50-59 years of age. *Am J Epidemiol*. 2021;190(3):365-375. doi:10.1093/aje/kwaa210

23. Henderson VW, St John JA, Hodis HN, et al. Cognitive effects of estradiol after menopause: a randomized trial of the timing hypothesis. *Neurology*. 2016;87(7):699-708. doi:10.1212/WNL.0000000000002980

24. Espeland MA, Rapp SR, Manson JE, et al; WHIMSY and WHIMS-ECHO Study Groups. Long-term effects on cognitive trajectories of postmenopausal hormone therapy in two age groups. *J Gerontol A Biol Sci Med Sci*. 2017;72(6):838-845. doi:10.1093/gerona/glw156

25. Chlebowski RT, Anderson GL, Sarto GE, et al. Continuous combined estrogen plus progestin and endometrial cancer: the Women's Health Initiative randomized trial. *J Natl Cancer Inst*. 2015;108(3):djv350. doi:10.1093/jnci/djv350

26. Chlebowski RT, Barrington W, Aragaki AK, et al. Estrogen alone and health outcomes in black women by African ancestry: a secondary analyses of a randomized controlled trial. *Menopause*. 2017;24(2):133-141. doi:10.1097/GME.0000000000000733

27. Kato I, Chlebowski RT, Hou L, et al. Menopausal estrogen therapy and non-Hodgkin's lymphoma: a post-hoc analysis of Women's Health Initiative randomized clinical trial. *Int J Cancer*. 2016;138(3):604-611. doi:10.1002/ijc.29819

28. Watts NB, Cauley JA, Jackson RD, et al; Women's Health Initiative Investigators. No increase in fractures after stopping hormone therapy: results from the Women's Health Initiative. *J Clin Endocrinol Metab*. 2017;102(1):302-308. doi:10.1210/jc.2016-3270

29. Chlebowski RT, Wakelee H, Pettinger M, et al. Estrogen plus progestin and lung cancer: follow-up of the Women's Health Initiative randomized trial. *Clin Lung Cancer*. 2016;17(1):10-7.e1. doi:10.1016/j.cllc.2015.09.004

30. Liu L, Klein L, Eaton C, et al. Menopausal hormone therapy and risks of first hospitalized heart failure and its subtypes during the intervention and extended postintervention follow-up of the Women's Health Initiative randomized trials. *J Card Fail*. 2020;26(1):2-12. doi:10.1016/j.cardfail.2019.09.006

31. Kantarci K, Tosakulwong N, Lesnick TG, et al. Effects of hormone therapy on brain structure: a randomized controlled trial. *Neurology*. 2016;87(9):887-896. doi:10.1212/WNL.0000000000002970

32. Prentice RL, Aragaki AK, Chlebowski RT, et al. Dual-outcome intention-to-treat analyses in the Women's Health Initiative randomized controlled hormone therapy trials. *Am J Epidemiol*. 2020;189(9):972-981. doi:10.1093/aje/kwaa033

33. Mørch LS, Kjaer SK, Keiding N, Løkkegaard E, Lidegaard Ø. The influence of hormone therapies on type I and II endometrial cancer: a nationwide cohort study. *Int J Cancer*. 2016;138(6):1506-1515. doi:10.1002/ijc.29878

34. Park SY, Wilkens LR, Kolonel LN, Henderson BE, Le Marchand L. Inverse associations of dietary fiber and menopausal hormone therapy with colorectal cancer risk in the Multiethnic Cohort Study. *Int J Cancer*. 2016;139(6):1241-1250. doi:10.1002/ijc.30172

35. Bethea TN, Palmer JR, Adams-Campbell LL, Rosenberg L. A prospective study of reproductive factors and exogenous hormone use in relation to ovarian cancer risk among Black women. *Cancer Causes Control*. 2017;28(5):385-391. doi:10.1007/s10552-016-0840-4

36. Hsia J, Criqui MH, Herrington DM, et al; Women's Health Initiative Research Group. Conjugated equine estrogens and peripheral arterial disease risk: the Women's Health Initiative. *Am Heart J*. 2006;152(1):170-176. doi:10.1016/j.ahj.2005.09.005

37. Hsia J, Criqui MH, Rodabough RJ, et al; Women's Health Initiative Investigators. Estrogen plus progestin and the risk of peripheral arterial disease: the Women's Health Initiative. *Circulation*. 2004;109(5):620-626. doi:10.1161/01.CIR.0000115309.63979.92

38. Tang JY, Spaunhurst KM, Chlebowski RT, et al. Menopausal hormone therapy and risks of melanoma and nonmelanoma skin cancers: Women's Health Initiative randomized trials. *J Natl Cancer Inst*. 2011;103(19):1469-1475. doi:10.1093/jnci/djr333

39. Espeland MA, Shumaker SA, Leng I, et al; WHIMSY Study Group. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. *JAMA Intern Med*. 2013;173(15):1429-1436. doi:10.1001/jamainternmed.2013.7727

40. Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA*. 1995;273(3):199-208. doi:10.1001/jama.1995.03520270033028

41. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med*. 2000;343(8):522-529. doi:10.1056/NEJM200008243430801

42. Tierney MC, Oh P, Moineddin R, et al. A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women. *Psychoneuroendocrinology*. 2009;34(7):1065-1074. doi:10.1016/j.psyneuen.2009.02.009

43. Yaffe K, Vittinghoff E, Ensrud KE, et al. Effects of ultra-low-dose transdermal estradiol on cognition and health-related quality of life. *Arch Neurol*. 2006;63(7):945-950. doi:10.1001/archneur.63.7.945

44. Waters DD, Alderman EL, Hsia J, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA*. 2002;288(19):2432-2440. doi:10.1001/jama.288.19.2432

45. Hsia J, Langer RD, Manson JE, et al; Women's Health Initiative Investigators. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med*. 2006;166(3):357-365. doi:10.1001/archinte.166.3.357

46. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. *J Clin Endocrinol Metab*. 2001;86(8):3618-3628. doi:10.1210/jcem.86.8.7703

47. Greenspan SL, Resnick NM, Parker RA. The effect of hormone replacement on physical performance in community-dwelling elderly women. *Am J Med*. 2005;118(11):1232-1239. doi:10.1016/j.amjmed.2005.03.004

48. Hodis HN, Mack WJ, Lobo RA, et al; Estrogen in the Prevention of Atherosclerosis Trial Research Group. Estrogen in the prevention of atherosclerosis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2001;135(11):939-953. doi:10.7326/0003-4819-135-11-200112040-00005

49. Veerus P, Hovi SL, Fischer K, Rahu M, Hakama M, Hemminki E. Results from the Estonian postmenopausal hormone therapy trial. [ISRCTN35338757]. *Maturitas*. 2006;55(2):162-173. doi:10.1016/j.maturitas.2006.01.012

50. Prentice RL, Manson JE, Langer RD, et al. Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. *Am J Epidemiol*. 2009;170(1):12-23. doi:10.1093/aje/kwp115

51. Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol*. 2012;13(5):476-486. doi:10.1016/S1470-2045(12)70075-X

52. Anderson GL, Judd HL, Kaunitz AM, et al; Women's Health Initiative Investigators. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA*. 2003;290(13):1739-1748. doi:10.1001/jama.290.13.1739

53. Bonds DE, Lasser N, Qi L, et al. The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative

randomised trial. *Diabetologia*. 2006;49(3):459-468. doi:10.1007/s00125-005-0096-0

54. Brunner RL, Gass M, Aragaki A, et al; Women's Health Initiative Investigators. Effects of conjugated equine estrogen on health-related quality of life in postmenopausal women with hysterectomy: results from the Women's Health Initiative randomized clinical trial. *Arch Intern Med*. 2005;165 (17):1976-1986. doi:10.1001/archinte.165.17.1976

55. Cauley JA, Robbins J, Chen Z, et al; Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA*. 2003;290(13):1729-1738. doi:10.1001/jama.290.13.1729

56. Chlebowski RT, Anderson GL, Gass M, et al; WHI Investigators. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA*. 2010;304(15): 1684-1692. doi:10.1001/jama.2010.1500

57. Chlebowski RT, Anderson GL, Manson JE, et al. Lung cancer among postmenopausal women treated with estrogen alone in the women's health initiative randomized trial. *J Natl Cancer Inst*. 2010; 102(18):1413-1421. doi:10.1093/jnci/djq285

58. Chlebowski RT, Hendrix SL, Langer RD, et al; WHI Investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA*. 2003;289 (24):3243-3253. doi:10.1001/jama.289.24.3243

59. Chlebowski RT, Schwartz AG, Wakelee H, et al; Women's Health Initiative Investigators. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. *Lancet*. 2009;374(9697):1243-1251. doi:10.1016/S0140-6736 (09)61526-9

60. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al; Women's Health Initiative Investigators. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med*. 2004;350(10):991-1004. doi:10.1056/NEJMoa032071

61. Culhane NS. Estrogen plus progestin may increase incidence of dementia. *J Fam Pract*. 2003; 52(10):754-755.

62. Curb JD, Prentice RL, Bray PF, et al. Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med*. 2006; 166(7):772-780. doi:10.1001/archinte.166.7.772

63. Cushman M, Kuller LH, Prentice R, et al; Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. *JAMA*. 2004;292(13):1573-1580. doi:10.1001/jama.292.13.1573

64. Espeland MA, Brunner RL, Hogan PE, et al; Women's Health Initiative Study of Cognitive Aging Study Group. Long-term effects of conjugated equine estrogen therapies on domain-specific cognitive function: results from the Women's Health Initiative Study of Cognitive Aging extension. *J Am Geriatr Soc*. 2010;58(7):1263-1271. doi:10.1111/j.1532-5415.2010.02953.x

65. Espeland MA, Rapp SR, Shumaker SA, et al; Women's Health Initiative Memory Study. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291 (24):2959-2968. doi:10.1001/jama.291.24.2959

66. Ettinger B, Ensrud KE, Wallace R, et al. Effects of ultralow-dose transdermal estradiol on bone mineral density: a randomized clinical trial. *Obstet Gynecol*. 2004;104(3):443-451. doi:10.1097/01.AOG.0000137833.43248.79

67. Grady D, Yaffe K, Kristof M, Lin F, Richards C, Barrett-Connor E. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. *Am J Med*. 2002;113(7):543-548. doi:10.1016/S0002-9343 (02)01270-6

68. Gramling R, Eaton CB, Rothman KJ, Cabral H, Silliman RA, Lash TL. Hormone replacement therapy, family history, and breast cancer risk among postmenopausal women. *Epidemiology*. 2009;20(5):752-756. doi:10.1097/EDE.0b013e3181a71279

69. Steinauer JE, Waetjen LE, Vittinghoff E, et al. Postmenopausal hormone therapy: does it cause incontinence? *Obstet Gynecol*. 2005;106(5, pt 1) (suppl 1):940-945. doi:10.1097/01.AOG.0000180394.08406.15

70. Vickers MR, Martin J, Meade TW; WISDOM Study Team. The Women's International Study of long-Duration Oestrogen after Menopause (WISDOM): a randomised controlled trial. *BMC Womens Health*. 2007;7(2):2. doi:10.1186/1472-6874-7-2

71. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al; WHI Investigators. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA*. 2003;289(20):2673-2684. doi:10.1001/jama.289.20.2673

72. Waetjen LE, Brown JS, Vittinghoff E, et al. The effect of ultralow-dose transdermal estradiol on urinary incontinence in postmenopausal women. *Obstet Gynecol*. 2005;106(5, pt 1):946-952. doi:10.1097/01.AOG.0000182576.48290.6d

73. Toh S, Hernández-Díaz S, Logan R, Rossouw JE, Hernán MA. Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: does the increased risk ever disappear? a randomized trial. *Ann Intern Med*. 2010;152(4):211-217. doi:10.7326/0003-4819-152-4-201002160-00005

74. Shumaker SA, Legault C, Rapp SR, et al; WHIMS Investigators. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*. 2003;289 (20):2651-2662. doi:10.1001/jama.289.20.2651

75. Shumaker SA, Legault C, Kuller L, et al; Women's Health Initiative Memory Study. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291(24): 2947-2958. doi:10.1001/jama.291.24.2947

76. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. [Published corection appears in *JAMA*. 2008;299(12):1426]. *JAMA*. 2007;297(13):1465-1477. doi:10.1001/jama.297.13.1465

77. Ritenbaugh C, Stanford JL, Wu L, et al; Women's Health Initiative Investigators. Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. *Cancer Epidemiol Biomarkers Prev*. 2008;17(10):2609-2618. doi:10.1158/1055-9965.EPI-08-0385

78. Resnick SM, Maki PM, Rapp SR, et al; Women's Health Initiative Study of Cognitive Aging Investigators. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *J Clin Endocrinol Metab*. 2006;91(5):1802-1810. doi:10.1210/jc.2005-2097

79. Resnick SM, Espeland MA, An Y, et al; Women's Health Initiative Study of Cognitive Aging Investigators. Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. *J Clin Endocrinol Metab*. 2009;94(11):4152-4161. doi:10.1210/jc.2009-1340

80. Rapp SR, Espeland MA, Shumaker SA, et al; WHIMS Investigators. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*. 2003;289(20):2663-2672. doi:10.1001/jama.289.20.2663

81. Grady D, Applegate W, Bush T, Furberg C, Riggs B, Hulley SB. Heart and Estrogen/progestin Replacement Study (HERS): design, methods, and baseline characteristics. *Control Clin Trials*. 1998;19 (4):314-335. doi:10.1016/S0197-2456(98)00010-5

82. Hulley S, Grady D, Bush T, et al; Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998;280(7):605-613. doi:10.1001/jama.280.7.605

83. Hendrix SL, Wassertheil-Smoller S, Johnson KC, et al; WHI Investigators. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation*. 2006;113(20):2425-2434. doi:10.1161/CIRCULATIONAHA.105.594077

84. Hendrix SL. The Women's Health Initiative estrogen plus progestin trial: the study and how it changes our practice. *J Am Osteopath Assoc*. 2003; 103(2)(suppl 2):S3-S5.

85. Hendrix SL, Cochrane BB, Nygaard IE, et al. Effects of estrogen with and without progestin on urinary incontinence. *JAMA*. 2005;293(8):935-948. doi:10.1001/jama.293.8.935

86. Margolis KL, Bonds DE, Rodabough RJ, et al; Women's Health Initiative Investigators. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia*. 2004;47(7):1175-1187. doi:10.1007/s00125-004-1448-x

87. Manson JE, Hsia J, Johnson KC, et al; Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med*. 2003;349(6):523-534. doi:10.1056/NEJMoa030808

88. Kanaya AM, Herrington D, Vittinghoff E, et al; Heart and Estrogen/progestin Replacement Study. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2003;138

(1):1-9. doi:10.7326/0003-4819-138-1-200301070-00005

89. Hulley S, Furberg C, Barrett-Connor E, et al; HERS Research Group. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA*. 2002;288(1):58-66. doi:10.1001/jama.288.1.58

90. Heiss G, Wallace R, Anderson GL, et al; WHI Investigators. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA*. 2008;299(9):1036-1045. doi:10.1001/jama.299.9.1036

91. Hays J, Ockene JK, Brunner RL, et al; Women's Health Initiative Investigators. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med*. 2003;348(19):1839-1854. doi:10.1056/NEJMoa030311

92. Johnson SR, Ettinger B, Macer JL, Ensrud KE, Quan J, Grady D. Uterine and vaginal effects of unopposed ultralow-dose transdermal estradiol. *Obstet Gynecol*. 2005;105(4):779-787. doi:10.1097/01.AOG.0000157116.23249.52

93. Cirillo DJ, Wallace RB, Rodabough RJ, et al. Effect of estrogen therapy on gallbladder disease. *JAMA*. 2005;293(3):330-339. doi:10.1001/jama.293.3.330

94. LaCroix AZ, Chlebowski RT, Manson JE, et al; WHI Investigators. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA*. 2011;305(13):1305-1314. doi:10.1001/jama.2011.382

95. Resnick SM, Coker LH, Maki PM, Rapp SR, Espeland MA, Shumaker SA. The Women's Health Initiative Study of Cognitive Aging (WHISCA): a randomized clinical trial of the effects of hormone therapy on age-associated cognitive decline. *Clin Trials*. 2004;1(5):440-450. doi:10.1191/1740774504cn040oa

96. Vickers MR, MacLennan AH, Lawton B, et al; WISDOM Group. Main morbidities recorded in the women's international study of long duration oestrogen after menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women. *BMJ*. 2007;335(7613):239. doi:10.1136/bmj.39266.425069.AD

97. Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. *PLoS Med*. 2015;12(6):e1001833. doi:10.1371/journal.pmed.1001833

98. Chlebowski RT, Rohan TE, Manson JE, et al. Breast cancer after use of estrogen plus progestin and estrogen alone: analyses of data from 2 women's health initiative randomized clinical trials. *JAMA Oncol*. 2015;1(3):296-305. doi:10.1001/jamaoncol.2015.0494

99. Canonico M, Plu-Bureau G, O'Sullivan MJ, et al. Age at menopause, reproductive history, and venous thromboembolism risk among postmenopausal women: the Women's Health Initiative hormone therapy clinical trials. *Menopause*. 2014;21(3):214-220. doi:10.1097/GME.0b013e31829752e0

100. Cherry N, McNamee R, Heagerty A, Kitchener H, Hannaford P. Long-term safety of unopposed estrogen used by women surviving myocardial infarction: 14-year follow-up of the ESPRIT randomised controlled trial. *BJOG*. 2014;121(6):700-705. doi:10.1111/1471-0528.12598

101. Cherry N, Gilmour K, Hannaford P, et al; ESPRIT Team. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet*. 2002;360(9350):2001-2008. doi:10.1016/S0140-6736(02)12001-0

102. Rimoin LP, Kwatra SG, Yosipovitch G. Female-specific pruritus from childhood to postmenopause: clinical features, hormonal factors, and treatment considerations. *Dermatol Ther*. 2013;26(2):157-167. doi:10.1111/dth.12034

103. Chlebowski RT, Anderson GL. Menopausal hormone therapy and cancer: changing clinical observations of target site specificity. *Steroids*. 2014;90:53-59. doi:10.1016/j.steroids.2014.06.001

104. Whitmer RA, Quesenberry CP, Zhou J, Yaffe K. Timing of hormone therapy and dementia: the critical window theory revisited. *Ann Neurol*. 2011;69(1):163-169. doi:10.1002/ana.22239

105. Hodis HN, Mack WJ, Henderson VW, et al; ELITE Research Group. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med*. 2016;374(13):1221-1231. doi:10.1056/NEJMoa1505241

106. Salpeter SR, Cheng J, Thabane L, Buckley NS, Salpeter EE. Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. *Am J Med*. 2009;122(11):1016-1022. doi:10.1016/j.amjmed.2009.05.021

107. Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, estrogen, and dementia: a 2014 update. *Mol Cell Endocrinol*. 2014;389(1-2):7-12. doi:10.1016/j.mce.2014.01.020

108. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *BMJ*. 2012;345:e6409. doi:10.1136/bmj.e6409