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

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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.


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The use of hormone therapy is recommended by clinical practice guidelines to manage menopause-associated symptoms. In the past, hormone therapy has also 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, 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.

Hormone therapy includes the use of various forms, doses, and regimens of estrogen with or without progestogen (progestin or progesterone). 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). 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.

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.

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, HSPrj, 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.

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).

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) 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 \( \chi^2 \) statistic and the \( I^2 \) statistic were calculated to assess the statistical heterogeneity in effects between studies.

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. 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. 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, reporting on the following: 2 new trials, 2 ancillary studies of the WHI, previously included trials, and 3 observational studies. Combined with articles that were carried forward from the previous review, 85 articles representing 20 unique fair- or good-quality trials (N = 39,145) and 3 large controlled cohort studies (N = 1155,410) 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.
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

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 trials44,46,47 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?

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

**Key Question 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)?

**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 RCTs3,16,40,41,46,48,50,51,54,94,98,100,101 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...
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 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, 9.5-51 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] and 4 events in the Women's International Study of Long Duration Estrogen After Menopause [WISDOM]). A prospective cohort study with data on 85,734 postmenopausal participants confirmed the WHI findings. 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).

Estrogen plus progestin therapy was associated with a lower risk of diabetes among participants in the HERS (n = 2029) and the WHI (n = 15,874). 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]).

Five trials with data on 20,499 participants reported on fractures with data on more than 20,000 persons. 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>
<thead>
<tr>
<th>Trial, source(s)</th>
<th>Country; participants and characteristics</th>
<th>Intervention; duration</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early vs Late Intervention Trial with Estradiol, Cognitive Endpoints (ELITE-Cog) Henderson et al,23 2016</td>
<td>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 &lt;25 pg/mL</td>
<td>17β-estradiol (1 mg/d) (n = 323) Placebo (n = 120) Women with a uterus: cyclic micronized progesterone (45 mg as a 4% vaginal gel) Mean, 4.8 y</td>
<td>Fair</td>
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<tr>
<td>Estrogen Memory Study (EMS) Tierney et al,42 2009</td>
<td>Canada Aged 61-87 y Last menstrual cycle &gt;12 mo before screening; fluent in English and able to read normal print and hear normal speech</td>
<td>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</td>
<td>Fair</td>
</tr>
<tr>
<td>Estrogen in the Prevention of Atherosclerosis (EPAT) Hodis et al,48 2001</td>
<td>US Postmenopausal women aged 46-80 y LDL-C level ≥130 mg/dL (3.37 mmol/L)</td>
<td>Micronized 17β-estradiol (1 mg/d) (n = 111) Placebo (n = 111) 2 y</td>
<td>Fair</td>
</tr>
<tr>
<td>Estonian Postmenopausal Hormone Therapy (EPHT) Veerus et al,49 2006</td>
<td>Estonia Aged 50-64 y ≥12 mo since last period at randomization stage</td>
<td>CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 404) Placebo (n = 373) Mean, 3.4 y</td>
<td>Fair</td>
</tr>
<tr>
<td>Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis (ERA) Herrington et al,41 2000</td>
<td>US Postmenopausal women aged 41-79 y Not receiving E replacement therapy; &gt;1 epicardial coronary stenosis of ≥30% of the luminal diameter</td>
<td>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</td>
<td>Good</td>
</tr>
<tr>
<td>Greenspan et al,47 2005</td>
<td>US Community-dwelling women aged 65-90 y</td>
<td>CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 121) CEE (0.625 mg/d) (n = 66) Placebo (n = 186) 3 y</td>
<td>Good</td>
</tr>
<tr>
<td>Heart and Estrogen/Progesterone Replacement Study (HERS) Grady et al,81 1998 Hulley et al,82 1998 Kanaya et al,88 2003 Steinauer et al,69,89 2005</td>
<td>US Postmenopausal, aged ≤80 y (mean, 66.7 y) Intact uterus; established coronary artery disease</td>
<td>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</td>
<td>Good</td>
</tr>
<tr>
<td>Kronos Early Estrogen Prevention Study-Cognitive and Affective Study (KEEPS-Cog) Gleason et al,97 2015</td>
<td>US Recently postmenopausal, aged 42-58 y Intact uterus; at risk for cardiovascular disease</td>
<td>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</td>
<td>Fair</td>
</tr>
<tr>
<td>Kronos Early Estrogen Prevention Study-MRI (KEEPS-MRI) Kantarci et al,31 2016</td>
<td>US Aged 42-59 y In good cardiovascular health; 5-36 mo past menopause; no MRI contraindication for safety and neurological disorders</td>
<td>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</td>
<td>Fair</td>
</tr>
<tr>
<td>Postmenopausal Estrogen/Progestin Interventions (PEPI) trial Writing Group for the PEPI trial,40 1995</td>
<td>US Aged 45-64 y With or without a uterus; naturally or surgically menopausal</td>
<td>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</td>
<td>Fair</td>
</tr>
<tr>
<td>STOP IT Gallagher et al,46 2001</td>
<td>US Aged 65-77 y Femoral neck density within normal range for age</td>
<td>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</td>
<td>Fair</td>
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</table>

(continued)
<table>
<thead>
<tr>
<th>Trial, source(s)</th>
<th>Country; participants and characteristics</th>
<th>Intervention; duration</th>
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</tr>
</thead>
</table>
| **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  
Johnson et al,92 2005 | 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,51 2012  
Anderson et al,52 2003  
Cauley 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  
Hsia et al,36 2006  
Manson et al,16 2013  
Margolis et al,86 2004  
Prentice et al,50 2009  
Prentice,22 2020  
Prentice,52 2020  
Ritven et al,77 2008  
Rosen et al,38 2011  
Toh et al,75 2010  
Wassertheil-Smoller et al,71 2003  
Tohe et al,73 2010 | US  
Postmenopausal, averaged 50-79 y  
Prior hysterectomy  
3-mo washout period required for women using HT at baseline | 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-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,52 2020 | US  
9666 WHI participants (90%) had any postintervention follow-up; 7645 (71%) consented to participate in the extension phase | CEE (0.625 mg/d) (n = 5310)  
Placebo (n = 5429)  
Median, 7.2 y | Fair |
| **WHI E + P trial**  
Anderson et al,51 2012  
Anderson et al,52 2003  
Cauley et al,99 2014  
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  
Hsia et al,36 2006  
Manson et al,16 2013  
Margolis et al,86 2004  
Prentice et al,50 2009  
Prentice,22 2020  
Prentice,52 2020  
Ritven et al,77 2008  
Rosen et al,38 2011  
Toh et al,75 2010  
Wassertheil-Smoller et al,71 2003  
Tohe 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 |
[95% CI, 0.40-0.88]) compared with persons who had received placebo. 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. 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,

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

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>WHI E + P postintervention and postintervention extension phases Chlebowski et al,29 2009 Chlebowski et al,26 2010 Gramling et al,49 2009 Heiss et al,80 2008 Manson et al,46 2013 Manson et al,19 2017 Prentice et al,22 2020 Prentice et al,32 2020</td>
<td>US 15 747 WHI participants (95%) had any postintervention follow-up; 12 788 (77%) consented to participate in the extension phase</td>
<td>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)</td>
<td>Good</td>
</tr>
<tr>
<td>Women's Health Initiative Memory Study (WHIMS) E only Espeland et al,63 2004 Shumaker et al,32 2004</td>
<td>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</td>
<td>CEE (0.625 mg/d) (n = 1464) Placebo (n = 1483) 5.2 y</td>
<td>Good</td>
</tr>
<tr>
<td>WHIMS E + P Culhane,63 2003 Rapp et al,80 2003 Shumaker et al,32 2004</td>
<td>US WHI participants aged 65-79 y enrolled in the E + P trial Free of probable dementia; able and willing to undergo annual cognitive assessment</td>
<td>CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 2229) Placebo (n = 2303) 5.4 y</td>
<td>Good</td>
</tr>
<tr>
<td>Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO) Espeland et al,24 2017</td>
<td>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</td>
<td>CEE (0.625 mg/d + MPA [2.5 mg/d]) or CEE (0.625 mg/d) only (n = 1402) 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</td>
<td>Good</td>
</tr>
<tr>
<td>Women's Health Initiative Memory Study of Younger Women (WHIMSY) Espeland et al,24,39 2013</td>
<td>US Postmenopausal, aged 50-55 y 3-mo washout period for women using HT at baseline</td>
<td>CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 696) Placebo (n = 630) 7.2 y</td>
<td>Good</td>
</tr>
<tr>
<td>Women's International Study of Long Duration Estrogen After Menopause (WISDOM) Vickers et al,96 2007</td>
<td>UK, Australia, New Zealand Postmenopausal, aged 50-69 y</td>
<td>CEE (0.625 mg/d + MPA [2.5 mg/d]) (n = 2196) CEE (0.625 mg/d) (n = 826) Placebo (n = 2189) 1 y</td>
<td>Fair</td>
</tr>
</tbody>
</table>

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.
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) and the WHI (n = 8376) 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 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], the Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis [ERA] trial [n = 205], and the WHI [n = 10 739]), 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) found higher risks of incidental 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]). The smaller Ultra-Low-Dose Transdermal Estrogen Assessment (ULTRA) trial (n = 239) did not find a statistically significant difference between groups at 2 years.

Based on the WHI (n = 10 739) results, 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 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 (Figure 2 in the Supplement; RR, 1.04 [95% CI, 0.89-1.21]) during a mean follow-up of 71 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 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]). 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]).

The risk of breast cancer mortality was numerically higher (median, 20.3 years; HR, 1.35 [95% CI, 0.94-1.95]). The HER 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]). The other trials reported inconclusive findings.

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of trials</th>
<th>No. of cases/total</th>
<th>Events per 10 000 persons (95% CI)</th>
<th>Benefits of hormone therapy</th>
<th>Harms of hormone therapy</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer (invasive)</td>
<td>1</td>
<td>104/5310</td>
<td>-52 (-97 to 4)</td>
<td></td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1</td>
<td>65/5310</td>
<td>-16 (-21 to 67)</td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1</td>
<td>62/5310</td>
<td>4 (-30 to 54)</td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Total cancer mortality</td>
<td>1</td>
<td>126/5310</td>
<td>-13 (-64 to 51)</td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>3</td>
<td>203/5396</td>
<td>-19 (-80 to 54)</td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Dementia (probable)</td>
<td>1</td>
<td>28/1464</td>
<td>63 (-21 to 213)</td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>449/4900</td>
<td>-134 (-237 to -18)</td>
<td></td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Fractures (osteoporotic)</td>
<td>1</td>
<td>544/5310</td>
<td>-388 (-489 to -277)</td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>1</td>
<td>461/4141</td>
<td>377 (234 to 540)</td>
<td></td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>169/5310</td>
<td>79 (15 to 159)</td>
<td></td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>1</td>
<td>773/3316</td>
<td>885 (659 to 1135)</td>
<td></td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>1</td>
<td>137/5310</td>
<td>77 (19 to 153)</td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3</td>
<td>309/5733</td>
<td>21 (-57 to 109)</td>
<td></td>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>

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 71 years except all-cause mortality, 2 to 7.2 years; fractures, 7.2 years; dementia, 5.2 years; and urinary incontinence, 1 year.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies/study designs; No. of participants</th>
<th>Summary of findings</th>
<th>Consistency and precision</th>
<th>Limitations</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive breast cancer</td>
<td>4 RCTs, during intervention period, 239 events in 10 739 persons contributed to effect estimate (based on 1 RCT)</td>
<td>Intervention follow-up of 7.2 y Non-significant lower risk with HT (HR, 0.79 [95% CI, 0.61-1.02])</td>
<td>Consistent; imprecise</td>
<td>Fair quality; 3 studies followed up participants for a relatively short duration (2-3 y)</td>
<td>Moderate for benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During cumulative follow-up, number of events that contributed to effect estimate NR (based on 1 RCT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>During cumulative follow-up, 239 events in 10 739 persons contributed to effect estimate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer mortality</td>
<td>1 RCT, during intervention period, 13 events in 10 739 persons contributed to effect estimate</td>
<td>Intervention follow-up of 7.2 y, similar risk (HR, 0.45 [95% CI, 0.14-1.46])</td>
<td>NA; imprecise</td>
<td>Fair quality; evidence is limited to a single study</td>
<td>Low for benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During cumulative follow-up, 63 events in 10 739 persons contributed to effect estimate</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>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])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1 RCT, during intervention period, 123 events in 10 739 persons contributed to effect estimate</td>
<td>Intervention follow-up of 7.2 y, no significant risk increase/reduction with HT (HR, 0.45 [95% CI, 0.81-1.64])</td>
<td>NA; imprecise</td>
<td>Fair quality; none</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During cumulative follow-up, 123 events in 9786 persons contributed to effect estimate</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>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])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer mortality</td>
<td>1 RCT, during intervention period, 33 events in 10 739 persons contributed to effect estimate</td>
<td>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, 1.24 [95% CI, 0.79-1.84])</td>
<td>NA; imprecise</td>
<td>Fair quality; estimates based on a single study</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During cumulative follow-up, 87 events in 10 739 persons contributed to effect estimate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1 RCT, during intervention phase, 123 events in 10 739 persons contributed to effect estimate</td>
<td>Intervention follow-up of 7.2 y, no significant risk increase/reduction with HT (HR, 1.05 [95% CI, 0.74-1.49])</td>
<td>NA; imprecise</td>
<td>Fair quality; none</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During cumulative follow-up, 223 events in 9786 persons contributed to effect estimate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>During cumulative follow-up of 13.0 y, no significant risk increase/reduction with HT (HR, 0.98 [95% CI, 0.75-1.27])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer mortality</td>
<td>1 RCT, 67 events in 10 379 persons contributed to effect estimate</td>
<td>Intervention follow-up of 7.9 y, no significant risk increase with HT (HR, 1.07 [95% CI, 0.66-1.72])</td>
<td>NA; imprecise</td>
<td>Fair quality; estimates based on a single study; short duration follow-up for a mortality outcome</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 RCT, 160 events in 10 685 persons contributed to effect estimate</td>
<td>Cumulative follow-up of 12.9 y, no significant risk increase/reduction with HT (HR, 1.02 [95% CI, 0.74-1.39])</td>
<td>NA; imprecise</td>
<td>Fair quality; none</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Total cancer mortality</td>
<td>1 RCT, during intervention period, 262 events in 10 739 persons contributed to effect estimate</td>
<td>Intervention follow-up of 7.2 y, no significant risk reduction/increase with HT (HR, 0.96 [95% CI, 0.75-1.22])</td>
<td>NA; imprecise</td>
<td>Fair quality; evidence is limited to a single study</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During cumulative follow-up, 863 events in 10 739 persons contributed to effect estimate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cumulative follow-up of 17.7 y, no significant risk reduction/increase with HT (HR, 0.99 [95% CI, 0.86-1.13])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>4 RCTs, during intervention period, 422 events in 11 310 persons contributed to meta-analysis (based on 3 RCTs)</td>
<td>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])</td>
<td>Consistent; precise</td>
<td>Fair quality; none</td>
<td>High for similar risks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During cumulative follow-up, 1071 events in 7645 persons contributed to effect estimate (based on 1 RCT)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Cumulative follow-up of 19.4 y, no significant risk reduction/increase with HT (HR, 0.97 [95% CI, 0.86-1.09])</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies/study designs; No. of participants</th>
<th>Summary of findings</th>
<th>Consistency and precision</th>
<th>Limitations</th>
<th>Strength of evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease mortality</td>
<td>1 RCT14, during intervention period, 517 events in 10 739 persons contributed to effect estimate (based on 1 RCT15)</td>
<td>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])</td>
<td>NA; precise</td>
<td>Fair quality; evidence is limited to a single study</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>1 RCT16; 144 events in 10 739 persons contributed to effect estimate</td>
<td>Intervention follow-up of 7.1 y, no significant risk reduction/increase with HT (HR, 1.35 [95% CI, 0.97 to 1.88])</td>
<td>NA; imprecise</td>
<td>Fair quality; evidence is limited to a single study</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Probable dementia</td>
<td>1 RCT17,51, 47 events in 2947 persons contributed to effect estimate</td>
<td>Intervention follow-up of 5.2 y, no significant risk increase/reduction with HT (HR, 1.49 [95% CI, 0.83-2.66])</td>
<td>NA; imprecise</td>
<td>Fair quality; none</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Alzheimer disease or other dementia mortality</td>
<td>1 RCT18, during intervention period, 11 events in 10 739 persons contributed to effect estimate</td>
<td>Intervention follow-up of 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])</td>
<td>NA; imprecise for intervention phase, precise for cumulative phase</td>
<td>Fair quality; few events and short-term follow-up for mortality outcome (intervention phase only)</td>
<td>Low for benefit</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 RCT19,52, during intervention period, 976 events in 9917 persons contributed to effect estimate</td>
<td>Intervention follow-up of 7.1 y, risk reduction with HT (HR, 0.86 [95% CI, 0.76-0.96]) Cumulative follow-up of 13.0 y, no significant risk increase/reduction with HT (HR, 0.94 [95% CI, 0.85-1.04])</td>
<td>NA; precise</td>
<td>Fair quality; diabetes is self-reported</td>
<td>Moderate for benefit</td>
</tr>
<tr>
<td>Fractures</td>
<td>2 RCTs20,22,41,53,94; during intervention period, 1311 events in 10 739 persons contributed to effect estimate (based on 1 RCT21) During postintervention follow-up, 699 events in 5 053 persons contributed to effect estimate (based on 1 RCT21)</td>
<td>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])</td>
<td>Consistent; precise</td>
<td>Fair quality; none</td>
<td>High for benefit</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>2 RCTs16,40; 773 events in 8376 persons contributed to effect estimate (based on 1 RCT15)</td>
<td>Intervention follow-up of 7.1 y, significant risk increase with HT (HR, 1.55 [95% CI, 1.34-1.79])</td>
<td>Consistent; precise</td>
<td>Fair quality; gallbladder disease is self-reported</td>
<td>Moderate for harm</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 RCTs41,48,94; during intervention period, 298 events in 10 739 persons contributed to effect estimate (based on 1 RCT21) During cumulative follow-up, 791 events in 10 739 persons contributed to effect estimate (based on 1 RCT21)</td>
<td>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])</td>
<td>Consistent; precise</td>
<td>Fair quality; 3 studies followed participants for a relatively short duration (2-3 y)</td>
<td>Moderate for harm</td>
</tr>
<tr>
<td>Stroke mortality</td>
<td>1 RCT10; during intervention period, 47 events in 10 739 persons contributed to effect estimate</td>
<td>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])</td>
<td>NA; imprecise</td>
<td>Fair quality; evidence is limited to a single study</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>2 RCTs16,72; during intervention period, 1272 events in 6767 persons contributed to effect estimate (based on 1 RCT15) During postintervention follow-up, 1456 events in 5644 persons contributed to effect estimate (based on 1 RCT15)</td>
<td>Intervention follow-up of 7.1 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])</td>
<td>Consistent; precise</td>
<td>Fair quality; urinary incontinence is self-reported</td>
<td>Moderate for harm</td>
</tr>
</tbody>
</table>
Table 2. Summary of Evidence by Outcome: Estrogen-Only Trials Enrolling Generally Healthy Postmenopausal Persons 50 Years or Older (continued)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies/study designs: No. of participants</th>
<th>Summary of findings</th>
<th>Consistency and precision</th>
<th>Limitations</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thrombembolism</td>
<td>2 RCTs17,18,28; 91 (PE) events in 10 739 persons</td>
<td>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])</td>
<td>Consistent; precise</td>
<td>Fair quality, none</td>
<td>High for similar risks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During cumulative follow-up, 471 events in 9939 persons contributed to effect estimates (based on 1 RCT 16)</td>
<td></td>
<td></td>
<td>Good for similar risks</td>
</tr>
<tr>
<td>Quality of life</td>
<td>1 RCT19; observed in 107 195 persons</td>
<td>Intervention follow-up of 7.1 y, similar scores on most items of the SF-36 subscales; precise risks</td>
<td>Consistent; precise</td>
<td>Fair quality, none</td>
<td>High for similar risks</td>
</tr>
</tbody>
</table>

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.

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 trials41,89,90 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.30,19,32,90

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
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]; \( P = .01 \)). 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 dementia107 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 results16 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies/study designs; No. of participants</th>
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<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive breast cancer</td>
<td>6 RCTs16, 18, 19, 40, 41, 49, 50, 56, 68, 74, 89, 90, 96; during intervention phase, 420 events in 25,442 persons contributed to effect estimate (based on 2 RCTs16, 89)</td>
<td>Intervention follow-up of 4.1-5.6 y, significant risk increase with HT (HR, 1.24 [95% CI, 1.01-1.52]) in WHI and nonsignificant increase with HT in HERS (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])</td>
<td>Consistent; precise</td>
<td>Fair; none</td>
<td>High for harm</td>
</tr>
<tr>
<td>Breast cancer mortality</td>
<td>1 RCT16; 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</td>
<td>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])</td>
<td>NA; imprecise</td>
<td>Fair; none</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>1 RCT17; 13 events in 16,608 persons contributed to effect estimate</td>
<td>Intervention follow-up of 5.6 y, no significant risk increase/reduction with HT (HR, 1.44 [95% CI, 0.47-4.42])</td>
<td>NA; imprecise</td>
<td>Fair; 1 study followed participants for a relatively short duration (5.6 y) to evaluate a rare cancer outcome</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>4 RCTs16, 22, 24, 50, 68, 90, 96; during intervention period, 152 events in 19,371 persons contributed to effect estimate (based on 2 RCTs16, 89)</td>
<td>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 (11.3 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])</td>
<td>Consistent; precise</td>
<td>Fair; long-term evidence is limited to the WHI</td>
<td>Moderate for benefit</td>
</tr>
<tr>
<td>Colorectal cancer mortality</td>
<td>1 RCT17; 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</td>
<td>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])</td>
<td>NA; imprecise</td>
<td>Fair; estimates based on a single study</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>4 RCTs16, 40, 41, 50, 52, 57, 89, 90; during intervention period, 64 events in 19,371 persons contributed to effect estimate (based on 2 RCTs16, 89) 1 retrospective cohort study102 with 4379 events in ≥900,000 persons</td>
<td>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])</td>
<td>Consistent; imprecise</td>
<td>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)</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>3 RCTs16, 26, 29, 39, 89; during intervention period, 191 events in 19,371 persons contributed to effect estimate (based on 2 RCTs16, 89)</td>
<td>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])</td>
<td>Consistent; precise</td>
<td>Fair; long-term evidence is limited to the WHI</td>
<td>Moderate for similar risks</td>
</tr>
<tr>
<td>Lung cancer mortality</td>
<td>1 RCT16, 52; 285 events in 16,608 persons contributed to effect estimate</td>
<td>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])</td>
<td>NA; imprecise</td>
<td>Fair; estimates based on a single study</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 RCT16, 52; 223 events in 16,544 persons contributed to effect estimate</td>
<td>Cumulative follow-up of 13.5 y, no significant risk increase/reduction with HT (HR, 0.98 [95% CI, 0.76-1.28])</td>
<td>NA; imprecise</td>
<td>Fair; none</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>1 RCT16, 52; 40 events in 16,608 persons contributed to effect estimate</td>
<td>Intervention follow-up of 5.6 y, no significant risk increase/reduction with HT (HR, 1.41 [95% CI, 0.73-2.66])</td>
<td>NA; imprecise</td>
<td>Fair; study followed participants for a relatively short duration (5.6 y) to evaluate a rare cancer outcome</td>
<td>Low for similar risks</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies/study designs; No. of participants</th>
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<th>Strength of evidence*</th>
</tr>
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<tr>
<td>Total cancer mortality</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt;; during intervention follow-up, 244 events in 16 608 persons contributed to effect estimate</td>
<td>Intervention follow-up of 5.6 y, no significant risk reduction/increase with HT (HR, 1.10 [95% CI, 0.86-1.42])</td>
<td>NA; precise</td>
<td>Fair; evidence is limited to a single study</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>6 RCTs&lt;sup&gt;16,40-42,49,96&lt;/sup&gt;; during intervention period, 487 events in 18 085 persons contributed to meta-analysis (based on 3 RCTs&lt;sup&gt;16,29,40,49&lt;/sup&gt;)</td>
<td>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])</td>
<td>Consistent; precise</td>
<td>Fair; none</td>
<td>High for similar risks</td>
</tr>
<tr>
<td>Coronary heart disease mortality</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt;; during intervention period, 80 events in 16 608 persons contributed to effect estimate</td>
<td>Intervention follow-up of 5.6 y, no significant risk reduction/increase with HT (HR, 1.05 [95% CI, 0.95-1.17])</td>
<td>NA; precise</td>
<td>Fair; evidence is limited to a single study</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt;; 98 events in 16 608 persons contributed to effect estimate</td>
<td>Intervention follow-up of 5.6 y, no significant risk reduction/increase with HT (HR, 0.89 [95% CI, 0.60 to 1.32])</td>
<td>NA; imprecise</td>
<td>Fair; evidence is limited to a single study</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Probable dementia</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt;; 61 events in 4532 persons contributed to effect estimate</td>
<td>Intervention follow-up of 4 y, significant risk increase with HT (HR, 2.05 [95% CI, 1.21-3.48])</td>
<td>NA; imprecise</td>
<td>Fair; evidence based on a single study</td>
<td>Low for harm</td>
</tr>
<tr>
<td>Alzheimer disease or other dementia mortality</td>
<td>1 RCT&lt;sup&gt;15&lt;/sup&gt;; during intervention period, there were 0 events in 16 608 persons</td>
<td>No events during intervention follow-up of 5.6 y</td>
<td>NA; imprecise</td>
<td>Fair; evidence based on a single study</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 RCTs&lt;sup&gt;16,40,48&lt;/sup&gt;; during intervention follow-up, 861 events in 17 903 persons contributed to effect estimates</td>
<td>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])</td>
<td>Consistent; precise</td>
<td>Fair; diabetes is self-reported</td>
<td>Moderate for benefit</td>
</tr>
<tr>
<td>Fractures</td>
<td>5 RCTs&lt;sup&gt;16,41,42,47,49,55,89,90&lt;/sup&gt;; during intervention period, 2004 events in 20 499 persons contributed to meta-analysis</td>
<td>Intervention follow-up of 2-5.6 y, significant risk reduction with HT (RR, 0.79 [95% CI, 0.66-0.94])</td>
<td>Consistent; precise</td>
<td>Fair; none</td>
<td>High for benefit</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>2 RCTs&lt;sup&gt;16,40&lt;/sup&gt;; 847 events in 14 203 persons contributed to effect estimate (based on 1 RCT&lt;sup&gt;15&lt;/sup&gt;)</td>
<td>Intervention follow-up of 5.6 y, significant risk increase with HT (HR, 1.57 [95% CI, 1.36-1.80])</td>
<td>Consistent; precise</td>
<td>Fair; gallbladder disease is self-reported</td>
<td>Moderate for harm</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 RCTs&lt;sup&gt;16,41,42,49&lt;/sup&gt;; during intervention period, 270 events in 17 385 persons contributed to effect estimates (based on 2 RCTs&lt;sup&gt;16,49&lt;/sup&gt;)</td>
<td>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])</td>
<td>Consistent; precise</td>
<td>Fair; outcome measures heterogeneous (stroke incidence vs composite risk of various cerebrovascular events)</td>
<td>Moderate for harm</td>
</tr>
</tbody>
</table>
### Table 3. Summary of Evidence by Outcome: Estrogen Plus Progestin Trials Enrolling Generally Healthy Postmenopausal Persons 50 Years or Older (continued)

<table>
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<tr>
<td><strong>Stroke mortality</strong></td>
<td>1 RCT(^{16}); during intervention period, 43 events in 16,608 persons contributed to effect estimate</td>
<td>Intervention follow-up of 5.6 y, no significant risk reduction/increase with HT (HR, 1.58 [95% CI, 0.85-2.94])</td>
<td>NA; imprecise</td>
<td>Fair; evidence is limited to a single study</td>
<td>Low for similar risks</td>
</tr>
<tr>
<td></td>
<td>During cumulative follow-up, 349 events in 16,608 persons contributed to effect estimate (based on 1 RCT(^{16}))</td>
<td>Cumulative follow-up of 17.7 y, no significant risk reduction/increase with HT (HR, 1.12 [95% CI, 0.91-1.38])</td>
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<tr>
<td><strong>Urinary incontinence</strong></td>
<td>2 RCTs(^{16,65}); during intervention period, 2346 events in 12,786 persons contributed to effect estimates</td>
<td>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])</td>
<td>Consistent; precise</td>
<td>Fair; urinary incontinence is self-reported</td>
<td>Moderate for harm</td>
</tr>
<tr>
<td></td>
<td>During postintervention follow-up, 2211 events in 10,073 persons contributed to effect estimate (based on 1 RCT(^{16}))</td>
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<tr>
<td><strong>Venous thromboembolism</strong></td>
<td>5 RCTs(^{11,42,49,63,87}); during intervention period, 216 DVT events and 143 PE events in 19,371 persons contributed to effect estimates (based on 2 RCTs(^{16}))</td>
<td>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</td>
<td>Consistent; precise</td>
<td>Fair; 3 studies followed participants for a relatively short duration (2-3 y)</td>
<td>Moderate for harm</td>
</tr>
<tr>
<td></td>
<td>During cumulative follow-up, 674 events in 15,730 persons contributed to effect estimate (based on 1 RCT(^{16}))</td>
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<tr>
<td><strong>Quality of life</strong></td>
<td>1 RCT(^{14}); observed in 16,608 persons</td>
<td>Intervention follow-up of 5.6 y, similar scores on most items of the SF-36</td>
<td>Inconsistent regarding subscales; precise</td>
<td>Fair; none</td>
<td>Moderate for similar risks</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>3 RCTs(^{41,89,90}); 751 events in 19,580 persons contributed to meta-analysis</td>
<td>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])</td>
<td>Consistent; precise</td>
<td>Fair; none</td>
<td>High for similar risks</td>
</tr>
<tr>
<td></td>
<td>1 RCT(^{32}); 5440 events in 16,608 persons contributed to effect estimate</td>
<td>Cumulative follow-up of 19.4 y, no significant risk reduction/increase with HT (HR, 1.02 [95% CI, 0.97-1.08])</td>
<td>NA; precise</td>
<td>Fair; evidence is limited to a single study</td>
<td></td>
</tr>
</tbody>
</table>

**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.

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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.

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Role of the Funder/Sponsor: AHRQ had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript. The opinions expressed in this document are those of the investigators and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

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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.

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