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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

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Abstract

Objective: Our objective was to determine whether metabolic syndrome (MetS) or its components modified the effect of hormone therapy (HT) on the risk of coronary heart disease (CHD) events in the Women's Health Initiative clinical trials.

Methods: We performed a nested case-control study of incident CHD events during the first 4 years of follow-up in the Women's Health Initiative HT trials (estrogen plus progestin therapy [EPT] and estrogen therapy [ET]). There were 359 incident cases of CHD during follow-up. After the exclusion of women with cardiovascular disease (n = 90), diabetes, or hypertension at baseline (n = 103), 166 CHD cases were matched to 524 controls on age, randomization date, and hysterectomy status. MetS classification required at least three of five Adult Treatment Panel III criteria. Analyses by χ^2 and *t* tests for heterogeneity and logistic regression were performed. Postmenopausal women (n = 27,347) aged 50 to 79 years from 40 US clinical centers participated. Daily conjugated equine estrogens (0.625 mg) and medroxyprogesterone acetate (2.5 mg; EPT) or conjugated equine estrogens (0.625 mg; ET) were compared with placebo. The main outcome measure was the odds for CHD with HT use versus placebo by MetS status.

Results: MetS modified the risk of CHD events with HT. In the pooled analysis, risk was increased with HT versus placebo in women with MetS (odds ratio, 2.26; 95% CI, 1.26-4.07), whereas women without MetS were not found to have an increased risk for a CHD event with HT (odds ratio, 0.97; 95% CI, 0.58-1.61; *P* for interaction = 0.03). Results of the EPT and ET trials, when examined separately, were similar. The constellation of MetS variables was more predictive of risk from HT than MetS components assessed individually. When women with diabetes or hypertension were included in the analysis, statistically significant effect modification was not detected.

Conclusions: MetS at baseline in women without prior cardiovascular disease, diabetes, or hypertension at baseline identifies women who are more likely to have had adverse coronary outcomes on HT. CHD risk stratification is recommended before initiating HT. The basis for the greater risk of CHD events with HT among women with MetS requires further study.

Key Words: Women's Health Initiative – Coronary heart disease – Hormone therapy – Metabolic syndrome – Effect modification.

Emerging evidence suggests that a woman's baseline clinical characteristics, including proximity to menopause[1] and coronary risk factor status, modify her risk of a coronary heart disease (CHD) event while she is taking menopausal hormone therapy (HT).[2,3] It is uncertain whether screening for cardiometabolic risk indicators, such as metabolic

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syndrome (MetS), may identify women who are at greater risk for an incident coronary event while using HT. Two clinical trials were conducted within the Women's Health Initiative (WHI) to assess CHD risk with HT. Conjugated equine estrogens (CEE) were compared with placebo in women who had undergone hysterectomy, and CEE plus medroxyprogesterone acetate (MPA) were compared with placebo in postmenopausal women who had an intact uterus. Neither of these trials demonstrated a protective effect of HT on CHD events.[4,5] To better estimate individual risk, we performed a nested case-control study of cardiometabolic risk status at baseline within both WHI clinical trials. The objective was to determine if the presence or absence of MetS identified women at greater or lesser risk for a CHD event while on HT during the trials.

METHODS

Study population

Eligibility criteria and recruitment methods for each of the WHI clinical trials are published.[6] Briefly 27,347 postmenopausal women aged 50 to 79 years from 40 US clinical centers were enrolled in the study between September 1, 1993, and December 31, 1998. CEE (0.625 mg) and MPA (2.5 mg; CEE + MPA) or CEE alone was given to 16,608 women with an intact uterus (estrogen plus progestin therapy [EPT] trial). The 10,739 women who had undergone hysterectomy received CEE (0.625 mg) alone (estrogen therapy [ET] trial). At baseline, women completed screening questionnaires by interview and self-report, and each participant underwent physical examination. Blood specimens were collected. Our analysis assessed variables during these baseline visits and evaluated events within the first 4 years of follow-up. The WHI randomized clinical trials (RCTs; EPT and ET) were approved by the human subjects review committees at each participating institution. All participants provided a written informed consent form. They randomly received a single daily tablet containing either placebo or active medication. Study drugs and placebo were supplied by Wyeth-Ayerst (St. Davids, PA). The planned end date of the trials was March 31, 2005, for a total follow-up of 8.4 years. However, CEE plus MPA trial medications were stopped on July 7, 2002, and CEE were stopped on March 1, 2004, after mean follow-up periods of 5.6 and 7.1 years, respectively.[1,2] All centrally adjudicated cases of CHD (nonfatal myocardial infarction [MI] or fatal CHD) occurring during the first 4 years of follow-up are included in our nested case-control study within both RCT cohorts. Clinical outcomes in the RCTs were identified by semiannual questionnaires and classified by centrally trained local adjudicators after medical records review. CHD included nonfatal and silent MI and CHD death. Definite and probable nonfatal MI required overnight hospitalization and was defined according to an algorithm based on standardized criteria using cardiac pain, cardiac enzyme and troponin levels, and electrocardiographic findings. This included MI occurring during surgical operation and aborted MI. CHD death was defined as death consistent with an underlying cause of CHD plus one or more of the following: hospitalization for MI within 28 days before death, previous angina or MI, death due to a procedure related to CHD, or a death certificate consistent with an underlying cause of atherosclerotic CHD. Definite silent MI was diagnosed at baseline and on years 3 and 6 (electrocardiograms; Nova codes 5.1 and 5.2.8).

We performed a case-control study nested within the two hormone clinical trial cohorts. There were 359 new CHD events in 4 years of follow-up. We were able to randomly select 817 control participants who did not have a CHD event at the same time that the cases were identified. Because prior cardiovascular disease (CVD) is such a strong risk factor for having a CHD event, we included in our analysis only women without a prior diagnosis of MI, angina, coronary revascularization, stroke, venous thromboembolism, or other major forms of CVD to help understand the risk of having MetS while on HT. Controls—those who did not experience a CVD event at the time that the cases were identified during follow-up in the WHI clinical trials—were matched on age and randomization date at baseline.

Blood samples were obtained in fasting state. Specimens were centrifuged, and serum and plasma were frozen at −70°C and shipped on dry ice for central processing. Lipids were measured in ethylenediaminetetraacetic acid anticoagulated plasma at the PPD Global Central Laboratories using a Hitachi 747 General Chemistry Analyzer. Triglycerides were measured using a chromogenic reaction after hydrolysis and oxidation. High-density lipoprotein (HDL) was measured after the removal of chylomicrons, very low-density lipoprotein, and low-density lipoprotein (LDL) from plasma. Our assessment of the presence or absence of MetS required at least three of five (Adult Treatment Panel III [ATPIII] National Cholesterol Education Program 2004) criteria at the baseline visit. The criteria for MetS included the following: waist size larger than 88 cm (or 80 cm for Asians and American Indians), systolic blood pressure higher than 130 mm Hg or diastolic blood pressure higher than 85 mm Hg (or hypertension), fasting glucose higher than 100 mg/dL (or diabetes), HDL cholesterol lower than 50 mg/dL, or triglycerides higher than 150 mg/dL.

There were 93 cases who had prior MI, 28 cases who had prior stroke, 133 cases who were diagnosed as having angina, 65 cases who had undergone a revascularization procedure, 17 cases who had prior deep vein thrombosis, and 3 cases who had prior pulmonary embolus. This left 269 cases who had no prior baseline CVD and who were matched with 695 controls. To help understand whether having MetS or its components at baseline modified the relationship between HT and CHD, we first analyzed effect modification in cases and controls who had no prior diagnosis of diabetes or hypertension. In this analysis, 166 cases were compared with 524 controls to test for effect modification by MetS. We assessed for the presence of MetS[7] as an effect modifier for active hormone treatment versus placebo as a risk for an incident CHD event during each of the clinical trials up to 4 years of follow-up. We calculated odds ratios (ORs) for women assigned to HT versus placebo and tested for effect modification by the individual MetS components as well. We further stratified these associations by years since menopause.

Knowing that diabetes incidence was reduced in HT users in the WHI, we next tested for effect modification by baseline, including those who also had a history of diabetes or hypertension (ATPIII National Cholesterol Education Program 2010 definition of MetS). In this analysis for effect modification, 269 cases were compared with 695 controls.

Statistical methods

χ^2 tests or *t* tests for heterogeneity were used to determine statistically significant differences between the groups. Logistic regression was used to calculate ORs and 95% CIs. The odds of CHD with HT treatment compared with placebo were determined in the combined cohort (HT trials) in those women who did or did not have MetS. Stepwise logistic analysis was performed to determine the covariates included in the final models. Participants with missing values for any covariates were excluded in the model. The final analysis was adjusted for smoking, age, and education. Full logistic analysis models checked for interactions. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

The baseline demographic characteristics of cases and controls in the ET and EPT trials and for the combined data set (HT), excluding women who developed CHD and had CVD at baseline, are displayed in Table 1. Those who went on to develop a CHD event had higher body mass index. MetS components, body mass index, LDL cholesterol, and high-sensitivity C-reactive protein were worse for clinical trial entrants who became cases than for those who became controls in the HT trials (Table 1). Higher mean systolic and diastolic blood pressure, fasting glucose, and/or diabetes or hypertension was found at baseline in those who became cases. Cases had less formal education and were more likely to be current smokers. Table 2 displays the odds for a coronary event in the combined data set with the presence or the absence of MetS and with each ATPIII MetS component compared with placebo when diabetes and hypertension were excluded. The *P* values refer to tests of interaction. We found that although, as reported previously, the overall risk of a CHD event in HT users compared with placebo was higher with hormone use (OR, 1.29; 95% CI, 1.00-1.66), the presence of MetS at baseline was a significant effect modifier. Tests for interaction showed significant effect modification for the pooled data set ($P = 0.03$). Women without MetS were not at increased risk for CHD while on HT versus placebo (OR, 0.97; 95% CI, 0.58-1.361). Women who had MetS, in contrast, were at significantly greater risk for a CHD event while on HT versus placebo (OR, 2.26; 95% CI, 1.26-4.07).

We performed the analysis for each individual trial as well. Despite limited power, we found in the EPT trial that although EPT users overall were significantly more likely to have had a CHD event (OR, 1.42; 95% CI, 1.02-1.97), those who had MetS at baseline were significantly more likely to have one (OR, 2.26; 95% CI, 1.05-4.85; Table 2). When MetS was not present, however, the OR was neutral (OR, 1.13; 95% CI, 0.61-2.13). The test for interaction in the EPT trial was not significant ($P = 0.173$).

In the ET trial, although the overall odds for an incident CHD event were higher (OR 1.15; 95% CI, 0.78-1.68) in ET users, there was no increased risk when MetS was not present (OR, 0.62; 95% CI, 0.27-1.42; Table 2). When MetS was present at baseline, the risk was (OR, 1.66; 95% CI, 0.84-3.27). The test for interaction was not significant ($P = 0.072$).

The same analysis was rerun to include diabetes and hypertension in the definition of MetS for those cases and controls who could have had a prior diagnosis of diabetes or hypertension. In this analysis, we could not find a statistically significant effect modification by MetS. When diabetes or hypertension was present, it seemed that the ability to detect effect modification was blunted (among women without MetS: OR, 0.95; 95% CI, 0.57-1.57; among women with MetS: OR, 1.49; 95% CI, 0.96-2.30; *P* for interaction = 0.19) in the pooled trial analysis. Analyses stratified by years since menopause could not reveal differences across strata. Power was very limited, however.

DISCUSSION

This investigation was designed to determine if the risk of a CHD event with HT was modified by baseline cardiometabolic risk status when menopausal HT was given in the WHI RCTs. By contrasting baseline demographic and metabolic parameters in those who became cases of CHD within 4 years of follow-up, we found that women with high baseline CVD risk fared worse on HT than those with lower CHD risk. When participants had MetS even without prior CVD, diabetes, or hypertension at baseline, HT was associated with a higher CHD risk. MetS was a predictor of an increased risk of an event with hormone use during the trials. Women who did not have MetS were not found to be at greater odds for CHD while taking HT.

It is interesting to speculate why we could not find effect modification when we included women who had diabetes or hypertension at baseline. The WHI showed a reduction in diabetes mellitus with the HT intervention during the clinical trials. There was a 21% significant reduction in the EPT arm (hazard ratio, 0.79; 95% CI, 0.67-0.93). In the ET arm, (hazard ratio, 0.88; 95% CI, 0.77-1.01).[8] It is possible that the HT-related reduction in diabetes incidence affected our ability to determine if effect modification occurred with HT. With larger numbers of women available, it would have been of interest to assess the CHD risk of HT in women who were diabetic and hypertensive. We did not have enough power to assess this in the current investigation.

Women younger than 60 years who are at risk for metabolic disease might have findings different from those for the group as a whole. The average age at baseline in cases and controls was 66 years. Findings might differ depending on age younger than 60 years and age older than 60 years. We did not have enough power to provide insight into this question in our investigation.

Of great interest is why these abnormal cardiometabolic indicators modify the risk for a CHD event with HT. Elevated non-HDL cholesterol levels found in MetS reflect altered

TABLE 1. *Baseline risk in women with no prior CVD at baseline*

	Estrogen therapy					Estrogen plus progestin therapy					Combined trial				
	Controls	n	Cases	n	*P*	Controls	n	Cases	n	*P*	Controls	n	Cases	n	*P*
Age at screening, mean (SD), y	66.29 (6.44)	273	66.92 (6.58)	112	0.386	66.59 (6.86)	422	65.76 (7.31)	157	0.200	66.47 (6.69)	695	66.24 (7.02)	269	0.632
Baseline body mass index, mean (SD), kg/m^2	29.18 (5.44)	273	30.17 (6.10)	112	0.118	27.73 (5.79)	419	28.64 (5.96)	157	0.097	28.30 (5.70)	692	29.28 (6.05)	269	0.020
Baseline hip circumference, mean (SD), cm	109.79 (12.58)	273	109.79 (13.00)	112	0.997	105.44 (11.38)	420	108.06 (13.55)	157	0.020	107.15 (12.05)	693	108.78 (13.33)	269	0.069
Baseline waist circumference, mean (SD), cm	90.60 (13.03)	273	94.61 (14.80)	112	0.009	86.18 (13.42)	420	90.30 (14.39)	157	0.001	87.92 (13.43)	693	92.09 (14.69)	269	<0.001
Baseline waist-to-hip ratio, mean (SD)	0.83 (0.09)	273	0.86 (0.08)	112	<0.005	0.82 (0.07)	420	0.83 (0.07)	157	0.006	0.82 (0.08)	693	0.85 (0.08)	269	<0.001
Baseline weight, mean (SD), kg	76.28 (15.09)	273	78.23 (17.41)	112	0.272	72.02 (16.01)	421	74.64 (16.68)	157	0.084	73.69 (15.78)	694	76.13 (17.05)	269	0.036
Baseline diastolic BP, mean (SD), mm Hg	76.13 (8.98)	272	77.80 (9.73)	112	0.108	74.80 (9.31)	422	76.81 (10.60)	157	0.0271	75.32 (9.20)	694	77.22 (10.24)	269	0.006
Baseline systolic BP, mean (SD), mm Hg	130.19 (16.91)	273	140.21 (18.05)	112	<0.001	129.04 (17.53)	422	133.86 (19.18)	157	0.004	129.49 (17.28)	695	136.50 (18.94)	269	<0.001
Baseline glucose, mean (SD), mg/dL	105.06 (27.99)	270	119.74 (50.05)	112	<0.003	102.55 (25.80)	422	115.31 (49.38)	155	<0.001	103.53 (26.68)	692	117.17 (49.62)	267	<0.001
Baseline HDL cholesterol, mean (SD), mg/dL	54.08 (14.16)	272	49.59 (13.11)	110	0.004	55.72 (14.77)	421	50.36 (13.45)	155	<0.001	55.07 (14.55)	693	50.04 (13.29)	265	<0.001
Baseline triglyceride, mean (SD), mg/dL	161.84 (86.36)	273	174.21 (91.83)	112	0.212	148.15 (77.41)	422	182.13 (109.70)	156	<0.001	153.53 (81.26)	695	178.82 (102.50)	268	<0.001
Baseline LDL cholesterol, mean (SD), mg/dL	143.45 (33.58)	266	153.38 (34.15)	105	0.011	141.43 (33.41)	416	154.22 (32.70)	148	<0.001	142.22 (33.47)	682	153.87 (33.25)	253	<0.001
Baseline total cholesterol, mean (SD), mg/dL	229.30 (37.44)	273	236.58 (39.19)	112	0.088	226.69 (36.38)	422	239.63 (37.26)	156	<0.002	227.72 (36.80)	695	238.36 (38.04)	268	<0.001
Baseline C-reactive protein, mean (SD), μg/mL	3.85 (4.38)	264	4.99 (4.60)	108	0.025	3.27 (4.63)	409	4.20 (4.65)	153	.034	3.50 (4.54)	673	4.53 (4.64)	261	0.002
Race/ethnicity, n (%)															
White	211 (77.29)		85 (75.89)		0.787	371 (87.91)		140 (89.17)		0.899	582 (83.74)		225 (83.64)		0.799
Black	42 (15.38)		16 (14.29)			23 (5.45)		7 (4.46)			65 (9.35)		23 (8.55)		
Hispanic	13 (4.76)		6 (5.36)			17 (4.03)		5 (3.18)			30 (4.32)		11 (4.09)		
Other	7 (2.56)		5 (4.46)			11 (2.61)		5 (3.18)			18 (2.59)		10 (3.72)		
Education, n (%)															
Up to high school diploma/GED	91 (33.58)		53 (48.62)		0.014	108 (25.71)		56 (35.90)		0.055	199 (28.80)		109 (41.13)		0.001
School after high school	111 (40.96)		39 (35.78)			166 (39.52)		54 (34.62)			277 (40.09)		93 (35.09)		
College degree or higher	69 (25.46)		17 (15.60)			146 (34.76)		46 (29.49)			215 (31.11)		63 (23.77)		

Smoking status, n (%)			<0.0003			<0.001			<0.001
Never	145 (54.92)	54 (49.54)		233 (55.88)	71 (46.71)		378 (55.51)	125 (47.89)	
Past	98 (37.12)	30 (27.52)		152 (36.45)	49 (32.24)		250 (36.71)	79 (30.27)	
Current	21 (7.95)	25 (22.94)		32 (7.67)	32 (21.05)		53 (7.78)	57 (21.84)	
Treated diabetes (pills or shots), n (%)			<0.001			0.007			<0.001
No	259 (94.87)	90 (80.36)		404 (95.73)	140 (89.74)		663 (95.40)	230 (85.82)	
Yes	14 (5.13)	22 (19.64)		18 (4.27)	16 (10.26)		32 (4.60)	38 (14.18)	
Hypertension, n (%)			0.021			0.002			<0.001
0	124 (49.40)	37 (35.92)		225 (59.21)	60 (43.48)		349 (55.31)	97 (40.25)	
1	127 (50.60)	66 (64.08)		155 (40.79)	78 (56.52)		282 (44.69)	144 (59.75)	
Use of antihyperlipidemic medication, n (%)			0.492			0.465			0.312
No	252 (92.31)	101 (90.18)		392 (92.89)	143 (91.08)		644 (92.66)	244 (90.71)	
Yes	21 (7.69)	11 (9.82)		30 (7.11)	14 (8.92)		51 (7.34)	25 (9.29)	
HT use status, n (%)			0.410			0.352			0.233
Never used	154 (56.41)	69 (61.61)		316 (74.88)	116 (73.89)		470 (67.63)	185 (68.77)	
Past user	88 (32.23)	35 (31.25)		79 (18.72)	35 (22.29)		167 (24.03)	70 (26.02)	
Current user	31 (11.36)	8 (7.14)		27 (6.40)	6 (3.82)		58 (8.35)	14 (5.20)	
Family history of premature MI (<55 y in men, <65 y in women), n (%)			0.027			0.052			0.003
No	196 (82.01)	66 (70.97)		309 (83.51)	97 (75.78)		505 (82.92)	163 (73.76)	
Yes	43 (17.99)	27 (29.03)		61 (16.49)	31 (24.22)		104 (17.08)	58 (26.24)	

Participants with baseline history of coronary heart disease, stroke, angina, revascularization, deep vein thrombosis, or pulmonary embolus were excluded from the analysis.
CVD, cardiovascular disease; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HT, hormone therapy; MI, myocardial infarction.

triglyceride metabolism, with more circulating atherogenic apolipoprotein B particles, including small dense LDLs.[9] Perhaps, in this setting, more fatty acids circulating could lead to greater insulin resistance. With higher circulating LDL particles, there may be a greater inflammatory response to these particles as they enter the arterial wall. This, along with circulating particles of higher triglyceride content, could be associated with a greater tendency for plaque rupture. Several recent investigations have assessed other CHD biomarkers as predictors of CHD with menopausal HT.[2,3,10] Many thrombotic, inflammatory, and lipid biomarkers are associated with a greater risk for a CHD event. Interleukin 6, matrix metalloproteinase 9, LDL cholesterol, total cholesterol, triglycerides, D-dimer, factor VIII, von Willebrand factor, leukocyte count, homocysteine, and fasting insulin have all been found to predict clinical CHD events. The genetic polymorphism glycoprotein IIIa leu33pro was significantly associated with incident CHD. These elevated biomarkers seem to reflect heightened inflammation and may be associated with central fat deposition. In a prior analysis of WHI data, however, none of these abnormal biomarkers, when analyzed individually, were found to be statistically significant effect modifiers for CHD outcomes with HT. The MetS milieu is associated with a constellation of risk factors, including insulin resistance and a hyperthrombotic, proinflammatory state, which, in combination, may be particularly deleterious and may adversely interact with HT to heighten thromboembolic risk.[11]

Prior investigations have determined that women with higher levels of LDL cholesterol are at higher risk for a CHD event when they receive HT.[2,3] Baseline LDL cholesterol has been shown to be an effect modifier.[2] Women with an LDL-to-HDL cholesterol ratio below 2.5 were not found to be at elevated risk when CEE with or without MPA were compared with placebo, whereas women with an LDL-to-HDL cholesterol ratio of 2.5 or higher were found to be at greater risk.[3] Of relevance to the findings here, prior investigations have found that neither unopposed estrogen nor estrogen with progestin lowered LDL particle concentration in the WHI clinical trials.[12] Elevated circulating small LDL particles are associated with having MetS.[13] Adiposity may be an important contributor to risk.[14] Obesity predisposes to the development of MetS. Our findings, coupled with the findings of Rossouw et al,[2] Bray et al,[3] and Hsia et al,[12] suggest that having elevated baseline cardiometabolic risk factors increased CHD risk when HT was given. These findings may have clinical utility in risk stratification and may help to identify women at increased risk for CHD events on HT. Measurement of lipids and assessment of other MetS parameters, including waist circumference, blood pressure, and fasting glucose, are readily available to most clinicians.

Our study within the RCT cohort of the WHI only assessed the CHD risk of oral HT versus placebo for the first 4 years of follow-up at doses that were in common use when each of the trials was conducted. Currently, other forms of HT that take advantage of different routes of delivery and deliver smaller steroid doses are increasingly being used, with prospects for

TABLE 2. *Risk according to baseline risk assessment (APTIII definition) in women with no baseline CVD, hypertension, or diabetes*

	Estrogen plus progestin therapy						Estrogen therapy						Combined trials					
	Placebo		Treatment				Placebo		Treatment				Placebo		Treatment			
	Controls	Cases	Controls	Cases	OR (95% CI)	*P* for interaction	Controls	Cases	Controls	Cases	OR (95% CI)	*P* for interaction	Controls	Cases	Controls	Cases	OR (95% CI)	*P* for interaction
Metabolic syndrome meeting three or more criteria in APTIII definition																		
No	100	23	137	34	1.13 (0.61-2.13)	0.173	58	17	51	13	0.75 (0.30-1.86)	0.123	158	40	188	47	0.97 (0.58-1.61)	0.032
Yes	56	18	39	30	2.26 (1.05-4.85)		44	11	35	20	2.11 (0.81-5.48)		100	29	74	50	2.26 (1.26-4.07)	
Waist >35 in. (80 cm for Asians and American Indians)																		
No	95	26	115	36	1.22 (0.66-2.26)	0.541	49	17	46	14	0.75 (0.30-1.87)	0.114	144	43	161	50	1.03 (0.62-1.70)	0.120
Yes	60	15	61	28	1.66 (0.78-3.53)		55	11	41	19	2.16 (0.84-5.52)		115	26	102	47	1.93 (1.08-3.44)	
Blood pressure ≥130/85 mm Hg																		
No	80	15	111	34	1.86 (0.90-3.83)	0.392	55	10	45	11	1.39 (0.50-3.92)	0.822	135	25	156	45	1.70 (0.95-3.05)	0.406
Yes	76	26	66	30	1.21 (0.62-2.34)		49	18	42	22	1.20 (0.51-2.79)		125	44	108	52	1.22 (0.73-2.04)	
Triglycerides >150 mg/dL																		
No	97	21	130	35	1.38 (0.72-2.61)	0.773	62	17	43	15	1.13 (0.48-2.68)	0.699	159	38	173	50	1.24 (0.75-2.04)	0.569
Yes	59	20	47	29	1.59 (0.76-3.31)		42	11	44	18	1.46 (0.55-3.88)		101	31	91	47	1.54 (0.87-2.75)	
HDL <50 mg/dL																		
No	97	19	124	31	1.37 (0.70-2.67)	0.753	64	12	52	12	1.32 (0.52-3.39)	0.693	161	31	176	43	1.33 (0.78-2.28)	0.895
Yes	59	22	52	33	1.60 (0.80-3.20)		39	16	35	20	1.02 (0.41-2.55)		98	38	87	53	1.40 (0.81-2.42)	
Fasting glucose ≥100 mg/dL																		
No	89	24	127	33	0.95 (0.51-1.77)	0.057	59	16	54	24	1.51 (0.67-3.41)	0.401	148	40	181	57	1.12 (0.69-1.83)	0.234
Yes	67	17	50	30	2.46 (1.15-5.24)		44	12	32	9	0.85 (0.28-2.54)		111	29	82	39	1.80 (0.99-3.29)	

Participants with baseline history of coronary heart disease, stroke, angina, revascularization, deep vein thrombosis, pulmonary embolus, diabetes, and hypertension were excluded from the analysis.
Values were adjusted for baseline smoking, age, education, hysterectomy status, and lipid-lowering medication.
APTIII, Adult Treatment Panel III; CVD, cardiovascular disease; OR, odds ratio; HDL, high-density lipoprotein.

greater safety.[15] Whether or not abnormal cardiometabolic risk indicators modify the risk of a CHD event when these newer HT preparations are taken is unknown and warrants further investigation.

Our findings emphasize the importance of assessing CVD risk status when HT is considered for relief of menopausal symptoms. Decisions to use HT are often multifaceted, complex, and challenging. Although HT should not be prescribed specifically for CHD protection, CVD risk assessment, including evaluation of the presence or absence of MetS, helps to identify women at higher or lower risk for a CHD event when taking HT.

CONCLUSIONS

MetS at baseline is an effect modifier for CHD risk with HT in the WHI clinical trials.

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