JAMA | Review | WOMEN'S HEALTH

The Women's Health Initiative Randomized Trials and Clinical Practice
A Review

JoAnn E. Manson, MD, DrPH; Carolyn J. Crandall, MD, MS; Jacques E. Rossouw, MD; Rowan T. Chlebowski, MD, PhD; Garnet L. Anderson, PhD; Marcia L. Stefanick, PhD; Aaron K. Aragaki, MS; Jane A. Cauley, DrPH; Gretchen L. Wells, MD, PhD; Andrea Z. LaCroix, PhD; Cynthia A. Thomson, PhD, RD; Marian L. Neuhouser, PhD; Linda Van Horn, PhD; Charles Kooperberg, PhD; Barbara V. Howard, PhD; Lesley F. Tinker, PhD; Jean Wactawski-Wende, PhD; Sally A. Shumaker, PhD; Ross L. Prentice, PhD

IMPORTANCE Approximately 55 million people in the US and approximately 1.1 billion people worldwide are postmenopausal women. To inform clinical practice about the health effects of menopausal hormone therapy, calcium plus vitamin D supplementation, and a low-fat dietary pattern, the Women's Health Initiative (WHI) enrolled 161 808 postmenopausal US women (N = 68 132 in the clinical trials) aged 50 to 79 years at baseline from 1993 to 1998, and followed them up for up to 20 years.

OBSERVATIONS The WHI clinical trial results do not support hormone therapy with oral conjugated equine estrogens plus medroxyprogesterone acetate for postmenopausal women or conjugated equine estrogens alone for those with prior hysterectomy to prevent cardiovascular disease, dementia, or other chronic diseases. However, hormone therapy is effective for treating moderate to severe vasomotor and other menopausal symptoms. These benefits of hormone therapy in early menopause, combined with lower rates of adverse effects of hormone therapy in early compared with later menopause, support initiation of hormone therapy before age 60 years for women without contraindications to hormone therapy who have bothersome menopausal symptoms. The WHI results do not support routinely recommending calcium plus vitamin D supplementation for fracture prevention in all postmenopausal women. However, calcium and vitamin D are appropriate for women who do not meet national guidelines for recommended intakes of these nutrients through diet. A low-fat dietary pattern with increased fruit, vegetable, and grain consumption did not prevent the primary outcomes of breast or colorectal cancer but was associated with lower rates of the secondary outcome of breast cancer mortality during long-term follow-up.

CONCLUSIONS AND RELEVANCE For postmenopausal women, the WHI randomized clinical trials do not support menopausal hormone therapy to prevent cardiovascular disease or other chronic diseases. Menopausal hormone therapy is appropriate to treat bothersome vasomotor symptoms among women in early menopause, without contraindications, who are interested in taking hormone therapy. The WHI evidence does not support routine supplementation with calcium plus vitamin D for menopausal women to prevent fractures or a low-fat diet with increased fruits, vegetables, and grains to prevent breast or colorectal cancer. A potential role of a low-fat dietary pattern in reducing breast cancer mortality, a secondary outcome, warrants further study.

JAMA. doi:10.1001/jama.2024.6542
Published online May 1, 2024.

Supplemental content

CME at jamacmelookup.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: JoAnn E. Manson, MD, DrPH, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Ave, 3rd Floor, Boston, MA 02215 (jmanson@bwh.harvard.edu).

Section Editor: Kristin Walter, MD, Deputy Editor.

Approximately 55 million women in the US[1] and 1.1 billion women worldwide[2] are postmenopausal. The Women's Health Initiative (WHI), the largest study of women's health in the US, enrolled 161 808 postmenopausal women aged 50 to 79 years in studies to inform clinical practice about prevention of chronic diseases, healthy aging, and the health effects of menopausal hormone therapy, calcium plus vitamin D supplementation, and low-fat dietary modification.[3-5] Overall, the WHI was designed to study strategies to prevent cardiovascular disease (CVD), cancer (especially breast and colorectal cancer), and hip fractures.[4] The 4 WHI randomized clinical trials (RCTs) included 68 132 women and were designed to study the benefits and risks of menopausal hormone therapy (2 trials), calcium plus vitamin D supplementation, and dietary modification. The study design, primary aims, and clinical messages of the WHI RCTs are summarized in the **Table**. The **Box** contains a brief list of frequently asked questions about the WHI RCTs. The WHI observational study addressed questions related to disease prevention in a racially, ethnically, and socioeconomically diverse cohort of postmenopausal women.

The WHI began recruitment in 1993, at a time when observational studies had reported that postmenopausal women who took hormone therapy had lower risks of coronary heart disease (CHD),[6,7] osteoporotic fractures,[8] and all-cause mortality[7] compared with postmenopausal women who did not take hormone therapy. Nearly 15 million US women received hormone therapy prescriptions annually,[9] and hormone therapy was increasingly prescribed to prevent CVD and other chronic diseases among women in both early and late menopause.[10] However, no RCTs had evaluated the benefits and risks of hormone therapy for chronic disease prevention.[4,11] Calcium and vitamin D supplements were studied in the WHI because previously they had been tested primarily in populations with osteoporosis or low bone mineral density (BMD),[12,13] and no prior RCT had evaluated the benefits and risks of calcium plus vitamin D supplementation among postmenopausal women with typical fracture risk. A low-fat dietary pattern was studied in the WHI because of epidemiologic evidence that people who consumed more dietary fat and fewer fruits and vegetables had higher rates of breast and colorectal cancer.[14,15] The dietary intervention in the WHI was designed to assess whether a diet low in fat and high in fruits, vegetables, and grains could reduce breast cancer and colorectal cancer. This Review summarizes the results of the 4 WHI RCTs and applications of the WHI results to current clinical practice.

WHI Methods and Design

Eligible postmenopausal women were recruited to participate in 1 of 2 hormone therapy trials and/or the low-fat dietary modification trial in 1993-1998, as detailed elsewhere.[4,5,16-18] After 1 year, women could join the calcium plus vitamin D supplementation trial (**Figure 1**; eFigure 1 in the Supplement). Therefore, depending on eligibility and informed consent, women could participate in a minimum of 1 and a maximum of 3 WHI RCTs; however, participants could participate in only 1 hormone therapy clinical trial. Sex, ethnicity, and race were

Table. Design, Primary Aims, and Clinical Messages of the Women's Health Initiative Randomized Clinical Trials[a]

	CEE plus MPA trial (N = 16 608)	CEE-alone trial (N = 10 739)	Calcium and vitamin D supplementation trial (N = 36 282)	Low-fat dietary modification trial (N = 48 835)
Trial-specific participant eligibility	In situ uterus; current hormone users required a 3-mo discontinuation; successful completion of 1-mo placebo run-in	Prior hysterectomy; current hormone users required a 3-mo discontinuation; successful completion of 1-mo placebo run-in	One year after randomization to hormone therapy and/or low-fat dietary modification trial, women could join the calcium and vitamin D supplementation trial.	Estimated fat intake ≥32% of energy at baseline based on a food frequency questionnaire
Interventions	Oral CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, vs placebo	Oral CEE alone, 0.625 mg/d, vs placebo	1000 mg/d of elemental calcium carbonate and 400 IU/d of vitamin D_3 vs placebo	Total fat reduction (20% of energy goal), increased vegetable and fruit intake (to ≥5 servings/d), and increased grain intake (to ≥6 servings/d) vs usual diet
Primary outcome	CHD	CHD	Hip fracture	Invasive breast cancer, colorectal cancer
Primary safety outcome	Invasive breast cancer	Invasive breast cancer		
Clinical application	Findings do not support use of CEE plus MPA to prevent CHD, stroke, dementia, or other chronic diseases, and the treatment significantly increased breast cancer risk in contrast to CEE alone. Findings in younger women support the FDA-approved indication of hormone therapy for treatment of moderate to severe vasomotor symptoms. Individualized patient care and shared decision-making are essential.	Findings do not support use of CEE alone to prevent CHD, stroke, dementia, or other chronic diseases. Findings in younger women support the FDA-approved indication of hormone therapy for treatment of moderate to severe vasomotor symptoms. Individualized patient care and shared decision-making are essential.	Calcium and vitamin D supplementation did not prevent hip fracture in postmenopausal women. Findings are consistent with the national recommended dietary allowances for intake of calcium (1200 mg/d) and vitamin D (600-800 IU/d) among postmenopausal women. Women not meeting these intake goals may benefit from supplementation.	A low-fat dietary pattern with an increase in vegetables, fruits, and grains did not significantly decrease the incidence of breast or colorectal cancer. A reduction in breast cancer mortality was observed with long-term follow-up. Such a diet provides an option for postmenopausal women seeking to reduce breast cancer risk.

Abbreviations: CEE, conjugated equine estrogens; CHD, coronary heart disease; FDA, Food and Drug Administration; MPA, medroxyprogesterone acetate.

[a] The overall population and eligibility included 68 132 postmenopausal women (mean age, 63 years) recruited at 40 US clinical centers from 1993 to 1998. All trials required that participants be postmenopausal women aged 50 to 79 years with no prior breast cancer, with an unremarkable baseline mammogram, and with expected 3-year or longer survival. Women were excluded for major comorbid conditions or substance use disorders that could affect adherence or safety.

Box. Frequently Asked Questions About the WHI Clinical Trials

Did Age Influence the Effects of Hormone Therapy on Health Outcomes?
In both of the WHI hormone therapy trials, women younger than 60 years had a more favorable benefit-risk ratio than women aged 60 to 69 years or 70 to 79 years. This was primarily because of lower absolute risks of adverse events in younger women but also because of lower hazard ratios for several clinical event outcomes in younger women than in older women (especially in the CEE-alone clinical trial).

Should Postmenopausal Women at Typical Risk of Fracture Routinely Take Calcium Plus Vitamin D Supplements for Fracture Prevention?
In the WHI, calcium and vitamin D supplementation did not significantly reduce hip fracture or other fractures in postmenopausal women. However, supplementation is appropriate for those who do not attain the recommended dietary intakes of these nutrients through food.

What Were the Effects of the WHI Low-Fat Dietary Intervention?
The WHI's low-fat dietary intervention was associated with a small weight loss (1.9 kg at year 1; 0.4 kg after 7 years) and was not associated with adverse effects. Although the intervention did not significantly reduce the incidence of breast cancer or colorectal cancer, a reduced risk of breast cancer mortality among women with breast cancer was observed during long-term follow-up.

Abbreviations: CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate; WHI, Women's Health Initiative.

self-identified. In the clinical trials, the proportion of women who identified as being of Hispanic ethnicity was 4.7% (n = 3231); for race, 10.0% (n = 6826) identified as Black, 84.4% (n = 57 528) as White, 2.1% (n = 1430) as Asian; for the remainder, participants identified as as other race, more than 1 race, or unknown race or the information was not reported. Detailed methods on the design, treatment assignment and delivery, follow-up, outcomes, and statistical analyses are in the eAppendix in the Supplement, and the key design features, primary aims, and clinical applications of each trial are summarized in the Table. Subgroup analyses by age at randomization (50-59, 60-69, or 70-79 years) were prespecified for each trial.

Menopausal Hormone Therapy Trials

The postmenopausal hormone therapy trials tested the benefits and risks of conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) vs placebo among women with uterus in situ and CEE alone vs placebo among women with prior hysterectomy. The primary aim of the postmenopausal hormone therapy clinical trials was to assess whether hormone therapy reduced the primary outcome of CHD compared with placebo. For safety, invasive breast cancer was the primary outcome. The planned duration of the RCTs was 9 years.

Because hormone therapy was established as an effective treatment for menopausal symptoms and this was a US Food and Drug Administration–approved indication,[10,19,20] assessing effects on vasomotor and other symptoms was not a WHI goal. The WHI tested the benefits and risks of oral CEE (0.625 mg/d) combined with MPA (2.5 mg/d) and CEE (0.625 mg/d) alone, the most commonly prescribed hormones at the time of trial inception,[19] for prevention of CHD and other chronic diseases.[21,22]

Estrogen Plus Progestin Among Postmenopausal Women With Uterus In Situ

The WHI RCT on CEE plus MPA included 16 608 women aged 50 to 79 years (mean age, 63.3 years); 5520 of the participants were aged 50 to 59 years. The trial was stopped in 2002, 3.3 years early (per recommendation of the data and safety monitoring board), after a median follow-up of 5.6 years because risks outweighed benefits. Specifically, the data and safety monitoring board concluded that the evidence for breast cancer harm, along with evidence for some increase in CHD, stroke, and pulmonary embolism, outweighed the evidence of benefit for fractures and possible benefit for colorectal cancer compared with placebo.[21] Results for the primary and secondary outcomes are presented in **Figure 2** as hazard ratios (HRs), annualized rates as percentages, and *P* values, along with attributable risks (differences in rates per 10 000 women per year), comparing CEE plus MPA with placebo for both the overall cohort and for younger women aged 50 to 59 years (ages at which women are more likely to seek hormone therapy for menopausal symptoms).[22] Incidence rates by 10-year age groups for CEE plus MPA vs placebo are shown in **Figure 3**, and the HRs for all 10-year age groups are shown in eFigure 2 in the Supplement.

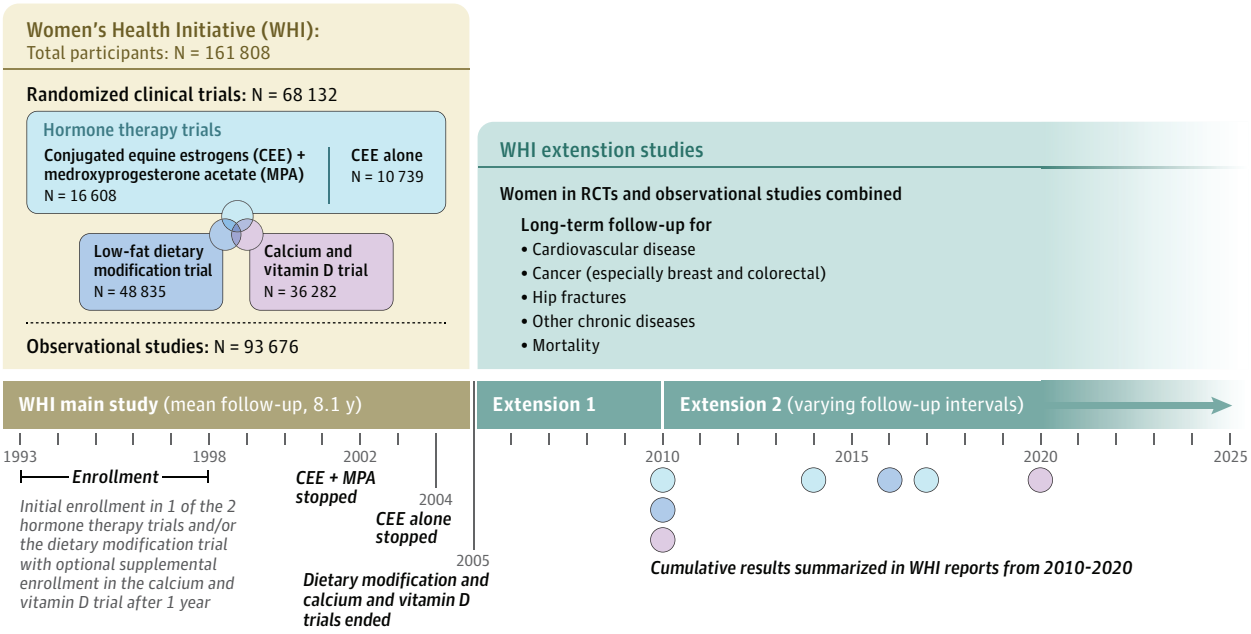
Effects of CEE Plus MPA on CVD Outcomes

When the trial was stopped early in 2002, CEE plus MPA, compared with placebo, significantly increased the prespecified secondary outcomes of stroke (annualized rate, 0.33% vs 0.24%; HR, 1.37; 95% CI, 1.07-1.76) and pulmonary embolism (0.18% vs 0.09%; HR, 1.98; 95% CI, 1.36-2.87) (Figure 2). Compared with placebo, CEE plus MPA nonsignificantly increased the primary outcome of CHD by 18% (0.41% vs 0.35%; HR, 1.18; 95% CI, 0.95-1.45) and had no significant effect on all-cause mortality (0.52% vs 0.53%; HR, 0.97; 95% CI, 0.81-1.16). (Figure 2).[21,22] Hazard ratios had similar patterns by age group (Figure 2; eFigure 2 in the Supplement), but absolute and attributable risks were lower in women aged 50 to 59 years compared with women aged 60 years or older (Figure 3; eFigure 2 in the Supplement). Effects of hormone therapy by age subgroups were prespecified in the trial protocol; these interactions were not statistically significant for CEE plus MPA.[22,23] After the intervention ended, at a cumulative follow-up of 13 years, CVD risks returned to baseline and there were no significant differences in HRs for all-cause mortality across age groups and no statistically significant interactions by age.[22] Women at lower baseline CVD risk, such as those with lower low-density lipoprotein cholesterol levels (≤130 mg/dL)[24] or without metabolic syndrome[25] at enrollment, tended to have more favorable CVD outcomes while taking hormone therapy than those at higher cardiometabolic risk, although these subgroup analyses were not prespecified in the protocol.

Effects of CEE Plus MPA on Cancer Outcomes

Breast cancer was the primary outcome for safety monitoring, and breast cancer mortality was a prespecified secondary outcome in the protocol. Compared with placebo, CEE plus MPA significantly increased breast cancer incidence by 24% at 5.6 years (0.43% vs 0.35% annually; HR, 1.24; 95% CI, 1.01-1.53).[22] At 20-year follow-

Figure 1. Design of the Women's Health Initiative (WHI) Randomized Clinical Trials (RCTs) and Observational Study



Intervention and postintervention phases of the RCTs through Extension 1 (2010) and at varying follow-up intervals during Extension 2. Cumulative results were summarized by key WHI reports, as indicated by trial color-coded symbols on the timeline. The RCT rectangles are not drawn to scale, but the sample size of each trial is included within the relevant rectangle.

up, CEE plus MPA, compared with placebo, significantly increased breast cancer incidence (0.45% vs 0.36%; HR, 1.28; 95% CI, 1.13-1.45).[26] Breast cancer mortality was significantly increased through 11-year follow-up,[27] but this effect was not statistically significant at 20-year follow-up.[26] CEE plus MPA also increased mammographic density,[28] frequency of abnormal mammograms,[29,30] and frequency of breast biopsies.[30] These results suggested that CEE plus MPA stimulated breast cancer growth and delayed breast cancer diagnosis.[29] Breast cancer HRs were similar by age (P = .68 for interaction by age),[22] but women 50 to 59 years old had lower attributable risks (Figure 2; eFigure 2 in the Supplement).[22]

Colorectal cancer and endometrial cancer were secondary outcomes. Although CEE plus MPA was initially associated with a significant 39% lower colorectal cancer incidence compared with placebo (0.10% vs 0.16%; HR, 0.61; 95% CI, 0.42-0.87),[31] the larger tumors at diagnosis in the CEE plus MPA group suggested delayed detection rather than clinical benefit,[32] and cumulative results over extended follow-up were no longer significantly reduced.[22] Compared with placebo, CEE plus MPA significantly reduced endometrial cancer incidence by 33% (0.07% vs 0.10%; HR, 0.67; 95% CI, 0.49-0.91) through long-term follow-up.[22,33]

Effects of CEE Plus MPA on Hip Fracture, Global Index, and Other End Points

Compared with placebo, CEE plus MPA significantly reduced hip fractures by 33% (0.11% vs 0.17%; HR, 0.67; 95% CI, 0.47-0.95) (Figure 2).[22] A lower rate of hip fracture in the CEE plus MPA group compared with placebo (0.23% vs 0.28%; HR, 0.81; 95% CI, 0.68-0.97) persisted after the intervention ended and at 13-year of cumulative follow-up.[22] Compared with placebo, CEE plus MPA increased rates of a prespecified global index, a composite outcome consisting of CHD, stroke, pulmonary embolism, hip fracture, breast cancer, colorectal cancer, endometrial cancer, or death from other causes (time to first event). Attributable risks from CEE plus MPA, compared with placebo, were 20 excess events for every 10 000 women per year in the overall cohort, 12 excess events per 10 000 women aged 50 to 59 years per year, and 38 excess events per 10 000 women aged 70 to 79 years per year (Figure 2 and Figure 3; eFigure 2 in the Supplement).[22] After the intervention was completed, at 13-year follow-up, CEE plus MPA had no significant effect on the global index outcome compared with placebo.[22] Compared with placebo, CEE plus MPA decreased diabetes (0.72% vs 0.88%; HR, 0.81; 95% CI, 0.70-0.94 [a self-reported and exploratory outcome]) and increased gallbladder disease (1.31% vs 0.84%; HR, 1.57; 95% CI, 1.36-1.80 [a self-reported safety outcome]).[22] Among 4532 women aged 65 years or older, compared with placebo, CEE plus MPA increased probable dementia incidence, assessed by in-person cognitive function testing (0.45% vs 0.22% annually; HR, 2.05; 95% CI, 1.21-3.48).[34] A subsequent WHI ancillary study among women randomized to CEE plus MPA at ages 50 to 55 years that used telephone-administered cognitive assessments performed about 7 years after the trial ended reported no effect of CEE plus MPA on cognition compared with placebo.[35]

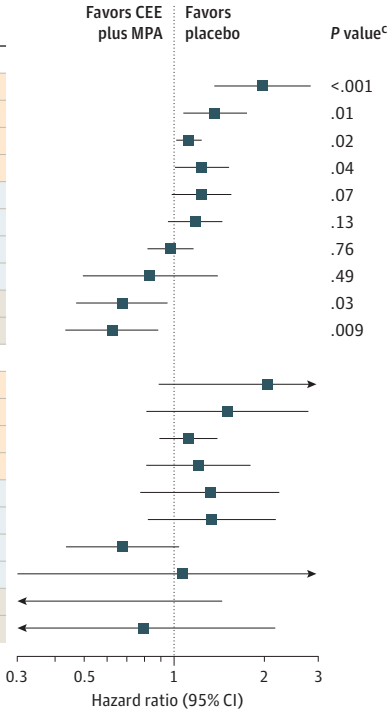
Estrogen Alone Among Postmenopausal Women With Prior Hysterectomy

Among 10 739 women aged 50 to 79 years (mean age, 63.6 years) with prior hysterectomy, the WHI RCT tested whether oral CEE alone (0.625 mg/d) reduced the primary outcome of CHD compared with placebo. A total of 3313 participants were aged 50 to 59 years. The trial was stopped 1 year early in 2004 by the National Institutes of

Figure 2. Health Outcomes in the Full Cohort and in Women Aged 50 to 59 Years in the Women's Health Initiative Hormone Therapy Trials

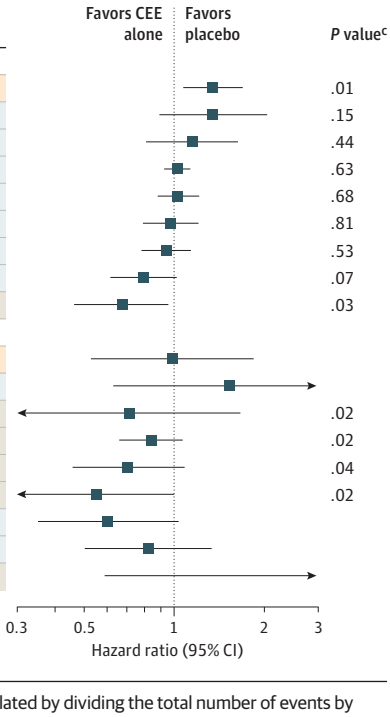
A CEE plus MPA

Health outcomes	Annualized rate, No. (%)[a] CEE plus MPA	Placebo	Difference per 10 000 person-years[b]	Hazard ratio (95% CI)	*P* value[c]
CEE plus MPA trial, full cohort (N = 16 608)					
Pulmonary embolism[d]	87 (0.18)	41 (0.09)	+9	1.98 (1.36-2.87)	<.001
Stroke[d]	159 (0.33)	109 (0.24)	+9	1.37 (1.07-1.76)	.01
Global index[d]	876 (1.89)	736 (1.68)	+20	1.12 (1.02-1.24)	.02
Invasive breast cancer[e]	206 (0.43)	155 (0.35)	+9	1.24 (1.01-1.53)	.04
Myocardial infarction[d]	168 (0.35)	129 (0.29)	+6	1.24 (0.98-1.56)	.07
Coronary heart disease[e]	196 (0.41)	159 (0.35)	+6	1.18 (0.95-1.45)	.13
All-cause mortality[d]	250 (0.52)	238 (0.53)	-1	0.97 (0.81-1.16)	.76
Endometrial cancer[d]	27 (0.06)	30 (0.07)	-1	0.83 (0.49-1.40)	.49
Hip fracture[d]	53 (0.11)	75 (0.17)	-6	0.67 (0.47-0.95)	.03
Colorectal cancer[d]	50 (0.10)	75 (0.17)	-6	0.62 (0.43-0.89)	.009
CEE plus MPA trial, age 50-59 y (n = 5520)					
Pulmonary embolism[d]	18 (0.11)	8 (0.05)	+6	2.05 (0.89-4.71)	
Stroke[d]	26 (0.15)	16 (0.10)	+5	1.51 (0.81-2.82)	
Global index[d]	170 (1.03)	141 (0.91)	+12	1.12 (0.89-1.40)	
Invasive breast cancer[e]	55 (0.33)	42 (0.27)	+6	1.21 (0.81-1.80)	
Myocardial infarction[d]	32 (0.19)	23 (0.15)	+4	1.32 (0.77-2.25)	
Coronary heart disease[e]	38 (0.23)	27 (0.17)	+5	1.34 (0.82-2.19)	
All-cause mortality[d]	35 (0.21)	48 (0.31)	-10	0.67 (0.43-1.04)	
Endometrial cancer[d]	6 (0.04)	5 (0.03)	0	1.07 (0.33-3.53)	
Hip fracture[d]	1 (0.01)	5 (0.03)	-3	0.17 (0.02-1.45)	
Colorectal cancer[d]	7 (0.04)	8 (0.05)	-1	0.79 (0.29-2.18)	



B CEE alone

Health outcomes	Annualized rate, No. (%)[a] CEE alone	Placebo	Difference per 10 000 person-years[b]	Hazard ratio (95% CI)	*P* value[c]
CEE-alone trial, full cohort (N = 10 739)					
Stroke[d]	169 (0.45)	130 (0.34)	+11	1.35 (1.07-1.70)	.01
Pulmonary embolism[d]	52 (0.14)	39 (0.10)	+4	1.35 (0.89-2.05)	.15
Colorectal cancer[d]	65 (0.17)	58 (0.15)	+2	1.15 (0.81-1.64)	.44
Global index[d]	753 (2.08)	755 (2.04)	+4	1.03 (0.93-1.13)	.63
All-cause mortality[d]	301 (0.80)	299 (0.77)	+3	1.03 (0.88-1.21)	.68
Myocardial infarction[d]	164 (0.44)	173 (0.45)	-1	0.97 (0.79-1.21)	.81
Coronary heart disease[e]	204 (0.55)	222 (0.58)	-3	0.94 (0.78-1.14)	.53
Invasive breast cancer[e]	104 (0.28)	135 (0.35)	-7	0.79 (0.61-1.02)	.07
Hip fracture[d]	48 (0.13)	74 (0.19)	-6	0.67 (0.46-0.96)	.03
CEE-alone trial, age 50-59 y (n = 3313)					
Stroke[d]	19 (0.16)	21 (0.17)	−1	0.99 (0.53-1.85)	
Pulmonary embolism[d]	12 (0.10)	8 (0.06)	+3	1.53 (0.63-3.75)	
Colorectal cancer[d]	9 (0.07)	13 (0.10)	-3	0.71 (0.30-1.67)	.02
Global index[d]	117 (0.98)	142 (1.17)	-19	0.84 (0.66-1.07)	.02
All-cause mortality[d]	35 (0.29)	50 (0.40)	-11	0.70 (0.46-1.09)	.04
Myocardial infarction[d]	17 (0.14)	31 (0.25)	-11	0.55 (0.31-1.00)	.02
Coronary heart disease[e]	21 (0.17)	35 (0.28)	-11	0.60 (0.35-1.04)	
Invasive breast cancer[e]	29 (0.24)	36 (0.29)	-5	0.82 (0.50-1.34)	
Hip fracture[d]	5 (0.04)	1 (0.01)	+3	5.01 (0.59-42.91)	



CEE indicates conjugated equine estrogens; MPA, medroxyprogesterone acetate. Full cohort outcomes are ordered from strongest statistical evidence for harm ($P \leq .05$; peach shading) to strongest evidence for benefit ($P \leq .05$; gray shading). Outcomes for age 50 to 59 years follow the same order as the full cohort; shading is identical unless superseded by statistically significant evidence for an age trend ($P \leq .05$ for interaction). Data are from Manson et al.[22] Summaries correspond to trial intervention phases (medians: 5.6 years for CEE plus MPA; 7.2 years for CEE alone).

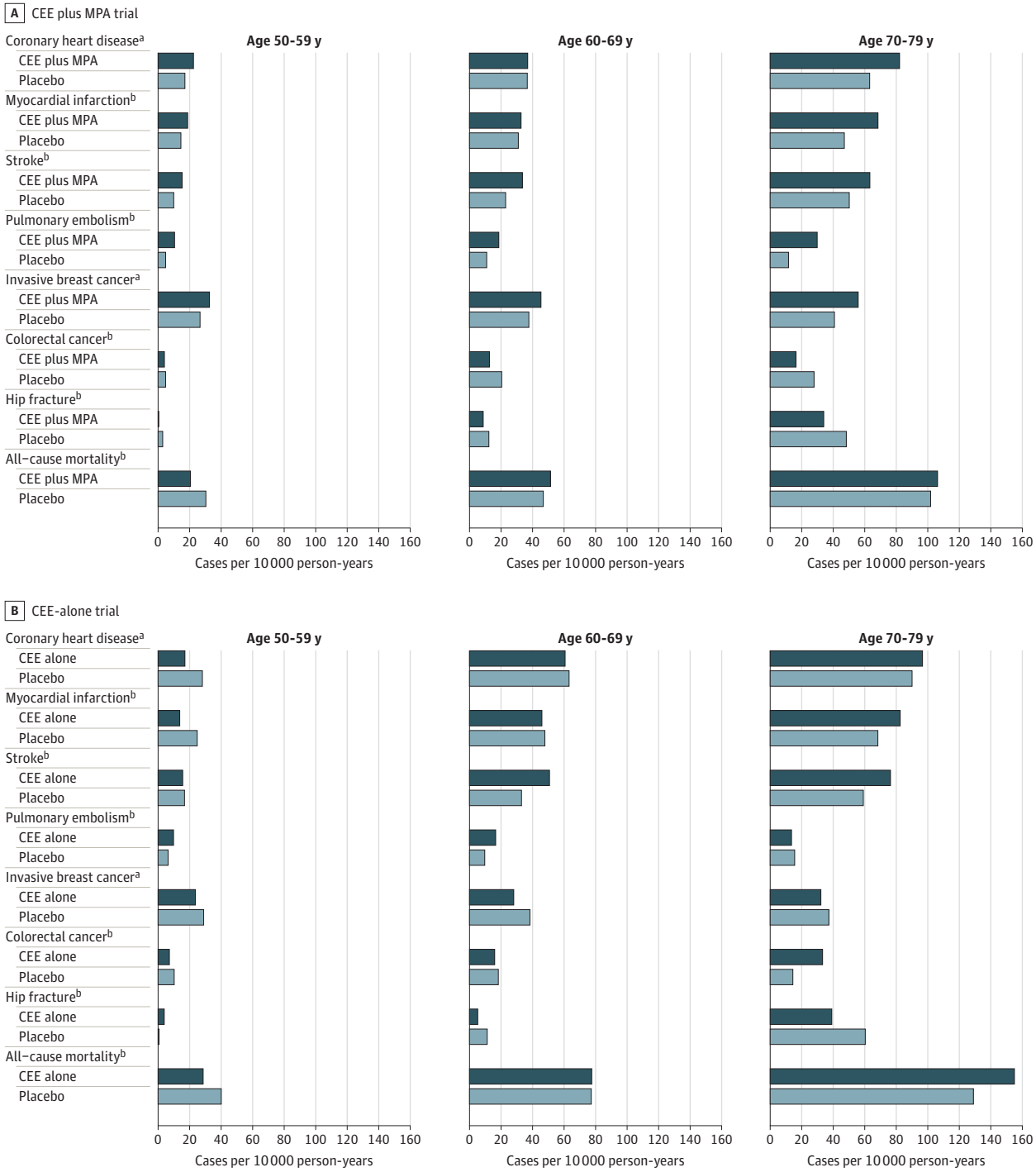
[a]Annualized rates were calculated by dividing the total number of events by total follow-up time in years and are expressed as percentages.

[b]Difference in estimated absolute excess risks (hormone therapy − placebo).

[c]*P* value for full cohort or significant interaction for trend by age group (other trends by age are nonsignificant).

[d]Secondary end points. [e]Primary end points.

Figure 3. Absolute Risks of Health Outcomes by 10-Year Age Groups in the Women's Health Initiative Hormone Therapy Trials



CEE indicates conjugated equine estrogens; MPA, medroxyprogesterone acetate. In the CEE plus MPA trial, no age interactions were statistically significant. In the CEE-alone trial, age interactions were statistically significant ($P \leq .05$ for interaction) for colorectal cancer, global index, all-cause mortality, and myocardial infarction (see Figure 2). Data are from Manson et al.[22]

Summaries correspond to the intervention phase of each trial, a median of 5.6 years in the CEE plus MPA trial and a median of 7.2 years in the CEE-alone trial.

[a]Primary end points.

[b]Secondary end points.

Health at a median follow-up of 7.2 years due to increased risk of stroke and no overall benefit for CHD (Figure 2 and Figure 3; eFigure 2 in Supplement).[36]

Effects of Estrogen Alone on CVD

During the intervention phase, compared with placebo, women in the overall cohort randomized to CEE compared with placebo had a 6% de-

crease in CHD (primary end point) and a 3% decrease in myocardial infarction (secondary end point), differences that were not statistically significant. During the intervention, compared with placebo, CEE significantly increased rates of stroke (secondary outcome) (0.45% vs 0.34%; HR, 1.35; 95% CI, 1.07-1.70). Compared with placebo, CEE nonsignificantly increased the secondary outcome of pulmonary embolism (0.14% vs 0.10% annually; HR, 1.35; 95% CI, 0.89-2.05) and had no effect on the secondary outcome of all-cause mortality (0.80% vs 0.77%; HR, 1.03; 95% CI, 0.88-1.21) (Figure 2).[22,36] There were statistically significant prespecified interactions by age for the effects of CEE on myocardial infarction compared with placebo (P = .02 for interaction), and all-cause mortality (P = .04 for interaction), reflecting more favorable results in younger women and more adverse effects in older women. Absolute risks were also lower in younger woman than in older women.[22] (Figure 3; eFigure 2 in the Supplement). No significant interactions by age were identified for total CHD, stroke, or pulmonary embolism. During the postintervention follow-up, risks of stroke, pulmonary embolism, CHD, and all-cause mortality were not significantly different between the CEE and placebo groups.[22] The favorable interaction by age for younger (aged 50-59 years) women compared with older women for myocardial infarction[22,37,38] persisted in follow-up after the intervention was completed (P = .007 for interaction by age). Also, at 18-year follow-up, 11 years after the intervention ended, compared with placebo, CEE was associated with reduced all-cause mortality among the 1129 women aged 50 to 59 years with prior bilateral oophorectomy (0.56% vs 0.79% annually; HR, 0.68; 95% CI, 0.48-0.96; P = .03 for interaction by age).[39] In an exploratory substudy conducted among women aged 50 to 59 years, 1.3 years after the intervention was completed and after a mean of 7.4 years of treatment, coronary artery calcium values were significantly lower among those randomized to CEE alone compared with those randomized to placebo.[40]

Effects of Estrogen Alone on Cancer

Among women with prior hysterectomy randomized to CEE alone compared with placebo, the rate of breast cancer, the primary outcome for safety, was nonsignificantly lower in the CEE group (0.28% vs 0.35%; HR, 0.79; 95% CI, 0.61-1.02) during the intervention (Figure 2).[22,41,42] There were no significant differences in outcomes by age group (Figure 2). At 10.7 years of follow-up, rates of breast cancer were significantly lower in the CEE group compared with the placebo group (0.27% vs 0.35%; HR, 0.77; 95% CI, 0.62-0.95),[38] with significant risk reductions persisting at 12- and 20-year follow-up.[26,41] Significant reductions in deaths from breast cancer among women assigned CEE alone vs placebo were observed at 12-year follow-up[41] and persisted in analyses at 20-year follow-up (0.031% vs 0.046%; HR, 0.60; 95% CI, 0.37-0.97).[26] Thus, the effects of CEE alone and CEE plus MPA on breast cancer were divergent during long-term follow-up, with women assigned to CEE alone having lower incidence of and mortality from breast cancer compared with those assigned to placebo, and women assigned to CEE plus MPA having higher breast cancer incidence compared with those assigned to placebo.[22,26] There were no significant differences in rates of colorectal cancer during the intervention (Figure 2) or at 13-year cumulative follow-up.[22]

Effects of Estrogen Alone on Hip Fracture, Global Index, and Other End Points

Among all women randomized to CEE vs placebo, during the median 7.2-year intervention, CEE reduced rates of hip fracture by 33% (0.13% vs 0.19%; HR, 0.67; 95% CI, 0.46-0.96) compared with placebo (Figure 2).[22] After the intervention, at 13-year follow-up, there was no significant effect of CEE compared with placebo on hip fracture (0.22% vs 0.24%; HR, 0.91; 95% CI, 0.72-1.15). In the overall cohort, there was no effect of CEE on the global index, which consisted of the same outcomes as for CEE plus MPA except endometrial cancer (due to prior hysterectomy) (Figure 2). However, in prespecified analyses, more favorable trends for younger women than older women were observed during the intervention phase (P = .02 for interaction by age), with 19 fewer global index events per 10 000 person-years among women aged 50 to 59 years randomized to CEE alone vs placebo compared with 51 excess global index events per 10 000 person-years for women aged 70 to 79 years randomized to CEE alone vs placebo (Figure 2; eFigure 2 in the Supplement).[22] After 13-year follow-up, the age differences in the global index persisted (P = .01 for interaction by age).[22] Compared with placebo, during the intervention, those randomized to CEE had 14% (95% CI, 2%-24%) lower rates of type 2 diabetes (exploratory outcome) and 55% (95% CI, 34%-79%) higher rates of gallbladder disease (safety outcome).[22] In the WHI Memory Study, among women aged 65 years or older (n = 2947), those randomized to CEE alone had a 49% (95% CI, −17% to 166%) increased rate of dementia as assessed by in-person cognitive function testing compared with those randomized to placebo, but this difference was not statistically significant.[34] A subsequent study of CEE alone and cognition among women randomized into the WHI at ages 50 to 55 years, using telephone-administered cognitive assessments performed about 7 years after the trial ended, reported neither benefit nor risk of CEE alone on cognition among women in early menopause.[35]

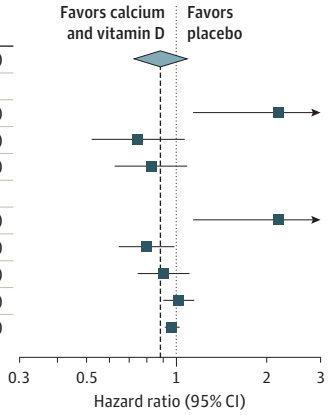
Key Clinical Messages From the WHI Hormone Therapy Trials

Results from the WHI do not support either CEE plus MPA or CEE alone for preventing CHD, stroke, dementia, or other chronic diseases in postmenopausal women. Younger menopausal women typically have low absolute risks of most of these chronic diseases, with low hormone therapy–related attributable risks in early menopause (generally less than 1 additional adverse event per 1000 women per year), and younger menopausal women may derive significant quality-of-life benefits from symptom relief. Differences in breast cancer outcomes with combination estrogen plus progestin vs estrogen alone have clinical implications, with risk increasing with longer duration of use of combination therapy. The WHI hormone therapy results should not be extrapolated to decision-making for women with premature or early onset of menopause (ie, age ≤45 years) because these individuals were not studied in the WHI and current guidelines recommend hormone therapy until the typical age of menopause onset in these settings (in the absence of contraindications).[19] Currently available formulations of hormone therapy (such as estradiol) include lower doses and transdermal routes of delivery, which may have lower risks of thrombotic events,[19,20] although these differences have not been demonstrated in RCTs. Individualized patient care and shared decision-making should be implemented, taking into account patient preferences, severity of symptoms, and cardiometabolic and general health status.

Figure 4. Fracture Outcomes in the Women's Health Initiative Calcium and Vitamin D Supplementation Trial

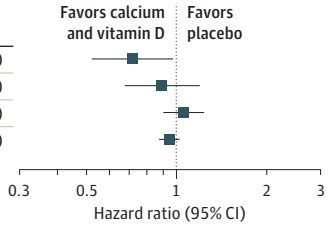
A Intention-to-treat analysis

Fracture outcomes (N = 36 282)	Annualized rate, No. (%)[a] Calcium and vitamin D	Placebo	Difference per 10 000 person-years[b]	Hazard ratio (95% CI)
Hip[c]	175 (0.14)	199 (0.16)	-2	0.88 (0.72-1.08)
Age, y (prespecified)				
50-59	29 (0.06)	13 (0.03)	+3	2.17 (1.13-4.18)
60-69	53 (0.09)	71 (0.13)	-4	0.74 (0.52-1.06)
70-79	93 (0.44)	115 (0.54)	-10	0.82 (0.62-1.08)
Age, y (post hoc)				
50-59	29 (0.06)	13 (0.03)	+3	2.17 (1.13-4.18)
60-79	146 (0.19)	186 (0.24)	-5	0.79 (0.64-0.98)
Clinical vertebral[d]	181 (0.14)	197 (0.15)	-1	0.90 (0.74-1.10)
Lower arm or wrist[d]	565 (0.44)	557 (0.44)	0	1.01 (0.90-1.14)
Total[d]	2102 (1.64)	2158 (1.70)	-6	0.96 (0.91-1.02)



B Adherence analysis[e]

Fracture outcomes (N = 36 282)	Annualized rate, No. (%)[a] Calcium and vitamin D	Placebo	Difference per 10 000 person-years[b]	Hazard ratio (95% CI)
Hip[c]	68 (0.10)	99 (0.14)	-4	0.71 (0.52-0.97)
Clinical vertebral[d]	91 (0.13)	104 (0.15)	-2	0.89 (0.67-1.19)
Lower arm or wrist[d]	312 (0.45)	308 (0.43)	+2	1.05 (0.90-1.23)
Total[d]	1119 (1.63)	1222 (1.72)	-9	0.94 (0.87-1.02)



Follow-up during the mean 7.0-year intervention phase. Data are from Jackson et al.[44]

[a]Annualized rates were calculated by dividing the total number of events by total follow-up time in years and are expressed as percentages.

[b]Difference in estimated absolute excess risks (calcium and vitamin D supplementation minus placebo).

[c]Primary end point.

[d]Secondary end points.

[e]Sensitivity analyses; participants were allowed to contribute follow-up time until 6 months after the first visit at which nonadherence (used <80% of study pills) was detected.

Calcium and Vitamin D Supplementation Trial

The WHI calcium and vitamin D supplementation trial was designed to test whether calcium plus vitamin D supplementation, compared with placebo, lowered the risk of hip fracture (primary end point) in postmenopausal women at typical fracture risk who were not preselected for low BMD. The clinical trial also tested whether calcium plus vitamin D supplementation lowered the risk of total fractures and colorectal cancer (secondary end points). Participants in the hormone therapy trial or the low-fat dietary modification trial were invited to join the calcium plus vitamin D supplementation trial beginning at their first annual follow-up visit.[43]

In this trial, 36 282 women were randomly assigned to 1000 mg/d of elemental calcium carbonate with 400 IU/d of vitamin D_3 or placebo. Personal supplementation of calcium (up to an additional 1000 mg/d) and/or vitamin D (initially up to 600 IU/d; later up to 1000 IU/d)[44] was permitted. The mean baseline intakes (diet and supplements) were 1150 mg/d of calcium and 370 IU/d of vitamin D.

Fracture and Bone Health

During the 7-year intervention, compared with placebo, calcium plus vitamin D supplementation did not significantly affect hip fractures rates (0.14% vs 0.16% annually; HR, 0.88; 95%CI, 0.72-1.08) (**Figure 4**). However, a reduction in hip fracture was observed among women aged 60 years or older (0.19% vs 0.24%; HR, 0.79; 95% CI, 0.64-0.98), and an increased risk of hip fracture was observed among younger women (HR, 2.17; 95% CI, 1.13-4.18; *P* = .05 for interaction by age) (analyses stratified by 10-year age groups were prespecified but analysis of <60 years vs ≥60 years was post hoc). Fractures at other sites were not significantly reduced. In sensitivity analyses among women who were adherent (ie, who took ≥80% of their study pills), calcium plus vitamin D supplementation reduced hip fracture in the overall cohort (0.10% vs 0.14%; HR, 0.71; 95% CI, 0.52-0.97) (Figure 4). Among women not taking calcium supplements outside of study interventions who were randomized to calcium plus vitamin D supplementation, the HR for hip fracture was 0.70 (95% CI, 0.51-0.98; *P* = .11 interaction by personal calcium supplementation [none, <500 mg/d, or ≥500 mg/d]) in post hoc analyses.[44] Women receiving calcium plus vitamin D supplementation had greater preservation of total hip BMD than women assigned to placebo but no statistically significant differences in bone density were observed for clinical spine or whole-body BMD.

Over the cumulative follow-up of 11.1 years (intervention plus postintervention), there was no statistically significant effect of calcium plus vitamin D supplementation on hip fractures.[45] However, compared with placebo, calcium plus vitamin D supplementation reduced hip fracture among women who had been adherent during the trial (HR, 0.77; 95% CI, 0.60-0.99).

Colorectal Cancer

During the 7-year intervention and follow-up, the incidence of invasive colorectal cancer did not significantly differ between women assigned to calcium plus vitamin D supplementation and those assigned to placebo (0.13% vs 0.12% annually; HR, 1.08; 95% CI,

0.86-1.34).[46] Similarly, there were no statistically significant differences in the incidence of invasive colorectal cancer at a mean follow-up of 11.1 years or in sensitivity analyses limited to women who were adherent to study medication during the trial.[45,46]

All-Cause Mortality and Other Outcomes

Compared with placebo, calcium plus vitamin D supplementation had no statistically significant effect on total mortality during the intervention period (0.58% vs 0.63%; HR, 0.91; 95% CI, 0.83-1.01) (secondary end point)[47] or over extended follow-up (0.88% vs 0.91%; HR, 0.96; 95% CI, 0.90-1.03).[45] Compared with placebo, calcium plus vitamin D supplementation also had no statistically significant effect on cardiovascular events during the intervention[48] or cumulative follow-up[45] and had no effects on coronary artery calcium measurements performed in a subgroup (n = 754) at the end of the intervention phase in 2005.[49] Compared with placebo, calcium plus vitamin D supplementation had no effect on invasive breast cancer, a secondary end point, during the intervention or cumulatively but reduced the risk of in situ breast cancer, an exploratory outcome (0.10% vs 0.12% annually; HR, 0.82; 95% CI, 0.68-0.99).[45] Compared with placebo, supplementation significantly increased the risk of kidney stones (0.35% vs 0.30% annually; HR, 1.17; 95% CI, 1.02-1.34) (safety end point).[50]

Key Clinical Messages From the WHI Calcium and Vitamin D Supplementation Trial

Overall, calcium plus vitamin D supplementation did not significantly reduce hip fractures in postmenopausal women compared with placebo among women not selected on the basis of low BMD. However, several lines of evidence in the clinical trial suggested bone health benefits of calcium plus vitamin D supplementation, including greater preservation of total hip BMD and reduction in hip fractures among women aged 60 years or older (who are more likely to have osteoporotic fracture) and among women adherent with study medications. Compared with placebo, calcium plus vitamin D supplementation had no effect on lower arm or wrist fracture, total fracture, colorectal cancer, CVD, or total mortality. The absolute increase in the risk of kidney stones among women randomized to calcium plus vitamin D supplementation was small (0.35% vs 0.30% annually; HR, 1.17; 5 extra cases per 10 000 women per year). Although these results did not support routine calcium plus vitamin D supplementation for postmenopausal women at typical risk of fracture and without regard to bone density, the Institute of Medicine recommends a dietary allowance for calcium of 1200 mg/d and for vitamin D of 600 to 800 IU/d for maintenance of bone health in postmenopausal women,[51] either with diet alone or in combination with supplements.

Dietary Modification Trial

This clinical trial tested whether a low-fat dietary pattern reduced the risk of invasive breast cancer or colorectal cancer (primary end points), and CHD (secondary end point).[4] The intervention was designed to reduce total fat consumption to 20% of total energy intake, increase vegetable and fruit intake to at least 5 servings per day, and increase grain intake to at least 6 servings per day. The diet intervention was not designed to change total caloric intake.

The low-fat dietary pattern intervention was a median 8.5-year behavioral intervention, delivered primarily by registered dietitians in small-group sessions (eTable in the Supplement). At 1-year follow-up, change from baseline in self-reported dietary intake in the intervention group (n = 19 541), compared with the usual-diet comparison group (n = 29 294),[52] showed significantly reduced intakes of each of the major subtypes of fat (saturated, monounsaturated, polyunsaturated, and total *trans* fatty acid), no significant differences in percentage reductions in each of these fat subtypes, and significant increases in vegetables, fruits, and grains (eFigure 3 in the Supplement). Differences in dietary fat intake persisted throughout the intervention period (absolute reductions of 10.7%, 9.5%, and 8.1% at years 1, 3, and 6, respectively) and modestly persisted after the intervention (3.6%).[53] The intervention group lost weight (a mean of 1.9 kg) compared with the control group at year 1 ($P < .001$). This difference was attenuated at a mean follow-up of 7.5 years, but a small (0.4-kg) statistically significant weight difference was evident throughout the intervention period.[54,55] A modestly higher physical activity level also was observed in the intervention group during trial follow-up; the intervention group had a 4% (95% CI, 2%-6%) higher mean number of episodes per week of moderate or vigorous recreational physical activity.[56]

Breast and Colorectal Cancer

Compared with usual diet, the low-fat diet high in fruits and vegetables did not significantly reduce breast cancer (0.42% vs 0.46%; HR, 0.92; 95% CI, 0.84-1.01; $P = .09$) or colorectal cancer (0.13% vs 0.12%; HR, 1.07; 95% CI, 0.90-1.27; $P = .45$) at 8.5-year follow-up (**Figure 5**).[52,58]

In post hoc analyses, during the intervention phase, all-cause mortality after a breast cancer diagnosis was reduced ($P = .02$) (Figure 5).[59] At 20-year cumulative follow-up, a reduction in breast cancer mortality, a secondary outcome, was observed (0.037% vs 0.047% annually; HR, 0.79; 95% CI, 0.64-0.97 $P = .02$).[57] Risk reductions were primarily in women with higher waist circumference and at higher cardiometabolic risk.[60] The breast cancer findings were likely mediated by a significant reduction in cancers that were estrogen receptor positive, progesterone receptor negative, which typically have a poorer prognosis.[57,59]

Coronary Heart Disease

Coronary heart disease, defined as nonfatal myocardial infarction plus coronary death, was not significantly reduced by the low-fat dietary pattern (Figure 5). However, compared with placebo, low-density lipoprotein cholesterol was slightly lower (by 3.55 mg/dL [$P < .05$]) in the intervention group.[52,61] Differential rates of statin use in the intervention group vs the comparison group (≥5% higher in the comparison group based on serial medication inventories) may have obscured the ability to detect differences in CHD outcomes between treatment groups (postrandomization confounding).[62]

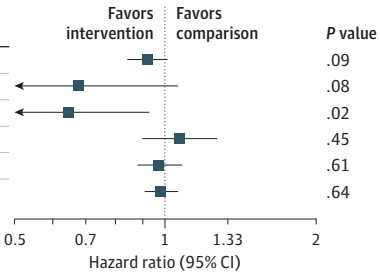
Other Outcomes

The dietary intervention did not significantly reduce endometrial, ovarian, or total cancer compared with usual diet.[63] The dietary intervention also did not significantly reduce stroke, coronary revascularization, or total CVD outcomes compared with usual diet.[52,61] In post hoc analyses, both serum insulin and glucose were lower in

Figure 5. Clinical Outcomes in the Women's Health Initiative Dietary Modification Trial

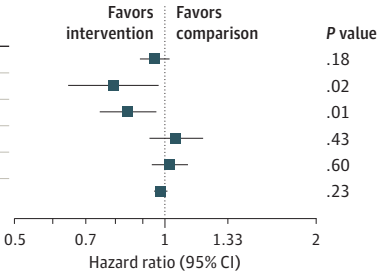
A Intervention phase

Clinical outcomes (N = 48 835)	Annualized rate, % (No.)[a]		Difference per 10 000 person-years[b]	Hazard ratio (95% CI)	P value
	Intervention	Comparison			
Invasive breast cancer[c]	0.42 (671)	0.46 (1093)	-4	0.92 (0.84-1.01)	.09
Breast cancer mortality[d]	0.016 (27)	0.024 (61)	-1	0.67 (0.43-1.06)	.08
Death (all causes) after breast cancer[e]	0.025 (40)	0.038 (94)	-1	0.64 (0.44-0.93)	.02
Colorectal cancer[c]	0.13 (216)	0.12 (303)	+1	1.07 (0.90-1.27)	.45
Coronary heart disease[d]	0.37 (591)	0.38 (914)	-1	0.97 (0.88-1.08)	.61
All-cause mortality[d]	0.59 (989)	0.61 (1520)	-2	0.98 (0.91-1.06)	.64



B Cumulative follow-up

Clinical outcomes (N = 48 835)	Annualized rate, % (No.)[a]		Difference per 10 000 person-years[b]	Hazard ratio (95% CI)	P value
	Intervention	Comparison			
Invasive breast cancer[c]	0.44 (1299)	0.46 (2075)	-2	0.95 (0.89-1.02)	.18
Breast cancer mortality[d]	0.037 (132)	0.047 (251)	-1	0.79 (0.64-0.97)	.02
Death (all causes) after breast cancer[e]	0.12 (359)	0.14 (652)	-2	0.84 (0.74-0.96)	.01
Colorectal cancer[c]	0.14 (417)	0.13 (604)	+1	1.05 (0.93-1.19)	.43
Coronary heart disease[d]	0.39 (929)	0.39 (1386)	0	1.02 (0.94-1.11)	.60
All-cause mortality[d]	1.49 (5337)	1.52 (8161)	-3	0.98 (0.95-1.01)	.23



Follow-up during the median 8.5-year intervention phase and over a cumulative follow-up of 19.6 years for most outcomes (see Methods section of text for details). Data are from Prentice et al[52] and Chlebowski et al.[57]

[a]Annualized rates were calculated by dividing the total number of events by total follow-up time in years and are expressed as percentages. Randomized allocation ratio was 40% for the intervention and 60% for the comparison group; annualized rates precede number of events.

[b]Difference in estimated absolute excess risks (intervention minus comparison).

[c]Primary end points.

[d]Secondary end points.

[e]Exploratory end point.

the intervention group than the comparison group during follow-up, and type 2 diabetes requiring insulin was also lower among participants assigned to the intervention group, a potential benefit related to glucose tolerance that requires further study.[52,64]

Key Clinical Messages From the WHI Diet Modification Trial

In the WHI, a low-fat dietary pattern with increased intake of vegetables, fruits, and grains did not significantly decrease the incidence of breast cancer or colorectal cancer (primary outcomes) or CHD (secondary outcome) in postmenopausal women. However, after 20 years of follow-up, lower rates of breast cancer mortality (a secondary outcome) were observed in the intervention group compared with the usual-diet group (0.037% vs 0.047%; HR, 0.79; 95% CI, 0.64-0.97; *P* = .02) No adverse outcomes associated with the low-fat dietary pattern were observed, and a small weight loss occurred (1.9 kg at year 1) compared with the usual-diet group.

Limitations

The WHI clinical trials had several limitations. First, the WHI hormone therapy trials tested CEE plus MPA and CEE alone, the most common hormone therapy formulations at WHI inception, but other hormone therapy formulations or routes of delivery may have yielded different results. Second, for the calcium plus vitamin D supplementation trial, the frequent use of nonstudy calcium and vitamin D supplements may have attenuated the effects of the intervention. Third, the dietary intervention did not achieve the target total fat reduction to 20% of total calories, which may have affected results. Fourth, in the clinical trial of diet, the effects of reducing dietary fat could not be distinguished from effects of increasing dietary intake of fruit, vegetables, and grains.

Conclusions

For postmenopausal women, the WHI RCTs did not support menopausal hormone therapy with oral CEE plus MPA or CEE alone for those with prior hysterectomy to prevent CVD or other chronic diseases. Menopausal hormone therapy is appropriate to treat bothersome vasomotor symptoms among women in early menopause, without contraindications, who are interested in taking hormone therapy. The WHI evidence does not support routine supplementation with calcium plus vitamin D for menopausal women to prevent fractures or a low-fat diet with increased fruits, vegetables, and grains to prevent breast or colorectal cancer. A potential role of a low-fat dietary pattern in reducing breast cancer mortality, a secondary outcome, warrants further study.

ARTICLE INFORMATION

Accepted for Publication: March 29, 2024.

Published Online: May 1, 2024. doi:10.1001/jama.2024.6542

Author Affiliations: Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Manson); Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles (Crandall); National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland (Rossouw); Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, California (Chlebowski); Division of Public Health Sciences, Fred Hutchinson Cancer Center, Seattle, Washington (Anderson, Aragaki, Neuhouser, Kooperberg, Tinker, Prentice); Stanford Prevention Research Center, Department of Medicine, Stanford University, Stanford, California (Stefanick); Department of Epidemiology, University of Pittsburgh School of Public Health|Epidemiology, Pittsburgh, Pennsylvania (Cauley); Department of Medicine, University of Alabama, Birmingham (Wells); Division of Epidemiology, Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, California (LaCroix); Department of Health Promotion Science, University of Arizona, Tucson (Thomson); Department of Preventive Medicine, Northwestern University, Chicago, Illinois (Van Horn); MedStar Health Research Institute and Department of Medicine, Georgetown University School of Medicine, Washington, DC (Howard); Department of Epidemiology and Environmental Health, University at Buffalo–SUNY, Buffalo, New York (Wactawski-Wende); Department of Gerontology and Geriatric Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina (Shumaker).

Author Contributions: Dr Manson and Mr Aragaki had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Manson, Crandall, Rossouw, Chlebowski, Anderson, Aragaki, Cauley, LaCroix, Thomson, Van Horn, Prentice.
Acquisition, analysis, or interpretation of data: Manson, Crandall, Rossouw, Chlebowski, Anderson, Stefanick, Cauley, Wells, LaCroix, Neuhouser, Van Horn, Kooperberg, Howard, Tinker, Wactawski-Wende, Shumaker, Prentice.
Drafting of the manuscript: Manson, Crandall, Rossouw, Chlebowski, Anderson, Aragaki, Wells, Thomson, Neuhouser, Van Horn, Tinker, Prentice.
Critical review of the manuscript for important intellectual content: Manson, Crandall, Rossouw, Chlebowski, Stefanick, Aragaki, Cauley, Wells, LaCroix, Thomson, Neuhouser, Van Horn, Kooperberg, Howard, Tinker, Wactawski-Wende, Shumaker, Prentice.
Statistical analysis: Stefanick, Aragaki, Prentice.
Obtained funding: Manson, Rossouw, Chlebowski, Anderson, Van Horn, Howard, Wactawski-Wende, Prentice.
Administrative, technical, or material support: Manson, Chlebowski, Cauley, Thomson, Neuhouser, Van Horn, Wactawski-Wende, Prentice.
Supervision: Manson, Chlebowski, Thomson, Neuhouser, Van Horn, Howard.

Conflict of Interest Disclosures: Dr Chlebowski reported receipt of personal fees from Novartis, AstraZeneca, Pfizer, Amgen, Genentech, Puma, and UpToDate. No other disclosures were reported.

Funding/Support: The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services, through contracts 75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D00004, and 75N92021D00005. Active and placebo study pills for the trials were donated by Wyeth Ayerst (hormone therapy trials) and GlaxoSmithKline Consumer Healthcare (calcium and vitamin D supplementation trial).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Disclaimer: The views expressed in the article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute, the National Institutes of Health, or the US Department of Health and Human Services.

Additional Contributions: This article is dedicated to the memory of Rebecca Jackson, MD, Gerardo Heiss, MD, PhD, and Lewis Kuller, MD, DrPH, who were beloved lead investigators on the WHI. They are deeply missed. We thank the WHI investigators, staff, and trial participants for their outstanding dedication and commitment. A short list of WHI investigators is as follows: *Program Office, National Heart, Lung, and Blood Institute:* Jacques Rossouw, Jared Reis, and Candice Price. *Clinical Coordinating Center, Fred Hutchinson Cancer Research Center:* Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg. *Investigators and academic centers*: Brigham and Women's Hospital, Harvard Medical School: JoAnn E. Manson; MedStar Health Research Institute/Howard University: Barbara V. Howard; Stanford Prevention Research Center: Marcia L. Stefanick; University of Arizona: Cynthia A. Thomson; University at Buffalo: Jean Wactawski-Wende; Wake Forest University School of Medicine: Sally Shumaker; University of Massachusetts: Brian Silver; Wake Forest University: Mara Vitolins; University of Alabama at Birmingham: Gretchen Wells; University at Buffalo: Amy Millen; University of Florida: Marian Limacher; The Ohio State University: Electra Paskett; Women's Health Initiative Memory Study, Wake Forest University School of Medicine: Mark Espeland. A list of all of the investigators who have contributed to WHI science is available at https://s3-us-west-2.amazonaws.com/www-whi-org/wp-content/uploads/WHI-Investigator-Long-List.pdf.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

REFERENCES

1. Blakeslee L, Caplan Z, Meyer JA. Rabe AM, Roberts AW. *Age and Sex Composition: 2020 Census Briefs*. US Census Bureau, US Dept of Commerce; 2023:C2020BR-06.

2. World Bank. World Bank, open data: population, female, 2024. Accessed February 2, 2024. https://data.worldbank.org

3. Healy proposes historic Women's Health Initiative. *The NIH Record*. May 4, 1991:4.

4. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19(1):61-109. doi:10.1016/S0197-2456(97)00078-0

5. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative study design. *Ann Epidemiol*. 2003;13(9)(suppl):S5-S17. doi:10.1016/S1047-2797(03)00043-7

6. Stampfer MJ, Willett WC, Colditz GA, Rosner B, Speizer FE, Hennekens CH. A prospective study of postmenopausal estrogen therapy and coronary heart disease. *N Engl J Med*. 1985;313(17):1044-1049. doi:10.1056/NEJM198510243131703

7. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. *Annu Rev Public Health*. 1998;19:55-72. doi:10.1146/annurev.publhealth.19.1.55

8. Manson JE, Martin KA. Clinical practice. Postmenopausal hormone-replacement therapy. *N Engl J Med*. 2001;345(1):34-40. doi:10.1056/NEJM200107053450106

9. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA*. 2004;291(1):47-53. doi:10.1001/jama.291.1.47

10. American College of Physicians. Guidelines for counseling postmenopausal women about preventive hormone therapy. *Ann Intern Med*. 1992;117(12):1038-1041. doi:10.7326/0003-4819-117-12-1038

11. Bergkvist L, Adami HO, Persson I, Hoover R, Schairer C. The risk of breast cancer after estrogen and estrogen-progestin replacement. *N Engl J Med*. 1989;321(5):293-297. doi:10.1056/NEJM198908033210505

12. Shea B, Wells G, Cranney A, et al; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analyses of therapies for postmenopausal osteoporosis, VII: meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. *Endocr Rev*. 2002;23(4):552-559. doi:10.1210/er.2001-7002

13. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA*. 2005;293(18):2257-2264. doi:10.1001/jama.293.18.2257

14. Prentice RL, Sheppard L. Dietary fat and cancer: consistency of the epidemiologic data, and disease prevention that may follow from a practical reduction in fat consumption. *Cancer Causes Control*. 1990;1(1):81-97. doi:10.1007/BF00053187

15. Hunter DJ, Spiegelman D, Adami HO, et al. Cohort studies of fat intake and the risk of breast cancer—a pooled analysis. *N Engl J Med*. 1996;334(6):356-361. doi:10.1056/NEJM199602083340603

16. Curb JD, McTiernan A, Heckbert SR, et al; WHI Morbidity and Mortality Committee. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol*. 2003;13

(9)(suppl):S122-S128. doi:10.1016/S1047-2797(03)00048-6

17. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol*. 2003;13(9)(suppl):S18-S77. doi:10.1016/S1047-2797(03)00042-5

18. Garcia L, Follis S, Thomson CA, et al. Taking action to advance the study of race and ethnicity: the Women's Health Initiative (WHI). *Womens Midlife Health*. 2022;8(1):1. doi:10.1186/s40695-021-00071-6

19. Faubion SS, Crandall CJ, Davis L, et al. The hormone therapy position statement of the North American Menopause Society. *Menopause*. 2022;29(7):767-794. doi:10.1097/GME.0000000000002028

20. Manson JE, Bassuk SS. Menopause and postmenopausal hormone therapy. In: Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. McGraw-Hill Education; 2018.

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

22. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310(13):1353-1368. doi:10.1001/jama.2013.278040

23. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;297(13):1465-1477. doi:10.1001/jama.297.13.1465

24. Rossouw JE, Prentice RL, Manson JE, et al. Relationships of coronary heart disease with 27-hydroxycholesterol, low-density lipoprotein cholesterol, and menopausal hormone therapy. *Circulation*. 2012;126(13):1577-1586. doi:10.1161/CIRCULATIONAHA.112.103218

25. Wild RA, Wu C, Curb JD, et al. Coronary heart disease events in the Women's Health Initiative hormone trials: effect modification by metabolic syndrome: a nested case-control study within the Women's Health Initiative randomized clinical trials. *Menopause*. 2013;20(3):254-260. doi:10.1097/gme.0b013e31826f80e0

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

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

28. McTiernan A, Martin CF, Peck JD, et al; Women's Health Initiative Mammogram Density Study Investigators. Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. *J Natl Cancer Inst*. 2005;97(18):1366-1376. doi:10.1093/jnci/dji279

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

30. Chlebowski RT, Anderson G, Pettinger M, et al; Women's Health Initiative Investigators. Estrogen plus progestin and breast cancer detection by means of mammography and breast biopsy. *Arch Intern Med*. 2008;168(4):370-377. doi:10.1001/archinternmed.2007.123

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

32. Simon MS, Chlebowski RT, Wactawski-Wende J, et al. Estrogen plus progestin and colorectal cancer incidence and mortality. *J Clin Oncol*. 2012;30(32):3983-3990. doi:10.1200/JCO.2012.42.7732

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

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

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

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

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

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

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

40. Manson JE, Allison MA, Rossouw JE, et al; WHI and WHI-CACS Investigators. Estrogen therapy and coronary-artery calcification. *N Engl J Med*. 2007;356(25):2591-2602. doi:10.1056/NEJMoa071513

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

42. Stefanick ML, Anderson GL, Margolis KL, et al; WHI Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA*. 2006;295(14):1647-1657. doi:10.1001/jama.295.14.1647

43. Jackson RD, LaCroix AZ, Cauley JA, McGowan J. The Women's Health Initiative calcium-vitamin D trial: overview and baseline characteristics of participants. *Ann Epidemiol*. 2003;13(9)(suppl):S98-S106. doi:10.1016/S1047-2797(03)00046-2

44. Jackson RD, LaCroix AZ, Gass M, et al; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354(7):669-683. doi:10.1056/NEJMoa055218

45. Cauley JA, Chlebowski RT, Wactawski-Wende J, et al. Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. *J Womens Health (Larchmt)*. 2013;22(11):915-929. doi:10.1089/jwh.2013.4270

46. Wactawski-Wende J, Kotchen JM, Anderson GL, et al; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med*. 2006;354(7):684-696. doi:10.1056/NEJMoa055222

47. LaCroix AZ, Kotchen J, Anderson G, et al. Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial. *J Gerontol A Biol Sci Med Sci*. 2009;64(5):559-567. doi:10.1093/gerona/glp006

48. Hsia J, Heiss G, Ren H, et al; Women's Health Initiative Investigators. Calcium/vitamin D supplementation and cardiovascular events. *Circulation*. 2007;115(7):846-854. doi:10.1161/CIRCULATIONAHA.106.673491

49. Manson JE, Allison MA, Carr JJ, et al; Women's Health Initiative and Women's Health Initiative–Coronary Artery Calcium Study Investigators. Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. *Menopause*. 2010;17(4):683-691. doi:10.1097/gme.0b013e3181d683b5

50. Wallace RB, Wactawski-Wende J, O'Sullivan MJ, et al. Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements. *Am J Clin Nutr*. 2011;94(1):270-277. doi:10.3945/ajcn.110.003350

51. Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. National Academies Press; 2011.

52. Prentice RL, Aragaki AK, Howard BV, et al. Low-fat dietary pattern among postmenopausal women influences long-term cancer, cardiovascular disease, and diabetes outcomes. *J Nutr*. 2019;149(9):1565-1574. doi:10.1093/jn/nxz107

53. Thomson CA, Van Horn L, Caan BJ, et al. Cancer incidence and mortality during the intervention and

postintervention periods of the Women's Health Initiative dietary modification trial. *Cancer Epidemiol Biomarkers Prev*. 2014;23(12):2924-2935. doi:10.1158/1055-9965.EPI-14-0922

54. Howard BV, Manson JE, Stefanick ML, et al. Low-fat dietary pattern and weight change over 7 years: the Women's Health Initiative dietary modification trial. *JAMA*. 2006;295(1):39-49. doi:10.1001/jama.295.1.39

55. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative randomized controlled dietary modification trial. *JAMA*. 2006;295(6):629-642. doi:10.1001/jama.295.6.629

56. Pan K, Aragaki AK, Michael Y, et al. Long-term dietary intervention influence on physical activity in the Women's Health Initiative dietary modification randomized trial. *Breast Cancer Res Treat*. 2022;195(1):43-54. doi:10.1007/s10549-022-06655-8

57. Chlebowski RT, Aragaki AK, Anderson GL, et al; Women's Health Initiative. Dietary modification and breast cancer mortality: long-term follow-up of the Women's Health Initiative randomized trial. *J Clin Oncol*. 2020;38(13):1419-1428. doi:10.1200/JCO.19.00435

58. Beresford SA, Johnson KC, Ritenbaugh C, et al. Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative randomized controlled dietary modification trial. *JAMA*. 2006;295(6):643-654. doi:10.1001/jama.295.6.643

59. Chlebowski RT, Aragaki AK, Anderson GL, et al. Low-fat dietary pattern and breast cancer mortality in the Women's Health Initiative randomized controlled trial. *J Clin Oncol*. 2017;35(25):2919-2926. doi:10.1200/JCO.2016.72.0326

60. Pan K, Aragaki AK, Neuhouser ML, et al. Low-fat dietary pattern and breast cancer mortality by metabolic syndrome components: a secondary analysis of the Women's Health Initiative (WHI) randomised trial. *Br J Cancer*. 2021;125(3):372-379. doi:10.1038/s41416-021-01379-w

61. Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative randomized controlled dietary modification trial. *JAMA*. 2006;295(6):655-666. doi:10.1001/jama.295.6.655

62. Prentice RL, Aragaki AK, Van Horn L, et al. Low-fat dietary pattern and cardiovascular disease: results from the Women's Health Initiative randomized controlled trial. *Am J Clin Nutr*. 2017;106(1):35-43. doi:10.3945/ajcn.117.153270

63. Prentice RL, Thomson CA, Caan B, et al. Low-fat dietary pattern and cancer incidence in the Women's Health Initiative dietary modification randomized controlled trial. *J Natl Cancer Inst*. 2007;99(20):1534-1543. doi:10.1093/jnci/djm159

64. Howard BV, Aragaki AK, Tinker LF, et al. A low-fat dietary pattern and diabetes: a secondary analysis from the Women's Health Initiative dietary modification trial. *Diabetes Care*. 2018;41(4):680-687. doi:10.2337/dc17-0534