## WEB MATERIAL

## Randomized Trial Evaluation of the Benefits and Risks of Menopausal Hormone

## Therapy Among Women 50-59 Years of Age

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#### Web Appendix 1. Saturated and Parsimonious Hazard Ratio (Cox) Models

Let z, a<sub>1</sub> ,a<sub>2</sub>, and s denote indicator variables for assignment to active hormone treatment, baseline age 60-69 years, baseline age 70-79 years, and inclusion in stratum s, respectively. The hazard rate for outcome k at time from randomization t for a participant having characteristics z, a<sub>1</sub>, a<sub>2</sub>, s under the 'saturated' hazard ratio (Cox) model is

 $h_k(t; z, a_1, a_2, s) = h_{ks}(t) \exp(zb_{1k} + za_1b_{2k} + za_2b_{3k})$ , for each outcome k.

The corresponding parsimonious hazard rate under the 'parsimonious' model is

 $h_k(t; z, a_1, a_2, s) = h_{ks}(t) \exp(zb_{1k} + za_1b_2 + za_2b_3)$ , for each outcome k.

In these expressions the stratification s involves cross classification by baseline characteristics of age (50-59, 60-69, 70-79), randomization status in the companion WHI Dietary Modification trial, prior diagnosis of outcome k, race/ethnicity, prior menopausal hormone therapy use, as well as by (follow-up time-dependent) study phase.

Regression parameters are estimated by partial likelihood, and P-values for the parsimonious model versus the saturated model are based on the partial likelihood ratio test.

**Web Figure 1**. Flow of participants in the WHI CEE-Alone and CEE+MPA trials through extended follow-up (entire cohort). Participants were postmenopausal and aged 50-79 when enrolled at 40 U.S. clinical centers during 1993-1998.

\*Fact of death is known for participants who did not provide consent for extended follow-up.



**Web Figure 2a**. Primary outcomes, other monitored outcomes, and global outcomes in the Women's Health Initiative CEE-alone trial during the intervention phase and cumulative follow-up among participants 60 to 69 years at randomization. Statistical models are similar to those described in Figure 1 for 50 to 59y participants in the CEE-alone trial. Participants were postmenopausal and aged 50-79 when enrolled at 40 U.S. clinical centers during 1993-1998.

	CEE-alone trial Subgroup 60- (N=10,739) (N=4,851)			p 60−69 y ,851)	Multivariate	marginal estimates o	HR (95%CI) for subgroup 60 to 69 y				
ntervention phase	# of even CEE-alone (N = 5.310)	ents (%*) Placebo (N = 5.429)	# of even CEE-alone (N = 2,386)	ents (%*) Placebo (N = 2.465)	Saturated mode solely derive	l (subgroup estimates ed from 60 to 69 y)	Parsimon I HR(95%CI)	ious model (sul everaged entire P-valuet	ogroup estimates cohort)		
Primary outcomes	(1 3,310)	11 3,423/	(11 2,000)	(1 2,403)	Indesticit		mgooner	1 Value			
Coronary heart disease	205(0.55)	222(0.58)	101(0.61)	108(0.63)	0.96(0.73.1.25)	<b>_</b> i	0.95(0.76.1.18)	0.12	<b></b>		
Invasive breast cancer	103(0.28)	135(0.35)	47(0.28)	66(0.39)	0.73(0.50,1.05)		0.80(0.60,1.06)	0.12	- <b>-</b> - <b>-</b>		
Other monitored outcomes											
Stroke	174(0.47)	130(0.34)	87(0.53)	57(0.33)	1.63(1.17,2.27)	⊧ —_ <b>∎</b>	1.37(1.06,1.76)		<b>↓</b>		
Pulmonary embolism	52(0.14)	39(0,10)	28(0.17)	17(0.098)	1.72(0.94.3.15)	<b>↓ →</b>	1.37(0.89.2.11)		_ <b></b>		
Colorectal cancer	65(0.17)	58(0.15)	27(0.16)	32(0.19)	0.87(0.52,1.45)	<b>_</b> .	1.13(0.78,1.64)		<b>i</b>		
Hip fracture	48(0.13)	74(0.19)	9(0.054)	20(0.12)	0.46(0.21.1.03) ←	- <b>e</b>	0.61(0.41.0.91)	_	<b></b> }		
All-cause mortality	301(0.80)	299(0.77)	130(0.78)	134(0.77)	1.01(0.80,1.29)	<b>_</b>	1.02(0.84,1.25)		- <b>+</b> -		
Global indices											
Univariate^	756(2.09)	754(2.04)	339(2.12)	347(2.11)	1.00(0.86.1.17)	<b></b>					
Multivariate <sup>1</sup>	948(2.51)	957(2.47)	429(2.57)	434(2.51)	1.03(0.88,1.20)	+	1.02(0.88,1.19)		+		

	# of events (%*)		%*) # of events (%*)		Saturated model (subgroup estimates				Parsimonious model (subgroup estimates				
	CEE-alone	Placebo	CEE-alone	Placebo	solely de	rived from (	60 to 69 y)			leverag	ed entire	+ cohort)	)
Cumulative follow-up	(N = 5,310)	(N = 5,429)	(N = 2,386)	(N = 2,465)	HR(95%CI)				HR(95%CI)	P-value†			
Primary outcomes											,	,	
Coronary heart disease	521(0.69)	550(0.71)	259(0.76)	276(0.78)	0.98(0.83,1.16)				1.00(0.88,1.15)	0.79		-	
Invasive breast cancer	231(0.30)	291(0.38)	107(0.31)	138(0.39)	0.80(0.62,1.03)		ьł		0.84(0.70,1.01)			╼┤	
Other monitored outcomes													
Stroke	399(0.53)	392(0.50)	197(0.58)	196(0.55)	1 07(0 88 1 30)		_ <b>_</b>		1 08(0 92 1 25)			╶┼┳╌	
Pulmonary embolism	153(0.20)	150(0 19)	83(0.24)	71(0.20)	1 26(0 91 1 73)				1 10(0 88 1 39)				
Colorectal cancer	119(0.15)	118(0.15)	57(0.16)	60(0.17)	0.99(0.69.1.42)	_	_		1 05(0 81 1 36)			_	
Hip fracture	208(0.27)	229(0.29)	87(0.25)	92(0.25)	0.97(0.73.1.31)	_	_		0.92(0.75.1.12)			_ <b>_</b>	
All-cause mortality**	1258(1.62)	1277(1.61)	559(1.59)	572(1.56)	1.03(0.92,1.16)		+		1.03(0.93,1.14)			+	
Global indices													
Univariate <sup>A</sup>	1997(2.84)	2078(2.91)	936(2.98)	985(3.02)	1.00(0.92.1.10)		4						
Multivariate‡	2889(3.72)	3007(3.79)	1349(3.84)	1405(3.84)	1.01(0.92,1.10)		<b>∔</b>		1.01(0.92,1.10)			+	
						· · ·	1			г			
					1	33 0.50	1.00 2.	00 3.00		0.3	3 0.50	1.00	2.00 3.00
						HR	(95%CI)				н	R(95%C	4)
						Favors	I	Favors		E	avors		Favors
					CE	E-alone	F	lacebo		CEE	E-alone		Placebo

**Web Figure 2b**. Primary outcomes, other monitored outcomes, and global outcomes in the Women's Health Initiative CEE-alone trial during the intervention phase and cumulative follow-up among participants 70 to 79 years at randomization. Statistical models are similar to those described in Figure 1 for 50 to 59y participants in the CEE-alone trial. Participants were postmenopausal and aged 50-79 when enrolled at 40 U.S. clinical centers during 1993-1998.

	CEE-al	one trial ),739)	Subgrou (N=2	р 70 <del>–</del> 79 у ,575)	Multivariate marginal estimates of HR (95%CI) for subgroup 70 to 79 y							
Intervention phase	# of events of e	ents (%*) Placebo (N = 5,429)	# of ev CEE-alone (N = 1.285)	ents (%*) Placebo (N = 1.290)	Saturated mo solely der HR(95%Cl)	del (subgroup estimates ived from 70 to 79 y)	Parsimon I HR(95%Cl)	ious model (su everaged entir P−value†	ıbgroup estimates e cohort)			
Primary outcomes	(11 0,010)	(11 0,4207	<u>(11 1,200)</u>	(11 1,200)				1 Value				
Coronary heart disease	205(0.55)	222(0.58)	83(0.97)	79(0.90)	1 13(0 83 1 55)	<b>_</b>	1 06(0 84 1 35)	0.12	<b>_</b>			
Invasive breast cancer	103(0.28)	135(0.35)	27(0.31)	33(0.37)	0.82(0.50,1.37)	<b>B</b>	0.90(0.66,1.22)					
Other monitored outcomes												
Stroke	174(0.47)	130(0.34)	68(0.79)	52(0.59)	1 30(0 91 1 88)		1 54(1 17 2 01)		¦∎			
Pulmonary embolism	52(0.14)	39(0.10)	12(0.14)	14(0.16)	0.86(0.40.1.84)	<b>_</b>	1.54(0.98,2.42)		· · · · · ·			
Colorectal cancer	65(0.17)	58(0.15)	29(0.33)	13(0.15)	2 19(1 14 4 22)	<b>_</b> →	1 27(0 87 1 86)					
Hip fracture	48(0.13)	74(0.19)	34(0.39)	53(0.60)	0.64(0.41.0.98)		0.68(0.47.0.99)	-	;			
All-cause mortality	301(0.80)	299(0.77)	136(1.55)	115(1.29)	1.21(0.95,1.55)		1.15(0.93,1.41)					
Global indices												
Univariate^	756(2.09)	754(2.04)	300(3.67)	265(3.16)	1.17(0.99.1.37)	-						
Multivariate‡	948(2.51)	957(2.47)	389(4.43)	359(4.03)	1.11(0.93,1.31)	+	1.08(0.91,1.28)		+			
							I	[]	I I			
					0.33	0.50 1.00 2.00 3.0	00	0.33 0.5	50 1.00 2.00 3.			

	# of events (%*)		# of ev	ents (%*)	Saturated mo	del (subgroup es	timates	Parsimonious model (subgroup estimates			
	CEE-alone Placebo		CEE-alone	Placebo	solely der	rived from 70 to 7	'9 у)		leveraged	l entire cohor	t)
Cumulative follow-up	(N = 5,310)	(N = 5,429)	(N = 1,285)	(N = 1,290)	HR(95%CI)			HR(95%CI)	P-value†		
Primary outcomes											
Coronary heart disease	521(0.69)	550(0.71)	191(1.22)	183(1.15)	1.07(0.88,1.32)			1.01(0.87,1.17)	0.79		
Invasive breast cancer	231(0.30)	291(0.38)	51(0.32)	61(0.38)	0.82(0.57,1.19)			0.85(0.69,1.03)			
Other monitored outcomes						1					
Stroke	399(0.53)	392(0.50)	153(0.97)	138(0.86)	1.11(0.88.1.40)			1.08(0.92.1.28)		- <b></b>	
Pulmonary embolism	153(0.20)	150(0.19)	35(0.22)	45(0.28)	0.77(0.50,1.20)	<b>B</b>		1.11(0.87.1.42)			
Colorectal cancer	119(0.15)	118(0.15)	44(0.27)	32(0.20)	1.35(0.86.2.11)	<b>_</b>		1.06(0.81,1.38)			
Hip fracture	208(0.27)	229(0.29)	102(0.64)	117(0.73)	0 85(0 65 1 10)	<b>_</b>		0.92(0.76.1.13)			
All-cause mortality**	1258(1.62)	1277(1.61)	543(3.32)	521(3.16)	1.04(0.92,1.17)			1.03(0.93,1.16)		-	
Global indices											
Univariate^	1997(2.84)	2078(2.91)	727(5 11)	700(4.83)	1 06(0 95 1 18)						
Multivariate‡	2889(3.72)	3007(3.79)	1119(6.84)	1097(6.65)	1.02(0.92,1.13)	+		1.01(0.91,1.12)		+	
					0.33	0.50 1.00	2.00 2.00		0.33 0	T T T	2.00 2.00
					0.55	0.50 1.00	2.00 5.00		0.55 0.	50 1.00	2.00 5.00
						HR(95%CI	)			HR(95%CI	.)
					Fa	vors	Favors		Favors	5	Favors
					CEE	-alone	Placebo		CEE-ald	one	Placebo

**Web Figure 3a**. Primary outcomes, other monitored outcomes, and global outcomes in the Women's Health Initiative CEE+MPA trial during the intervention phase and cumulative follow-up among participants 60 to 69 years at randomization. Statistical models are similar to those described in Figure 2 for 50 to 59y participants in the CEE+MPA trial. Participants were postmenopausal and aged 50-79 when enrolled at 40 U.S. clinical centers during 1993-1998.

	CEE+M (N=16	PA trial 6,608)	Subgrou (N=7	р 60–69 у (,509)	Multivariate marginal estimates of HR (95%CI) for subgroup 60 to 69 y								
Intervention phase	# of ev CEE+MPA (N = 8,506)	ents (%*) Placebo (N = 8,102)	*)		Saturated mo solely der HR(95%CI)	del (subgroup estimates ived from 60 to 69 y)	Pars HR(95%CI)	simonious model (subgroup estii leveraged entire cohort) P−value†	mates				
Primary outcomes Coronary heart disease Invasive breast cancer	196(0.41) 205(0.43)	159(0.35) 155(0.35)	79(0.37) 96(0.45)	73(0.37) 75(0.38)	0.97(0.70,1.35) 1.19(0.88,1.61)		1.15(0.90,1.46) 1.22(0.96,1.54)	0.76					
Other monitored outcomes Stroke Pulmonary embolism Colorectal cancer Endometrial cancer Hip fracture All-cause mortality	159(0.33) 87(0.18) 50(0.10) 27(0.056) 53(0.11) 250(0.52)	110(0.24) 41(0.091) 76(0.17) 30(0.066) 75(0.17) 238(0.53)	72(0.34) 40(0.19) 27(0.13) 14(0.065) 19(0.088) 111(0.51)	47(0.24) 22(0.11) 42(0.21) 17(0.085) 25(0.12) 94(0.47)	1.44(0.99,2.09) 1.69(1.01,2.86) 0.59(0.36,0.96) 0.74(0.36,1.53) 0.70(0.39,1.26) 1.09(0.83,1.43)		1.33(1.01,1.74) 1.96(1.33,2.90) 0.60(0.41,0.87) 0.81(0.48,1.39) 0.63(0.43,0.93) 0.96(0.77,1.18)		∎				
Global indices Univariate^ Multivariate‡	875(1.88) 1027(2.13)	737(1.68) 884(1.96)	392(1.89) 458(2.12)	326(1.68) 395(1.97)	1.13(0.97,1.30) 1.07(0.92,1.24)	3 0.50 100 200 3.00	1.07(0.92,1.25)	033 0.50 1.00 2	2.00 3.00				

	# of events (%*) # of e		# of ev	ents (%*)	Saturated mod	lel (subgroup es	timates	Parsimonious model (subgroup estimates			
Cumulative follow-up	CEE+MPA (N = 8,506)	Placebo (N = 8,102)	CEE+MPA (N = 3,854)	Placebo (N = 3,655)	solely deri HR(95%CI)	ved from 60 to 6	9 у)	HR(95%CI)	leveraged P-value†	l entire coho	rt)
Primary outcomes											
Coronary heart disease	710(0.55)	652(0.53)	300(0.51)	298(0.54)	0.96(0.82,1.13)			1.04(0.92,1.17)	0.74		
Invasive breast cancer	574(0.45)	432(0.36)	255(0.44)	203(0.37)	1.20(1.00,1.45)	-	-	1.25(1.09,1.44)		-	8-
Other monitored outcomes											
Stroke	579(0.45)	492(0.40)	280(0.47)	230(0.41)	1.15(0.96,1.37)			1.10(0.96,1.25)		÷∎-	-
Pulmonary embolism	235(0.18)	199(0.16)	112(0.19)	98(0.17)	1.09(0.83,1.43)	<b></b>		1.11(0.91,1.35)		-∔∎-	_
Colorectal cancer	178(0.14)	197(0.16)	90(0.15)	100(0.18)	0.83(0.63,1.11)	_ <b>_</b> _		0.84(0.68,1.03)		_ <b>∎</b> ∔	
Endometrial cancer	97(0.074)	127(0.10)	42(0.070)	56(0.099)	0.71(0.47,1.06)	<b>_</b> _		0.72(0.55,0.94)			
Hip fracture	394(0.30)	421(0.34)	187(0.32)	175(0.31)	0.98(0.80,1.21)	<b>_</b>		0.87(0.75,1.01)		- <b>e</b> -i	
All-cause mortality**	1870(1.42)	1793(1.44)	852(1.42)	818(1.44)	0.98(0.89,1.08)	+		0.98(0.90,1.06)		+	
Global indices											
Univariate^	3265(2.78)	3009(2.67)	1523(2.85)	1400(2.74)	1.04(0.97.1.12)	•					
Multivariate‡	4637(3.52)	4313(3.45)	2118(3.52)	1978(3.47)	1.01(0.94,1.09)	+		1.01(0.94,1.08)		<b>•</b>	
						1			Г	1 1	
					0.33	0.50 1.00	2.00 3.00		0.33	0.50 1.00	2.00 3.00
						HR(95%C	I)			HR(95%	CI)
					Fa	vors	Favors		Favo	ors	Favors
					CEE	+MPA	Placebo		CEE+	MPA	Placebo

**Web Figure 3b**. Primary outcomes, other monitored outcomes, and global outcomes in the Women's Health Initiative CEE+MPA trial during the intervention phase and cumulative follow-up among participants 70 to 79 years at randomization. Statistical models are similar to those described in Figure 2 for 50 to 59y participants in the CEE+MPA trial. Participants were postmenopausal and aged 50-79 when enrolled at 40 U.S. clinical centers during 1993-1998.

	CEE+M (N=16	IPA trial 6,608)	Subgrou (N=3	р 70–79 у 5,579)	Multivariate marginal estimates of HR (95%CI) for subgroup 70 to 79 y							
Intervention phase	# of events (%*) CEE+MPA Placebo (N = 8,506) (N = 8,102)		# of ev CEE+MPA (N = 1.815)	ents (%*) Placebo (N = 1.764)	Saturated mo solely der HR(95%CI)	del (subgroup estimates ived from 70 to 79 y)	Pars HR(95%Cl)	imonious m leverag P−value†	odel (subgroup estimates ed entire cohort)			
Primary outcomes Coronary heart disease	196(0.41)	159(0.35)	79(0.82)	59(0.63)	1.33(0.96,1.86)		1.22(0.96,1.57)	0.76	+			
Invasive breast cancer	205(0.43)	155(0.35)	54(0.56)	38(0.41)	1.34(0.88,2.03)		1.30(1.00,1.69)					
Stroke	159(0.33)	110(0.24)	61(0.63)	47(0.50)	1.22(0.83.1.79)		1.42(1.08.1.88)					
Pulmonary embolism	87(0.18)	41(0.091)	29(0.30)	11(0.12)	2.48(1.23,4.99)	<b>→</b>	2.10(1.42,3.12)		$\longrightarrow$			
Colorectal cancer	50(0.10)	76(0.17)	16(0.16)	26(0.28)	0.58(0.31,1.10)	← ■	0.64(0.43,0.94)		<b>_</b>			
Endometrial cancer	27(0.056)	30(0.066)	7(0.072)	8(0.085)	0.83(0.30,2.32)	← ■ !	0.87(0.50,1.50)					
Hip fracture	53(0.11)	75(0.17)	33(0.34)	45(0.48)	0.69(0.44,1.10)		0.68(0.47,0.97)					
All-cause mortality	250(0.52)	238(0.53)	104(1.06)	96(1.02)	1.01(0.77,1.34)	<b>+</b>	1.02(0.82,1.27)		<b>#</b>			
Global indices												
Univariate^	875(1.88)	737(1.68)	313(3.42)	270(3.03)	1.11(0.94,1.30)	<b>•</b>						
Multivariate‡	1027(2.13)	884(1.96)	383(3.92)	330(3.51)	1.10(0.94,1.30)	+	1.09(0.92,1.29)		+			
								Г				
					0	.33 0.50 1.00 2.00 3.00		0.3	3 0.50 1.00 2.00 3.00			

	# of events (%*)			ents (%*) Placebo	Saturated model (subgroup estimates solely derived from 70 to 79 y)				Parsimonious model (subgroup estimates leveraged entire cohort)				estimates
Cumulative follow-up	(N = 8,506)	(N = 8,102)	(N = 1,815)	(N = 1,764)	HR(95%CI)			- ]/	HR(95%CI)	P-value†		,	
Primary outcomes			· · · · ·		· · · · · · · · · · · · · · · · · · ·	,			i		,	,	
Coronary heart disease	710(0.55)	652(0.53)	281(1.21)	240(1.05)	1.16(0.97,1.37	)	<u>+</u> ∎-		1.07(0.95,1.22)	0.74		- <b> </b> =	
Invasive breast cancer	574(0.45)	432(0.36)	121(0.52)	93(0.41)	1.27(0.97,1.68	)	-		1.30(1.12,1.51)				-
Other monitored outcomes												l.	
Stroke	579(0.45)	492(0.40)	212(0.91)	185(0.81)	1.11(0.91,1.35	)			1.14(0.99,1.31)				
Pulmonary embolism	235(0.18)	199(0.16)	68(0.29)	53(0.23)	1.25(0.88,1.80	)	- <b> </b> -		1.15(0.94,1.41)				
Colorectal cancer	178(0.14)	197(0.16)	44(0.18)	62(0.27)	0.68(0.46,1.00	) — –	•		0.87(0.70,1.07)			<b>_</b> ∎ <u>¦</u>	
Endometrial cancer	97(0.074)	127(0.10)	16(0.066)	24(0.10)	0.66(0.35,1.27	) — —	• <del> </del>		0.75(0.56,0.99)			<b>.</b>	
Hip fracture	394(0.30)	421(0.34)	164(0.70)	198(0.87)	0.82(0.67,1.01	) -	_ <b>∎</b> _¦		0.91(0.78,1.05)			- <b>-</b>	
All-cause mortality**	1870(1.42)	1793(1.44)	752(3.11)	708(3.00)	1.03(0.93,1.14	)	+		1.01(0.92,1.11)			÷.	
Global indices													
Univariate^	3265(2.78)	3009(2.67)	1069(5.24)	997(4.97)	1.05(0.96,1.14	)	•					i	
Multivariate‡	4637(3.52)	4313(3.45)	1658(6.86)	1563(6.62)	1.04 0.95, 1.13	)	+		1.04(0.95,1.13)			+	
						<u>г т т</u>	1			г			
						0.33 0.50	1.00	2.00 3.00		0.3	3 0.50	1.00	2.00 3.00
						F	HR(95%C	1)			н	R(95%C	I)
						Favors		Favors		F	avors		Favors
					(	CEE+MPA		Placebo		CEI	E+MPA		Placebo

Web Figure 4. Breakout of hazard ratios (95% CIs) for CEE according to whether gap time from menopause to first use of menopausal hormone therapy is <5 years or ≥5 years, as an extension of the parsimonious hazard ratio analysis of Figure 1. Participants were postmenopausal and aged 50-79 when enrolled at 40 U.S. clinical centers during 1993-1998.

# of eve -alone <u>1,059)</u> (0.15) (0.25)	ents (%*) Placebo (N = 1,086) 18(0.22) 17(0.21)	HR(95%CI) 0.87(0.56,1.34) 0.93(0.58,1.49)		# of eve CEE-alone (N = 580) 9(0.21) 9(0.21)	ents (%*) Placebo (N = 588) 17(0.40) 19(0.45)	HR(95%CI) 0.60(0.38,0.94) 0.42(0.26,0.68)	
(0.15) (0.25)	18(0.22) 17(0.21)	0.87(0.56,1.34) 0.93(0.58,1.49)		9(0.21) 9(0.21)	17(0.40) 19(0.45)	0.60(0.38,0.94) 0.42(0.26,0.68)	
(0.15) (0.25)	18(0.22) 17(0.21)	0.87(0.56,1.34) 0.93(0.58,1.49)		9(0.21) 9(0.21)	17(0.40) 19(0.45)	0.60(0.38,0.94) 0.42(0.26,0.68)	
0.25)	17(0.21)	0.93(0.58,1.49)		9(0.21)	19(0.45)	0.42(0.26,0.68)	< <b>-</b>
.076)	11(0.14)	0.95(0.60,1.52)		13(0.31)	10(0.23)	1.01(0.63,1.63)	· · · · ·
0.13)	4(0.049)	1.61(0.81,3.17)		2(0.047)	4(0.093)	0.70(0.36,1.38)	
.076)	7(0.086)	0.99(0.54,1.81)	<b>_</b>	3(0.071)	6(0.14)	0.71(0.39,1.29)	
.050)	<b>`</b> 0 ´	0.39(0.19,0.82)	<∎	1(0.023)	1(0.023)	0.48(0.26,0.89)	<∎
0.25)	30(0.37)	0.84(0.57,1.24)		15(0.35)	20(0.46)	0.68(0.44,1.05)	
0.98)	87(1.07)	0.96(0.69,1.33)		52(1.22)	77(1.78)	0.64(0.43,0.96)	
0.98)	87(1.07)	0.92(0.66,1.28)		52(1.22)	77(1.78)	0.64(0.43,0.95)	-
	076) 050) 0.25) 0.98) 0.98)	076) 7(0.086)   050) 0   0.25) 30(0.37)   0.98) 87(1.07)   0.98) 87(1.07)	076) 7(0.086) 0.99(0.54,1.81)   050) 0 0.39(0.19,0.82)   0.25) 30(0.37) 0.84(0.57,1.24)   0.98) 87(1.07) 0.96(0.69,1.33)   0.98) 87(1.07) 0.92(0.66,1.28)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

0.33 0.50 1.00 2.00 3.00



Cumulative follow−up	# of ev CEE−alone <u>(</u> N = 1,059)	ents (%*) Placebo (N = 1,086)	HR(95%CI)			# of ev CEE−alone _(N = 580)	ents (%*) Placebo (N = 588)	_HR(95%CI)	1				
Primary outcomes													
Coronary heart disease	39(0.23)	48(0.28)	0.87(0.67,1.12)	<b></b>		32(0.36)	43(0.49)	0.79(0.60,1.0	3)	_	<b>∳</b> -}		
Invasive breast cancer	47(0.28)	50(0.30)	0.77(0.58,1.04)			26(0.30)	42(0.49)	0.61(0.45,0.8	3)		- - -		
Other monitored outcomes													
Stroke	27(0.16)	33(0.19)	0.87(0.66,1.16)			22(0.25)	25(0.29)	0.88(0.66,1.1	7)	-			
Pulmonary embolism	22(0.13)	24(0.14)	0.92(0.64,1.32)	<b>_</b>		13(0.15)	10(0.11)	0.89(0.60.1.3	1)		-		
Colorectal cancer	11(0.064)	15(0.088)	0.89(0.59,1.34)			7(0.079)	11(0.12)	0.83(0.55,1.2	4)		- <b>i</b>		
Hip fracture	12(0.070)	12(0.070)	0.72(0.51,1.01)			7(0.078)	8(0.090)	0.77(0.55,1.0	9)		<b>_</b>		
All-cause mortality**	90(0.52)	110(0.64)	0.81(0.66,1.01)			66(0.74)	74(0.83)	0.85(0.66,1.0	8)	_	÷∎+		
Multivariate global indices													
Parsimonious (averaged) Saturated (solely 50−59 y)	248(1.44) 248(1.44)	292(1.70) 292(1.70)	0.83(0.69,1.00) 0.83(0.69,1.00)	•		173(1.93) 173(1.93)	213(2.38) 213(2.38)	0.78(0.62,0.9 0.79(0.63,1.0	9) 0)				
				1 1									
			0.33 0	0.50 1.00	2.00 3.00				0.33	0.50	1.00	2.00 3.00	0
				HR(95%CI)						H	R(95%C	l)	
			Favor	ſS	Favors				Fav	ors		Favors	s
			CEE-al	one	Placebo				CEE-	alone		Placeb	00

Web Figure 5. Breakout of hazard ratios (95% CIs) for CEE+MPA according to whether gap time from menopause to first use of menopausal hormone therapy is <5 years or ≥5 years, as an extension of the parsimonious hazard ratio analysis of Figure 2. Participants were postmenopausal and aged 50-59 when enrolled at 40 U.S. clinical centers during 1993-1998.

	Gap−tir (N=2	me < 5 y 2,870)	Multivariate mar Parsimoni	rginal estimates: ious model	Gap−tim (N=2	ie >= 5 y ,650)	Multivariate margir Parsimoniou	nal estimates: s model
Intervention phase	# of ev CEE+MPA <u>(N = 1,503)</u>	ents (%*) Placebo (N = 1,367)			# of eve CEE+MPA (N = 1,334)	ents (%*) Placebo <u>(N = 1,316)</u>	HR(95%CI)	
Primary outcomes Coronary heart disease Invasive breast cancer	16(0.18) 28(0.31)	18(0.22) 14(0.17)	0.97(0.58,1.63) 1.51(0.93,2.47)		22(0.28) 27(0.35)	9(0.12) 28(0.37)	1.32(0.90,1.93) 1.20(0.84,1.73)	+ <u>+</u>
Other monitored outcomes Stroke Pulmonary embolism Colorectal cancer Endometrial cancer Hip fracture All-cause mortality	16(0.18) 7(0.077) 1(0.011) 1(0.011) 0 13(0.14)	7(0.086) 5(0.062) 5(0.062) 2(0.025) 1(0.012) 27(0.33)	$\begin{array}{c} 1.18(0.66,2.11)\\ 0.93(0.45,1.94)\\ 0.22(0.07,0.71)\\ 0.47(0.17,1.30)\\ 0.18(0.06,0.57)\\ 0.66(0.42,1.06) \end{array}$		10(0.13) 11(0.14) 6(0.077) 5(0.064) 1(0.013) 22(0.28)	9(0.12) 3(0.040) 3(0.040) 3(0.040) 4(0.053) 21(0.28)	$\begin{array}{c} 1.52(1.00,2.31)\\ 2.75(1.62,4.68)\\ 0.76(0.47,1.25)\\ 1.05(0.53,2.06)\\ 0.84(0.51,1.39)\\ 1.14(0.80,1.64)\end{array}$	
Multivariate global indices Parsimonious (averaged) Saturated (solely 50–59 y)	82(0.90) 82(0.90)	79(0.97) 79(0.97)	0.97(0.69,1.35) 0.94(0.67,1.32)		104(1.33) 104(1.33)	80(1.06) 80(1.06)	1.25(0.91,1.71) 1.26(0.92,1.71)	

0.33	0.50	1.00	2.00	3.00

2.00 3.00

Placebo

1.00

0.33 0.50

CEE+MPA

	# of ev	ents (%*)			# of events (%*)					
Cumulative follow-up	CEE+MPA (N = 1,503)	Placebo (N = 1,367)	HR(95%CI)		CEE+MPA (N = 1,334)	Placebo (N = 1,316)	HR(95%CI)			
Primary outcomes					-					
Coronary heart disease	54(0.22)	60(0.27)	0.96(0.74,1.26)	<b></b>	75(0.35)	54(0.25)	1.12(0.93,1.35)		-+∎	
Invasive breast cancer	106(0.43)	53(0.24)	1.52(1.17,1.98)		92(0.44)	83(0.39)	1.24(1.02,1.51)			
Other monitored outcomes										
Stroke	47(0.19)	32(0.14)	1.24(0.92,1.68)		40(0.18)	45(0.21)	1.13(0.93,1.39)			
Pulmonary embolism	29(0.11)	23(0.10)	0.93(0.62,1.41)		26(0.12)	25(0.12)	1.24(0.96,1.60)			_
Colorectal cancer	21(0.083)	16(0.071)	0.96(0.59,1.56)	<b></b>	23(0.11)	19(0.088)	0.87(0.66,1.14)		<b>∎</b> ¦:	
Endometrial cancer	18(0.071)	23(0.10)	0.70(0.43,1.14)	<b></b>	21(0.097)	24(0.11)	0.75(0.54,1.06)	_	<b>_∎_</b> _{:	
Hip fracture	16(0.063)	22(0.098)	0.67(0.46,0.95)	İ	27(0.12)	26(0.12)	0.98(0.79,1.21)		<b></b> ;	
All-cause mortality**	116(0.46)	119(0.53)	0.94(0.77,1.15)		150(0.69)	148(0.68)	1.05(0.89,1.24)			
Multivariate global indices										
Parsimonious (averaged)	407(1.60)	348(1.54)	1.05(0.90,1.24)	•••	454(2.08)	424(1.95)	1.08(0.93,1.26)		-	
Saturated (solely 50–59 y)	407(1.60)	348(1.54)	1.04(0.88,1.22)	+	454(2.08)	424(1.95)	1.08(0.93,1.26)		+	
				0.33 0.50 1.00 2.00 3.00			0	.33 0.50	1.00	2.00 3.00
				HR(95%CI)				1	HR(95%CI	)
				Favors Favors			F	avors		Favors

Placebo

