Supplementary Online Content

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*. doi:10.1001/jama.2017.16952

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Search strategies

PubMed, September 28, 2015

#1	Search "Hormone Replacement Therapy"[Mesh] OR "Estrogen Replacement Therapy"[Mesh] OR "Estrogens"[Mesh] OR "Estradiol Congeners"[Mesh]	153213
#2	Search "Perimenopause"[Mesh] OR "Climacteric"[Mesh] OR "Menopause"[Mesh]	50740
#3	Search (#1 AND #2)	18187
#4	Search (#1 AND #2) Filters: Humans	17486
#5	Search (#4) AND ("2011/06/01"[Date - Entrez]: "3000"[Date - Entrez]) Filters: Humans	1558
#6	Search (#4) AND ("2011/06/01"[Date - Entrez]: "3000"[Date - Entrez]) Filters: Humans; English	1449
#9	Search (#5 NOT #6) NON ENGLISH	109

PubMed (English) = 1449 = (2 appeared in the original report and have been removed)
PubMed (English) = 1447

Cochrane, September 28, 2015
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric)
Reviews = 9 = 4 NEW
Other reviews = 5 = 1 NEW
Trials = 62 = 33 NEW

Embase, September 28, 2015
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) = 459 = 327 NEW

ClinicalTrials.gov, September 28, 2015
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) = 12

WHO ICTRP, September 28, 2015
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) = 7 = 4 NEW

TOTAL NON-DUPLICATE DATABASE = 1828

Drugs@FDA.gov, September 28, 2015
Will do targeted searches for "harms" as indicated

NON-ENGLISH
PubMed (non-English) = 109 = NEW
Embase = 16 = 13 NEW
Total = 122

IPA, September 28, 2015
IPA (held as separate file) = ‘hormone replacement therapy’ AND (menopause OR perimenopause OR climacteric) = 6 = 4 NEW

Pubmed, August 1, 2016

#15	Search ("Hormone Replacement Therapy"[Mesh] OR "Estrogen Replacement Therapy"[Mesh] OR "Estrogens"[Mesh] OR "Estradiol Congeners"[Mesh])	157162
#16	Search "Perimenopause"[Mesh] OR "Climacteric"[Mesh] OR "Menopause"[Mesh]	52591
#17	Search (#15 AND #16)	18650
#21	Search (#15 AND #16) Filters: Publication date from 2015/06/01	223
#22	Search (#15 AND #16) Filters: Publication date from 2015/06/01; Humans	216
#23	Search (#15 AND #16) Filters: Publication date from 2015/06/01; Humans; English	204
#30	Search (#21 NOT #23)	19
#32	Search (#21 NOT #23) Filters: Humans	12

PubMed (English) = 204 = 189 NEW
PubMed (non-English) = 12

Cochrane, August 1, 2016
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric)
Reviews = 3 = 3 NEW
Other reviews = 0 = 0 NEW
Trials = 26 = 22 NEW

Embase, August 1, 2016
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) = 29 = 19 NEW

ClinicalTrials.gov, August 1, 2016
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) = 2

WHO ICTRP, August 1, 2016
'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) = 2 NEW

TOTAL NON-DUPLICATE DATABASE = 237

Drugs@FDA.gov, August 1, 2016
Will do targeted searches for “harms” as indicated

NON-ENGLISH
PubMed (non-English) = 12
Embase = 0 = NEW
Total = 12

IPA, August 1, 2016
IPA (held as separate file) = 'hormone replacement therapy' AND (menopause OR perimenopause OR climacteric) = 0 New

eTable 1. Eligibility Criteria

	Include	Exclude
Population	Generally healthy perimenopausal and postmenopausal women who are eligible for hormone therapy; women with and without menopausal symptoms will be included if the focus of the analysis is on the prevention of chronic conditions	Animals; men; premenopausal women; postmenopausal women with contraindications for hormone therapy use, such as history of breast cancer, coronary heart disease, previous venous thromboembolic event or stroke, active liver disease, or women who are at high risk of these complications; populations that are not applicable to US primary care
Interventions	Systemic therapy with estrogen-only formulations or estrogen plus progestin for the prevention of chronic conditions; US Food and Drug Administration–approved medications that are available for use in the United States	Localized (nonsystemic) treatments, such as rings or gels, contraceptives, and other hormones or treatments of menopausal symptoms (such as over-the-counter preparations that are not approved by the US Food and Drug Administration)
Comparators	Placebo, no treatment	Active comparator
Outcomes	KQ 1/2: Benefits and harms Cancer (breast, cervical, colorectal, endometrial, nonsmall cell lung, and ovarian) Coronary heart disease Cognitive functioning and dementia Diabetes Gallbladder disease Fractures Stroke Urinary incontinence Venus thromboembolism Quality of life (if related to chronic conditions of interest)	Any outcomes that are not health outcomes of chronic conditions associated with hormone therapy (eg, intermediate outcomes, such as bone density and cholesterol level)
	Functional capacity All-cause mortality Disease-specific mortality (if related to chronic conditions of interest) KQ 3: Any of the outcomes listed above by subgroups of interest	
Timing: Duration of intervention	≥1 year of treatment	<1 year of treatment
Setting	Primary care or primary care–like settings	Inpatient facilities, nursing homes, and specialist settings (such as endocrinology)
Geography	US adult population or comparable populations (ie, those categorized as “Very High” on the Human Development Index, as defined by the United Nations Development Programme)	Settings not comparable or applicable to US adult population

eTable 1. Eligibility Criteria (continued)

Study design	**All outcomes:** **Randomized controlled trials** **Controlled clinical trials** **Systematic reviews** **Large cohort studies (>10 000 women) for outcomes with no evidence from trials or systematic reviews**	**All other study designs**
Publication language	English	Non-English language
Publication type	Published or unpublished original research	Nonsystematic review article, letter, or editorial; results reported elsewhere; no original data
Start date of search	January 2011 onward	Before January 2011

KQ = key question; US = United States.

eTable 2. Ratings for Domains of Quality Ratings of Randomized Controlled Trials

Trial	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care providers masked?	Patient masked?	Loss to follow-up ≤20% and differential attrition ≤15%?	Intention-to-treat analysis?	Other biases?	Quality rating
DOPS[1, 2]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes[a]	Poor
Clarke 2002[3]	Unclear	Unclear	Yes	Yes	No	No	No	Yes	No	Poor
EMS[4]	Yes	Yes	Mostly, except for prior hormone therapy use and amnestic mild cognitive impairment	Yes	Yes	Yes	Yes	Unclear	No	Fair
EPAT[5]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[b]	Fair
EPHT[6]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Fair
ERA[7]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes[c]	Fair
ESPRIT[8]	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Fair
Greenspan 2005[9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
Notelovitz 2002[10]	Unclear	Unclear	Yes	Yes	Yes	Yes	No	No	Yes[d]	Poor
HERS;[11-14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
KEEPS-Cog[15]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
Pefanco 2007[16]	Yes	Unclear	Yes	Yes	Unclear	Yes	No	No	No	Poor
PEPI[17]	Yes	Unclear	Unclear	Yes	Unclear	Yes	Unclear	No	Yes[e]	Fair
STOP-IT[18]	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Fair
ULTRA[19-22]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
WAVE[23]	Yes	Unclear	Yes	Yes	Yes	Yes	No	Unclear	No	Fair
WHI[24-41 42-45 46, 47 48-57]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
WHIMS[58-62]	Yes	Yes	Mostly, except for history of stroke, and hypertension	Yes	Yes	Yes	Yes	Yes	No	Good
WHIMSY[63]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
WHISCA[64-66]	Yes	Yes	Mostly, except for smoking status	Yes	Yes	Yes	Yes	Yes	No	Good
WISDOM[67]	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Fair

[a] High risk of selection bias and contamination. Invited participants chose whether or not to be part of randomized trial (those who preferred a treatment option where followed in the cohort study). Among those who were randomized to no-HRT and attended 5 -year follow-up, 15% had initiated HRT. Among those randomized to HRT, 18% had changed the type of HRT and 22% had stopped HRT at 5 years.

[b] Although the trial conducted an ITT analysis, it was only for evaluable patients (199/222) from the larger set of randomized patients.

[c] There was a statistically significant difference between placebo and CEE in adherence.

[d] Risk of measurement bias. Some outcome (eg, breast cancer) were assessed as adverse events; ascertainment of these outcomes is unclear. Although mammograms were performed as part of the study protocol, cases of breast cancer appear to have been self-reported. Some were assessed to be benign; method of determining cancer severity were not described.

DOPS = Danish Osteoporosis Prevention Study; E = estrogen only; EMS = Estrogen Memory Study; EPAT = Estrogen in the Prevention of Atherosclerosis; EPHT = Estonian Postmenopausal Hormone Therapy Trial; ERA = Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HERS = Heart and Estrogen/ Progestin Replacement Study; KEEPS-Cog = Kronos Early Estrogen Prevention Study–Cognitive and Affective Study; PEPI = Postmenopausal Estrogen and Progestin Interventions Trial (PEPI); STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; ULTRA = Ultra-Low-Dose Transdermal Estrogen Assessment; WAVE = The Women's Angiographic Vitamin and Estrogen Trial; WHI = Women's Health Initiative E Trial; WHIMS = Women's Health Initiative Memory Study E; WHIMSY = The Women's Health Initiative Memory Study of Younger Women; WHISCA = Women's Health Initiative Study of Cognitive Aging; WISDOM = International Study of Long Duration Oestrogen After Menopause.

eTable 3. Evidence Table of Trials Reporting Incidence of Breast Cancer

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
EPAT Estrogen-only trial Hodis, 2001[5]	111 Estrogen 111 Placebo	**Follow-up: 2 years** **Breast cancer** 0 vs. 1
EPHT Estrogen plus progestin trial Veerus, 2006[6]	404 Estrogen plus progestin 373 Placebo	**Follow-up: Mean 3.4 years** **Breast cancer** 1 vs. 2; HR, 0.55 (95% CI, 0.05-6.06)
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[7]	100 Estrogen alone 104 Estrogen plus progestin 105 Placebo	**Follow-up: Mean 3.2 years** **Breast cancer (not defined)** 1 vs. 0 vs. 0; *P* = .35
ESPRIT Estrogen-only trial Cherry (ESPRIT Team), 2002[8]; Cherry, 2014[68]	513 Estrogen[b] 504 Placebo	**Follow-up: 2 years**[8] **Any breast cancer (measured via ICD codes)** 4 (0.8%) vs. 4 (0.8%); RR, 0.98 (95% CI, 0.25-3.91); *P* = 1.00 **Cumulative follow-up: Mean 12.6 years**[c68] **Any breast cancer (measured via ICD codes)** HR, 0.47 (95% CI, 0.19-1.15)
Greenspan et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[9]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Follow-up: 3 years** **Breast cancer** *Analysis did not stratify by treatment regimen* 2 (hormone therapy) vs. 2; *P* = 1.0
HERS Estrogen plus progestin trial Hulley, 2002[69]	1380 Estrogen plus progestin 1383 Placebo Cumulative follow-up: 1156 Estrogen plus progestin 1383 Placebo	**Follow-up: 4.1 years** 34 (2.5%) vs. 25 (1.8%); HR, 1.38 (95% CI, 0.82-2.31); *P* = .22 **Follow-up: Mean 2.7 years postintervention** HR, 1.08 (95% CI, 0.52-2.24); *P* = .83 **Cumulative follow-up: 6.8 years** HR, 1.27 (95% CI, 0.84-1.94); *P* = .26

eTable 3. Evidence Table of Trials Reporting Incidence of Breast Cancer (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995[17]	175 Estrogen 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Follow-up: 3 years** **Breast cancer** 1 (estrogen) vs. 2 (estrogen plus progestin) vs. 4 (estrogen plus micronized progestin) vs. 1 (placebo); *P* = .29
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[18]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Follow-up: 3 years** **Breast cancer (not defined)** *Analysis did not stratify by treatment regimen* 0 (hormone therapy with or without calcitriol) vs. 4 (calcitriol only and placebo)
WAVE Estrogen-only and estrogen plus progestin trial Waters, 2002[23]	124 Estrogen 86 Estrogen plus progestin 213 Placebo	**Follow-up: Mean 2.8 years** **Breast cancer (any)** *Analysis did not stratify by treatment regimen* 3 vs. 1; *P* = .37
WHI Estrogen-only trial Anderson, 2004;[24] Anderson, 2012;[38] LaCroix, 2011[37] Prentice 2009[50] Manson, 2013[33] Chlebowski, 2015[70]	5310 Estrogen 5429 Placebo Postintervention extension follow-up: 3778 Estrogen 3867 Placebo	**Follow-up: Median 7.2 years**[33, 37] **Invasive breast cancer** 104 (2.0%) vs. 135 (2.5%); HR, 0.79 (95% CI, 0.61-1.02); *P* = .07 **Subgroups:** No significant difference by age at randomization[33] Biennial analysis (2, 4, 6, and 8 years since randomization)[70] P for trend = .29[70] **Risk for invasive breast cancer based on timing of intervention:**[50] No significant association; p for gap time interaction = .20 **Follow-up: Median 6.6 years postintervention and postintervention extension**[33] **Invasive breast cancer** HR, 0.80 (95% CI, 0.58-1.11); *P* = .19 **Cumulative follow-up: Median 13.0 years**[33] **Invasive breast cancer** HR, 0.79 (95% CI, 0.65-0.97); *P* = .02

eTable 3. Evidence Table of Trials Reporting Incidence of Breast Cancer (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen plus progestin trial Writing Group for the WHI, 2002;[51] Heiss, 2008;[57] Chlebowski, 2003;[42] Chlebowski, 2010;[36] Gramling, 2009;[56] Prentice 2009[50] Manson, 2013[33] Chlebowski, 2015[70]	8506 Estrogen plus progestin 8102 Placebo Postintervention extension follow-up: 6545 Estrogen plus progestin 6243 Placebo	**Follow-up: Median 5.6 years**[33] **Invasive breast cancer** 206 (2.4%) vs. 155 (1.9%); HR, 1.24 (95% CI, 1.01-1.53) **Overall breast cancer mortality**[36] 25 (0.3%) vs. 12 (0.2%); HR, 1.96 (95% CI, 1.00-4.04); *P* = .049 **Subgroups:** No significant difference by age[33] Time since randomization[70] 2 years since randomization: HR, 0.71 (95% CI, 0.47-1.08) 4 years since randomization: HR, 1.36 (95% CI, 0.95-1.94) 6 years since randomization: HR, 1.65 (1.17-2.32) P for trend = 0.008 **Risk for invasive breast cancer based on timing of intervention:**[50] Initiation of hormone therapy within 5 years of menopause: HR, 2.06 (95% CI, 1.30-3.27) Initiation of hormone therapy after 5 years of menopause: HR, 1.30 (95% CI, 0.57-2.99) P for gap time interaction = 0.03 **Follow-up: Mean 2.4 years postintervention**[57] **Invasive breast cancer** HR, 1.27 (95% CI, 0.91-1.78) **Follow-up: Median 8.2 years postintervention and postintervention extension**[33] HR, 1.32 (95% CI, 1.08 vs. 1.61); *P* = .007 **Cumulative follow-up: 13.2 years**[33] HR, 1.28 (95% CI, 1.11-1.48); *P* < 0.001

eTable 3. Evidence Table of Trials Reporting Incidence of Breast Cancer (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WISDOM Estrogen plus progestin trial Vickers, 2007[67]	2196 Estrogen plus progestin 2189 Placebo	**Follow-up: Mean 1 year** **Breast cancer incidence** 5 vs. 7 **Breast cancer mortality** 0 vs. 0

[a] Intervention dosages are listed in Table 2 by trial.
[b] All women enrolled in the initial trial were followed by data linkage to UK mortality and cancer records.
[c] At enrollment, 24% of women reported having a hysterectomy. After the 2-year intervention period, women with an intact uterus were sent a letter each year for the first 5 years after stopping treatment to remind them to seek medical attention if they experienced vaginal bleeding. No attempt was made after the end of the 2-year intervention to obtain medical information from women or their physicians about the use of medications or health events.

CI = confidence interval; ERA = Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis; EPAT = Estrogen in the Prevention of Atherosclerosis; EPHT = Estonian Postmenopausal Hormone Therapy Trial; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; ICD = International Classification of Diseases; PEPI = Postmenopausal Estrogen and Progestin Interventions Trial; RR = relative risk; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; UK = United Kingdom; vs. = versus; WAVE = Women's Angiographic Vitamin and Estrogen; WHI = Women's Health Initiative; WISDOM = Women's International Study of Long-Duration Oestrogen After Menopause.

eTable 4. Evidence Table of Trials Reporting Incidence of Cervical Cancer

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
ESPRIT Estrogen-only trial Cherry, 2014[68]	513 Estrogen only[b] 504 Placebo[b]	**Cumulative follow-up: Mean 12.6 years**[c] 0 vs. 1
WHI Estrogen plus progestin trial Anderson, 2003[39]	8506 Estrogen plus progestin 8102 Placebo	**Follow-up: Median 5.6 years** 8 (0.09%) vs. 5 (0.06%); HR, 1.44 (95% CI, 0.47-4.42)

[a] Intervention dosages are listed in Table 2 by trial.
[b] At enrollment, 24% of enrolled women reported having a hysterectomy. After the 2-year intervention period, women with an intact uterus were sent a letter each year for the first 5 years after stopping treatment to remind them to seek medical attention if they experienced vaginal bleeding. No attempt was made after the end of the 2-year intervention to obtain medical information from women or their physicians about the use of medications or health events.
[c] Cancer incidence was determined by data linkage to UK cancer records for a mean 12.6 years after enrollment.

CI = confidence interval; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HR = hazard ratio; vs. = versus; WHI = Women's Health Initiative.

eTable 5. Evidence Table of Trials Reporting Incidence of Colorectal Cancer

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
EMS Estrogen plus progestin trial Tierney, 2009[4]	70 Estrogen plus progestin 72 Placebo	**Follow-up: 2 years** 0 vs. 0
Greenspan et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[9]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Follow-up: 3 years** *Analysis did not stratify by treatment regimen* 3 vs. 1; *P* = .62
HERS Estrogen plus progestin trial Hulley, 2002[69]	1380 Estrogen plus progestin 1,383 Placebo Cumulative follow-up: 1156 Estrogen plus progestin 1383 Placebo	**Follow-up: Mean 4.1 years** 11 (0.80%) vs. 16 (1.16%); HR, 0.69 (95% CI, 0.32-1.49); *P* = .43 **Cumulative follow-up: Mean 6.8 years** HR, 0.81 (95% CI, 0.46-1.45); *P* = .48
PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995[17]	175 Estrogen only 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Follow-up: 3 years** *Analysis did not stratify by treatment regimen* 2 colon cancer cases
STOP-IT Estrogen-only and Estrogen plus progestin trial Gallagher, 2001[18]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Follow-up: 3 years** *Analysis did not stratify by treatment regimen* 1 (hormone therapy with or without calcitriol) vs. 6 (calcitriol only and placebo)

eTable 5. Evidence Table of Trials Reporting Incidence of Colorectal Cancer (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen-only trial Anderson, 2004;[24] Ritenbaugh, 2008;[34] Prentice, 2009;[50] LaCroix, 2011;[37] Manson, 2013[33]	5310 Estrogen only 5429 Placebo Postintervention follow-up: 4794 Estrogen only 4872 Placebo Postintervention extension follow-up: 4851 Estrogen only 4935 Placebo	**Follow-up: Median 7.2 years** 65 (1.22%) vs. 58 (1.07%); HR, 1.15 (95% CI, 0.81-1.64); *P* = .44[33] **Invasive colorectal cancer**[34,b] HR, 1.12 (95% CI, 0.77-1.63); *P* = .55 **Invasive colon cancer**[34,b] HR, 1.26 (95% CI, 0.84-1.88); *P* = .26 **Invasive rectal cancer**[34,b] HR, 0.53 (95% CI, 0.18-1.56); *P* = .25 **Subgroups:**[34, b] No significant difference by race or ethnic group, bilateral oophorectomy status, family history of colorectal cancer, treated diabetes status Age at randomization[33] Among women 50-59 years at randomization: HR, 0.71 (95% CI, 0.30-1.67) Among women 60-69 years at randomization: HR, 0.88 (95% CI, 0.53-1.47) Among women 70-79 years at randomization: HR, 2.24 (95% CI, 1.16-4.30) *P* for trend = .02 **Risk for colorectal cancer based on timing of intervention:**[50] No significant association; *P* for gap time interaction = .34 **Follow-up: Median 6.6 years postintervention and postintervention extension**[33] HR, 1.10 (95% CI, 0.68-1.78); *P* = .69 **Cumulative follow-up: Median 13.0 years**[33] HR, 1.13 (95% CI, 0.85-1.51); *P* = .39 **Subgroups:**[33] No significant difference by age at randomization

eTable 5. Evidence Table of Trials Reporting Incidence of Colorectal Cancer (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen plus progestin trial Writing Group for the Women's Health Initiative Investigators, 2002;[51] Chlebowski, 2004;[43] Heiss, 2008;[57] Prentice, 2009;[50] Manson, 2013[33]	8506 Estrogen plus progestin 8102 Placebo Postintervention follow-up: 8060 Estrogen plus progestin 7687 Placebo Postintervention extension follow-up:[e] 6545 Estrogen plus progestin 6243 Placebo	**Follow-up: Median 5.6 years** 50 (0.59%) vs. 75 (0.93%); HR, 0.62 (95% CI, 0.43-0.89); *P* = .009[33] **Invasive colorectal cancer**[43,d] HR, 0.56 (95% CI, 0.38-0.81); *P* = .003 **Invasive colon cancer**[43,d] HR, 0.54 (95% CI, 0.36-0.82); *P* = .004 **Invasive rectal cancer**[43,d] HR, 0.66 (95% CI, 0.26-1.64); *P* = .37 **Subgroups:** No significant difference by age at randomization,[33] race or ethnic group, family history of colorectal cancer[43, 50, d] **Risk for colorectal cancer based on timing of intervention:**[50] No significant association; p for gap time interaction = .42 **Follow-up: Median 8.2 years postintervention and postintervention extension**[33] HR, 0.97 (95% CI, 0.70-1.33); *P* = .83 **Cumulative follow-up: Median 13.2 years**[33] HR, 0.80 (95% CI, 0.63-1.01); *P* = .06 **Subgroups:**[33] No significant difference by age at randomization
WISDOM Estrogen plus progestin trial Vickers 2007[67]	2196 Estrogen plus progestin[f] 2189 Placebo[f]	**Follow-up: Median 11.9 months** 2 vs. 2

[a] Intervention dosages are listed in Table 2 by trial.
[b] The mean follow-up for some of these analyses (Ritenbaugh et al., 2008 and Prentice et al., 2009) was 7.1 years, suggesting that the results are based on an earlier adjudication of intervention phase data than the most recent intervention data from Manson (2013).[33]
[c] Women were ineligible if they were deceased or provided no contact through the postintervention phase. By the end of the postintervention phase, 7878/8506 (93% of women randomized to estrogen plus progestin) and 7530/8102 (93% of women randomized to placebo) were eligible for the postintervention extension phase.
[d] The analysis was based on 122 centrally adjudicated colorectal cancers, which were diagnosed before 7/8/2002, the date participants were instructed to discontinue their study medication.
[e] The mean follow-up for this analysis was 5.5 years, suggesting that the results are based on an earlier adjudication of intervention phase data than the most recent intervention data from Manson (2013).[33]
[f] The estrogen plus progestin arm includes 1862 women with an intact uterus and 334 women with a prior hysterectomy who had agreed to be randomized to estrogen plus progestin, estrogen only, or placebo (the women randomized to estrogen only included women who agreed to

placebo (n = 341) and women who did not agree to placebo (n = 485), so there is a selection bias that precludes us from including any results for the estrogen-only women.

CI = confidence interval; EMS = Estrogen Memory Study; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; PEPI = Postmenopausal Estrogen/Progestin Interventions Trail; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WHI = Women's Health Initiative; WISDOM = Women's International Study of Long-Duration Oestrogen After Menopause.

eTable 6. Evidence Table of Trials Reporting Incidence of Endometrial Cancer

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
EPAT Estrogen-only trial Hodis, 2001[5]	133 (60%) of enrolled women had an intact uterus 111 Estrogen only 111 Placebo	**Follow-up: 2 years**[b] 0 (0.0%) vs. 0 (0.0%)
ERA Estrogen only and estrogen plus progestin trial Herrington, 2000[7]	120 (39%) of enrolled women had an intact uterus, including 44 (44%) women in the estrogen-only arm, 40 (38%) women in the estrogen plus progestin arm, and 36 (34%) women in the placebo arm 100 Estrogen only 104 Estrogen plus progestin 105 Placebo	**Follow-up: 3.2 years** 0 (0.0%) vs. 0 (0.0%) vs. 0 (0.0%)
ESPRIT Estrogen-only trial Cherry, 2002;[8] Cherry, 2014[68]	At enrollment, 24% of women had an intact uterus, including 373 (73%) of women in the active treatment arm[d] 513 Estrogen only 504 Placebo	**Follow-up: 2 years**[8] 0 (0.0%) vs. 0 (0.0%) **Cumulative follow-up: Mean 12.6 years**[68] HR, 0.52 (95% CI, 0.05-5.80)
Greenspan et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[9]	243 (65%) of enrolled women had an intact uterus, including 121 (65%) in the hormone therapy arm and 122 (66%) in the placebo arm. Women with an intact uterus received estrogen plus progestin; women with a hysterectomy received estrogen only. 187 Hormone therapy 186 Placebo	**Follow-up: 3 years** 1 vs. 0; *P* = 1.0[d]

eTable 6. Evidence Table of Trials Reporting Incidence of Endometrial Cancer (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
HERS Estrogen plus progestin trial Hulley, 2002[69]	All enrolled women had an intact uterus 1380 Estrogen plus progestin 1383 Placebo Cumulative follow-up: 1156 Estrogen plus progestin 1383 Placebo	**Follow-up: Mean 4.1 years** 2 (0.14%) vs. 5 (0.36%); HR, 0.39 (95% CI, 0.08-2.02); *P* = .26 **Cumulative follow-up: Mean 6.8 years** HR, 0.25 (95% CI, 0.05-1.18); *P* = .08
PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995[17]	Approximately 68% of women had an intact uterus; women with an intact uterus had to have a normal endometrial biopsy at baseline 175 Estrogen only 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Follow-up: 3 years** 1 (estrogen only) vs. 0 (estrogen plus progestin) vs. 0 (estrogen plus micronized progestin) vs. 0 (placebo)
STOP-IT Estrogen only and estrogen plus progestin Gallagher, 2001[18]	199 (41%) of enrolled women had an intact uterus; women with a prior hysterectomy who were randomized to receive estrogen plus progestin, with or without calcitriol, received estrogen only 121 Estrogen plus progestin 122 Estrogen plus progestin plus calcitriol 123 Calcitriol only 123 Placebo	**Follow-up: 3 years** *Analysis did not stratify by treatment regimen* 0 (hormone therapy with or without calcitriol) vs. 1 (calcitriol only or placebo)

eTable 6. Evidence Table of Trials Reporting Incidence of Endometrial Cancer (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
ULTRA Estrogen-only trial Johnson, 2005[20]	All enrolled women had an intact uterus 208 Estrogen only 209 Placebo	**Follow-up: 2 years** 0 (0.0%) vs. 0 (0.0%); difference, 0.0 (95% CI, -4.2-3.1); *P* = 1.000[e]
WHI Estrogen plus progestin trial Writing Group for the Women's Health Initiative Investigators, 2002;[51] Anderson, 2003;[39] Heiss, 2008;[57] Prentice, 2009;[50] Chlebowski, 2010;[27] Manson, 2013[33, 71]	Women with an intact uterus 8506 Estrogen plus progestin 8102 Placebo Postintervention follow-up: 8060 Estrogen plus progestin 7687 Placebo Postintervention extension follow-up:[f] 6545 Estrogen plus progestin 6243 Placebo	**Follow-up: Median 5.6 years**[33] 27 (0.32%) vs. 30 (0.37%); HR, 0.83 (95% CI, 0.49-1.40); *P* = .49 **Subgroups:**[33] No significant difference by age at randomization **Follow-up: Median 8.2 years postintervention and postintervention extension**[33] HR, 0.58 (95% CI, 0.40-0.86); *P* = .007 **Cumulative follow-up: Median 13.2 years**[33] HR, 0.67 (95% CI, 0.49-0.91); *P* = .01 **Subgroups:**[33] No significant difference by age at randomization

[a] Intervention dosages are listed in Table 2 by trial.
[b] Adverse event reporting was only among women who received uterine biopsies (30 women in the estrogen-only arm and 5 women in the placebo arm).
[c] Women with an intact uterus were sent an annual letter for 5 years reminding them to seek medical attention if they experienced vaginal bleeding.
[d] The mean follow-up was 5.5 years, suggesting that the results are based on an earlier adjudication of intervention phase data than the most recent intervention data from Manson (2013).[33]
[d] Because women with an intact uterus received estrogen plus progestin if they were randomized to the hormone therapy arm, this woman had received estrogen plus progestin.
[e] Analysis focused on women with endometrial biopsy results, including 188 women in the estrogen-only arm and 177 women in the placebo arm.
[f] Women were ineligible if they were deceased or provided no contact through the postintervention phase. By the end of the postintervention phase, 7878/8506 (93% of women randomized to estrogen plus progestin) and 7530/8102 (93% of women randomized to placebo) were eligible for the postintervention extension phase.

CI = confidence interval; EPAT = Estrogen in the Prevention of Atherosclerosis Trial; ERA = Estrogen Replacement and Atherosclerosis; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; PEPI = Postmenopausal Estrogen/Progestin Interventions Trial; STOP IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; ULTRA = Ultra-Low-Dose Transdermal Estrogen Replacement Assessment; vs. = versus; WHI = Women's Health Initiative.

eTable 7. Evidence Table of Trials Reporting Incidence of Lung Cancer

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
EMS Estrogen plus progestin trial Tierney, 2009[4]	70 Estrogen plus progestin 72 Placebo	**Follow-up: 2 years** 1 vs. 0
HERS Estrogen plus progestin trial Hulley, 2002[69]	1380 Estrogen plus progestin 1383 Placebo Cumulative follow-up: 1156 Estrogen plus progestin 1383 Placebo	**Follow-up: Mean 4.1 years** 24 (1.74%) vs. 19 (1.37%); HR, 1.28 (95% CI, 0.70-2.33); *P* = .43 **Cumulative follow-up: Mean 6.8 years** Unadjusted ITT: HR, 1.39 (95% CI, 0.84-2.28); *P* = .20 Adjusted ITT: HR, 1.43 (95% CI, 0.87-2.37) Adjusted As-Treated: HR, 1.73 (95% CI, 0.93-3.21)
PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995[17]	175 Estrogen only 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Follow-up: 3 years** *Analysis did not stratify by treatment regimen* 2 lung cancer cases

eTable 7. Evidence Table of Trials Reporting Incidence of Lung Cancer (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen-only trial Chlebowski, 2010;[27] Manson, 2013[33]	5310 Estrogen only 5429 Placebo Postintervention follow-up: 4794 Estrogen only 4872 Placebo Postintervention extension follow-up: 4851 Estrogen only 4935 Placebo	**Follow-up: Median 7.2 years**[33] 62 (1.17 %) vs. 61 (1.12%); HR, 1.05 (95% CI, 0.74-1.49); *P* = .79 **Subgroups:**[33] No significant difference by age at randomization **Follow-up: Mean 7.9 years**[27,b] **Lung cancer** HR, 1.17 (95% CI, 0.81-1.69); *P* = .39 **Nonsmall cell lung cancer** HR, 1.10 (95% CI, 0.74-1.64); *P* = .62 **Small cell lung cancer** HR, 1.57 (95% CI, 0.56-4.41); *P* = .39 **Follow-up: Median 6.6 years postintervention and postintervention extension**[33] HR, 0.90 (95% CI, 0.61-1.34); *P* = .61 **Cumulative follow-up: Median 13.0 years**[33] HR, 0.98 (95% CI, 0.75-1.27); *P* = .87 **Subgroups:**[33] No significant difference by age at randomization

eTable 7. Evidence Table of Trials Reporting Incidence of Lung Cancer (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen plus progestin trial Chlebowski, 2009;[55] Manson, 2013[33]	8506 Estrogen plus progestin 8102 Placebo Postintervention follow-up: 8060 Estrogen plus progestin 7687 Placebo Postintervention extension follow-up:[c] 6545 Estrogen plus progestin 6243 Placebo	**Follow-up: Median 5.6 years**[33] 78 (0.92%) vs. 70 (0.86%); HR, 1.05 (95% CI, 0.76-1.45); *P* = .78 **Subgroups:**[33] No significant difference by age at randomization **Follow-up: Mean 7.9 years**[55, b] **Lung cancer** HR, 1.23 (95% CI, 0.92-1.63); *P* = .16 **Nonsmall cell** HR, 1.28 (95% CI, 0.94-1.73); *P* = .12 **Small cell lung cancer** HR, 0.96 (95% CI, 0.44-2.07); *P* = .91 **Follow-up: Median 8.2 years postintervention and postintervention extension**[33] HR, 1.13 (95% CI, 0.86-1.47); *P* = .38 **Cumulative follow-up: Median 13.2 years**[33] HR, 1.10 (95% CI, 0.89-1.35); *P* = .38 **Subgroups:**[33] No significant difference by age at randomization

[a] Intervention dosages are listed in Table 2 by trial.
[b] Authors state ascertainment of lung cancer cases is through 3/31/2005, which is the end of the postintervention phase according to Manson[33]; this would mean these results are for trial and posttrial phases combined together.
[c] Women were ineligible if they were deceased or provided no contact through the postintervention phase. By the end of the postintervention phase, 7878/8506 (93% of women randomized to estrogen plus progestin) and 7530/8102 (93% of women randomized to placebo) were eligible for the postintervention extension phase.

CI = confidence interval; EMS = Estrogen Memory Study; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; ITT = intention to treat; PEPI = Postmenopausal Estrogen/Progestin Interventions; vs. = versus; WHI = Women's Health Initiative.

eTable 8. Evidence Table of Trials Reporting Incidence of Ovarian Cancer

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
ESPRIT Estrogen-only trial Cherry, 2014[68]	513 Estrogen only[b] 504 Placebo[b]	**Follow-up: Mean 12.6 years** 4 (0.78%) vs. 1 (0.20%); Fisher's exact test *P* = .37
WHI Estrogen plus progestin trial Anderson, 2003;[39] Manson, 2013[33]	8506 Estrogen plus progestin 8102 Placebo Postintervention follow-up: 8060 Estrogen plus progestin 7687 Placebo Postintervention extension follow-up:[c] 6545 Estrogen plus progestin 6243 Placebo	**Follow-up: Median 5.6 years**[33] 24 (0.28%) vs.16 (0.20%); HR, 1.41 (95% CI, 0.75-2.66); *P* = .28 **Subgroups:**[33] No significant difference by age at randomization **Follow-up: Median 8.2 years postintervention and postintervention extension**[33] HR, 1.12 (95% CI, 0.65-1.90); *P* = .69 **Cumulative follow-up: Median 13.2 years**[33] HR, 1.24 (95% CI, 0.83-1.87); *P* = .30 **Subgroups:**[33] Among women 50-59 years at randomization: HR, 0.55 (95% CI, 0.24-1.25) Among women 60-69 years at randomization: HR, 1.25 (95% CI, 0.72-2.18) Among women 70-79 years at randomization: HR, 3.82 (95% CI, 1.27-11.52) p for trend = .005

[a] Intervention dosages are listed in Table 2 by trial.
[b] Women were ineligible if they were deceased or provided no contact through the postintervention phase. By the end of the postintervention phase, 7878/8506 (93% of women randomized to estrogen plus progestin) and 7530/8102 (93% of women randomized to placebo) were eligible for the postintervention extension phase.
[c] At enrollment, 24% of women reported having a hysterectomy. After the 2-year intervention period, women with an intact uterus were sent a letter each year for the first 5 years after stopping treatment to remind them to seek medical attention if they experienced vaginal bleeding. No attempt was made after the end of 2-year intervention to obtain medical information from women or their physicians about the use of medications or health events.

CI = confidence interval; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HR = hazard ratio; vs. = versus; WHI = Women's Health Initiative.

eTable 9. Evidence Table of Trials Reporting Incidence of Coronary Heart Disease

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
EMS Estrogen plus progestin trial Tierney, 2009[4]	70 Estrogen plus progestin 72 Placebo	**Follow-up: Mean 2 years** **Any cardiovascular event** 11 (15.7%) vs. 8 (11.1%); no statistically significant differences between groups
EPAT Estrogen-only trial Hodis,2001[5]	111 Estrogen 111 Placebo	**Follow-up: Mean 2 years** **Cardiovascular events** 3 (2.7%) vs. 4 (3.6%); p>0.2
EPHT Estrogen plus progestin trial Veerus, 2006[6]	404 Estrogen plus progestin 373 Placebo	**Follow-up: Mean 3.4 years** **CHD** 66 (16.3%) vs. 62 (16.6%); HR 1.03 (95% CI, 0.73-1.46)
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[7]	Women with angiographically verified coronary disease 100 Estrogen 104 Estrogen plus progestin 105 Placebo	**Follow-up: Mean 3.2 years** **Cardiovascular events** 29 (29.0%) vs. 28 (26.9%) vs. 34 (32.4%); *P* = .69
Greenspan et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[9]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Follow-up: Mean 3 years** **Myocardial infarction** *Analysis did not stratify by treatment regimen* 1 (0.5%) vs. 3 (1.6%); *P* = .37
PEPI Estrogen-only and estrogen plus progestin trial Writing Group for PEPI trial, 1995[17]	175 Estrogen only 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Follow-up: Mean 3 years** **CHD** 1 (estrogen: 0.6%) vs. 1 (estrogen plus progestin: 0.3%) vs. 3 (estrogen plus micronized progestin: 1.7%) vs. 0 (placebo); *P* = .29
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[18]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Follow-up: Mean 3 years** **Cardiovascular events** *Analysis did not stratify by treatment regimen* 8 (hormone therapy with or without calcitriol: 3.3%) vs. 7 (calcitriol only or placebo: 2.8%)

eTable 9. Evidence Table of Trials Reporting Incidence of Coronary Heart Disease (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WAVE Estrogen-only and estrogen plus progestin trial Waters, 2002[23]	Women with a coronary stenosis of 15%–75% 124 Estrogen (with or without vitamins C and E) 86 Estrogen plus progestin (with or without vitamins C and E) 213 Placebo (with or without vitamins C and E)	**Follow-up: Mean 2.8 years** **Nonfatal myocardial infarction or cardiovascular death** *Analysis did not stratify by treatment regimen* 18 (8.6%) vs. 12 (5.6%)
WHI Estrogen-only trial Anderson, 2004;[24] Manson, 2003;[48] Rossouw, 2007;[35] Hsia, 2006;[32] Prentice 2009;[50] LaCroix, 2011;[37] Manson, 2013[33]	5310 Estrogen 5429 Placebo Postintervention follow-up: 3778 Estrogen 3867 Placebo	**Follow-up: Mean 7.1 years** **Overall CHD (nonfatal myocardial infarction, death due to CHD)** [32] 201 (3.8%) vs. 217 (4.0%); HR, 0.95 (95% CI, 0.79-1.16) **Subgroups:**[32,33] No significant difference by race or ethnic group, age, years since bilateral oophorectomy, hypertension, diabetes, high cholesterol requiring medication, coronary risk factors, CVD at baseline, or CHD at baseline Younger women had a lower risk for myocardial infarction than older women relative to placebo (*P* = .02) [33] **Risk for CHD based on timing of intervention:** No significant association; p for gap time interaction = .40[50] No significant association; p for trend = .16[33] **Follow-up: Mean 3.9 years postintervention**[37] **Overall CHD (nonfatal myocardial infarction, death due to CHD)** HR, 0.97 (95% CI, 0.75-1.25)

eTable 9. Evidence Table of Trials Reporting Incidence of Coronary Heart Disease (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen plus progestin trial Writing Group for the WHI, 2002;[51] Manson, 2003;[48] Rossouw, 2007;[35] Heiss, 2008;[57] Prentice 2009;[50] Manson, 2013[33]	8506 Estrogen plus progestin 8102 Placebo Postintervention follow-up: 8052 Estrogen plus progestin 7678 Placebo	**Follow-up: Mean 5.2 years**[33] **Overall CHD (nonfatal myocardial infarction, death due to CHD)** 196 (2.0%) vs. 159 (2.0%); HR, 1.18 (95% CI, 0.95-1.45) **Nonfatal myocardial infarction** 151 (1.8%) vs. 114 (1.4%); HR, 1.28 (95% CI, 1.00-1.63) **CHD death** 39 (0.5%) vs. 34 (0.4%); HR, 1.10 (95% CI, 0.70-1.75) **Subgroups:**[33, 48] No significant difference by race or ethnic group, age, hypertension, diabetes, CVD at baseline, or CHD at baseline **Risk based on timing of intervention:** **Overall CHD** No significant association; p for gap time interaction = .42[50] No significant association; p for trend = .08[33] **Nonfatal myocardial infarction**[33] <10 years after menopause: HR, 0.91 10–<20 years after menopause: HR, 1.16 ≥20 years after menopause: HR, 1.99 p for trend = .01 **Follow-up: Mean 2.4 years postintervention**[57] **Overall CHD** HR, 1.04 (95% CI, 0.89-1.21)
WISDOM Estrogen plus progestin trial Vickers, 2007[67]	826 Estrogen 2196 Estrogen plus progestin 2189 Placebo	**Follow-up: Mean 1 year** **Cardiovascular events** 2 (0.2%) vs. 7 (0.3%) vs. 0 (0.0%); *P* = .016

[a] Intervention dosages are listed in Table 2 by trial.

CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; DOPS = Danish Osteoporosis Prevention Study; EMS = Estrogen Memory Study; EPAT = Estrogen in the Prevention of Atherosclerosis Trial; EPHT = Estonian Postmenopausal Hormone Therapy Trial; ERA = Estrogen Replacement and Atherosclerosis; HR = hazard ratio; PEPI = Postmenopausal Estrogen/Progestin Interventions Trial; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WHI = Women's Health Initiative; WISDOM = Women's International Study of Long Duration Oestrogen After Menopause.

eTable 10. Evidence Table of Trials Reporting Incidence of Cognitive Function and Dementia

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)				
		PD Incidence	MCI Incidence	Other Dementia Diagnosis Outcomes	3MSE Scores (0-100, Higher Better)	Other Measures
EMS Estrogen plus progestin trial Tierney, 2009[4]	Women with normal to just below normal scores on cognitive battery tests, but free of dementia: 70 Estrogen plus progestin 72 Placebo	NR	NR	NR	NR	**Follow-up: 1 year** **CVLT short-delay verbal recall** *P* = .15 **Follow-up: 2 years** **CVLT short-delay verbal recall** *P* = .11
HERS Estrogen plus progestin trial Grady, 2002[72]	662 Estrogen plus progestin 666 Placebo	NR	NR	NR	**Follow-up: 4.2 years** 93.1 (SD, 6.4) vs. 93.4 (SD, 6.4); difference, -0.4 (95% CI, -1.1-0.4); *P* = .36	**Follow-up: 4.2 years** **Verbal fluency** (0-∞, higher better) 15.9 (SD, 4.8) vs. 16.6 (SD, 4.8); difference, -0.7 (95% CI, -1.3--0.1); *P* = .02 No other differences between groups for Boston Naming, Word List Memory, Word List Recall, or Trials B
KEEPS-Cog Estrogen plus progestin trial Gleason, 2015[15]	431 Estrogen plus progestin 262 Placebo	NR	NR	NR	**Follow-up: 4 years** **Oral estrogen** Beta estimate, 1.02×10^{-2} (CI, -4.45×10^{-3} to 2.48×10^{-2}); *P* = .178 **Transdermal estrogen** Beta estimate, -9.40×10^{-4} (CI, -1.57×10^{-2} to 1.38×10^{-2}); *P* = .840	NR

eTable 10. Evidence Table of Trials Reporting Incidence of Cognitive Function and Dementia (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)				
		PD Incidence	MCI Incidence	Other Dementia Diagnosis Outcomes	3MSE Scores (0-100, Higher Better)	Other Measures
ULTRA Estrogen-only trial Yaffe, 2006[22]	417 Enrolled 208 Estrogen 209 Placebo	NR	NR	NR	**Follow-up: 2 years** Baseline 3MSE ≤90: 5.90 vs. 7.10; difference, -1.21 (95% CI, -5.05-2.64); *P* = .53 Baseline 3MSE >90: 0.57 vs. 0.87; difference, -0.30 (95% CI, -0.74-0.14); *P* = .18	**Follow-up: 2 years** No differences between groups on Logical Memory, Brief Visuospatial Memory Test, Word List, Trails B, Modified Boston Naming Test, Verbal Fluency
WHIMS Estrogen-only trial Shumaker, 2004,[59] Espeland, 2004[58]	Women without probable dementia Dementia outcomes, WHI:[59] 1464 Estrogen 1483 Placebo General cognitive function, enrolled in WHIMS >6 months after initiation of assigned WHI therapy and with >1 post-randomization 3MSE score:[58] 1387 Estrogen 1421 Placebo Subgroup analysis: 1464 Estrogen 1483 Placebo	**Follow-up: 5.2 years**[59] 28 (1.9%) vs. 19 (1.3%); cumulative HR, 1.49 (95% CI, 0.83-2.66); *P* = .18 **Subgroups:**[59] No difference in the hazard rate for probable dementia by race or history of cardiovascular disease, diabetes, hypertension, or stroke	**Follow-up: 5.2 years**[59] 76 (5.2%) vs. 58 (3.9%); cumulative HR, 1.34 (95% CI, 0.95-1.89); *P* = NS	**Follow-up: 5.2 years**[59] PD or MCI: 93 (6.4%) vs. 69 (4.7%); cumulative HR, 1.38 (95% CI, 1.01-1.89); *P* = .04	**Follow-up: Mean 5.4 years**[58] Mean difference in change from baseline, -0.26 (95% CI, -0.52-0.00); *P* = .04	NR

eTable 10. Evidence Table of Trials Reporting Incidence of Cognitive Function and Dementia (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)				
		PD Incidence	MCI Incidence	Other Dementia Diagnosis Outcomes	3MSE Scores (0-100, Higher Better)	Other Measures
WHIMS Estrogen plus progestin trial Shumaker, 2003;[62], Shumaker, 2004;[59], Rapp, 2003[61]; Espeland, 2004[58]	Women without probable dementia Dementia and cognitive impairment outcomes:[62] 2229 Estrogen plus progestin 2303 Placebo Cognitive function outcomes:[58] 2131 Estrogen plus progestin 2213 Placebo	**Follow-up: ~4 years**[62] 40 (1.8%) vs. 21 (0.9%); cumulative HR, 2.05 (95% CI, 1.21-3.48); *P* = .01 **Subgroups:**[62] No difference in the hazard rate for probable dementia by race or history of cardiovascular disease, diabetes, hypertension, or stroke	**Follow-up: ~4 years**[62] 56 (2.5%) vs. 55 (2.4%); cumulative HR, 1.07 (95% CI, 0.74-1.55); *P* = .72	**Follow-up: ~4 years**[62] PD or MCI: 85 (3.8%) vs. 66 (2.9%); cumulative HR, 1.37 (95% CI, 0.99 to1.89)	**Follow-up: 5.4 years**[58] Mean difference in change from baseline, -0.18 (95% CI, -0.37-0.00); *P* = .055 **Subgroups:**[61] No difference in the rate of change by race, length of use, or history of cardiovascular disease, diabetes, or hypertension **Timing:**[61] No difference in the rate of change by time to initiation of therapy after last menstrual period	NR

eTable 10. Evidence Table of Trials Reporting Incidence of Cognitive Function and Dementia (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)				
		PD Incidence	MCI Incidence	Other Dementia Diagnosis Outcomes	3MSE Scores (0-100, Higher Better)	Other Measures
WHIMSY Estrogen-only and estrogen plus progestin trial Espeland, 2013[63]	696 Hormone therapy 630 Placebo	NR	NR	NR	NR	**Follow-up: 7.2 years postintervention** **Verbal fluency** 18.90 (estrogen: SE 0.33) vs. 19.91 (placebo: SE 0.34) No other differences between groups for Telephone Interview for Cognitive Status–modified, East Boston Memory Test, Verbal Memory, Attention, Executive Function, Working Memory, Composite
WHIMSY Estrogen-only and estrogen plus progestin trial Espeland, 2013[63]	696 Hormone therapy 630 Placebo	NR	NR	NR	NR	**Follow-up: 7.2 years** **Verbal fluency** 21.04 (estrogen plus progestin: SE 0.25) vs. 20.65 (placebo: SE 0.27) No other differences between groups for Telephone Interview for Cognitive Status–modified, East Boston Memory Test, Verbal Memory, Attention, Executive Function, Working Memory, Composite

eTable 10. Evidence Table of Trials Reporting Incidence of Cognitive Function and Dementia (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)				
		PD Incidence	MCI Incidence	Other Dementia Diagnosis Outcomes	3MSE Scores (0-100, Higher Better)	Other Measures
WHISCA Estrogen-only trial Resnick, 2009[65]; Espeland, 2010[64]	Dementia outcomes, WHISCA:[65] 434 Estrogen 452 Placebo Cognitive measures, WHISCA extension:[64] 601 Hormone therapy 612 Placebo	**Follow-up: 2.7 years** (during WHISCA, after being enrolled in WHI for 3 years)[65] 4 (0.9%) vs. 2 (0.4%); calculated RR, 2.08 (95% CI, 0.38-11.31); *P* = .40	**Follow-up: 2.7 years** (during WHISCA, after being enrolled in WHI for 3 years)[65] 18 (4.1%) vs. 15 (3.3%); calculated RR, 1.25 (95% CI, 0.64-2.45); *P* = .52	NR	**Follow-up: 3.6 years** (during WHISCA, after being enrolled in WHI for 3 years)[64] Mean decrement in global cognitive function, -0.092 (SE, 0.039); *P* = .02 **Follow-up: Mean 2.4 years posttrial** (after being enrolled in WHI for 3 years and WHISCA for .36 years)[64] Mean decrement in global cognitive function, -0.081 (SE 0.047); *P* = .09	**Follow-up: Mean 3.6 years** (during trial)[64] **Verbal knowledge** -0.100 (SE, 0.051); *P* = .05 **Verbal fluency** -0.118 (SE, 0.054); *P* = .03 **Figural memory** -0.132 (SE, 0.048); *P* = .006 **Spatial ability** -0.137 (SE, 0.057); *P* = .02 Verbal memory and attention and working memory not significant at *P* = .05 **Follow-up: 2.4 years postintervention**[64] **Spatial ability** -0.179 (SE, 0.063); *P* = .004 Verbal knowledge, verbal fluency, verbal memory, figural memory, attention and working memory differences not significant at *P* = .05

eTable 10. Evidence Table of Trials Reporting Incidence of Cognitive Function and Dementia (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)				
		PD Incidence	MCI Incidence	Other Dementia Diagnosis Outcomes	3MSE Scores (0-100, Higher Better)	Other Measures
WHISCA Estrogen plus progestin trial Resnick, 2006;[66] Espeland, 2010[64]	Probable dementia or cognitive impairment, WHIMS:[66] 690 Estrogen plus progestin 726 Placebo Cognitive measures, WHISCA extension:[64] 601 Hormone therapy 612 Placebo	**Follow-up: 1.4 years** (during WHISCA, after being enrolled in WHI for 3 years)[66] 5 (0.7%) vs. 6 (0.8%); calculated RR, 0.88 (95% CI, 0.27-2.86); *P* = .83	**Follow-up: 1.4 years** (during WHISCA, after being enrolled in WHI for 3 years)[66] 6 (0.9%) vs. 13 (1.8%); calculated RR, 0.49 (95% CI, 0.19-1.27); *P* = .14	NR	**Follow-up: Mean 2 years** (during WHISCA, after being enrolled in WHI for 3 years)[64] Mean decrement in global cognitive function, -0.080 (SE, 0.034); *P* = .02 **Follow-up: Mean 4 years post-trial** (after being enrolled in WHI for 3 years and in WHISCA for 2 years)[64] Mean decrement in global cognitive function, -0.059 (SE, 0.032); *P* = .06	**Follow-up: Mean 3 years** (pre-WHISCA, 2 years during WHISCA trial)[64] Spatial ability, verbal knowledge, verbal fluency, verbal memory, figural memory, attention and working memory not statistically significant at *P* = .05 **Follow-up: Mean 4 years post-trial**[64] Spatial ability, verbal knowledge, verbal fluency, verbal memory, figural memory, attention and working memory not statistically significant at *P* = .05

[a] Intervention dosages are listed in Table 2 by trial.

3MSE = Modified Mini-Mental State Examination; CI = confidence interval; CVLT = California Verbal Learning Test; EMS = Estrogen Memory Study; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; KEEPS-Cog = Kronos Early Estrogen Prevention Study–Cognitive and Affective Study; MCI = mild cognitive impairment; NR = not reported; NS = not significant; PD = probable dementia; RR = relative risk; SD = standard deviation; SE = standard error; ULTRA = Ultra-Low-Dose Transdermal Estrogen Replacement Assessment; WHI = Women's Health Initiative; WHIMS = Women's Health Initiative Memory Study; WHIMSY = Women's Health Initiative Memory Study of Younger Women; WHISCA = Women's Health Initiative Study of Cognitive Aging; vs. = versus.

eTable 11. Evidence Table of Trials Reporting Incidence of Diabetes

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
Greenspan et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[9]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Follow-up: 3 years** *Analysis did not stratify by regimen* 2 (1.1%) vs. 6 (3.2%); *P* = .17
HERS Estrogen plus progestin trial Kanaya, 2003[13]	Women without self-reported diabetes at baseline 999 Estrogen plus progestin 1030 Placebo	**Follow-up: Mean 4.1 years** **Overall** 62 (6.2%) vs. 98 (9.5%); NNT, 30 (95% CI, 18-103); *P* = .006 **Of those with normal glucose at baseline** 38/904 (4.2%) vs. 52/907 (5.7%); *P* = .13 **Of those with impaired fasting glucose at baseline** 24/95 (25.3%) vs. 46/123 (37.4%); *P* = .06 **Risk for incident diabetes** HR, 0.65 (95% CI, 0.48-0.89)
WHI Estrogen-only trial Bonds, 2006;[25] Manson, 2013[33]	Women not receiving treatment for diabetes at baseline 4900 Estrogen 5017 Placebo	**Follow-up: Mean 7.1/median 7.2 years** **Overall**[33] 449 (9.2%) vs. 527 (10.5%); HR, 0.86; 95% CI, 0.76-0.98); *P* = .02 **Of those who adhered to ≥80% of medication**[25] HR, 0.73 (95% CI, 0.60-0.88) **Subgroups:**[25] No significant difference by race/ethnicity, age at screening, hypertension, or metabolic syndrome at baseline **Follow-up: Median 6.6 years postintervention**[33] HR, 1.07; 95% CI, 0.92-1.25
WHI Estrogen plus progestin trial Margolis, 2004;[49] Manson, 2013[33]	Women not receiving treatment for diabetes at baseline 8132 Estrogen plus progestin 7742 Placebo	**Follow-up: Mean 5.6 years**[49] 328 (4.0%) vs. 373 (4.8%); HR, 0.81 (95% CI, 0.70-0.94); *P* = .005 **Subgroups:**[49] No significant difference by race/ethnicity, age at screening, or hypertension at baseline **Follow-up: Median 8.2 years postintervention**[33] HR, 1.19, 95% CI, 1.05-1.34

[a] Intervention dosages are listed in Table 2 by trial.

CI = confidence interval; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; NNT = number needed to treat; s. = versus; WHI = Women's Health Initiative.

eTable 12. Evidence Table of Trials Reporting Incidence of Fractures

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
EMS Estrogen plus progestin trial Tierney 2009[4]	70 Estrogen plus progestin 72 Placebo	**Follow-up: 2 years** **Hip fractures** 0 (0.0%) vs. 1 (1.4%)
EPHT Estrogen plus progestin trial Veerus, 2006[6]	404 Estrogen plus progestin 373 Placebo	**Follow-up: 5 years** **Bone fractures[b]** 15 (3.7%) vs. 25 (6.7%) HR, 0.52 (95% CI, 0.27-0.98)
ERA Estrogen-only and estrogen plus progestin trial Herrington 2000[7]	100 Estrogen 104 Estrogen plus progestin 105 Placebo	**Follow-up: 3.2 years** **Fractures (all sites)** 6 (6.0%) vs. 7 (6.7%) vs. 15 (14.3%) Estrogen: Calculated RR, 0.42 (95% CI, 0.17-1.04); *P* = .06 Estrogen plus progestin: Calculated RR, 0.47 (95% CI, 0.24-1.11); *P* = .09
HERS Estrogen plus progestin trial Hulley, 2002[69]	1380 Estrogen plus progestin 1383 Placebo	**Follow-up: Mean 4.1 years** **Hip** 15 vs. 13; HR, 1.16 (95% CI, 0.55-2.44); *P* = .69 **Wrist** 29 vs. 29; HR, 1.01 (95% CI, 0.60-1.68); *P* = .98 **Vertebral** 14 vs. 19; HR, 0.74 (95% CI, 0.37-1.48); *P* = .40 **Other** 91 vs. 101; HR, 0.91 (95% CI, 0.69-1.21); *P* = .52 **Any** 140 vs. 148; HR, 0.96 (95% CI, 0.76-1.20); *P* = .70
STOP-IT Estrogen plus progestin trial Gallagher 2001[18]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Follow-up: 3 years** **Vertebral fractures** *Analysis did not stratify by regimen* 2 (hormone therapy with or without calcitriol) vs. 1 (calcitriol only or placebo)

eTable 12. Evidence Table of Trials Reporting Incidence of Fractures (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen-only trial LaCroix, 2011;[37] Anderson, 2004;[39] Manson, 2013[33]	5310 Estrogen 5429 Placebo Postintervention follow-up: 3778 Estrogen 3867 Placebo	**Follow-up time: Median 7.2 years**[33, 39] **Vertebral** 44 (0.8%) vs. 70 (1.3%); HR, 0.64 (95% CI, 0.44-0.93) **Hip** 48 (0.9%) vs. 74 (1.4%); HR, 0.67 (95% CI, 0.46-0.96) **Total** 544 (10.2%) vs. 767 (14.1%); HR, 0.72 (95% CI, 0.64-0.80) **Subgroups:** No significant difference by age **Follow-up: Mean 5.9 years**[37] **Hip fractures** HR, 0.67 (95% CI, 0.46-0.96) **Follow-up: Mean 10.7 years postintervention**[37] **Hip fractures** HR, 1.27 (95% CI, 0.88-1.82) **Cumulative follow-up: Median 13.0 years**[37] **Hip fractures** HR, 0.92 (95% CI, 0.71-1.18) **Subgroups:** No significant difference by age

eTable 12. Evidence Table of Trials Reporting Incidence of Fractures (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen plus progestin trial Heiss, 2008;[57], Cauley, 2003;[41]. Rossouw, 2002[51]	8506 Estrogen plus progestin 8102 Placebo Postintervention follow-up: 8052 Estrogen plus progestin 7678 Placebo	**Follow-up: Mean 5.6 years**[33, 57] **Hip fractures** 53 vs. 75; HR, 0.67 (95% CI, 0.47-0.96) **Vertebral fractures** 56 vs. 78; HR, 0.68 (95% CI, 0.48-0.96) **Other osteoporotic fractures** 650 vs. 800; HR, 0.75 (95% CI, 0.68-0.83) **Total (hip, vertebral, or other osteoporotic fractures)** 741 vs. 903; HR, 0.76 (95% CI, 0.69-0.83) **Follow-up: Mean 2.4 years postintervention**[57] **Hip fractures** HR, 0.92 (95% CI, 0.64-1.34) **Vertebral fractures** HR, 0.96 (95% CI, 0.64-1.44) **Other osteoporotic fractures** HR, 0.87 (95% CI, 0.74-1.03) **Total (hip, vertebral, or other osteoporotic fractures)** HR, 0.91 (95% CI, 0.78-1.06)

[a] Intervention dosages are listed in Table 2 by trial.
[b] Bone fractures defined as diagnoses Sx2 (x = 1-9) according to ICD-10 (fracture of neck, fractures of ribs, sternum and thoracic spine, fracture of lumbar spine and pelvis, fracture of shoulder and upper arm, fracture of forearm, fracture at wrist and hand level, fracture of femur, fracture of lower leg, including ankle).

CI = confidence interval; EMS = Estrogen Memory Study; EPHT – Estonian Postmenopausal Hormones Therapy Trial; ERA = Estrogen Replacement and Atherosclerosis Trial; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; RR = relative risk; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WHI = Women's Health Initiative.

eTable 13. Evidence Table of Trials Reporting Incidence of Gallbladder Disease

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
Greenspan et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[9]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Followup: 3 years** **Gallstones** *Analysis did not stratify by regimen* 1 (0.5%) vs. 1 (0.5%)
PEPI Estrogen-only and estrogen plus progestin trial PEPI, 1995[17]	175 Estrogen only 174 Estrogen plus progestin (cyclic) 174 Estrogen plus progestin (continuous) 178 Estrogen plus progestin (micronized) 174 Placebo	**Follow-up: 3 years** **Gallbladder disease** 2 (estrogen: 1.1%) vs. 9 (estrogen plus progestin: 2.6%) vs. 4 (estrogen plus micronized progestin 2.2%) vs. 2 (placebo: 1.1%)
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[18]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Follow-up: 3 years** **Gallstones or cholecystitis** *Analysis did not stratify by regimen* 8 (hormone therapy with or without calcitriol: 3.3%) vs. 3 (calcitriol only or placebo: 1.2%)
WHI Estrogen-only trial Cirillo, 2005;[28] LaCroix, 2011;[37] Manson, 2013[33]	Women without cholecystectomy or gallbladder disease at baseline 4141 Estrogen 4235 Placebo	**Follow-up: Mean 7.1 years**[28] **Gallbladder event incidence** 228 (5.5%) vs. 143 (3.4%); HR, 1.67 (95% CI, 1.35-2.06); p<0.001 **Cholecystectomy** 192 (4.6%) vs. 104 (2.5%); HR, 1.93 (95% CI, 1.52-2.44); p<0.001 **Global gallbladder disease** 223 (5.4%) vs. 130 (3.1%); HR, 1.79 (95% CI, 1.44-2.22); p<0.001 **Cholecystitis** 186 (4.5%) vs. 107 (2.5%); HR, 1.80 (95% CI, 1.42-2.28); p<0.001 **Subgroups:**[28] No significant difference by age **Follow-up: Median 6.6 years postintervention**[33] **Gallbladder disease** HR, 0.98 (95% CI, 0.68-1.41); *P* = .92

eTable 13. Evidence Table of Trials Reporting Incidence of Gallbladder Disease (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen plus progestin trial Cirillo, 2005;[28] Manson, 2013[33]	Women without cholecystectomy or gallbladder disease at baseline 7308 Estrogen plus progestin 6895 Placebo	**Follow-up: Mean 5.6 years**[28] **Gallbladder event incidence** 228 (3.1%) vs. 135 (2.0%); HR, 1.59 (95% CI, 1.28-1.97); p<0.001 **Cholecystectomy** 190 (2.6%) vs. 107 (1.6%); HR, 1.67 (95% CI, 1.32-2.11); p<0.001 **Global gallbladder disease** 223 (3.1%) vs. 130 (1.9%); HR, 1.61 (95% CI, 1.30-2.00); p<0.001 **Cholecystitis** 192 (2.6%) vs. 117 (1.7%); HR, 1.54 (95% CI, 1.22-1.94); p<0.001 **Subgroups:**[28] No significant difference by age **Follow-up: Median 8.2 years postintervention**[33] **Gallbladder disease** HR, 1.24 (95% CI, 1.01-1.52); *P* = .04

[a] Intervention dosages are listed in Table 2 by trial.

CI = confidence interval; HR = hazard ratio; PEPI = Postmenopausal Estrogen/Progestin Interventions; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WHI = Women's Health Initiative.

eTable 14. Evidence Table of Trials Reporting Incidence of Stroke

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
EMS Estrogen plus progestin trial Tierney, 2000[4]	70 Estrogen plus progestin 72 Placebo	**Follow-up: 2 years** **Intracerebral hemorrhage** 1 (1.4%) (fatal) vs. 0; *P* = NS **Transient ischemic attack** 1 (1.4%) vs. 1 (1.4%); *P* = NS
EPAT Estrogen-only trial Hodis,2001[5]	111 Estrogen[b] 111 Placebo[b]	**Follow-up: 2 years** **Cerebrovascular accidents** 0 vs. 1
EPHT Estrogen plus progestin trial Veerus, 2006[6]	404 Estrogen plus progestin 373 Placebo	**Follow-up: Mean 3.4 years** **Any cerebrovascular disease**[c] 23 (5.7%) vs. 9 (2.4%); HR 2.46 (1.14-5.34) **Stroke** 1 (0.2%) vs 1 (0.3%); HR 1.06 (0.07-17.2)
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[7]	Women with angiographically verified coronary disease 100 Estrogen 104 Estrogen plus progestin 105 Placebo	**Follow-up: Mean 3.2 years** **Stroke or transient ischemic attack** 5 vs. 6 vs. 6; *P* = 1.0
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[18]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Follow-up: Mean 3 years** **Cerebrovascular accidents** *Analysis did not stratify by regimen* 10 (hormone therapy with or without calcitriol) vs. 7 (calcitriol only or placebo)
WAVE Estrogen-only and estrogen plus progestin trial Waters, 2002[23]	Women with a coronary stenosis of 15%–75% 124 Estrogen (with or without vitamins C and E) 86 Estrogen plus progestin (with or without vitamins C and E) 213 Placebo (with or without vitamins C and E)	**Follow-up: Mean 2.8 years** **Stroke** *Analysis did not stratify by regimen* 9 (4.3%) vs. 4 (1.9%); *P* = .17

eTable 14. Evidence Table of Trials Reporting Incidence of Stroke (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen-only trial Hendrix, 2006;[31] LaCroix, 2011;[37] Manson, 2013;[33] Prentice, 2009[50]	5310 Estrogen 5429 Placebo Postintervention follow-up: 3778 Estrogen 3867 Placebo	**Follow-up: Median 7.2 years**[33] **All stroke** 169 (3.2%) vs. 129 (2.4%); HR, 1.35 (95% CI, 1.07-1.70); *P* = .01 **Subgroups:**[31] No significant difference by race or ethnicity, age, prior CVD, diabetes, hypertension **Risk for stroke based on timing of intervention:**[50] No significant association; *P* for gap time interaction = .96 **Follow-up: Mean 3.9 years postintervention**[37] **All stroke** HR, 0.89 (95% CI, 0.64-1.24) **Cumulative follow-up: Median 13.0 years**[33, 37] **All stroke** HR, 1.15 (95% CI, 0.97-1.37)

eTable 14. Evidence Table of Trials Reporting Incidence of Stroke (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen plus progestin trial Wassertheil-Smoller, 2003[54] Heiss, 2008;[57] Cushman, 2004;[44]Manson, 2013[33]	8506 Estrogen plus progestin 8102 Placebo Postintervention follow-up: 8052 Estrogen plus progestin 7678 Placebo	**Follow-up: Mean 5.6 years** **All stroke**[33] 159 (1.9%) vs. 109 (1.3%); HR, 1.37 (95% CI, 1.07-1.76) **Ischemic stroke**[54] 125 vs. 81; HR, 1.44 (95% CI, 1.09-1.90) **Hemorrhagic stroke**[54] 18 vs. 20; HR, 0.82 (95% CI, 0.43-1.56) **Subgroups:** No significant difference by race or ethnicity, age, diabetes, or hypertension **Risk for stroke based on timing of intervention:**[50] No significant association; p for gap time interaction = 1.00 **Follow-up: Mean 2.4 years postintervention**[33] **All Stroke** HR, 1.04 (95% CI, 0.89-1.23) **Cumulative follow-up: Median 13.2 years**[33] **All stroke** HR, 1.16 (95% CI, 1.00-1.35)

[a] Intervention dosages are listed in Table 2 by trial.
[b] Unopposed micronized 17V-estradiol (1 mg/d).
[c] Defined as diagnoses of one of the following (ICD-10 or 160-169 codes): subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, stroke, occlusion and stenosis of precerebral arteries, occlusion and stenosis of cerebral arteries, other cerebrovascular diseases, cerebrovascular disorders, sequelae of cerebrovascular disease.

CI = confidence interval; CVD = cardiovascular disease; EMS = Estrogen Memory Study; EPAT = Estrogen in the Prevention of Atherosclerosis; EPHT = Estonian Postmenopausal Hormone Therapy Trial; ERA = Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis; HR = hazard ratio; NS = not significant; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WAVE = The Women's Angiographic Vitamin and Estrogen Trial; WHI = Women's Health Initiative.

eTable 15. Evidence Table of Trials Reporting Incidence of Urinary Incontinence

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
HERS Estrogen plus progestin trial Steinauer, 2005[14]	Women reporting no episodes of incontinence in the past week at baseline 597 Estrogen plus progestin 611 Placebo	**Follow-up: 4.2 years** **Weekly urinary incontinence** 382 vs. 302, OR,1.6 (95% CI, 1.3-1.9); p<0.001 **Stress urinary incontinence** OR, 1.7 (95% CI, 1.5-2.1); p<0.001 **Urge urinary incontinence** OR, 1.5 (95% CI, 1.2-1.8); p<0.001
ULTRA Estrogen-only trial Waetjen, 2005[21]	Women who were continent at baseline 122 Estrogen (calculated) 117 Placebo (calculated)	**Follow-up: 2 years** 39.0% vs. 36.8%; OR, 1.2 (95% CI, 0.7-2.2); *P* = .74
WHI Estrogen-only trial Hendrix, 2005[30]	Women with urinary incontinence data at baseline and 1 year 1526 Estrogen (all continent at baseline, 96 continent at 1 year) 1547 Placebo (all continent at baseline, 136 continent at 1 year)	**Follow-up: 1 year** **Incident urinary incontinence** 557 (36.5%) vs. 368 (23.8%); RR, 1.53 (95% CI, 1.37-1.71) **Stress urinary incontinence** 266 (17.4%) vs. 131 (8.5%); RR, 2.15 (95% CI, 1.77-2.62); p<0.001 **Urge urinary incontinence** 210 (13.8%) vs. 184 (11.9%); RR, 1.32 (95% CI, 1.10-1.58); *P* = .003 **Mixed urinary incontinence** 76 (5.0%) vs. 50 (3.2%); RR, 1.79 (95% CI, 1.26-2.53); *P* = .001 **Follow-up: 3 years** 27/96 (28.1%) vs. 26/136 (19.1%) of continent women at baseline and 1 year reported incident urinary incontinence at 3 years; RR, 1.47 (95% CI, 0.92-2.36)
WHI Estrogen plus progestin trial Hendrix, 2005[30]	Women with urinary incontinence data at baseline and 1 year 2675 Estrogen plus progestin (all continent at baseline, 153 continent at 1 year) 2507 Placebo (all continent at baseline, 185 continent at 1 year)	**Follow-up: 1 year** **Incident urinary incontinence** 834 (31.2%) vs. 563 (22.5%); RR, 1.39 (95% CI, 1.27-1.52) **Stress urinary incontinence** 429 (16.0%) vs. 218 (8.7%); RR, 1.87 (95% CI, 1.61-2.18); p<0.001 **Urge urinary incontinence** 304 (11.4%) vs. 272 (10.8%); RR, 1.15 (95% CI, 0.99-1.34); *P* = .06 **Mixed urinary incontinence** 99 (3.7%) vs. 69 (2.8%); RR, 1.49 (95% CI, 1.10-2.01); *P* = .01 **Follow-up: 3 years** 39/153 (25.5%) vs. 26/185 (14.1%) of continent women at baseline and 1 year reported incident urinary incontinence at 3 years; RR, 1.81 (95% CI, 1.16-2.84)

[a] Intervention dosages are listed in Table 2 by trial.

CI = confidence interval; HERS = Heart and Estrogen/Progestin Replacement Study; OR = odds ratio; RR = relative risk; ULTRA = Ultra Low-Dose Transdermal Estrogen Replacement Assessment; vs. = versus; WHI = Women's Health Initiative.

eTable 16. Evidence Table of Trials Reporting Incidence of Venous Thromboembolism

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
EMS Estrogen plus progestin trial Tierney, 2000[4]	70 Estrogen plus progestin 72 Placebo	**Follow-up: 2 years** **Deep vein thrombosis** 1 vs. 0; *P* = NS
EPAT Estrogen-only trial Hodis, 2001[5]	111 Estrogen 111 Placebo	**Follow-up: 2 years** **Deep vein thrombosis or pulmonary embolism** 0 (0.0%) vs. (0.0%)
EPHT Estrogen plus progestin trial Veerus, 2006[6]	404 Estrogen plus progestin 373 Placebo	**Follow-up: Mean 3.4 years** **Venous thromboembolism** 0 (0.0%) vs. 0 (0.0%)
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[7]	100 Estrogen 104 Estrogen plus progestin 105 Placebo	**Follow-up: 3.2 years** 1 vs. 0 vs. 0; *P* = .35
Greenspan et al. Estrogen-only and estrogen plus progestin trial Greenspan, 2005[9]	66 Estrogen 121 Estrogen plus progestin 186 Placebo	**Follow-up: 3 years** **Deep vein thrombosis** *Analysis did not stratify by regimen* 2 vs. 1; *P* = 1.0
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[18]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Follow-up: 3 years** **Deep vein thrombosis** *Analysis did not stratify by regimen* 4 (hormone therapy with or without calcitriol) vs. 1 (calcitriol only or placebo)
WAVE Estrogen-only and estrogen plus progestin trial Waters, 2002[23]	Women with a coronary stenosis of 15%–75% 124 Estrogen (with or without vitamins C and E) 86 Estrogen plus progestin (with or without vitamins C and E) 213 Placebo (with or without vitamins C and E)	**Follow-up: 2.8 years** **Deep vein thrombosis or pulmonary embolism** *Analysis did not stratify by treatment regimen* 4 vs. 4; *P* = .93

eTable 16. Evidence Table of Trials Reporting Incidence of Venous Thromboembolism (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen-only trial LaCroix, 2011;[37] Curb, 2006[29] Prentice, 2009;[50] Manson, 2013[33]	5310 Estrogen 5429 Placebo Postintervention follow-up: 3778 Estrogen 3867 Placebo	**Follow-up: Mean 7.1 years**[33, 37] **Deep vein thrombosis** 85 (1.6%) vs. 59 (1.0%); HR, 1.48 (95% CI, 1.06-2.07); *P* = .02 **Pulmonary embolism** 52 (0.98%) vs. 39 (0.72%); HR, 1.35 (95% CI, 0.89-2.05); *P* = .15 **Subgroups:**[29] No significant difference by race or ethnicity, age, or history of CVD **Risk for venous thromboembolism based on timing of intervention:**[50] No significant association; p for gap time interaction = .65 **Follow-up: Mean 3.9 years postintervention**[37] **Deep vein thrombosis** HR, 0.63 (95% CI, 0.41-0.98); *P* = .003 **Pulmonary embolism** HR, 0.98 (95% CI, 0.62-1.55); *P* = .29 **Cumulative follow-up: Median 13.0 years**[33] **Deep vein thrombosis** HR 1.05 (95% CI, 0.82-1.33) **Pulmonary embolism** HR, 1.15 (95% CI, 0.87-1.51)

eTable 16. Evidence Table of Trials Reporting Incidence of Venous Thromboembolism (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen plus progestin trial Heiss, 2008;[57] Cushman, 2004;[44] Manson, 2013;[33] Prentice, 2009[50]	8506 Estrogen plus progestin 8102 Placebo Postintervention follow-up: 8052 Estrogen plus progestin 7678 Placebo	**Follow-up: Median 5.6 years** **Venous thrombosis**[44] 167 vs. 76; HR, 2.06 (95% CI, 1.57-2.70) **Deep vein thrombosis**[33] 122 (1.4%) vs. 61 (0.8%); HR, 1.87 (95% CI, 1.37-2.54); p<0.001 **Pulmonary embolism**[33] 87 (1.0%) vs. 41(0.5%); HR, 1.98 (95% CI, 1.36-2.87); p<0.001 **Subgroups:**[33] No significant difference by age **Risk for venous thromboembolism based on timing of intervention:**[50] No significant association; *P* for gap time interaction = .45 **Follow-up: Mean 2.4 years postintervention**[57] **Deep vein thrombosis** HR, 1.07 (95% CI, 0.66-1.75) **Pulmonary embolism** HR 1.07 (95% CI, 0.62-1.86) **Cumulative follow-up: Median 13.0 years**[33, 44, 57] **Deep vein thrombosis** HR, 1.05 (95% CI, 0.82-1.33) **Pulmonary embolism** HR 1.15 (95% CI, 0.87-1.51)

[a] Intervention dosages are listed in Table 2 by trial.

CI = confidence interval; CVD = cardiovascular disease; EMS = Estrogen Memory Study; EPAT = Estrogen in the Prevention of Atherosclerosis; EPHT = Estonian Postmenopausal Hormone Therapy Trial; ERA = Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis; HR = hazard ratio; NS = not significant; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WAVE = The Women's Angiographic Vitamin and Estrogen Trial; WHI = Women's Health Initiative.

eTable 17. Evidence Table of Trials Reporting Quality of Life

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen-only trial Manson, 2013[33]	5310 Estrogen 5429 Placebo	**Follow-up: Mean 7.1 years**[33] RAND 36: Similar scores on all items except for emotional role (81.0 vs. 82.2, *P* = .04) and social functioning (85.8 vs. 86.9, *P* = .01) for which women on placebo had statistically significantly better scores than women on estrogen-only therapy
WHI Estrogen plus progestin trial Manson, 2013;[33] Hays, 2003[45]	8506 Estrogen plus progestin 8102 Placebo	**Follow-up: Mean 5.6 years**[33] RAND 36: Similar scores on all items except for physical functioning (82.6 vs. 81.8, *P* < 0.001), physical role (77.4 vs. 76.2, *P* = .02), bodily pain (77.6 vs. 75.6, *P* < 0.001), and general health (76.6 vs. 76.1, *P* = .02) for which women on hormone therapy had statistically significantly better scores than women on placebo

[a] Intervention dosages are listed in Table 2 by trial.

vs. = versus; WHI = Women's Health Initiative.

eTable 18. Evidence Table of Trials Reporting Incidence of All-Cause Mortality

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
ERA Estrogen-only and estrogen plus progestin trial Herrington, 2000[7]	100 Estrogen 104 Estrogen plus progestin 105 Placebo	**Follow-up: Mean 3.2 years** 8 (8.0%) vs. 3 (2.9%) vs. 6 (5.7%); *P* = .28
ESPRIT Estrogen-only trial Cherry, 2002;[8] Cherry, 2014[68]	513 Estrogen 504 Placebo	**Follow-up: 2 years**[8] 32 (6.2%) vs. 39 (7.7%); Rate ratio, 0.79 (95% CI, 0.50-1.27); *P* = .34 **Cumulative follow-up: Mean 14.1 years**[68] HR, 1.07 (95% CI, 0.88-1.29)
HERS Estrogen plus progestin trial Hulley, 2002[69]	1380 Estrogen plus progestin 1383 Placebo Cumulative follow-up: 1156 Estrogen plus progestin 1383 Placebo	**Follow-up: Mean 4.1 years** 130 (9.4%) vs. 123 (8.9%); HR, 1.06 (95% CI, 0.83-1.36); *P* = .62 **Cumulative follow-up: Mean 6.8 years** HR, 1.10 (95% CI, 0.92-1.31); *P* = .29
STOP-IT Estrogen-only and estrogen plus progestin trial Gallagher, 2001[18]	121 Hormone therapy 122 Hormone therapy plus calcitriol 123 Calcitriol only 123 Placebo	**Follow-up: 3 years** *Analysis did not stratify by regimen* 3 (hormone therapy with or without calcitriol: 1.2%) vs. 2 (calcitriol only or placebo: 0.8%)
WAVE Estrogen-only and estrogen plus progestin trial Waters, 2002[23]	124 Estrogen (with or without vitamins C and E) 86 Estrogen plus progestin (with or without vitamins C and E) 213 Placebo (with or without vitamins C and E)	**Follow-up: Mean 2.8 years** *Analysis did not stratify by treatment regimen* 14 (6.7%) vs. 8 (3.8%)

eTable 18. Evidence Table of Trials Reporting Incidence of All-Cause Mortality (continued)

Study Author, Year	Population	Results (number of cases in treatment[a] vs. placebo arm)
WHI Estrogen-only trial LaCroix, 2011;[37] Manson, 2013;[33] Prentice, 2009[50]	5310 Estrogen 5429 Placebo	**Follow-up: Mean 7.1 years**[37] 300 (5.6%) vs. 297 (5.5%); HR, 1.04 (95% CI, 0.89-1.22) **Subgroups:**[33] Among women 50–59 years at randomization: HR, 0.70 (95% CI, 0.46-1.09) Among women 60–69 years at randomization: HR, 1.01 (95% CI, 0.79-1.49) Among women 70–79 years at randomization: HR, 1.21 (95% CI, 0.95-1.56) p for trend = .04 **Risk for death based on timing of intervention:**[50] **Among women without prior HT use** No significant association; p for gap time interaction = .14 **Follow-up: Mean 3.9 years postintervention**[37] HR, 1.00 (95% CI, 0.84-1.18) **Cumulative follow-up: Mean 10.7 years**[37] HR, 1.02 (95% CI, 0.91-1.15)
WHI Estrogen plus progestin trial Heiss, 2008;[57] Manson, 2013;[33] Prentice, 2009[50]	8506 Estrogen plus progestin 8102 Placebo	**Follow-up: Mean 5.6 (weighted mean 5.2) years**[57] 250 (2.9%) vs. 239 (2.9%); HR, 0.97 (95% CI, 0.81-1.16) **Risk for death based on timing of intervention:**[50] No significant association; p for gap time interaction = .36 **Follow-up: Mean 2.4 years postintervention**[57] HR, 1.15 (95% CI, 0.95-1.39) **Of those who adhered to ≥80% of medication**[57] HR, 1.53 (95% CI, 1.04-2.24) **Follow-up: Median 8.2 years postintervention**[33] HR, 1.01 (95% CI, 0.91-1.11); *P* = .90

[a] Intervention dosages are listed in Table 2 by trial.

CI = confidence interval; ERA = Estrogen Replacement and Atherosclerosis Trial; ESPRIT = Oestrogen in the Prevention of Reinfarction Trial; HERS = Heart and Estrogen/Progestin Replacement Study; HR = hazard ratio; HT = hormone therapy; STOP-IT = Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection; vs. = versus; WAVE = Women's Angiographic Vitamin and Estrogen Trial; WHI = **Women's Health Initiative**

eTable 19. Summary of Evidence: Subgroups

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency[a]/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations[b]	EPC Assessment of Strength of Evidence	Applicability
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[33, 70] 600 events in 27,347 women	**Invasive Breast Cancer:** Age: Similar treatment effects in subgroups based on age	NA/ reasonably precise	Undetected	Fair	None	Moderate	Generally healthy post-menopausal women 50 years or older
			Duration: The risk of invasive breast cancer increased for women who initiated estrogen plus progestin with increasing time since randomization (p for trend=0.008).	NA/reasonably precise	Undetected	Fair	Post-hoc analysis	Low	Generally healthy post-menopausal women 50 years or older
			Timing: Women who initiated estrogen plus progestin closer to menopause had a higher risk of invasive breast cancer than those who initiated later (p for interaction=0.03)	NA/reasonably precise	Undetected	Fair	Post-hoc analysis; for women with hysterect-omy without oophorect-omy, exact timing of menopause is often difficult to determine	Low	Generally healthy post-menopausal women 50 years or older
			No difference in timing or duration of HRT use for women on estrogen-only therapy	NA/reasonably precise	Undetected	Fair	Post-hoc analysis; for women with hysterect-omy without oophorect-omy, exact timing of menopause is often difficult to determine	Low	Generally healthy post-menopausal women 50 years or older

eTable 19. Summary of Evidence: Subgroups (continued)

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency[a]/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations[b]	EPC Assessment of Strength of Evidence	Applicability
KQ 3	Menopausal women with intact uterus Estrogen plus progestin therapy	No evidence	**Cervical Cancer:** No evidence	NA	Undetected	NA	N	Insufficient	NA
			Timing: No evidence	NA	Undetected	NA	NA	Insufficient	NA
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[33, 34, 43, 50] 248 events in 27,347 women	**Colorectal Cancer**: Age: For estrogen-only, there was a significant trend towards lower risk among younger women compared to older women, relative to placebo (p for interaction= 0.02); similar risks for estrogen plus progestin	NA/imprecise	Undetected	Fair	Estimates based on 2 studies with few events; lack of power to detect subgroup effects	Low	Generally healthy post-menopausal women 50 years or older
			Race or ethnicity or family history of colorectal cancer: Similar treatment effects in subgroups for both treatment regimens	NA/imprecise	Undetected	Fair	Estimates based on 2 studies with few events; lack of power to detect subgroup effects	Low	Generally healthy post-menopausal women 50 years or older
			Timing: Similar treatment effects in subgroups based on timing of intervention since menopause for both treatment regimens	NA/imprecise	Undetected	Fair	Post-hoc analysis; for women with hysterect-omy without oophorect-omy, exact timing of menopause is often difficult to determine	Low	Generally healthy post-menopausal women 50 years or older

eTable 19. Summary of Evidence: Subgroups (continued)

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency[a]/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations[b]	EPC Assessment of Strength of Evidence	Applicability
KQ 3	Menopausal women with intact uterus Estrogen plus progestin therapy	1 RCT[33] 57 events in 16,608 women	**Endometrial Cancer:** Similar treatment effects in subgroups based on age in the estrogen plus progestin and placebo groups	NA/imprecise	Undetected	Fair	Estimates based on a single study with few events; lack of power to detect subgroup effects	Insufficient	Generally healthy post-menopausal women 50 years or older
			Timing: No evidence	NA/NA	Undetected	NA	NA	Insufficient	NA
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[33] 271 events in 27,347 women	**Lung Cancer:** Similar treatment effects in subgroups based on age for both treatment regimens	NA/imprecise	Undetected	Fair	Estimates based on 2 studies with few events; lack of power to detect subgroup effects	Low	Generally healthy post-menopausal women 50 years or older
			Timing: No evidence	NA/NA	Undetected	NA	NA	Insufficient	NA
KQ 3	Menopausal women with intact uterus Estrogen plus progestin therapy	1 RCT[33] 40 events in 16,608 women	**Ovarian Cancer:** No subgroup effects with respect to age for estrogen plus progestin	NA/imprecise	Undetected	Fair	Very few events	Insufficient	Generally healthy post-menopausal women 50 years or older
			Timing: No evidence	NA/NA	Undetected	NA	NA	Insufficient	NA

eTable 19. Summary of Evidence: Subgroups (continued)

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency[a]/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations[b]	EPC Assessment of Strength of Evidence	Applicability
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[32, 35, 48] 711 event in >27,000 women	**Coronary Heart Disease:** Risk attributable to HT increased numerically with age for estrogen plus progestin, test of interaction was not statistically significant; there was a significant trend towards lower risk among younger women on estrogen only for myocardial infarction compared to older women, relative to placebo	NA/ reasonably precise	Undetected	Fair	None	Low	Generally healthy post-menopausal women 50 years or older
			Similar treatment effects in subgroups based on race or ethnicity	Consistent/ reasonably precise	Undetected	Fair	None	Moderate	Generally healthy post-menopausal women 50 years or older
			Similar treatment effects in subgroups based on: hypertension, diabetes, high cholesterol requiring medication, coronary risk factors, years since bilateral oophorectomy, years since hysterectomy, or body mass index for both treatment regimens	Consistent/ reasonably precise	Undetected	Fair	Post-hoc analysis	Low	Generally healthy post-menopausal women 50 years or older

eTable 19. Summary of Evidence: Subgroups (continued)

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency[a]/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations[b]	EPC Assessment of Strength of Evidence	Applicability
			Timing: Risk attributable to HT increased with time since menopause; test of interaction was not statistically significant (p=0.40)	Consistent/ reasonably precise	Undetected	Fair	Post-hoc analysis; for women with hysterect-omy without oophorect-omy, exact timing of menopause is often difficult to determine	Low	Generally healthy post-menopausal women 50 years or older
KQ 3	Menopausal women with intact uterus Estrogen only or estrogen plus progestin therapy	1 RCT[59, 61, 62] 108 events in 7,479 women	**Probable Dementia:** Similar treatment effects in subgroups based on race, history of diabetes, stroke, hypertension, or cardiovascular disease for estrogen only	NA/imprecise	Undetected	Fair	Estimates based on a single study	Low	Generally healthy post-menopausal women 50 years or older
			Timing: Similar treatment effects in subgroups based on timing of intervention since menopause for estrogen plus progestin	NA/imprecise	Undetected	Fair	Post hoc analysis; for women with hyster-ectomy without oophorec-tomy, exact timing of menopause is often difficult to determine	Low	Generally healthy post-menopausal women 50 years or older

eTable 19. Summary of Evidence: Subgroups (continued)

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency[a]/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations[b]	EPC Assessment of Strength of Evidence	Applicability
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	1 RCT[25, 33, 49] 1,677 events in 25,791 women	**Diabetes:** Similar treatment effects in subgroups based on age, race/ethnicity for both treatment regimens	NA/precise	Undetected	Fair	None	Moderate	Generally healthy post-menopausal women 50 years or older
			Similar treatment effects in subgroups based on hypertension, metabolic syndrome for estrogen only	NA/precise	Undetected	Fair	Post-hoc analysis	Low	NA
			Timing: No evidence	NA	Undetected	NA	NA	Insufficient	NA
KQ 3	Menopausal women with intact uterus Estrogen only or estrogen plus progestin therapy	1 RCT[39] 1,227 events in 10,739 women Timing: 1 RCT[6] 40 events in 777 women[6]	**Fractures:** No significant difference by age for estrogen only	NA	Undetected	NA	None	Moderate	NA
			Timing: Similar treatment effects based on timing of intervention since menopause for estrogen plus progestin	NA/precise	Undetected	Fair	Post-hoc analysis; for women with hysterect-omy without oophorect-omy, exact timing of menopause is often difficult to determine	Low	Generally healthy post-menopausal women 50 years or older
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[28] 734 events in 22,579 women	**Gallbladder disease:** Similar treatment effects in subgroups based on age for both treatment regimens	NA/precise	Undetected	Fair	None	Moderate	Generally healthy post-menopausal women 50 years or older
			Timing: No evidence	NA	NA	NA	NA	Insufficient	NA
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[33] 567 events in 27,347 women	**Stroke:** Similar treatment effects in subgroups based on age, race/ethnicity	NA/precise	Undetected	Fair	None	Moderate	Generally healthy post-menopausal women 50 years or older

eTable 19. Summary of Evidence: Subgroups (continued)

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency[a]/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations[b]	EPC Assessment of Strength of Evidence	Applicability
			Similar treatment effects in subgroups based on hypertension for both treatment regimens	NA/precise	Undetected	Fair	Post-hoc analysis	Low	Generally healthy post-menopausal women 50 years or older
			Timing: Similar treatment effects in subgroups based on timing of intervention since menopause for both treatment regimens	NA/precise	Undetected	Fair	Post-hoc analysis; for women with hysterect-omy without oophorect-omy, exact timing of menopause is often difficult to determine	Low	Generally healthy post-menopausal women 50 years or older
KQ 3	Menopausal women with intact uterus Estrogen plus progestin therapy	No evidence	**Urinary incontinence:** No evidence	NA	Undetected	NA	NA	Insufficient	
			Timing: No evidence	NA	Undetected	NA	NA	Insufficient	NA
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[33] 546 events in 27,347 women	**Venous Thromboembolism:** Similar treatment effects in subgroups based on age and race/ethnicityfor both treatment regimens	NA/precise	Undetected	Fair	None	Moderate	Generally healthy post-menopausal women 50 years or older
			Similar treatment effects in subgroups based on history of cardiovascular disease for estrogen only	NA/precise	Undetected	Fair	Post-hoc analysis	Low	Generally healthy post-menopausal women 50 years or older

eTable 19. Summary of Evidence: Subgroups (continued)

Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency[a]/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations[b]	EPC Assessment of Strength of Evidence	Applicability
			Timing: Similar treatment effects in subgroups based on timing of intervention since menopause for both treatment regimens	NA/precise	Undetected	Fair	Post-hoc analysis; for women with hysterect-omy without oophorect-omy, exact timing of menopause is often difficult to determine	Low	Generally healthy post-menopausal women 50 years or older
KQ 3	Menopausal women with intact uterus Estrogen plus progestin therapy	No evidence	**Quality of life:** No evidence	NA	Undetected	NA	NA	Insufficient	NA
KQ 3	Menopausal women Estrogen only or estrogen plus progestin therapy	2 RCTs[37, 50] 1086 events in 27,347 women	**All-cause mortality:** There was a significant trend towards lower risk among younger compared to older women using estrogen only, relative to placebo (p for interaction=0.04); in women on estrogen plus progestin difference did not reach statistical significance.	NA/precise	Undetected	Fair	None	Low	Generally healthy post-menopausal women 50 years or older

eTable 19. Summary of Evidence: Subgroups (continued)

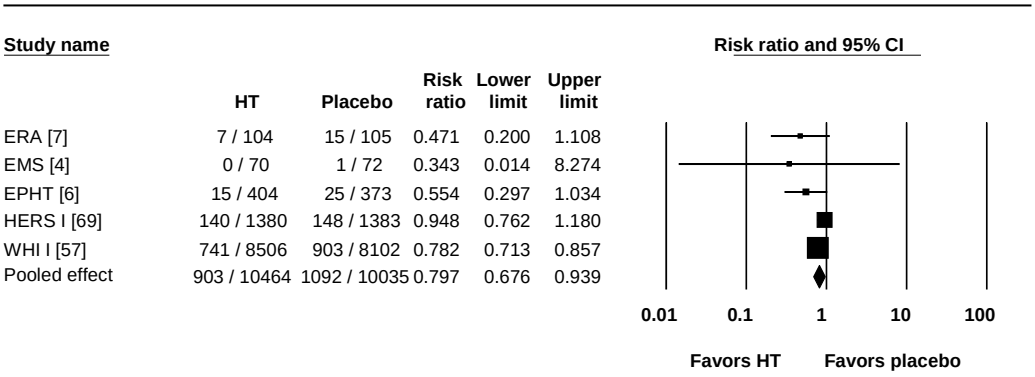
Key Question	Population, Intervention	No. of Studies; No. of Observations	Summary of Findings by Outcome	Consistency[a]/ Precision	Reporting Bias	Overall Quality of Studies	Body of Evidence Limitations[b]	EPC Assessment of Strength of Evidence	Applicability
			Timing: Similar treatment effects in subgroups based on timing of intervention since menopause for both treatment regimens	NA/precise	Undetected	Fair	Post-hoc analysis; for women with hysterecto-my without oophorecto-my, exact timing of menopause is often difficult to determine	Low	Generally healthy post-menopausal women 50 years or older

[a] Ratings of consistency pertain to effects of the same treatment regimen (i.e., either estrogen only or combination therapy). In situations where only a single study is available for each regimen, consistency was rated as not applicable (NA). [b]We downgraded all subgroup analyses for multiplicity; in addition, we further downgraded post hoc subgroup analyses.

EPC = Evidence-based Practice Center; HT = hormone therapy; KQ = Key Question; NA = not applicable; No. = number; RCT = randomized controlled tria

eFigures

eFigure 1. Fractures (Osteoporotic), Estrogen plus Progestin Therapy vs. Placebo



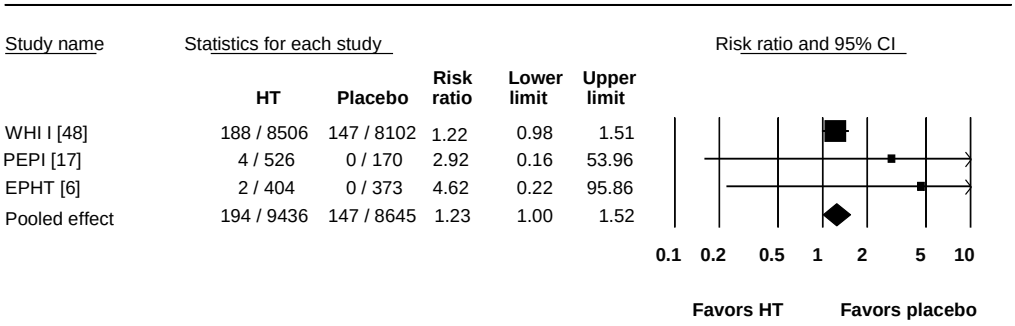
Random effects meta analysis; I-squared 28.7%; [] = reference number.

Squares in the figure represent the effects of individual studies. The size of the squares reflects the weight that a particular study has in the meta-analysis.

For studies with zero events in one arm, we added a continuity correction of 0.5 to each cell of the 2 by 2 table.

CI = confidence interval; ERA = Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis; EMS = Estrogen Memory Study; EPHT = Estonian Postmenopausal Hormone Therapy Trial; HERS = Heart and Estrogen/ Progestin Replacement Study; HT = hormone therapy; WHI = Women's Health Initiative.

eFigure 2. Coronary Heart Disease, Estrogen plus Progestin Therapy vs Placebo



Random effects meta analysis; I-squared 0%; [ ] = reference number.

Squares in the figure represent the effects of individual studies. The size of the squares reflects the weight that a particular study has in the meta-analysis.

For studies with zero events in one arm, we added a continuity correction of 0.5 to each cell of the 2 by 2 table.

CI = confidence interval; EPHT = Estonian Postmenopausal Hormone Therapy Trial; HT = hormone therapy; PEPI = Postmenopausal Estrogen/Progestin Interventions; WHI = Women's Health Initiative.

eReferences

1. Mosekilde L, Beck-Nielsen H, Sorensen OH, et al. Hormonal replacement therapy reduces forearm fracture incidence in recent postmenopausal women - results of the Danish Osteoporosis Prevention Study. *Maturitas*. 2000 Oct 31;36(3):181-93. PMID: 11063900.
2. 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. PMID: 23048011.
3. Clarke SC, Kelleher J, Lloyd-Jones H, et al. A study of hormone replacement therapy in postmenopausal women with ischaemic heart disease: the Papworth HRT atherosclerosis study. *BJOG*. 2002 Sep;109(9):1056-62. PMID: 12269682.
4. 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 Aug;34(7):1065-74. doi: 10.1016/j.psyneuen.2009.02.009. PMID: 19297102.
5. Hodis HN, Mack WJ, Lobo RA, et al. Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2001 Dec 4;135(11):939-53. PMID: 11730394.
6. Veerus P, Hovi SL, Fischer K, et al. Results from the Estonian postmenopausal hormone therapy trial [ISRCTN35338757]. *Maturitas*. 2006 Sep 20;55(2):162-73. doi: 10.1016/j.maturitas.2006.01.012. PMID: 16504428.
7. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med*. 2000 Aug 24;343(8):522-9. doi: 10.1056/nejm200008243430801. PMID: 10954759.
8. Cherry N, Gilmour K, Hannaford P, et al. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet*. 2002 Dec 21-28;360(9350):2001-8. PMID: 12504395.
9. Greenspan SL, Resnick NM, Parker RA. The effect of hormone replacement on physical performance in community-dwelling elderly women. *Am J Med*. 2005 Nov;118(11):1232-9. doi: 10.1016/j.amjmed.2005.03.004. PMID: 16271907.
10. Notelovitz M, John VA, Good WR. Effectiveness of Alora estradiol matrix transdermal delivery system in improving lumbar bone mineral density in healthy, postmenopausal women. *Menopause*. 2002 Sep-Oct;9(5):343-53. PMID: 12218723.
11. Grady D, Applegate W, Bush T, et al. Heart and Estrogen/progestin Replacement Study (HERS): design, methods, and baseline characteristics. *Control Clin Trials*. 1998 Aug;19(4):314-35. PMID: 9683309.
12. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA*. 1998 Aug;280(7):605-13. PMID: 9718051.
13. Kanaya AM, Herrington D, Vittinghoff E, et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial.[Summary for patients in Ann Intern Med. 2003 Jan 7;138(1):I10; PMID: 12513063]. *Ann Intern Med*. 2003 Jan 7;138(1):1-9. PMID: 12513038.
14. Steinauer JE, Waetjen LE, Vittinghoff E, et al. Postmenopausal hormone therapy: does it cause incontinence? *Obstet Gynecol*. 2005 Nov;106(5 Pt 1):940-5. PMID: 16260510.
15. 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 Jun;12(6):e1001833; discussion e. doi: 10.1371/journal.pmed.1001833 [doi]; PMEDICINE-D-14-01484 [pii]. PMID: 26035291.
16. Pefanco MA, Kenny AM, Kaplan RF, et al. The effect of 3-year treatment with 0.25 mg/day of micronized 17beta-estradiol on cognitive function in older postmenopausal women. *J Am Geriatr Soc*. 2007 Mar;55(3):426-31. doi: 10.1111/j.1532-5415.2007.01085.x. PMID: 17341247.
17. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA*. 1995 Jan 18;273(3):199-208. PMID: 7807658.
18. Gallagher JC, Fowler SE, Detter JR, et al. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. *J Clin Endocrinol Metab*. 2001 Aug;86(8):3618-28. doi: 10.1210/jcem.86.8.7703. PMID: 11502787.
19. 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 Sep;104(3):443-51. PMID: 15339752.
20. Johnson SR, Ettinger B, Macer JL, et al. Uterine and vaginal effects of unopposed ultralow-dose transdermal estradiol. *Obstet Gynecol*. 2005;105(4):779-87. PMID: 15802405.

21. Waetjen LE, Brown JS, Vittinghoff E, et al. The effect of ultralow-dose transdermal estradiol on urinary incontinence in postmenopausal women. *Obstet Gynecol*. 2005 Nov;106(5 Pt 1):946-52. PMID: 16260511.
22. 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 Jul;63(7):945-50. doi: 10.1001/archneur.63.7.945. PMID: 16831962.
23. 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 Nov 20;288(19):2432-40. PMID: 12435256.
24. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004 Apr 14;291(14):1701-12. PMID: 15082697.
25. 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 Mar;49(3):459-68. PMID: 16440209.
26. Brunner RL, Gass M, Aragaki A, et al. Effects of conjugated equine estrogen on health-related quality of life in postmenopausal women with hysterectomy: results from the Women's Health Initiative Randomized Clinical Trial. *Arch Intern Med*. 2005 Sep 26;165(17):1976-86. PMID: 16186467.
27. 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 Sep 22;102(18):1413-21. PMID: 20709992.
28. Cirillo DJ, Wallace RB, Rodabough RJ, et al. Effect of estrogen therapy on gallbladder disease. *JAMA*. 2005;293:330-9. PMID: 15657326.
29. Curb JD, Prentice RL, Bray PF, et al. Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med*. 2006 Apr 10;166(7):772-80. PMID: 16606815.
30. Hendrix SL, Cochrane BB, Nygaard IE, et al. Effects of estrogen with and without progestin on urinary incontinence. *JAMA*. 2005 Feb 23;293(8):935-48. PMID: 15728164.
31. Hendrix SL, Wassertheil-Smoller S, Johnson KC, et al. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation*. 2006 May 23;113(20):2425-34. PMID: 16702472.
32. Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med*. 2006 Feb 13;166(3):357-65. doi: 10.1001/archinte.166.3.357. PMID: 16476878.
33. 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 Oct 2;310(13):1353-68. doi: 1745676 [pii]; 10.1001/jama.2013.278040 [doi]. PMID: 24084921.
34. Ritenbaugh C, Stanford JL, Wu L, et al. Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. *Cancer Epidemiol Biomarkers Prev*. 2008 Oct;17(10):2609-18. PMID: 18829444.
35. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause.[Erratum appears in JAMA. 2008 Mar 26;299(12):1426]. *JAMA*. 2007 Apr 4;297(13):1465-77. PMID: 17405972.
36. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA*. 2010 Oct 20;304(15):1684-92. PMID: 20959578.
37. LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA*. 2011 Apr 6;305(13):1305-14. PMID: 21467283.
38. 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 May;13(5):476-86. doi: 10.1016/s1470-2045(12)70075-x. PMID: 22401913.
39. Anderson GL, Judd HL, Kaunitz AM, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA*. 2003 Oct 1;290(13):1739-48. PMID: 14519708.
40. 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 Mar;21(3):214-20. doi: 10.1097/GME.0b013e31829752e0 [doi]. PMID: 23760439.
41. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA*. 2003 Oct 1;290(13):1729-38. PMID: 14519707.

42. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA*. 2003 Jun 25;289(24):3243-53. PMID: 12824205.
43. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med*. 2004 Mar 4;350(10):991-1004. PMID: 14999111.
44. Cushman M, Kuller LH, Prentice R, et al. Estrogen plus progestin and risk of venous thrombosis. *JAMA*. 2004 Oct 6;292(13):1573-80. PMID: 15467059.
45. Hays J, Ockene JK, Brunner RL, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med*. 2003 May 8;348(19):1839-54. PMID: 12642637.
46. Hendrix SL. The Women's Health Initiative estrogen plus progestin trial: the study and how it changes our practice. *J Am Osteopath Assoc*. 2003 Feb;103(2 Suppl 2):S3-5. PMID: 12625631.
47. Hsia J, Criqui MH, Rodabough RJ, et al. Estrogen plus progestin and the risk of peripheral aerterial disease. *Circulation*. 2004;109(5):620-26. PMID: 14769684.
48. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med*. 2003 Aug 7;349(6):523-34. PMID: 12904517.
49. Margolis KL, Bonds DE, Rodabough RJ, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia*. 2004 Jul;47(7):1175-87. PMID: 15252707.
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 Jul 1;170(1):12-23. doi: 10.1093/aje/kwp115. PMID: 19468079.
51. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002 Jul 17;288(3):321-33. PMID: 12117397.
52. 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 Oct 5;103(19):1469-75. doi: djr333 [pii]; 10.1093/jnci/djr333 [doi]. PMID: 21878677.
53. Toh S, Hernandez-Diaz S, Logan R, et al. Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: does the increased risk ever disappear? A randomized trial.[Summary for patients in Ann Intern Med. 2010 Feb 16;152(4):I-40; PMID: 20157120]. *Ann Intern Med*. 2010 Feb 16;152(4):211-7. PMID: 20157135.
54. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA*. 2003 May 28;289(20):2673-84. PMID: 12771114.
55. Chlebowski RT, Schwartz AG, Wakelee H, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. *Lancet*. 2009 Oct 10;374(9697):1243-51. PMID: 19767090.
56. Gramling R, Eaton CB, Rothman KJ, et al. Hormone replacement therapy, family history, and breast cancer risk among postmenopausal women. *Epidemiology*. 2009 Sep;20(5):752-6. PMID: 19451819.
57. Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA*. 2008 Mar 5;299(9):1036-45. PMID: 18319414.
58. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004 Jun 23;291(24):2959-68. PMID: 15213207.
59. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004 Jun 23;291(24):2947-58. PMID: 15213206.
60. Culhane NS. Estrogen plus progestin may increase incidence of dementia. *J Fam Pract*. 2003 Oct;52(10):754-5. PMID: 14529594.
61. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*. 2003 May 28;289(20):2663-72. PMID: 12771113.
62. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*. 2003 May 28;289(20):2651-62. PMID: 12771112.
63. Espeland MA, Shumaker SA, Leng I, et al. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. JAMA internal medicine; 2013. p. 1429-36.
64. Espeland MA, Brunner RL, Hogan PE, et al. Long-term effects of conjugated equine estrogen therapies on domain-specific cognitive function: results from the Women's Health Initiative study of cognitive aging extension. *J Am Geriatr Soc*. 2010 Jul;58(7):1263-71. PMID: 20649689.

65. Resnick SM, Espeland MA, An Y, et al. Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. *J Clin Endocrinol Metab*. 2009 Nov;94(11):4152-61. PMID: 19850684.
66. Resnick SM, Maki PM, Rapp SR, et al. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *J Clin Endocrinol Metab*. 2006 May;91(5):1802-10. PMID: 16522699.
67. Vickers MR, MacLennan AH, Lawton B, et al. 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 Aug 4;335(7613):239. doi: 10.1136/bmj.39266.425069.AD. PMID: 17626056.
68. Cherry N, McNamee R, Heagerty A, et al. Long-term safety of unopposed estrogen used by women surviving myocardial infarction: 14-year follow-up of the ESPRIT randomised controlled trial. *BJOG*. 2014 May;121(6):700-5; discussion 5. doi: 10.1111/1471-0528.12598. PMID: 24533510.
69. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA*. 2002 Jul 3;288(1):58-66. PMID: 12090863.
70. 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 Jun;1(3):296-305. doi: 2250347 [pii]; 10.1001/jamaoncol.2015.0494 [doi]. PMID: 26181174.
71. 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*. 2016 Mar;108(3)doi: djv350 [pii]; 10.1093/jnci/djv350 [doi]. PMID: 26668177.
72. Grady D, Yaffe K, Kristof M, et al. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. *Am J Med*. 2002 Nov;113(7):543-8. PMID: 12459399.