Original Investigation

Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials

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IMPORTANCE Menopausal hormone therapy continues in clinical use but questions remain regarding its risks and benefits for chronic disease prevention.

OBJECTIVE To report a comprehensive, integrated overview of findings from the 2 Women's Health Initiative (WHI) hormone therapy trials with extended postintervention follow-up.

DESIGN, SETTING, AND PARTICIPANTS A total of 27 347 postmenopausal women aged 50 to 79 years were enrolled at 40 US centers.

INTERVENTIONS Women with an intact uterus received conjugated equine estrogens (CEE; 0.625 mg/d) plus medroxyprogesterone acetate (MPA; 2.5 mg/d) (n = 8506) or placebo (n = 8102). Women with prior hysterectomy received CEE alone (0.625 mg/d) (n = 5310) or placebo (n = 5429). The intervention lasted a median of 5.6 years in CEE plus MPA trial and 7.2 years in CEE alone trial with 13 years of cumulative follow-up until September 30, 2010.

MAIN OUTCOMES AND MEASURES Primary efficacy and safety outcomes were coronary heart disease (CHD) and invasive breast cancer, respectively. A global index also included stroke, pulmonary embolism, colorectal cancer, endometrial cancer, hip fracture, and death.

RESULTS During the CEE plus MPA intervention phase, the numbers of CHD cases were 196 for CEE plus MPA vs 159 for placebo (hazard ratio [HR], 1.18; 95% CI, 0.95-1.45) and 206 vs 155, respectively, for invasive breast cancer (HR, 1.24; 95% CI, 1.01-1.53). Other risks included increased stroke, pulmonary embolism, dementia (in women aged ≥65 years), gallbladder disease, and urinary incontinence; benefits included decreased hip fractures, diabetes, and vasomotor symptoms. Most risks and benefits dissipated postintervention, although some elevation in breast cancer risk persisted during cumulative follow-up (434 cases for CEE plus MPA vs 323 for placebo; HR, 1.28 [95% CI, 1.11-1.48]). The risks and benefits were more balanced during the CEE alone intervention with 204 CHD cases for CEE alone vs 222 cases for placebo (HR, 0.94; 95% CI, 0.78-1.14) and 104 vs 135, respectively, for invasive breast cancer (HR, 0.79; 95% CI, 0.61-1.02); cumulatively, there were 168 vs 216, respectively, cases of breast cancer diagnosed (HR, 0.79; 95% CI, 0.65-0.97). Results for other outcomes were similar to CEE plus MPA. Neither regimen affected all-cause mortality. For CEE alone, younger women (aged 50-59 years) had more favorable results for all-cause mortality, myocardial infarction, and the global index (nominal $P < .05$ for trend by age). Absolute risks of adverse events (measured by the global index) per 10 000 women annually taking CEE plus MPA ranged from 12 excess cases for ages of 50-59 years to 38 for ages of 70-79 years; for women taking CEE alone, from 19 fewer cases for ages of 50-59 years to 51 excess cases for ages of 70-79 years. Quality-of-life outcomes had mixed results in both trials.

CONCLUSIONS AND RELEVANCE Menopausal hormone therapy has a complex pattern of risks and benefits. Findings from the intervention and extended postintervention follow-up of the 2 WHI hormone therapy trials do not support use of this therapy for chronic disease prevention, although it is appropriate for symptom management in some women.

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The Women's Health Initiative (WHI) trials were designed to determine the benefits and risks of hormone therapy when taken for chronic disease prevention by predominantly healthy postmenopausal women.[1-3] Although originally prescribed primarily to treat vasomotor symptoms, menopausal hormone therapy had been increasingly viewed as a way to prevent many chronic diseases of aging, including coronary heart disease (CHD) and cognitive impairment.[4,5] At least 40% of postmenopausal women in the United States were using hormone therapy shortly before the publication of the initial WHI findings.[6] Even though observational studies had suggested net benefit for hormone therapy use,[4,5] no previous large-scale randomized prevention trial had addressed the balance of risks and benefits. In this context, the WHI hormone therapy trials were conceived and the most commonly used hormone therapy formulations in the United States at that time, conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) and CEE alone, were chosen as the interventions.[1]

Findings from the 2 hormone therapy trials have been published in numerous journals during the past decade[2,3,7-15] (a full listing of previous reports appears in the Supplement), but no previous WHI publication has synthesized results for primary, secondary, and quality-of-life outcomes of the 2 trials during their intervention and postintervention phases. In addition, for some end points, analyses have not been previously stratified by age or time since menopause. The goal of this report is to provide a comprehensive, integrated overview of findings from the 2 WHI hormone therapy trials with extended postintervention follow-up (median, 13 years of cumulative follow-up) and stratification by age and other important variables.

Methods

Study Design

Details of the 2 WHI hormone therapy trial designs and outcome adjudication procedures have been published.[1-3] Briefly, 27 347 postmenopausal women aged 50 to 79 years were recruited from 1993 to 1998 at 40 US clinical centers; 16 608 women with a uterus were randomized to oral CEE (0.625 mg/d) plus MPA (2.5 mg/d) (Prempro) or placebo and 10 739 women with prior hysterectomy were randomized to oral CEE (0.625 mg/d) alone (Premarin) or placebo. The primary efficacy and safety outcomes of the trial were CHD and invasive breast cancer, respectively. The sample sizes were based on power to detect effects on these outcomes.[1]

Institutional review board approval was obtained at each clinical center and all participants provided written informed consent. Race and ethnicity were self-reported. Postintervention follow-up through September 30, 2010, is based on 81.1% of surviving participants who provided additional written informed consent. Following stopping of the interventions, fewer than 4% of women reported personal use of hormone therapy. Comparisons during the postintervention phase need to be interpreted in the context of possible selection due to effects in the preceding intervention phase and partial consent to further follow-up after 2005.

Statistical Analysis

For each trial, intervention phase analyses included all randomized participants according to their randomization assignment until last intervention contact, using time-to-event methods based on the intention-to-treat principle. A global index of the monitored clinical events was calculated as time to first event for CHD, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, endometrial cancer (for CEE plus MPA only), hip fractures, and death from all other causes.

Hazard ratios (HRs) were estimated using Cox proportional hazards models stratified by age, prior disease (if appropriate), and randomization status in the WHI dietary modification trial. Models were constructed for each clinical end point with women contributing follow-up time until the end of the study phase, date of their first relevant clinical event, death, or withdrawal from the study, whichever came first. Comparisons during the postintervention phase include randomized participants in active follow-up and at risk for an initial diagnosis of the relevant outcome. Cumulative results represent overall findings. The HRs may exhibit time dependencies within or between phases, as previously reported.[14,15]

All statistical tests are 2-sided and nominal *P* values of .05 or less are regarded as significant. The *P* values do not adjust for multiple outcomes, sequential monitoring, or multiple subgroup comparisons due to the large number of tests conducted; therefore, the *P* values should be interpreted cautiously. Inference on subgroup analyses rely primarily on tests for interaction, which are also subject to multiple testing limitations when a large number of tests are conducted. Subgroup analyses, stratifying on age and time since menopause, are reported for most outcomes. Tests were based on a 1 degree of freedom for trend in which models included a randomization group × baseline group interaction term, which was coded ordinally.

Adherence sensitivity analyses, conducted by censoring follow-up 6 months after nonadherence (taking <80% of study pills or starting nonprotocol hormone therapy), included time-varying weights (inversely proportional to the estimated probability of continued adherence) in proportional hazards models that adjusted for changes in the distribution of sample characteristics during follow-up. For secondary and quality-of-life outcomes, results are provided for the intervention phase and, when available, for the postintervention and cumulative follow-up period.

Additional analyses were conducted among women with no prior hormone therapy use before entry as well as stratified by vasomotor symptoms at enrollment. All statistical analyses were conducted using SAS software version 9.3 (SAS Institute Inc) and R software version 2.15 (R Foundation for Statistical Computing).

Results

Baseline Characteristics

Baseline characteristics for the 2 randomization groups in each trial were well balanced according to demographic and disease risk factors (**Table**). However, several differences are seen when comparing characteristics between trials. Compared with CEE plus MPA trial participants, women in the CEE alone trial

Table. Baseline Characteristics of Participants in the 2 WHI Hormone Therapy Trials

	No. (%) of Participants[a]			
	CEE + MPA Trial		CEE Alone Trial	
	CEE + MPA (n = 8506)	Placebo (n = 8102)	CEE Alone (n = 5310)	Placebo (n = 5429)
Age at screening, mean (SD), y	63.2 (7.1)	63.3 (7.1)	63.6 (7.3)	63.6 (7.3)
Age group at screening, y				
50-59	2837 (33.4)	2683 (33.1)	1639 (30.9)	1674 (30.8)
60-69	3854 (45.3)	3655 (45.1)	2386 (44.9)	2465 (45.4)
70-79	1815 (21.3)	1764 (21.8)	1285 (24.2)	1290 (23.8)
Race/ethnicity				
White	7141 (84.0)	6805 (84.0)	4009 (75.5)	4075 (75.1)
Black	548 (6.4)	574 (7.1)	781 (14.7)	835 (15.4)
Hispanic	471 (5.5)	415 (5.1)	319 (6.0)	332 (6.1)
American Indian	25 (0.3)	30 (0.4)	41 (0.8)	34 (0.6)
Asian/Pacific Islander	194 (2.3)	169 (2.1)	86 (1.6)	78 (1.4)
Unknown	127 (1.5)	109 (1.3)	74 (1.4)	75 (1.4)
Years since menopause, y				
<10	2780 (36.2)	2711 (36.1)	827 (18.4)	817 (17.6)
10-<20	3049 (39.7)	2992 (39.9)	1438 (32.0)	1500 (32.4)
≥20	1850 (24.1)	1805 (24.0)	2230 (49.6)	2319 (50.0)
Hormone use				
Never	6277 (73.8)	6022 (74.4)	2769 (52.2)	2769 (51.0)
Past	1671 (19.7)	1587 (19.6)	1871 (35.2)	1947 (35.9)
Current[b]	554 (6.5)	490 (6.1)	669 (12.6)	709 (13.1)
Vasomotor symptoms				
None	5162 (61.3)	4928 (61.5)	2962 (56.4)	3004 (56.0)
Mild	2190 (26.0)	2115 (26.4)	1377 (26.2)	1441 (26.9)
Moderate or severe	1072 (12.7)	974 (12.1)	913 (17.4)	917 (17.1)
Body mass index[c]				
Median (IQR)	27.5 (24.2-31.7)	27.5 (24.3-31.7)	29.2 (25.7-33.7)	29.2 (25.7-33.5)
No. (%)				
<25	2579 (30.4)	2479 (30.8)	1110 (21.0)	1096 (20.3)
25-29	2992 (35.3)	2835 (35.2)	1798 (34.0)	1915 (35.5)
≥30	2899 (34.2)	2737 (34.0)	2375 (45.0)	2385 (44.2)
Blood pressure, mean (SD), mm Hg				
Systolic	127.6 (17.6)	127.8 (17.5)	130.4 (17.5)	130.2 (17.6)
Diastolic	75.6 (9.1)	75.8 (9.1)	76.5 (9.2)	76.5 (9.4)
Smoking				
Never	4178 (49.6)	3999 (50.0)	2723 (51.9)	2705 (50.4)
Past	3362 (39.9)	3157 (39.5)	1986 (37.8)	2090 (38.9)
Current	880 (10.5)	838 (10.5)	542 (10.3)	571 (10.6)
Never pregnant or no term pregnancy	860 (11.2)	833 (11.5)	491 (10.4)	463 (9.5)
Age at time of first birth (among those ever pregnant), y				
<20	1124 (16.4)	1117 (17.3)	1193 (28.1)	1234 (28.0)
20-29	4996 (73.0)	4698 (73.0)	2846 (67.0)	2914 (66.1)
≥30	727 (10.6)	624 (9.7)	210 (4.9)	260 (5.9)
Age at time of hysterectomy, y				
<40			2100 (39.8)	2148 (39.8)
40-49			2280 (43.2)	2275 (42.2)
50-54			501 (9.5)	566 (10.5)
≥55			401 (7.6)	404 (7.5)
Bilateral oophorectomy	29 (0.3)	24 (0.3)	1938 (39.5)	2111 (42.0)

(continued)

Table. Baseline Characteristics of Participants in the 2 WHI Hormone Therapy Trials (continued)

	No. (%) of Participants[a]			
	CEE + MPA Trial		CEE Alone Trial	
	CEE + MPA (n = 8506)	Placebo (n = 8102)	CEE Alone (n = 5310)	Placebo (n = 5429)
Receiving treatment for				
Diabetes	374 (4.4)	360 (4.4)	410 (7.7)	412 (7.6)
Hypertension or systolic/diastolic blood pressure ≥140/90 mm Hg	3377 (43.2)	3283 (42.7)	2651 (53.3)	2647 (52.6)
Elevated cholesterol levels	1018 (12.0)	1027 (12.7)	763 (14.4)	829 (15.3)
Statin use at baseline	580 (6.8)	535 (6.6)	397 (7.5)	430 (7.9)
Aspirin use (≥80 mg/d) at baseline	1652 (19.4)	1654 (20.4)	1050 (19.8)	1081 (19.9)
Medical history				
Myocardial infarction	139 (1.6)	157 (1.9)	165 (3.1)	173 (3.2)
Angina	318 (3.8)	331 (4.1)	402 (7.6)	388 (7.2)
CABG or PCI	95 (1.1)	120 (1.5)	120 (2.3)	114 (2.1)
Stroke	61 (0.7)	77 (1.0)	76 (1.4)	92 (1.7)
Deep vein thrombosis or pulmonary embolism	79 (0.9)	62 (0.8)	87 (1.6)	84 (1.5)
Fracture at age ≥55 y[d]	1030 (16.6)	1027 (16.7)	676 (17.3)	643 (16.4)
Family history of breast cancer[e]	1286 (16.0)	1175 (15.3)	892 (17.9)	870 (17.1)
Education >high school degree or GED	6272 (74.1)	5899 (73.3)	3488 (66.3)	3678 (68.3)
Family income ≥$50 000	2447 (30.4)	2401 (31.4)	1148 (22.9)	1167 (22.9)

Abbreviations: CABG, coronary artery bypass graft; CEE, conjugated equine estrogens; GED, general equivalency diploma; IQR, interquartile range; MPA, medroxyprogesterone acetate; PCI, percutaneous coronary intervention; WHI, Women's Health Initiative.

[a] Unless otherwise indicated.

[b] Required a 3-month washout period prior to randomization.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Excludes finger or toe fractures.

[e] In mother, sister, daughter, or grandmother.

were more racially diverse, more distant from menopause onset, had less favorable cardiovascular risk profiles, and more commonly had oophorectomy and prior hormone therapy use.

The intervention phase of the CEE plus MPA trial ended on July 7, 2002 (after a median of 5.6 years [interquartile range {IQR}, 4.8-6.5 years]) due to increased breast cancer risk and an unfavorable risk-to-benefit ratio with CEE plus MPA.[2] The intervention phase of the CEE alone trial ended on February 29, 2004 (after a median of 7.2 years [IQR, 6.4-8.1 years]) due to increased stroke incidence that was not offset by lower CHD risk in the hormone therapy group.[3] Some HRs differ slightly from those previously reported due to the more complete outcome ascertainment in the present report. After the intervention phases ended, the follow-up phases continued through September 30, 2010, among surviving participants who provided additional written consent. The cumulative results reported herein include a median postintervention follow-up of 8.2 years (IQR, 6.6-8.2 years) for the CEE plus MPA trial and a median cumulative follow-up of 13.2 years (IQR, 10.5-14.2 years); for the CEE alone trial, the median postintervention follow-up was 6.6 years (IQR, 3.8-6.6 years) and the median cumulative follow-up was 13.0 years (IQR, 9.1-14.1 years) (**Figure 1**).

Primary End Points in the 2 Trials: Intervention, Postintervention, and Cumulative Results

The intervention results for CHD and invasive breast cancer (the primary efficacy and safety outcomes, respectively) in the 2 trials are presented in **Figure 2**. The higher absolute risks for these and other major health outcomes among women in older compared with younger age groups appear in **Figure 3**. Results for the postintervention and cumulative follow-up phases appear in **Figure 4** and eFigure 1 in Supplement. The figures include the number of incident cases (events), absolute risk differences (cases per 10 000 person-years for each end point in the CEE plus MPA or CEE alone groups minus the placebo groups), HRs, 95% confidence intervals, and forest plots of the HRs and 95% confidence intervals for the 2 trials.

Coronary Heart Disease

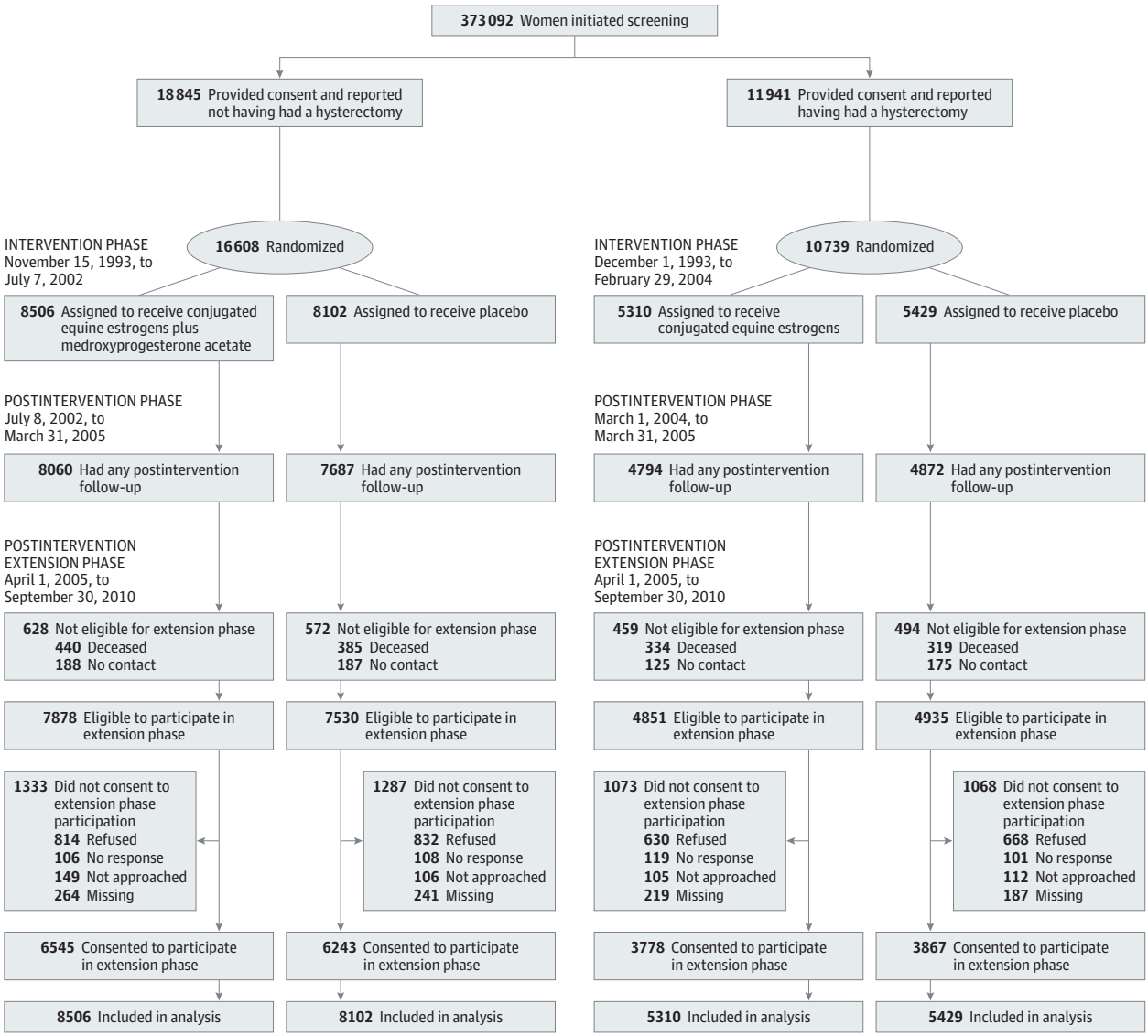
Coronary heart disease was defined as nonfatal myocardial infarction (MI) or coronary death. Results for total MI, which was a secondary end point, are reported separately below.

Intervention Phase | Results for CHD differed between the 2 trials (Figure 2). Women assigned to CEE plus MPA had an HR of 1.18 (95% CI, 0.95-1.45) compared with placebo. The HR at year 1 was 1.80 (95% CI, 1.08-2.99), but was less elevated or neutral in subsequent years (P = .03 for trend by time). Women assigned to CEE alone had an HR of 0.94 (95% CI, 0.78-1.14) compared with placebo; the HRs did not differ appreciably by year since randomization (P = .21 for trend by time).

Postintervention and Cumulative Follow-up Phases | The postintervention results in both trials were neutral (Figure 4). During cumulative 13-year follow-up, the HRs for CHD were 1.09 (95% CI, 0.96-1.24) for CEE plus MPA and 0.94 (95% CI, 0.82-1.09) for CEE alone compared with the placebo groups (Figure 4).

Stratified Analyses by Age and Time Since Menopause | In the CEE plus MPA trial, the HRs were similar by age (**Figure 5**); however, there was a nonsignificant difference by time since menopause onset compared with the placebo group (P = .08 for trend), with significantly elevated risk among women who were more than 20 years past menopause onset (eFigure 2 in Supplement). In the CEE alone trial, a nonsignificant but lower CHD risk in younger women was suggested compared with the pla-

Figure 1. Women's Health Initiative Trials of Menopausal Hormone Therapy Through Extended Follow-up



There were 342 306 women who were ineligible or unwilling to participate in the hormone therapy trials. The postintervention phase began on the day after participants were instructed to stop study medication use and continued through the original trial completion date. During the extension phase, there was follow-up for those who provided additional consent (conjugated equine estrogens plus medroxyprogesterone acetate or placebo trial: 83% of those eligible and 2.8% dropped out; conjugated equine estrogens alone or placebo trial: 78% of those eligible and 3.0% dropped out).

cebo group (P = 0.08 for trend; Figure 5). Statistically significant differences by age or proximity to menopause for MI are described later.

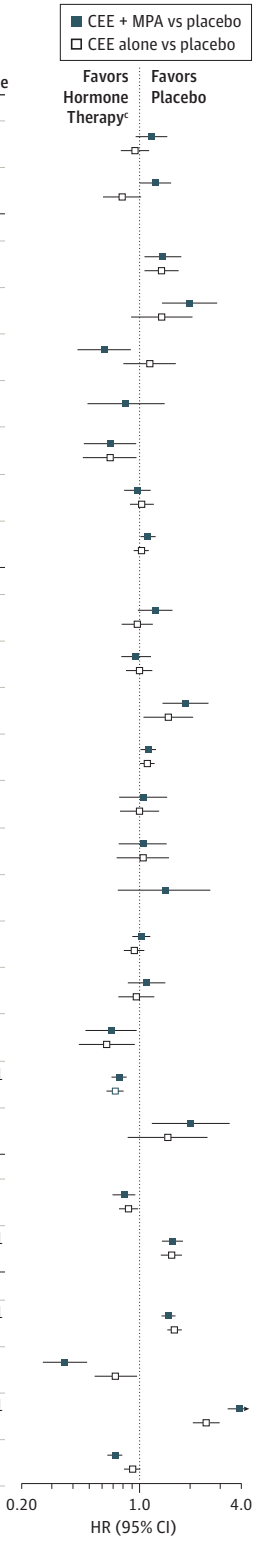
Invasive Breast Cancer

Intervention Phase | Results for invasive breast cancer differed between the 2 trials. Women assigned to CEE plus MPA had an HR of 1.24 (95% CI, 1.01-1.53) for breast cancer compared with the placebo group (Figure 2). The HRs progressively increased by time since randomization (P = .005 for time trend), with cancer cases diagnosed at more advanced stages.[16] In contrast, women assigned to CEE alone had an HR of 0.79 (95% CI, 0.61-1.02) compared with the placebo group and the HRs did not differ by time since randomization.

Postintervention and Cumulative Follow-up | The HR for invasive breast cancer with CEE plus MPA remained statistically significantly elevated during postintervention and cumulative follow-up compared with the placebo group (HR for cumulative follow-up, 1.28 [95% CI, 1.11-1.48]; Figure 4 and eFigure 1 in Supplement); however, more detailed time-dependent analyses identified risk attenuation with time since cessation of hormone therapy use.[17] For women assigned to CEE alone, the risk reduction became

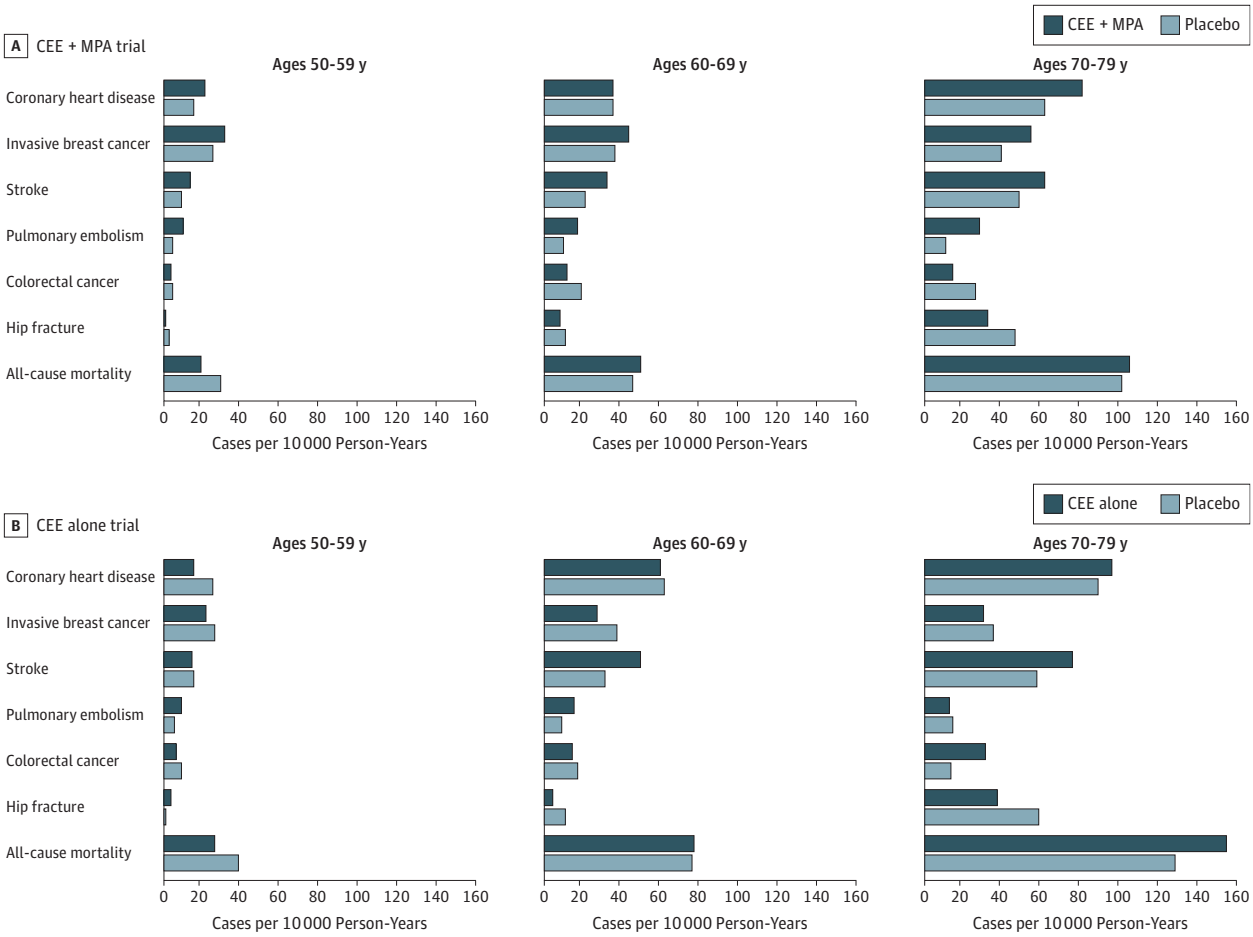
Figure 2. Health Outcomes in the Overall Study Population in the Women's Health Initiative Hormone Therapy Trials During the Intervention Phase

	CEE + MPA Trial					CEE Alone Trial				
	No. (%) of Events[a]					No. (%) of Events[a]				
	CEE + MPA (n = 8506)	Placebo (n = 8102)	Difference/ 10 000 PY[b]	HR (95% CI)	*P* Value	CEE (n = 5310)	Placebo (n = 5429)	Difference/ 10 000 PY[b]	HR (95% CI)	*P* Value
Primary end points										
Coronary heart disease	196 (0.41)	159 (0.35)	6	1.18 (0.95-1.45)	.13	204 (0.55)	222 (0.58)	-3	0.94 (0.78-1.14)	.53
Invasive breast cancer	206 (0.43)	155 (0.35)	9	1.24 (1.01-1.53)	.04	104 (0.28)	135 (0.35)	-7	0.79 (0.61-1.02)	.07
Other end points in global index										
Stroke	159 (0.33)	109 (0.24)	9	1.37 (1.07-1.76)	.01	169 (0.45)	130 (0.34)	11	1.35 (1.07-1.70)	.01
Pulmonary embolism	87 (0.18)	41 (0.09)	9	1.98 (1.36-2.87)	<.001	52 (0.14)	39 (0.10)	4	1.35 (0.89-2.05)	.15
Colorectal cancer	50 (0.10)	75 (0.17)	-6	0.62 (0.43-0.89)	.009	65 (0.17)	58 (0.15)	2	1.15 (0.81- 1.64)	.44
Endometrial cancer	27 (0.06)	30 (0.07)	-1	0.83 (0.49-1.40)	.49	NA	NA	NA	NA	NA
Hip fracture	53 (0.11)	75 (0.17)	-6	0.67 (0.47-0.95)	.03	48 (0.13)	74 (0.19)	-6	0.67 (0.46-0.96)	.03
All-cause mortality	250 (0.52)	238 (0.53)	-1	0.97 (0.81-1.16)	.76	301 (0.80)	299 (0.77)	3	1.03 (0.88-1.21)	.68
Global index	876 (1.89)	736 (1.68)	20	1.12 (1.02-1.24)	.02	753 (2.08)	755 (2.04)	4	1.03 (0.93-1.13)	.63
Secondary end points										
Total MI	168 (0.35)	129 (0.29)	6	1.24 (0.98-1.56)	.07	164 (0.44)	173 (0.45)	-1	0.97 (0.79-1.21)	.81
CABG or PCI	198 (0.42)	200 (0.45)	-3	0.95 (0.78-1.16)	.64	249 (0.68)	255 (0.67)	0	1.00 (0.83-1.19)	.96
Deep vein thrombosis	122 (0.25)	61 (0.14)	12	1.87 (1.37-2.54)	<.001	85 (0.23)	59 (0.15)	7	1.48 (1.06-2.07)	.02
All cardiovascular events	786 (1.70)	663 (1.52)	19	1.13 (1.02-1.25)	.02	877 (2.51)	813 (2.24)	27	1.11 (1.01-1.22)	.03
Cardiovascular deaths	79 (0.16)	70 (0.15)	1	1.05 (0.76-1.45)	.77	109 (0.29)	112 (0.29)	0	1.00 (0.77-1.31)	.98
Lung cancer	78 (0.16)	70 (0.16)	1	1.05 (0.76-1.45)	.78	62 (0.16)	61 (0.16)	1	1.05 (0.74-1.49)	.79
Ovarian cancer	24 (0.05)	16 (0.04)	1	1.41 (0.75-2.66)	.28	NR	NR	NR	NR	NR
All cancer types[d]	598 (1.27)	543 (1.24)	4	1.02 (0.91-1.15)	.69	399 (1.09)	438 (1.17)	-8	0.93 (0.81-1.07)	.30
Cancer deaths	133 (0.28)	111 (0.25)	3	1.10 (0.86-1.42)	.45	126 (0.33)	135 (0.35)	-1	0.96 (0.75-1.22)	.73
Vertebral fracture	56 (0.12)	78 (0.17)	-6	0.68 (0.48-0.96)	.03	44 (0.12)	70 (0.18)	-6	0.64 (0.44-0.93)	.02
All fracture	741 (1.61)	903 (2.12)	-51	0.76 (0.69-0.83)	<.001	544 (1.53)	767 (2.14)	-61	0.72 (0.64-0.80)	<.001
Probable dementia[e]	40 (0.46)	21 (0.23)	23	2.01 (1.19-3.42)	.01	33 (0.44)	22 (0.29)	15	1.47 (0.85-2.52)	.17
Self-reported end points[f]										
Diabetes	328 (0.72)	373 (0.88)	-16	0.81 (0.70-0.94)	.005	449 (1.34)	527 (1.55)	-21	0.86 (0.76-0.98)	.02
Gallbladder disease	528 (1.31)	319 (0.84)	47	1.57 (1.36-1.80)	<.001	461 (1.64)	312 (1.06)	58	1.55 (1.34-1.79)	<.001
Self-reported symptoms[g]										
Urinary incontinence[f]	1021 (16.61)	641 (11.12)	549	1.49 (1.36-1.63)	<.001	773 (22.55)	499 (14.03)	852	1.61 (1.46-1.79)	<.001
Vasomotor symptoms[h]	46 (16.36)	109 (44.52)	-2816	0.36 (0.27-0.49)	<.001	52 (29.15)	71 (41.21)	-1205	0.72 (0.54-0.96)	.03
Breast tenderness[f]	712 (9.08)	173 (2.31)	678	3.93 (3.34-4.63)	<.001	388 (8.22)	160 (3.30)	491	2.48 (2.08-2.97)	<.001
Joint pain[f]	607 (9.84)	810 (13.70)	-386	0.72 (0.65- 0.79)	<.001	527 (15.73)	595 (17.33)	-160	0.91 (0.81-1.01)	.07



CABG indicates coronary artery bypass graft; CEE, conjugated equine estrogens; HR, hazard ratio; MI, myocardial infarction; MPA, medroxyprogesterone acetate; NA, not applicable due to hysterectomy; NR, not reported due to small numbers; PCI, percutaneous coronary intervention; PY, person-years. [a]Percentages are annualized. [b]Difference in estimated absolute excess risks (hormone therapy minus placebo). [c]Indicates CEE alone or CEE plus MPA. [d]Excludes non–melanoma skin cancer. [e]In women aged 65 years or older. [f]In women not reporting condition at baseline. [g]Collected at year 1. [h]In symptomatic women aged 50 to 54 years.

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



None of the age interactions were statistically significant (at the $P < .05$ level), except for colorectal cancer, all-cause mortality, myocardial infarction, and the global index in the CEE alone trial (details appear in Figure 5). CEE indicates conjugated equine estrogens; MPA, medroxyprogesterone acetate.

statistically significant during cumulative follow-up (HR, 0.79 [95% CI, 0.65-0.97]; Figure 4).

Stratified Analyses | No appreciable differences by age or time since menopause onset emerged (Figure 5 and **Figure 6**; eFigure 2 in Supplement).

Other End Points in the Global Index: Intervention and Postintervention Results

Stroke

Intervention Phase | Stroke risk was increased with CEE plus MPA (HR, 1.37) and with CEE alone (HR, 1.35) compared with the placebo groups (Figure 2), reflecting increased ischemic but not hemorrhagic stroke risk.[10,11]

Postintervention and Cumulative Follow-up | The postintervention results were neutral in both trials (eFigure 1 in Supplement). Cumulatively, the HRs for stroke were higher in the hormone therapy groups compared with the placebo groups in both trials (HR, 1.16 for CEE plus MPA; HR, 1.15 for CEE alone) (Figure 4).

Stratified Analyses | No appreciable differences by subgroups were seen in either trial (Figures 5-6 and eFigure 2 in Supplement).

Pulmonary Embolism

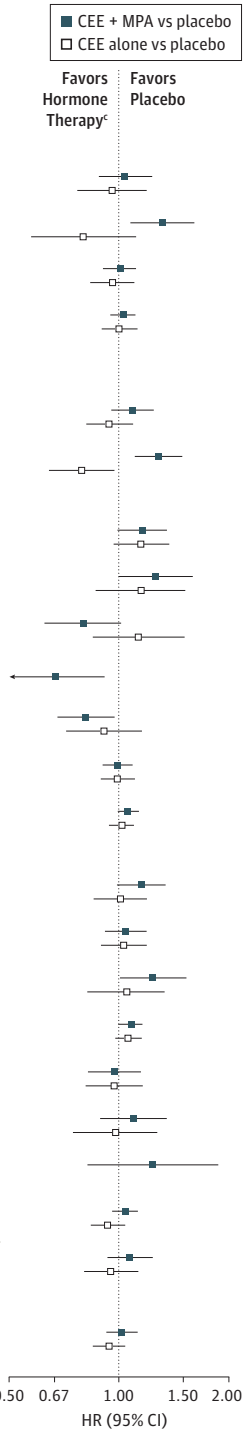
Intervention Phase | A statistically significant increase in pulmonary embolism risk was seen in women assigned to CEE plus MPA (HR, 1.98) compared with the placebo group (Figure 2), whereas the increase in pulmonary embolism risk was not statistically significant in women assigned to CEE alone (HR, 1.35).

Postintervention and Cumulative Follow-up | Poststopping results were neutral in both trials (eFigure 1 in Supplement). Cumulatively, the HRs were 1.26 (95% CI, 1.00-1.59) for CEE plus MPA and 1.15 (95% CI, 0.87-1.51) for CEE alone compared with the placebo groups (Figure 4).

Stratified Analyses | No appreciable differences by age or time since menopause onset were seen in either trial (Figures 5-6 and eFigure 2 in Supplement).

Figure 4. Postintervention Health Outcomes and Overall Combined Outcomes (Cumulative Follow-up) in the Overall Study Population in the Women's Health Initiative Hormone Therapy Trials

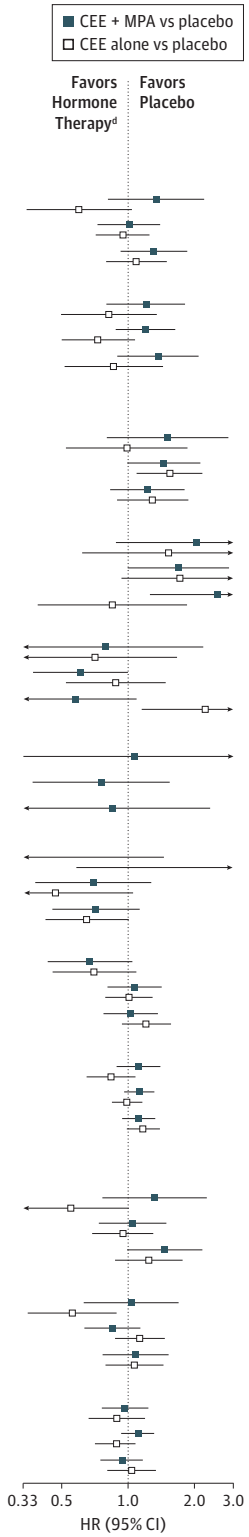
	CEE + MPA Trial					CEE Alone Trial				
	No. (%) of Events[a]					No. (%) of Events[a]				
	CEE + MPA (n = 8506)	Placebo (n = 8102)	Difference/ 10 000 PY[b]	HR (95% CI)	*P* Value	CEE (n = 5310)	Placebo (n = 5429)	Difference/ 10 000 PY[b]	HR (95% CI)	*P* Value
Postintervention										
Coronary heart disease	291 (0.55)	271 (0.53)	2	1.04 (0.89-1.23)	.61	159 (0.68)	171 (0.72)	-4	0.96 (0.77-1.19)	.70
Invasive breast cancer	228 (0.43)	168 (0.33)	10	1.32 (1.08-1.61)	.007	64 (0.27)	81 (0.34)	-7	0.80 (0.58-1.11)	.19
All-cause mortality	761 (1.39)	728 (1.39)	0	1.01 (0.91-1.11)	.90	403 (1.66)	426 (1.73)	-7	0.96 (0.84-1.10)	.54
Global index	1322 (2.75)	1261 (2.70)	4	1.03 (0.95-1.11)	.50	621 (2.90)	642 (2.96)	-6	1.00 (0.90-1.12)	.95
Cumulative follow-up (overall combined phases)										
Primary end points										
Coronary heart disease	487 (0.48)	430 (0.45)	3	1.09 (0.96-1.24)	.19	363 (0.60)	393 (0.63)	-4	0.94 (0.82-1.09)	.43
Invasive breast cancer	434 (0.43)	323 (0.34)	9	1.28 (1.11-1.48)	<.001	168 (0.28)	216 (0.35)	-7	0.79 (0.65-0.97)	.02
Other end points in global index										
Stroke	376 (0.37)	311 (0.32)	5	1.16 (1.00-1.35)	.06	278 (0.46)	253 (0.41)	5	1.15 (0.97-1.37)	.10
Pulmonary embolism	172 (0.17)	128 (0.13)	4	1.26 (1.00-1.59)	.05	107 (0.17)	96 (0.15)	2	1.15 (0.87-1.51)	.34
Colorectal cancer	126 (0.12)	150 (0.16)	-3	0.80 (0.63-1.01)	.06	100 (0.16)	90 (0.14)	2	1.13 (0.85-1.51)	.39
Endometrial cancer	68 (0.07)	96 (0.10)	-3	0.67 (0.49-0.91)	.01	NA	NA	NA	NA	NA
Hip fracture	232 (0.23)	270 (0.28)	-5	0.81 (0.68-0.97)	.02	134 (0.22)	148 (0.24)	-2	0.91 (0.72-1.15)	.44
All-cause mortality	1011 (0.98)	966 (0.99)	-1	0.99 (0.91-1.08)	.87	704 (1.14)	725 (1.14)	-1	0.99 (0.90-1.10)	.92
Global index	2198 (2.32)	1997 (2.21)	12	1.06 (1.00-1.13)	.05	1374 (2.39)	1397 (2.38)	1	1.02 (0.94-1.09)	.68
Secondary end points										
Total MI	389 (0.39)	324 (0.34)	5	1.15 (0.99-1.34)	.06	285 (0.47)	288 (0.47)	1	1.01 (0.86-1.19)	.90
CABG or PCI	506 (0.50)	471 (0.50)	1	1.04 (0.92-1.18)	.50	405 (0.68)	396 (0.65)	3	1.03 (0.90-1.19)	.65
Deep vein thrombosis	212 (0.21)	162 (0.17)	4	1.24 (1.01-1.53)	.04	135 (0.22)	133 (0.21)	1	1.05 (0.82-1.33)	.71
All cardiovascular events	1606 (1.70)	1446 (1.60)	10	1.08 (1.00-1.15)	.05	1267 (2.30)	1227 (2.15)	15	1.06 (0.98-1.15)	.12
Cardiovascular deaths	293 (0.28)	286 (0.29)	-1	0.97 (0.83-1.14)	.73	243 (0.39)	257 (0.41)	-1	0.97 (0.82-1.16)	.75
Lung cancer	198 (0.19)	171 (0.18)	2	1.10 (0.89-1.35)	.38	109 (0.18)	114 (0.18)	0	0.98 (0.75-1.27)	.87
Ovarian cancer	53 (0.05)	41 (0.04)	1	1.24 (0.83-1.87)	.30	NR	NR	NR	NR	NR
All cancer types[d]	1351 (1.40)	1233 (1.35)	5	1.04 (0.96-1.12)	.33	685 (1.16)	746 (1.24)	-8	0.93 (0.84-1.04)	.19
Cancer deaths	428 (0.42)	379 (0.39)	3	1.07 (0.93-1.23)	.32	260 (0.42)	278 (0.44)	-2	0.95 (0.81-1.13)	.58
Self-reported end points[e]										
Diabetes	931 (0.99)	855 (0.96)	3	1.02 (0.93-1.12)	.66	772 (1.45)	833 (1.55)	-10	0.94 (0.85-1.04)	.22



The all cardiovascular events outcome is defined in the Results section. CABG indicates coronary artery bypass graft; CEE, conjugated equine estrogens; HR, hazard ratio; MI, myocardial infarction; MPA, medroxyprogesterone acetate; NA, not applicable because women have had hysterectomy; NR, not reported due to small numbers; PCI, percutaneous coronary intervention; PY, person-years. [a]The percentages are annualized. [b]Difference in estimated absolute excess risks (CEE plus MPA or CEE alone minus placebo). [c]Indicates CEE alone or CEE plus MPA. [d]Excludes non-melanoma skin cancer. [e]Includes participants who did not report a prevalent condition at baseline.

Figure 5. Health Outcomes in the Women's Health Initiative Hormone Therapy Trials During the Intervention Phase According to 10-Year Age Groups at Randomization

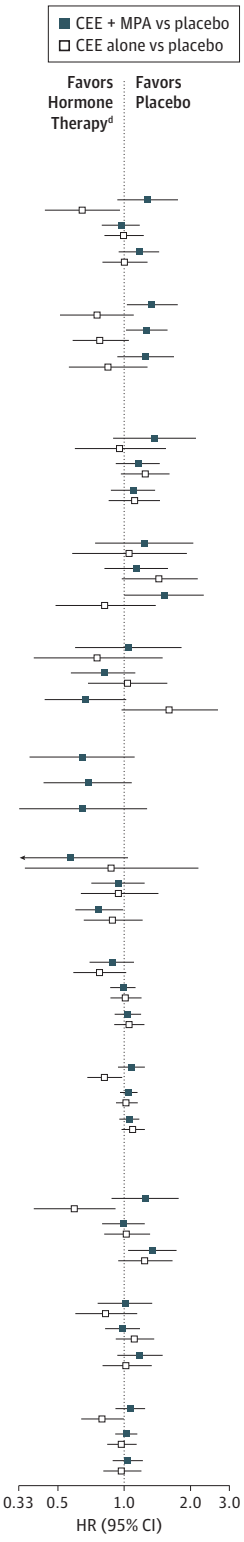
	CEE + MPA Trial					CEE Alone Trial				
	No. (%) of Events[a]					No. (%) of Events[a]				
	CEE + MPA (n = 8506)	Placebo (n = 8102)	Difference/ 10 000 PY[b]	HR (95% CI)	*P* for Trend[c]	CEE (n = 5310)	Placebo (n = 5429)	Difference/ 10 000 PY[b]	HR (95% CI)	*P* for Trend[c]
Primary end points										
Coronary heart disease										
50-59 y	38 (0.23)	27 (0.17)	5	1.34 (0.82-2.19)		21 (0.17)	35 (0.28)	-11	0.60 (0.35-1.04)	
60-69 y	79 (0.37)	73 (0.37)	0	1.01 (0.73-1.39)	.81	100 (0.61)	108 (0.63)	-3	0.95 (0.72-1.24)	.08
70-79 y	79 (0.82)	59 (0.63)	19	1.31 (0.93-1.84)		83 (0.97)	79 (0.90)	7	1.09 (0.80-1.49)	
Invasive breast cancer										
50-59 y	55 (0.33)	42 (0.27)	6	1.21 (0.81-1.80)		29 (0.24)	36 (0.29)	-5	0.82 (0.50-1.34)	
60-69 y	97 (0.45)	75 (0.38)	8	1.20 (0.89-1.62)	.68	47 (0.28)	66 (0.39)	-10	0.73 (0.51-1.07)	.89
70-79 y	54 (0.56)	38 (0.41)	15	1.37 (0.90-2.07)		28 (0.32)	33 (0.37)	-5	0.86 (0.52-1.43)	
Other end points in global index										
Stroke										
50-59 y	26 (0.15)	16 (0.10)	5	1.51 (0.81-2.82)		19 (0.16)	21 (0.17)	-1	0.99 (0.53-1.85)	
60-69 y	72 (0.34)	46 (0.23)	11	1.45 (1.00-2.11)	.50	84 (0.51)	57 (0.33)	18	1.55 (1.10-2.16)	.77
70-79 y	61 (0.63)	47 (0.50)	13	1.22 (0.84-1.79)		66 (0.77)	52 (0.59)	17	1.29 (0.90-1.86)	
Pulmonary embolism										
50-59 y	18 (0.11)	8 (0.05)	6	2.05 (0.89-4.71)		12 (0.10)	8 (0.06)	3	1.53 (0.63-3.75)	
60-69 y	40 (0.19)	22 (0.11)	8	1.69 (1.01-2.85)	.61	28 (0.17)	17 (0.10)	7	1.72 (0.94-3.14)	.28
70-79 y	29 (0.30)	11 (0.12)	18	2.54 (1.27-5.09)		12 (0.14)	14 (0.16)	-2	0.85 (0.39-1.84)	
Colorectal cancer										
50-59 y	7 (0.04)	8 (0.05)	-1	0.79 (0.29-2.18)		9 (0.07)	13 (0.10)	-3	0.71 (0.30-1.67)	
60-69 y	27 (0.13)	41 (0.21)	-8	0.61 (0.37-0.99)	.66	27 (0.16)	32 (0.19)	-2	0.88 (0.53-1.47)	.02
70-79 y	16 (0.16)	26 (0.28)	-11	0.58 (0.31-1.08)		29 (0.33)	13 (0.15)	19	2.24 (1.16-4.30)	
Endometrial cancer										
50-59 y	6 (0.04)	5 (0.03)	0	1.07 (0.33-3.53)						
60-69 y	14 (0.07)	17 (0.08)	-2	0.76 (0.37-1.53)	.81	NA	NA	NA	NA	NA
70-79 y	7 (0.07)	8 (0.09)	-1	0.85 (0.31-2.35)						
Hip fracture										
50-59 y	1 (0.01)	5 (0.03)	-3	0.17 (0.02-1.45)		5 (0.04)	1 (0.01)	3	5.01 (0.59-42.91)	
60-69 y	19 (0.09)	25 (0.12)	-4	0.70 (0.38-1.27)	.38	9 (0.05)	20 (0.12)	-6	0.47 (0.22-1.04)	.33
70-79 y	33 (0.34)	45 (0.48)	-14	0.71 (0.46-1.12)		34 (0.39)	53 (0.60)	-21	0.65 (0.42-1.00)	
All-cause mortality										
50-59 y	35 (0.21)	48 (0.31)	-10	0.67 (0.43-1.04)		35 (0.29)	50 (0.40)	-11	0.70 (0.46-1.09)	
60-69 y	111 (0.51)	94 (0.47)	5	1.07 (0.81-1.41)	.20	130 (0.78)	134 (0.77)	0	1.01 (0.79-1.29)	.04
70-79 y	104 (1.06)	96 (1.02)	4	1.03 (0.78-1.36)		136 (1.55)	115 (1.29)	26	1.21 (0.95-1.56)	
Global index										
50-59 y	170 (1.03)	141 (0.91)	12	1.12 (0.89-1.40)		117 (0.98)	142 (1.17)	-19	0.84 (0.66-1.07)	
60-69 y	393 (1.89)	325 (1.67)	22	1.13 (0.97-1.31)	>.99	336 (2.10)	348 (2.11)	-1	0.99 (0.85-1.15)	.02
70-79 y	313 (3.42)	270 (3.03)	38	1.12 (0.95-1.32)		300 (3.67)	265 (3.16)	51	1.17 (0.99-1.39)	
Selected secondary end points										
Total MI										
50-59 y	32 (0.19)	23 (0.15)	4	1.32 (0.77-2.25)		17 (0.14)	31 (0.25)	-11	0.55 (0.31-1.00)	
60-69 y	70 (0.33)	62 (0.31)	2	1.05 (0.74-1.47)	.55	76 (0.46)	82 (0.48)	-2	0.95 (0.69-1.30)	.02
70-79 y	66 (0.69)	44 (0.47)	21	1.46 (1.00-2.15)		71 (0.83)	60 (0.69)	14	1.24 (0.88-1.75)	
CABG or PCI										
50-59 y	34 (0.20)	32 (0.20)	0	1.03 (0.63-1.68)		29 (0.24)	51 (0.41)	-17	0.56 (0.35-0.88)	
60-69 y	92 (0.43)	103 (0.52)	-9	0.85 (0.64-1.13)	.67	129 (0.79)	116 (0.69)	11	1.13 (0.88-1.46)	.06
70-79 y	72 (0.75)	65 (0.70)	5	1.08 (0.77-1.51)		91 (1.07)	88 (1.02)	5	1.07 (0.79-1.43)	
All cancer types[e]										
50-59 y	138 (0.83)	130 (0.84)	-1	0.97 (0.76-1.23)		85 (0.71)	96 (0.79)	-8	0.89 (0.66-1.19)	
60-69 y	298 (1.42)	249 (1.28)	15	1.11 (0.93-1.31)	.77	185 (1.14)	216 (1.29)	-15	0.89 (0.73-1.08)	.39
70-79 y	162 (1.71)	164 (1.82)	-11	0.94 (0.75-1.17)		129 (1.52)	126 (1.47)	6	1.04 (0.81-1.33)	



CABG indicates coronary artery bypass graft; CEE, conjugated equine estrogens; HR, hazard ratio; MI, myocardial infarction; MPA, medroxyprogesterone acetate; NA, not applicable because women have had hysterectomy; PCI, percutaneous coronary intervention; PY, person-years. [a]The percentages are annualized. [b]Difference in estimated absolute excess risks (CEE plus MPA or CEE alone minus placebo). [c]For trend by age group. [d]Indicates CEE alone or CEE plus MPA. [e]Excludes non–melanoma skin cancer.

Figure 6. Health Outcomes in the Women's Health Initiative Hormone Therapy Trials for the Overall Combined Phases (Cumulative Follow-up) According to 10-Year Age Groups at Randomization

	CEE + MPA Trial					CEE Alone Trial				
	No. (%) of Events[a]					No. (%) of Events[a]				
	CEE + MPA (n = 8506)	Placebo (n = 8102)	Difference/ 10 000 PY[b]	HR (95% CI)	*P* for Trend[c]	CEE (n = 5310)	Placebo (n = 5429)	Difference/ 10 000 PY[b]	HR (95% CI)	*P* for Trend[c]
Primary end points										
Coronary heart disease										
50-59 y	93 (0.26)	69 (0.21)	5	1.27 (0.93-1.74)		42 (0.21)	64 (0.32)	-11	0.65 (0.44-0.96)	
60-69 y	201 (0.44)	199 (0.46)	-2	0.97 (0.79-1.18)	.99	183 (0.67)	188 (0.67)	0	1.00 (0.82-1.23)	.12
70-79 y	193 (0.98)	162 (0.84)	14	1.17 (0.95-1.44)		138 (1.03)	141 (1.03)	0	1.01 (0.80-1.28)	
Invasive breast cancer										
50-59 y	132 (0.37)	93 (0.28)	9	1.34 (1.03-1.75)		46 (0.23)	61 (0.30)	-7	0.76 (0.52-1.11)	
60-69 y	198 (0.43)	149 (0.34)	9	1.27 (1.02-1.57)	.72	80 (0.29)	105 (0.37)	-8	0.78 (0.58-1.05)	.70
70-79 y	104 (0.53)	81 (0.42)	11	1.25 (0.94-1.67)		42 (0.31)	50 (0.36)	-5	0.85 (0.56-1.28)	
Other end points in global index										
Stroke										
50-59 y	52 (0.15)	35 (0.10)	4	1.37 (0.89-2.11)		33 (0.16)	36 (0.18)	-1	0.96 (0.60-1.55)	
60-69 y	168 (0.36)	138 (0.32)	5	1.16 (0.92-1.45)	.40	134 (0.49)	114 (0.40)	9	1.25 (0.97-1.60)	.87
70-79 y	156 (0.79)	138 (0.72)	8	1.10 (0.87-1.38)		111 (0.82)	103 (0.75)	7	1.12 (0.85-1.46)	
Pulmonary embolism										
50-59 y	35 (0.10)	26 (0.08)	2	1.24 (0.74-2.06)		22 (0.11)	21 (0.10)	1	1.06 (0.58-1.93)	
60-69 y	79 (0.17)	65 (0.15)	2	1.14 (0.82-1.58)	.46	59 (0.21)	42 (0.15)	7	1.45 (0.97-2.15)	.43
70-79 y	58 (0.29)	37 (0.19)	10	1.52 (1.01-2.30)		26 (0.19)	33 (0.24)	-5	0.82 (0.49-1.38)	
Colorectal cancer										
50-59 y	27 (0.08)	24 (0.07)	0	1.05 (0.60-1.81)		15 (0.07)	20 (0.10)	-2	0.76 (0.39-1.49)	
60-69 y	63 (0.14)	74 (0.17)	-3	0.81 (0.58-1.13)	.21	45 (0.16)	45 (0.16)	1	1.04 (0.69-1.57)	.07
70-79 y	36 (0.18)	52 (0.27)	-9	0.67 (0.44-1.02)		40 (0.29)	25 (0.18)	11	1.61 (0.98-2.66)	
Endometrial cancer										
50-59 y	22 (0.06)	31 (0.09)	-3	0.65 (0.37-1.12)						
60-69 y	32 (0.07)	44 (0.10)	-3	0.69 (0.44-1.08)	.97	NA	NA	NA	NA	NA
70-79 y	14 (0.07)	21 (0.11)	-4	0.65 (0.33-1.27)						
Hip fracture										
50-59 y	17 (0.05)	28 (0.08)	-4	0.57 (0.31-1.04)		9 (0.04)	10 (0.05)	0	0.88 (0.36-2.17)	
60-69 y	103 (0.22)	100 (0.23)	-1	0.94 (0.71-1.24)	.93	46 (0.17)	49 (0.17)	0	0.95 (0.64-1.43)	.89
70-79 y	112 (0.57)	142 (0.75)	-18	0.77 (0.60-0.99)		79 (0.58)	89 (0.65)	-7	0.89 (0.66-1.21)	
All-cause mortality										
50-59 y	141 (0.39)	149 (0.44)	-5	0.88 (0.70-1.11)		90 (0.45)	115 (0.56)	-12	0.78 (0.59-1.03)	
60-69 y	452 (0.97)	429 (0.97)	-1	0.99 (0.87-1.13)	.23	301 (1.08)	308 (1.07)	1	1.02 (0.87-1.19)	.10
70-79 y	418 (2.07)	388 (1.97)	9	1.04 (0.91-1.20)		313 (2.26)	302 (2.15)	11	1.06 (0.90-1.24)	
Global index										
50-59 y	431 (1.27)	377 (1.17)	10	1.08 (0.94-1.24)		214 (1.10)	264 (1.36)	-26	0.82 (0.68-0.98)	
60-69 y	999 (2.33)	906 (2.21)	11	1.05 (0.96-1.15)	.83	637 (2.47)	637 (2.40)	8	1.03 (0.92-1.15)	.01
70-79 y	768 (4.36)	714 (4.12)	24	1.06 (0.96-1.17)		523 (4.23)	496 (3.90)	33	1.10 (0.97-1.25)	
Selected secondary end points										
Total MI										
50-59 y	75 (0.21)	57 (0.17)	4	1.25 (0.88-1.76)		35 (0.17)	58 (0.29)	-11	0.60 (0.39-0.91)	
60-69 y	165 (0.36)	158 (0.36)	0	0.99 (0.80-1.24)	.46	140 (0.52)	139 (0.49)	2	1.03 (0.82-1.31)	.007
70-79 y	149 (0.76)	109 (0.57)	19	1.34 (1.05-1.72)		110 (0.82)	91 (0.67)	16	1.25 (0.95-1.65)	
CABG or PCI										
50-59 y	102 (0.29)	96 (0.29)	0	1.01 (0.76-1.34)		71 (0.36)	83 (0.42)	-6	0.83 (0.60-1.14)	
60-69 y	246 (0.54)	244 (0.57)	-3	0.98 (0.82-1.18)	.34	212 (0.80)	192 (0.69)	10	1.12 (0.92-1.37)	.40
70-79 y	158 (0.81)	131 (0.69)	12	1.18 (0.94-1.49)		122 (0.93)	121 (0.90)	2	1.03 (0.80-1.33)	
All cancer types[e]										
50-59 y	366 (1.07)	321 (1.00)	7	1.07 (0.92-1.24)		147 (0.75)	182 (0.93)	-18	0.80 (0.64-0.99)	
60-69 y	644 (1.47)	595 (1.44)	4	1.02 (0.92-1.14)	.80	336 (1.27)	358 (1.31)	-4	0.98 (0.84-1.14)	.18
70-79 y	341 (1.81)	317 (1.75)	7	1.04 (0.89-1.21)		202 (1.53)	206 (1.55)	-2	0.98 (0.81-1.19)	



CABG indicates coronary artery bypass graft; CEE, conjugated equine estrogens; HR, hazard ratio; MI, myocardial infarction; MPA, medroxyprogesterone acetate; NA, not applicable because women have had hysterectomy; PCI, percutaneous coronary intervention; PY, person-years. [a]The percentages are annualized. [b]Difference in estimated absolute excess risks (CEE plus MPA or CEE alone minus placebo). [c]For trend by age group. [d]Indicates CEE alone or CEE plus MPA. [e]Excludes non–melanoma skin cancer.

Colorectal Cancer

Intervention Phase | Results for colorectal cancer differed between the 2 trials. For women assigned to CEE plus MPA, the HR was 0.62 (95% CI, 0.43-0.89) compared with the placebo group (Figure 2), but the cancer cases were diagnosed at a more advanced stage.[18] For women assigned to CEE alone, hormone therapy did not affect colorectal cancer incidence (HR, 1.15; 95% CI, 0.81-1.64).

Postintervention and Cumulative Follow-up | Poststopping and cumulative HRs were neutral in both trials (Figure 4 and eFigure 1 in Supplement).

Stratified Analyses | For women assigned to CEE alone, results were more adverse in older compared with younger women (P = .02 for trend), but age differences were not apparent for those assigned to CEE plus MPA (Figure 5).

Endometrial Cancer

Intervention Phase | Women in the CEE plus MPA group compared with the placebo group had an HR of 0.83 (95% CI, 0.49-1.40; Figure 2).

Postintervention and Cumulative Follow-up | A reduced risk of endometrial cancer with CEE plus MPA emerged postintervention (HR, 0.58; 95% CI, 0.40-0.86) compared with the placebo group (eFigure 1 in Supplement) and for cumulative follow-up (HR, 0.67 [95% CI, 0.49-0.91]; Figure 4).

Hip Fracture

Intervention Phase | Women in the CEE plus MPA and CEE alone groups compared with the placebo groups had statistically significant 33% reductions in hip fracture (Figure 2).

Postintervention and Cumulative Follow-up | The risk reductions were attenuated in both trials postintervention (eFigure 1 in Supplement); however, a significant fracture benefit persisted over 13 years for women assigned to CEE plus MPA (HR, 0.81 [95% CI, 0.68-0.97]; Figure 4).

Stratified Analyses | Results in the CEE alone trial were more favorable for women with greater time since menopause onset (eFigure 2 in Supplement).

All-Cause Mortality

Intervention Phase | Neither CEE plus MPA nor CEE alone affected all-cause mortality (Figure 2).

Postintervention and Cumulative Follow-up | All-cause mortality remained neutral postintervention and during cumulative follow-up in both trials (Figure 4). The cumulative follow-up HR was 0.99 (95% CI, 0.91-1.08) for CEE plus MPA compared with placebo and 0.99 (95% CI, 0.90-1.10) for CEE alone compared with placebo (Figure 4).

Stratified Analyses | In both trials, patterns of more favorable results for all-cause mortality in younger than older women were apparent during the intervention phase. Among women aged 50 to 59 years, the HRs were 0.67 (95% CI, 0.43-1.04) in the CEE plus MPA trial and 0.70 (95% CI, 0.46-1.09) in the CEE alone trial; however, the HRs ranged from 1.01 to 1.21 among women aged 60 to 79 years (Figure 5). The nominal P value for trend by age was only significant (P = .04) in the CEE alone trial. Trends with time since menopause onset were similar but not significant (eFigure 2 in Supplement).

Global Index

Intervention Phase | Overall, the health risks of CEE plus MPA significantly outweighed the benefits. For the global index of monitored events, which included the outcomes listed above, the HR was elevated for CEE plus MPA at 1.12 (95% CI, 1.02-1.24) compared with placebo (Figure 2). In absolute terms, for every 10 000 women taking CEE plus MPA per year, there were 6 more coronary events, 9 more strokes, 9 more pulmonary emboli, 9 more cases of breast cancer, 6 fewer cases of colorectal cancer, 1 fewer case of endometrial cancer, 6 fewer hip fractures, and 1 fewer death, yielding a net effect of 20 additional adverse events per 10 000 person-years (Figure 2 and Figure 3). The corresponding HR for the global index for CEE alone was 1.03 (95% CI, 0.93-1.13) with a net of 4 adverse events.

Postintervention and Cumulative Follow-up | Because most risks became attenuated after stopping therapy, the global index was neutral for both trials postintervention and cumulatively (Figure 4 and eFigure 1 in Supplement).

Stratified Analyses | The global index HR for women assigned to CEE plus MPA was not modified by age (P > .99 for trend); however, for women assigned to CEE alone, the HR was more favorable in younger women (P = .02 for trend; Figure 5). The absolute risks of adverse events were lower in both trials in younger than older women. For CEE plus MPA compared with placebo, women aged 50 to 59 years had 12 more adverse events per 10 000 person-years; 60 though 69 years, 22 more; and 70 to 79 years, 38 more. For CEE alone compared with placebo, women aged 50 to 59 years had 19 fewer adverse events per 10 000 person-years, whereas women aged 70 to 79 years had 51 more adverse events per 10 000 person-years (Figure 5).

Effect modification by age for CEE alone was more pronounced during cumulative follow-up (P = .01 for trend by age). Compared with placebo, there were 26 fewer adverse events per 10 000 person-years among women aged 50 to 59 years assigned to CEE alone and 33 more adverse events per 10 000 person-years among those aged 70 to 79 years (Figure 6).

Secondary End Points in the 2 Trials: Intervention and Postintervention Results

The results for other clinical end points in the trial are summarized herein but more details are available in the Supplement.

Myocardial Infarction

Overall, results for MI were similar to those for CHD (Figure 2). However, differences by age or time since menopause onset emerged during the intervention phase of both trials. For CEE plus MPA, statistically significant differences were apparent by time since menopause onset (HRs were 0.91, 1.16, and 1.99 with increasing decade past menopause onset, respectively; P = .01 for trend; eFigure 2 in Supplement) but not by age (Figure 5). For CEE alone, the HRs increased with increasing decade of age (HRs of 0.55 for 50-59 years, 0.95 for 60-69 years, and 1.24 for 70-79 years; P = .02 for trend; Figure 5 and eFigure 3 in Supplement). Cumulatively, the differences by time since menopause onset for CEE plus MPA persisted (P = .02 for trend) and the differences by age for CEE alone became more pronounced (P = .007 for trend; Figure 6).

Other Secondary Cardiovascular Disease Outcomes

Results for coronary artery bypass graft or percutaneous coronary intervention were neutral in both trials; findings for deep vein thrombosis generally paralleled those for pulmonary embolism (Figure 2 and Figure 4). The all cardiovascular events outcome in Figure 2 includes MI, stroke, coronary artery bypass graft or percutaneous coronary intervention, angina, heart failure, carotid artery disease, peripheral vascular disease, venous thromboembolism, and cardiovascular death. The HRs were significantly elevated for total cardiovascular events during the intervention phase of both trials, but were neutral during the postintervention phase. For cardiovascular death, results were neutral throughout the trial phases (Figure 2, Figure 4, and eFigure 1 in Supplement).

Secondary Cancer Outcomes

The incidence of lung and ovarian cancer did not differ significantly between randomization groups (Figure 2 and Figure 4). An adverse effect of CEE plus MPA, but not CEE alone, on lung cancer mortality has been observed in the WHI.[19,20] Neither intervention was associated with total cancer incidence (ie, all cancer types in Figure 2 and Figure 4); the cumulative HR was 1.04 (95% CI, 0.96-1.12) for CEE plus MPA and 0.93 (95% CI, 0.84-1.04) for CEE alone (Figure 4). Women aged 50 to 59 years in the CEE alone group had a lower cumulative incidence of total cancer compared with the placebo group (HR, 0.80 [95% CI, 0.64-0.99]; ie, all cancer types in Figure 6), but age interactions were not significant.

During the intervention phase, total cancer mortality did not differ between randomization groups in either trial (Figure 2); during cumulative follow-up, the HRs were 1.07 (95% CI, 0.93-1.23) for CEE plus MPA and 0.95 (95% CI, 0.81-1.13) for CEE alone. When examined by age, the HRs for total cancer mortality in the CEE alone trial were more adverse for women older than 70 years (HRs for increasing age groups were 0.77, 0.77, 1.36; P = .05 for trend; eFigure 3 in Supplement), but this trend was not significant in cumulative results (eFigure 4 in Supplement). No effect modification by age or time since menopause onset was detected for cancer mortality in the CEE plus MPA trial.

Clinical Vertebral and Total Fractures

In both trials, results for clinical vertebral and total fractures paralleled those for hip fracture (Figure 2 and eFigure 3 in Supplement).

Dementia

A subset of WHI participants aged 65 years or older at enrollment underwent cognitive testing in the WHI memory study.[21,22] The HRs for probable dementia were 2.01 (95% CI, 1.19-3.42) during the intervention phase of the CEE plus MPA trial and 1.47 (95% CI, 0.85-2.52) for the CEE alone trial (Figure 2). For women aged 50 to 55 years at randomization, cognitive assessments that were conducted an average of 7.2 years postintervention showed neutral results.[23]

Self-reported End Points, Self-reported Symptoms, and Quality-of-Life Outcomes in the 2 Trials

In both trials, women assigned hormone therapy had significantly lower rates of treated diabetes than women assigned placebo (HR, 0.81 [95% CI, 0.70-0.94] for CEE plus MPA and 0.86 [95% CI, 0.76-0.98] for CEE alone; Figure 2). However, rates of gallbladder disease were approximately 50% higher among women assigned to hormone therapy in both trials (Figure 2). Self-reported urinary incontinence[24] (at least once/week) was also higher in women assigned to CEE plus MPA (HR, 1.49; 95% CI, 1.36-1.63) or CEE alone (HR, 1.61; 95% CI, 1.46-1.79) than in those assigned to placebo (Figure 2) and were attenuated but still higher poststopping in both trials (eFigure 1 in Supplement). The reductions in diabetes dissipated postintervention in both trials (Figure 4 and eFigure 1 in Supplement), whereas the HRs for gallbladder disease were attenuated but still elevated for CEE plus MPA and became neutral for CEE alone. No significant differences by age group were observed for these outcomes.

Among younger women (aged 50-54 years) experiencing moderate or severe hot flashes, night sweats, or both at enrollment (n = 979), those in both the CEE plus MPA and CEE alone groups had substantial reductions in symptoms (64% and 28%, respectively, vs placebo at 1 year; Figure 2). In the overall cohort, women assigned to CEE plus MPA and CEE alone reported less sleep disturbances (assessed by a 5-item validated scale[25,26]), but more breast tenderness than in those receiving placebo (Figure 2 and eFigure 5 in Supplement). Women receiving CEE plus MPA were less likely to have joint pain than those receiving placebo.

Regarding health-related quality of life (RAND 36-Item Short Form Health Survey),[9,27] treatment with CEE plus MPA compared with placebo was associated with a small but statistically significant benefit for physical functioning, role physical, bodily pain, and general health, and neutral results for the other subscales at 1 year (eFigure 5 in Supplement). Treatment with CEE alone was associated with nominally significant adverse effects for social functioning and emotional role (eFigure 5 in Supplement). No significant differences in depressive symptom scores were observed. Postintervention symptoms of breast tenderness were similar between treatment groups in both trials but the direction of some of the other associations was reversed (eFigure 1 in Supplement), particu-

larly joint pain. Additional information about other patient-reported outcomes appears in the Supplement.

Additional Analyses Conducted in the 2 Trials

Women Without Prerandomization Use of Hormone Therapy

Approximately one-quarter of CEE plus MPA trial participants and half of CEE alone trial participants had used hormone therapy prior to randomization. To simulate first initiation of hormone therapy in clinical practice, secondary analyses were conducted to assess women without hormone therapy use prior to randomization, stratified by age group (eFigure 6 in Supplement). The age-stratified findings remained similar to the primary analysis for the CEE plus MPA trial, but were slightly more favorable for younger women in the CEE alone trial. Among women aged 50 to 59 years without prior hormone therapy use, the global index was significantly better for those assigned CEE alone compared with placebo (HR, 0.71; 95% CI, 0.50-0.99). There were 40 fewer adverse events per 10 000 person-years in this age group in the CEE alone group compared with 34 excess events per 10 000 person-years among women aged 70 to 79 years.

Analyses Stratified by Vasomotor Symptoms at Baseline

Women aged 70 to 79 years with moderate to severe vasomotor symptoms at baseline assigned to CEE plus MPA had an HR for CHD of 5.79 (95% CI, 1.29-25.97), whereas women in younger age groups (with or without vasomotor symptoms) did not have significantly elevated CHD risks (eFigure 7 in Supplement). Similarly, women aged 70 to 79 years who had moderate to severe vasomotor symptoms and were assigned to CEE alone had an HR for CHD of 4.34 (95% CI, 1.43-13.14) compared with women assigned placebo, whereas women in younger age groups (with or without vasomotor symptoms) had no excess risk. Thus, CHD risk with both hormone therapy regimens was particularly high in the small group of women aged 70 years or older with moderate to severe vasomotor symptoms (n = 392; 4.8% and 8.7% of women in this age group in the CEE plus MPA and CEE alone trials, respectively), but the 3-way interactions by age and vasomotor symptoms were nominally significant only when CEE was taken alone (P = .04). Such interactions were not observed for other disease outcomes.

Sensitivity Analyses Censoring for Noncompliance With Study Pills

Secondary analyses among adherent women (censoring women within 6 months of reporting <80% compliance with study pills) were generally similar to intention-to-treat results but tended to accentuate the findings in each trial. For example, the intervention phase adherence-adjusted HR for CHD was 1.32 (95% CI, 1.00-1.75) in the CEE plus MPA trial and 0.85 (95% CI, 0.64-1.14) in the CEE alone trial, whereas the HR for breast cancer was 1.52 (95% CI, 1.15-2.00) in the CEE plus MPA trial and 0.58 (95% CI, 0.39-0.84) in the CEE alone trial.

Other Analyses

A detailed presentation of biomarker findings and analyses stratified by other baseline characteristics is beyond the scope of this article. However, several additional analyses with potential relevance to clinical decision making about hormone therapy appear in the Supplement.

Discussion

This report provides a comprehensive overview of findings from the intervention and extended postintervention phases of the CEE plus MPA and CEE alone trials of the WHI, representing 13 years of cumulative follow-up. Key findings include differences in the benefit-to-risk profile for CEE plus MPA compared with CEE alone, and the role of age, time since menopause onset, and other factors in modifying the effects of hormone therapy on some outcomes.

Overall, the risks of CEE plus MPA therapy during the intervention phase outweighed the benefits. Most risks and benefits from CEE plus MPA dissipated postintervention; however, cardiovascular disease events remained nonsignificantly elevated, a reduction in endometrial cancer emerged, hip fractures remained cumulatively reduced, and breast cancer HRs remained above unity. Among women with prior hysterectomy, the benefits and risks of CEE alone therapy during the intervention phase were more balanced, with increased risks of stroke and venous thrombosis, reduced risk of hip and total fractures, and a nonsignificant reduction in invasive breast cancer. A significant decrease in breast cancer emerged postintervention among women assigned CEE alone, but most other outcomes were neutral. Thus, breast cancer findings were divergent between the 2 trials and, for both cancer and cardiovascular disease outcomes, results tended to be more adverse for CEE plus MPA than for CEE alone.

The effects of hormone therapy on clinical outcomes were influenced in some cases by age or time since onset of menopause. For CEE alone during the intervention phase, results were more favorable for younger than older women for all-cause mortality, MI, deaths due to cancer, and the global index. Both regimens, however, were associated with increased risk of stroke, venous thrombosis, gallbladder disease, and urinary incontinence, without clear differences by age. For CEE plus MPA, invasive breast cancer was an additional adverse effect and, although risk of MI varied by time since menopause onset, the overall risks outweighed the benefits across all age groups.

The potential influence of age or time since menopause onset on the relationship between hormone therapy and vascular disease has received considerable attention.[28-32] It has been postulated that estrogen may slow down the early stages of atherosclerosis and have favorable endothelial effects in women with recent onset of menopause but have adverse and plaque-destabilizing effects on advanced atherosclerotic lesions.[28,32] Overall, the WHI findings suggest that hormone therapy has a harmful effect on CHD risk among older women, whereas the results in younger women remain inconclusive. Lower absolute risks of adverse events with hormone therapy in younger women, however, lead to lower attributable risks in these age groups. Whether menopausal hormone therapy has a particularly adverse effect on coronary risk in older women with vasomotor symptoms remains unclear.[33-35] These symptoms have

been associated with higher coronary risk in some reports,[33,35] and have been previously linked to adverse outcomes with hormone therapy among women with prevalent CHD.[36] Due to the small sizes of these subgroups in the WHI and other studies, however, further research is needed.

Treatment with CEE plus MPA increased breast cancer incidence and cancer cases were diagnosed at a higher cancer stage, likely reflecting diagnostic delay due to interference with mammographic detection.[37] Although a residual elevation in breast cancer risk was seen with CEE plus MPA postintervention, analyses demonstrated year-to-year reductions in HRs after stopping hormone therapy. In contrast, the significant reduction in breast cancer seen with CEE alone[38,39] was unexpected and differs from the results of many observational studies.[40,41] Although differential mammography use in those with hormone therapy use compared with those with nonuse of hormone therapy in observational studies may explain some of the differences, the opposite findings for CEE alone compared with CEE plus MPA in the randomized trials points to a determinant influence of progestin on the breast epithelium.[42] Full discussion of the complex processes mediating these differences[43,44] is beyond the scope of this report.

Fewer colorectal cancer cases were diagnosed during the CEE plus MPA intervention phase but the cancer cases were diagnosed at a higher stage, potentially reflecting differential detection (Supplement).[18] Treatment with CEE plus MPA reduced the risk of endometrial cancer; however, both hormone therapy regimens may increase ovarian cancer risk.[45] Women treated with CEE plus MPA had increased rates of death from (but not incidence of) lung cancer, whereas no effect on these outcomes was seen in women treated with CEE alone.[20] Neither treatment with CEE plus MPA nor CEE alone influenced total cancer incidence or total cancer mortality.

Both CEE plus MPA and CEE alone reduced diabetes risk during the intervention phase, which is when improvements in measured glucose and insulin levels also were documented[46,47]; however, the risk reductions dissipated postintervention. Both regimens increased risks for venous thrombosis and gallbladder disease. Among participants aged 65 years or older, hormone therapy increased probable dementia risk, with results for CEE plus MPA more adverse than for CEE alone. Women aged 50 to 54 years with moderate to severe vasomotor symptoms at baseline experienced symptom reductions with hormone therapy, and women overall had fewer sleep disturbances and joint pain, although incidence of rheumatoid arthritis was not reduced.[48] Overall, results for self-reported symptoms with both interventions were mixed and few additional quality-of-life benefits were observed.

Despite the large size and numerous strengths of the WHI randomized hormone therapy trials, some limitations warrant consideration. Only 1 dose, formulation, and route of administration in each trial was assessed; thus, results are not necessarily generalizable to other hormone preparations. Event information collected poststopping represents unblinded reporting and nearly 20% of surviving participants did not consent to extended follow-up. Multiple outcomes and subgroups (some with low power) were examined, potentially leading to both false-positive and false-negative results. Thus, the nominal *P* values and 95% confidence intervals presented herein should be interpreted cautiously.

Conclusion

In summary, current WHI findings based on results from the intervention, postintervention, and cumulative follow-up phases do not support the use of either CEE plus MPA or CEE alone for chronic disease prevention. The risks of CEE plus MPA outweigh the benefits irrespective of a woman's age; however, a more favorable risk-to-benefit ratio was seen in younger women with prior hysterectomy who received CEE alone. Increased risks of stroke and venous thrombosis, as well as gallstones and urinary incontinence, in both younger and older women remain a concern with both regimens. Even though hormone therapy is a reasonable option for the management of moderate to severe menopausal symptoms among generally healthy women during early menopause, the risks associated with hormone therapy, in conjunction with the multiple testing limitations attending subgroup analyses, preclude a recommendation in support of its use for disease prevention even among younger women. Current findings also suggest caution when considering hormone therapy treatment in older age groups, even in the presence of persistent vasomotor symptoms, given the high risk of CHD and other outcomes associated with hormone therapy use in this setting.

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Additional Information: A full list of all the investigators who have contributed to Women's Health Initiative science appears at https://cleo.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf.

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