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CHD Events in the WHI Hormone Trials: Effect Modification by Metabolic Syndrome A Nested Case/Control Study within the WHI RCTs

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Abstract

Objective—Our objective was to determine if metabolic syndrome (MetS), or its components, modified the effect of HT on risk of CHD events in the Women's Health Initiative (WHI) clinical trials.

Methods—We performed a nested case/control study of incident CHD events during the first 4 years of follow up in the WHI HT trials (estrogen plus progestin [E+P] and estrogen-alone [E-

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Conflicts of Interest and Sources of Funding

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alone)). There were 359 incident cases of CHD during follow up. After excluding women with cardiovascular disease (CVD) (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 3 of 5 ATPIII criteria. Analyses by Chi-square, t-tests for heterogeneity and logistic regression were performed. Postmenopausal women (n=27,347) ages 50 to 79 from 40 US clinical centers participated.

Daily conjugated equine estrogens (0.625 mg) and medroxyprogesterone acetate (2.5mg) (EPT) or conjugated equine estrogens (0.625 mg) (ET) was compared to placebo. The Main Outcome Measure was the odds for CHD with HT use vs. placebo by MetS status.

Results—MetS modified the risk of CHD events with HT. In the pooled analysis, with MetS, risk was increased with HT vs. placebo (OR=2.26[95% CI, 1.26, 4.07]), whereas women without MetS were not found to have increased risk for a CHD event with HT (OR=0.97 [95% CI, 0.58, 1.61]) (p for interaction = 0. 03). Results were similar in the EPT and ET trials, when examined separately. The constellation of MetS variables was more predictive of risk from HT than MetS components assessed individually. When patients with diabetes or hypertension were included in the analysis we could not detect statistically significant effect modification.

Conclusion—MetS at baseline, in women without prior CVD, diabetes, or hypertension at baseline, identified women more likely to have had adverse coronary outcomes on HT. CHD risk stratification is recommended prior to initiating HT. The basis for the greater risk of CHD events with HT among patients with the metabolic syndrome requires further study.

Keywords

WHI; CHD; HT; Metabolic syndrome; Effect Modification

Emerging evidence suggests that a woman's baseline clinical characteristics, including proximity to menopause(1) and her coronary risk factor status, modify her risk of having a coronary heart disease (CHD) event when she is taking menopausal hormone therapy (HT) (2; 3). It is uncertain whether screening for cardio-metabolic risk indicators, such as the metabolic syndrome, may identify women who are at greater risk of an incident coronary event when using HT. Two clinical trials were conducted within the Women's Health Initiative (WHI) to assess CHD risk with HT. Conjugated equine estrogens (CEE) was compared to placebo in women with hysterectomy and CEE + medroxyprogesterone acetate (MPA) was compared to 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 cardio-metabolic risk status at baseline within both WHI clinical trials. The objective was to determine if presence or absence of the metabolic syndrome identified women at greater or lesser risk for a CHD event on HT during the trials.

Methods

Study population

Eligibility criteria and recruitment methods are published for each of the Women's Health Initiative clinical trials (6). Briefly 27, 347 postmenopausal women aged 50 to 79 years were

enrolled between September 1, 1993, and December 31, 1998 at 40 US clinical centers. Conjugated equine estrogens (0.625 mg) and medroxyprogesterone acetate (2.5mg) (CEE + MPA) or CEE-alone were given to 16, 608 women with an intact uterus (EPT trial). The 10, 739 women who had undergone hysterectomy, received conjugated equine estrogens (0.625 mg) alone (CEE) (ET trial). At baseline, women completed screening questionnaires by interview and self-report and each participant underwent a 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 RCTs studies (EPT and ET) were approved by the human subjects review committees at each participating institution. All participants provided written informed consent. They randomly received either a single daily tablet containing placebo or active medication. Study drugs and placebo were supplied by Wyeth-Ayerst (St. Davids, Pennsylvania). The planned end date of the trials was March 31, 2005, for a total follow-up of 8.4 years. However, conjugated equine estrogens plus medroxyprogesterone trial medications were stopped on July 7, 2002, and conjugated equine estrogens 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 or fatal CHD) occurring during the first 4 years of follow-up are included in our nested case-control study within both of the RCT cohorts. Clinical outcomes in the RCTs were identified by semi-annual questionnaires and were classified by centrally trained local adjudicators after medical record review. Coronary heart disease 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 surgery and aborted MI. Coronary heart disease death was defined as death consistent with an underlying cause of CHD plus 1 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 from baseline and years 3 and 6 electrocardiograms (Nova code 5.1 and 5.2.8).

We performed a case/control study nested within the 2 hormone clinical trials cohorts. There were 359 new CHD events in 4 years of follow up. We were able to randomly select 817 control subjects identified at the same time that the case was identified who did not have a CHD event. To help understand the risk of having the MetS when HT was used, because prior CVD is such a strong a risk factor for having a CHD event, we included only women without a prior diagnosis of myocardial infarction, angina, coronary revascularization, stroke, venous thromboembolism, or other major forms of cardiovascular disease in our analysis. Controls, those who did not experience a cardiovascular disease event at the time the case was identified during follow-up in the Women's Health Initiative clinical trials, were matched on age, randomization date, at baseline.

Blood samples were obtained in a 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-anti-coagulated plasma at PPD Global Central labs on a Hitachi 747 General Chemistry Analyzer. Triglycerides were measured using a chromogenic reaction after hydrolysis and oxidation. HDL was measured after removal of

chylomicrons, VLDL, and LDL from plasma. Our assessment for presence or absence of the metabolic syndrome required at least 3 of 5 (ATPIII NCEP 2004) criteria at the baseline visit. The criteria for MetS included: waist size >88cm (or 80 cm for Asian and American Indians), blood pressure >130 mmHg systolic or diastolic > 85 mmHg (or hypertension), fasting glucose > 100 mg/dL (or diabetes), HDL cholesterol <50 mg/dL, or triglycerides >150 mg/dL.

There were 93 cases who had a prior MI, 28 who had a prior stroke, 133 who were diagnosed with angina, 65 who had undergone a revascularization procedure, and 17 who had a prior deep vein thrombosis and 3 who had a prior pulmonary embolus. This left 269 cases who had no prior baseline CVD 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 for effect modification in cases and controls who had no prior diagnosis of diabetes or hypertension. In this analysis 166 cases were compared to 524 controls to test for effect modification by having the MetS. We assessed for presence of the metabolic syndrome (7) as an effect modifier for active hormone treatment vs. placebo as to risk for an incident CHD event during each of the clinical trials up to four years of follow up. We calculated odds ratios for women assigned to HT vs. placebo and tested for effect modification by the individual metabolic syndrome 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 of baseline including those who also had a prior history of diabetes or hypertension (ATPIII NCEP 2010 definition of MetS). In this analysis for effect modification, 269 cases were compared to 695 controls.

Statistical Methods

Chi-square tests or t-test for heterogeneity were used to determine the statistical significance of difference between the groups. Logistic regression was used to calculate odds ratios and 95% CIs. The odds of CHD with HT treatment compared to placebo were determined in the combined cohort (HT trials) in those patients who did or did have the metabolic syndrome. Stepwise logistic analysis was performed to determine the covariates included in the final models. Participants with missing value for any covariates are 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, North Carolina).

Results

Baseline demographic characteristic of cases and controls in the ET, the EPT trials and for the combined data set (HT) excluding patients who developed CHD and had CVD at baseline are displayed in (Table 1). Those who went on to develop a CHD event had greater BMIs. MetS components, BMI, LDL-cholesterol and hs-C-reactive protein were worse for clinical trial entrants who became a case than for those who became controls in the HT trials (Table 1). Higher mean systolic and diastolic blood pressure, fasting glucose and/or more 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 for the combined data set for presence or absence of the metabolic syndrome and for each ATPIII MetS component compared to 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 for a CHD event for HT users compared to placebo was higher with hormone use (1.29 [95% CI, 1.00, 1.66]), presence of the metabolic syndrome at baseline was a significant effect modifier. Test for interaction showed significant effect modification for the pooled data set ($p=.03$). Women without the metabolic syndrome were not at increased risk of CHD on HT vs. placebo (OR=0.97 [95% CI, 0.58, 1.361]). Women who had the metabolic syndrome, in contrast, were at significantly greater risk for a CHD event while on HT vs. placebo (OR=2.26 [95% CI, 1.26, 4.07]).

We performed the analysis for each individual trial as well. Although power was more limited, 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 the 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 (1.13 [0.61, 2.13]). Test for interaction in the EPT trial was not significant ($P=.173$).

In the ET trial, although overall the odds for an incident CHD event were higher (1.15 [95% CI 0.78, 1.68]) in ET users, when MetS was not present there was no increased risk (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 .84, 3.27]). Test for interaction was not significant ($P=.072$).

The same analysis was rerun including diabetes and hypertension as part of the definition of MetS on those cases and controls who could have had a prior diagnosis of diabetes or hypertension. In this analysis we could not find statistically significant effect modification by having metabolic syndrome. When diabetes or hypertension was present it appeared that the ability to detect effect modification was blunted (OR=0.95 [95% CI 0.57, 1.57] among women without MetS and OR=1.49 [95% CI 0.96, 2.30] among women with MetS (p -value 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 cardio metabolic risk status when menopausal hormone therapy was given in the Women's Health Initiative randomized clinical trials. By contrasting baseline demographic and metabolic parameters in those who became cases of CHD within four 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 the metabolic syndrome even without prior CVD, diabetes or hypertension at baseline, hormone therapy was associated with higher CHD risk. Metabolic syndrome was a predictor of an increased risk of an event with hormone use during the trials. Women who did not have the metabolic syndrome were not found to be at greater odds for CHD when taking HT.

It is interesting to speculate why we could not find effect modification when we included patients who had diabetes or hypertension at baseline. The WHI showed a reduction in DM with the HT intervention during the clinical trials. In the EPT arm there was a 21% significant reduction. The HR was (0.79 [95% CI 0.67, 0.93]). In the ET arm the HR was (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 patients available it would have been of interest to assess CHD risk of HT in patients who were diabetic and hypertensive. We did not have enough power to assess this in the current investigation.

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

Of great interest is why do these abnormal cardio metabolic indicators modify the risk for a CHD event with HT? Elevated non hdl cholesterol levels found in MetS reflect altered triglyceride metabolism, with more circulating atherogenic ApoB particles including small dense ldl(9). Perhaps in this setting more fatty acids circulating could lead to more insulin resistance. With higher circulating ldl particles there may be more of an inflammatory response to these particles as they enter the artery wall. Along with particles circulating with higher triglyceride content this could be associated with a greater tendency for plaque rupture. Several recent investigations have assessed other coronary heart disease biomarkers as predictors of CHD with menopause hormone therapy (2; 3; 10). Many thrombotic, inflammatory, and lipid biomarkers are associated with greater risk for a CHD event. Interleukin 6, matrix metalloproteinase 9, low-density lipoprotein 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 prior analysis of WHI data, however, none of these abnormal biomarkers, when analyzed individually, were found to be statistically significant effect modifiers of CHD outcomes with HT. The MetS milieu is associated with a constellation of risk factors, including insulin resistance and a hyper-thrombotic, pro-inflammatory state, which in combination may be particularly deleterious and 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 hormone therapy (HT) (2; 3). Baseline ldl cholesterol has been shown to be an effect modifier (2). Women with a ratio of low-density lipoprotein (ldl) to high-density lipoprotein (hdl) cholesterol ratio below 2.5 were not found to be at elevated risk when CEE with or without MPA was compared to placebo, whereas women with an ldl/hdl cholesterol ratio > 2.5 were found to be at greater risk(3). Of relevance to the findings here, prior investigations found that neither unopposed estrogen nor estrogen with progestin lowered low- density ldl particle concentration in the WHI clinical trials (12). Elevated circulating small ldl particles are associated with having the

MetS(13). Adiposity may be an important contributor to risk (14). Obesity predisposes to development of the metabolic syndrome (MetS). Our findings coupled with findings by Rossouw et al (2) Bray et al (3) and Hsia et al (12) suggest that having elevated baseline cardio metabolic 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 of CHD events on HT. Measurement of lipids and assessment of other metabolic syndrome parameters, including waist circumference, blood pressure and fasting glucose, are readily available to most clinicians.

Our study within the RCTs cohort of the WHI only assessed the CHD risk of oral HT above placebo for the first four years of follow up at the 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 that deliver smaller steroid doses are increasingly used with prospects for greater safety(15). Whether or not abnormal cardio metabolic 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 hormone therapy should not be prescribed specifically for CHD protection, CVD risk assessment, including evaluation for the presence or absence of MetS, helps to identify women at higher or lower risk for a CHD event when taking HT.

Conclusion

Metabolic syndrome at baseline was an effect modifier for CHD risk when HT was given during the WHI HT clinical trials.

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Table 1

Baseline Risk in patients with no prior CVD at baseline

	Estrogen Alone				Estrogen + Progestin				Combined Trial				Cases					
	Controls		Cases		Controls		Cases		Controls		Cases		Controls		Cases			
	N	Mean	SD	N	Mean	SD	p-value	N	Mean	SD	N	Mean	SD	p-value	N	Mean	SD	p-value
Age at screening	273	66.29	6.44	112	66.92	6.58	0.386	422	66.59	6.86	157	65.76	7.31	0.200	695	66.47	6.69	0.632
Body-mass index (kg/m ²), baseline	273	29.18	5.44	112	30.17	6.10	0.118	419	27.73	5.79	157	28.64	5.96	0.097	692	28.30	5.70	0.020
Hip circumference (cm), baseline	273	109.79	12.58	112	109.79	13.00	0.997	420	105.44	11.38	157	108.06	13.55	0.020	693	107.15	12.05	0.069
Waist circumference (cm), baseline	273	90.60	13.03	112	94.61	14.80	0.009	420	86.18	13.42	157	90.30	14.39	0.001	693	87.92	13.43	<.001
Waist/hip ratio, baseline	273	0.83	0.09	112	0.86	0.08	<0.005	420	0.82	0.07	157	0.83	0.07	0.006	693	0.82	0.08	<.001
Weight (kg), baseline	273	76.28	15.09	112	78.23	17.41	0.272	421	72.02	16.01	157	74.64	16.68	0.084	694	73.69	15.78	0.036
Diastolic BP (mm Hg), baseline	272	76.13	8.98	112	77.80	9.73	0.108	422	74.80	9.31	157	76.81	10.60	0.0271	694	75.32	9.20	0.006
Systolic BP (mm Hg), baseline	273	130.19	16.91	112	140.21	18.05	<0.001	422	129.04	17.53	157	133.86	19.18	0.004	695	129.49	17.28	<.001
BL Glucose, mg/dL	270	105.06	27.99	112	119.74	50.05	<0.003	422	102.55	25.80	155	115.31	49.38	<.001	692	103.53	26.68	<.001
BL HDL-C, mg/dL (MRL)	272	54.08	14.16	110	49.59	13.11	0.004	421	55.72	14.77	155	50.36	13.45	<.001	693	55.07	14.55	<.001
BL Triglyceride, mg/dL (MRL)	273	161.84	86.36	112	174.21	91.83	0.212	422	148.15	77.41	156	182.13	109.70	<.001	695	153.53	81.26	<.001
BL LDL-C, mg/dL	266	143.45	33.58	105	153.38	34.15	0.011	416	141.43	33.41	148	154.22	32.70	<.001	682	142.22	33.47	<.001
BL Total Cholesterol, mg/dL	273	229.30	37.44	112	236.58	39.19	0.088	422	226.69	36.38	156	239.63	37.26	<.002	695	227.72	36.80	<.001
BL C-reactive protein, ug/ml	264	3.85	4.38	108	4.99	4.60	0.025	409	3.27	4.63	153	4.20	4.65	.034	673	3.50	4.54	0.002

	Estrogen Alone					Estrogen + Pro					Combined Trial				
	Controls		Cases			Controls		Cases			Controls		Cases		
	N	%	N	%	p-value	N	%	N	%	p-value	N	%	N	%	p-value
Race/ethnicity	211	77.29	85	75.89	0.787	371	87.91	140	89.17	0.899	582	83.74	225	83.64	0.799
	42	15.38	16	14.29		23	5.45	7	4.46		65	9.35	23	8.55	
	13	4.76	6	5.36		17	4.03	5	3.18		30	4.32	11	4.09	
	7	2.56	5	4.46		11	2.61	5	3.18		18	2.59	10	3.72	
Education	91	33.58	53	48.62	0.014	108	25.71	56	35.90	0.055	199	28.80	109	41.13	0.001
	111	40.96	39	35.78		166	39.52	54	34.62		277	40.09	93	35.09	
Smoking status	69	25.46	17	15.60		146	34.76	46	29.49		215	31.11	63	23.77	
	145	54.92	54	49.54	<.0003	233	55.88	71	46.71	<.001	378	55.51	125	47.89	<.001
	98	37.12	30	27.52		152	36.45	49	32.24		250	36.71	79	30.27	
	21	7.95	25	22.94		32	7.67	32	21.05		53	7.78	57	21.84	
Treated diabetes (pills or shots)	259	94.87	90	80.36	<.001	404	95.73	140	89.74	0.007	663	95.40	230	85.82	<.001
	14	5.13	22	19.64		18	4.27	16	10.26		32	4.60	38	14.18	
Hypertension	124	49.40	37	35.92	0.021	225	59.21	60	43.48	0.002	349	55.31	97	40.25	<.001
	127	50.60	66	64.08		155	40.79	78	56.52		282	44.69	144	59.75	
Anti-hyperlipidemic medication use	252	92.31	101	90.18	0.492	392	92.89	143	91.08	0.465	644	92.66	244	90.71	0.312
	21	7.69	11	9.82		30	7.11	14	8.92		51	7.34	25	9.29	
HRT use status	154	56.41	69	61.61	0.410	316	74.88	116	73.89	0.352	470	67.63	185	68.77	0.233
	88	32.23	35	31.25		79	18.72	35	22.29		167	24.03	70	26.02	
	31	11.36	8	7.14		27	6.40	6	3.82		58	8.35	14	5.20	
	196	82.01	66	70.97	0.027	309	83.51	97	75.78	0.052	505	82.92	163	73.76	0.003
Family history of premature MI (<55 male, <65 female)	43	17.99	27	29.03		61	16.49	31	24.22		104	17.08	58	26.24	

Table 2
Risk according to baseline Risk Assessment (APTHI definition) in patients with no baseline CVD, hypertension or diabetes

	Estrogen + Progestin										Estrogen alone					
	Placebo					Treatment					P value for interaction	Placebo		Treatment		P value for interaction
	Controls	Cases	Controls	Cases	OR	lower CL	upper CL	Controls	Cases	OR		lower CL	upper CL			
MBS, meeting three or more criteria, APTIII definition	No	100	23	137	34	1.13	(0.61, 2.13)	0.173	58	17	13	0.75	(0.30, 1.86)	0.123		
	Yes	56	18	39	30	2.26	(1.05, 4.85)		44	11	35	2.11	(0.81, 5.48)			
Waist > 35 inches (80 cm for Asian and American Indian)	No	95	26	115	36	1.22	(0.66, 2.26)	0.541	49	17	46	0.75	(0.30, 1.87)	0.114		
	Yes	60	15	61	28	1.66	(0.78, 3.53)		55	11	41	2.16	(0.84, 5.52)			
Elevated blood pressure	No	80	15	111	34	1.86	(0.90, 3.83)	0.392	55	10	45	1.39	(0.50, 3.92)	0.822		
>=130/85	Yes	76	26	66	30	1.21	(0.62, 2.34)		49	18	42	1.20	(0.51, 2.79)			
Elevated triglycerides > 150 mg/dL	No	97	21	130	35	1.38	(0.72, 2.61)	0.773	62	17	43	1.13	(0.48, 2.68)	0.699		
	Yes	59	20	47	29	1.59	(0.76, 3.31)		42	11	44	1.46	(0.55, 3.88)			
reduced HDL < 50 mg/dL	No	97	19	124	31	1.37	(0.70, 2.67)	0.753	64	12	52	1.32	(0.52, 3.39)	0.693		
	Yes	59	22	52	33	1.60	(0.80, 3.20)		39	16	35	1.02	(0.41, 2.55)			
Elevated fasting glucose	No	89	24	127	33	0.95	(0.51, 1.77)	0.057	59	16	54	1.51	(0.67, 3.41)	0.401		
	Yes	67	17	50	30	2.46	(1.15, 5.24)		44	12	32	0.85	(0.28, 2.54)			

Combined Trials														
	Placebo					Treatment					P value for interaction			
	Controls	Cases	Controls	Cases	OR	lower CL	upper CL							
MBS, meeting three or more criteria, APTHI definition	No	158	40	188	47	0.97	(0.58, 1.61)	0.032						
Waist > 35 inches (80 cm for Asian and American Indian)	Yes	100	29	74	50	2.26	(1.26, 4.07)							
Elevated blood pressure $\geq 130/85$	No	144	43	161	50	1.03	(0.62, 1.70)	0.120						
	Yes	115	26	102	47	1.93	(1.08, 3.44)							
	No	135	25	156	45	1.70	(0.95, 3.05)	0.406						
	Yes	125	44	108	52	1.22	(0.73, 2.04)							

	Combined Trials							
	Placebo		Treatment					
	Controls	Cases	Controls	Cases	OR	lower CL	upper CL	P value for interaction
Elevated triglycerides > 150 mg/dL	No Yes	38 31	173 91	50 47	1.24 1.54	(0.75, 0.87)	(2.04, 2.75)	0.569
reduced HDL < 50 mg/dL	No Yes	31 38	176 87	43 53	1.33 1.40	(0.78, 0.81)	(2.28, 2.42)	0.895
Elevated fasting glucose >= 100 mg/dL	No Yes	40 111	181 82	57 39	1.12 1.80	(0.69, 0.99)	(1.83, 3.29)	0.234

Participants with baseline history of CHD, stroke, angina, re-vascularization, DVT, PE, diabetes, and hypertension were excluded from analysis Adjusted for baseline smoking, age, education, hysterectomy status, and lipid lowering medication.