



Lipoprotein particles and size, total and high molecular weight adiponectin, and leptin in relation to incident coronary heart disease among severely obese postmenopausal women: The Women's Health Initiative Observational Study ^{☆, ☆, ☆, ☆}



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ABSTRACT

Background: We hypothesized that higher concentrations of LDL particles (LDL-P) and leptin, and lower concentrations of HDL particles (HDL-P), and total and high molecular weight (HMW) adiponectin, would predict incident coronary heart disease (CHD) among severely obese postmenopausal women.

Methods: In a case-cohort study nested in the Women's Health Initiative Observational Study, we sampled 677 of the 1852 white or black women with body mass index (BMI) ≥ 40 kg/m² and no prevalent cardiovascular disease (CVD), including all 124 cases of incident CHD over mean 5.0 year follow-up. Biomarkers were assayed on stored blood samples.

Results: In multivariable-adjusted weighted Cox models, higher baseline levels of total and small LDL-P, and lower levels of total and medium HDL-P, and smaller mean HDL-P size were significantly associated with incident CHD. In contrast, large HDL-P levels were inversely associated with CHD only for women without diabetes, and higher total and HMW adiponectin levels and lower leptin levels were associated with CHD only for women with diabetes. Higher total LDL-P and lower HDL-P were associated with CHD risk independently of confounders including CV risk factors and other lipoprotein measures, with adjusted HR (95% CIs) of 1.55 (1.28, 1.88) and 0.70 (0.57, 0.85), respectively, and similar results for medium HDL-P.

Conclusions: Higher CHD risk among severely obese postmenopausal women is strongly associated with modifiable concentrations of LDL-P and HDL-P, independent of diabetes, smoking, hypertension, physical activity,

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BMI and waist circumference.

General significance: Severely obese postmenopausal women should be considered high risk candidates for lipid lowering therapy.

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1. Introduction

The prevalence of extreme, or severe, obesity (body mass index [BMI] ≥ 40 kg/m²) [1] is higher for women than men, and for black than white women among US adults [2]. We have previously shown that among postmenopausal women in the Women's Health Initiative (WHI), incident coronary heart disease (CHD) and total mortality rates are doubled for severe obesity compared with normal BMI [3]. In WHI, within the category of severe obesity, CHD incidence was unrelated to BMI, but was strongly associated with smoking, diabetes, and hypertension [3]. Similarly, among severely obese adults in the Swedish Obesity Study (SOS), risk of myocardial infarction (MI) and cardiovascular disease (CVD) were not related to BMI, but were related to diabetes, smoking, systolic blood pressure (SBP), and total cholesterol [4]. However, individuals with severe obesity are rarely included in non-bariatric surgery cohort studies, so that there is little data on CVD risk factors among women with severe obesity, particularly for novel biomarkers [5].

Obesity is strongly related to higher levels of leptin and lower levels of total and high molecular weight (HMW) adiponectin, all of which have been proposed as risk factors and possible therapeutic targets for the prevention of obesity or its metabolic and cardiovascular effects. Although several studies have reported that higher leptin levels were associated with increased CHD risk, a meta-analysis suggested that the risk was largely dependent on the strong association of leptin with BMI [6]. Adiponectin, both the total and the HMW form, are inversely associated with obesity and particularly with insulin resistance, but associations are mixed in relation to CHD and mortality [7–9]. The SOS has reported that higher baseline and greater 2 year increases in adiponectin were associated with lower CHD risk for severely obese patients who did not receive bariatric surgery, but not for those who did [10]. However, the relation of leptin, and total and HMW adiponectin to CHD risk among severely obese postmenopausal women remains unclear.

Finally, associations with CHD events are similar or stronger for concentrations of low density lipoprotein particles (LDL-P) and high density lipoprotein (HDL) particles (HDL-P) compared with concentrations of the cholesterol carried by those particles, i.e., LDL cholesterol (LDL-C) and HDL-C [11–16]. Under- or over-estimation of atherosclerotic CHD risk by LDL-C compared with LDL-P or apoB, which approximates LDL-P, is common, particularly among postmenopausal women [15–17]. In the Dallas Heart Study, HDL-P was similarly associated with lower CHD risk among white and black participants, but HDL-C was not associated with CHD risk among black participants, who had higher HDL-C and larger mean HDL size than white participants [18]. Smaller LDL and HDL particle sizes are also associated with incident CVD, but several studies have shown that these associations are not independent of correlated levels of total LDL-P, apoB, apoA-1 or HDL-P [12,14,19–22]. However, associations of LDL-P and HDL-P, subclasses and mean particle sizes with incident CHD in severe obesity have not been reported.

Therefore we conducted a case-cohort study nested in the WHI Observational Study (WHI-OS), to evaluate concentrations of lipoprotein particles, total and HMW adiponectin, leptin, as predictors of incident CHD among black and white postmenopausal women with severe obesity. Specifically, we hypothesized that among severely obese postmenopausal women without baseline CVD, incident CHD would be related to lower levels of total and HMW adiponectin, and to

higher levels of leptin, independent of BMI and diabetes, but that higher levels of total LDL-P and lower levels of total HDL-P would be the strongest determinants of incident CHD.

2. Methods

2.1. Participants and data

The 677 participants in the current case-cohort study were sampled from the WHI-OS (Fig. 1). As previously described in detail [23], the WHI-OS recruited 93,676 postmenopausal women aged 50 to 79 at centers in the United States between 1993 and 1998 who chose not to or were ineligible to participate in WHI hormone or diet clinical trials. The current study was restricted to the 1852 black and white postmenopausal women in WHI-OS with BMI ≥ 40 kg/m² and no prevalent CVD (MI, angina, revascularization, congestive heart failure, stroke or peripheral vascular disease) and sufficient blood sample. According to case-cohort methodology [24], a subcohort (n = 579) was sampled from this subset without regard to incident CHD, using stratified random sampling to obtain approximately equal numbers in strata defined by ethnicity, waist circumference tertiles (waist circumference [WC] <111.6, 111.6–<121 and ≥ 121 cm), and age groups: 50–59, 60–69 and 70–79 (see Fig. 1). Incident CHD events were defined as adjudicated fatal and non-fatal MI, angina and/or angioplasty and bypass surgery [25]. All cases of incident CHD that occurred after the baseline blood draw date through August 2006 were also selected, n = 124, of whom 26 had also been selected in the subcohort, per case-cohort design [24]. Participants provided informed consent and institutional review

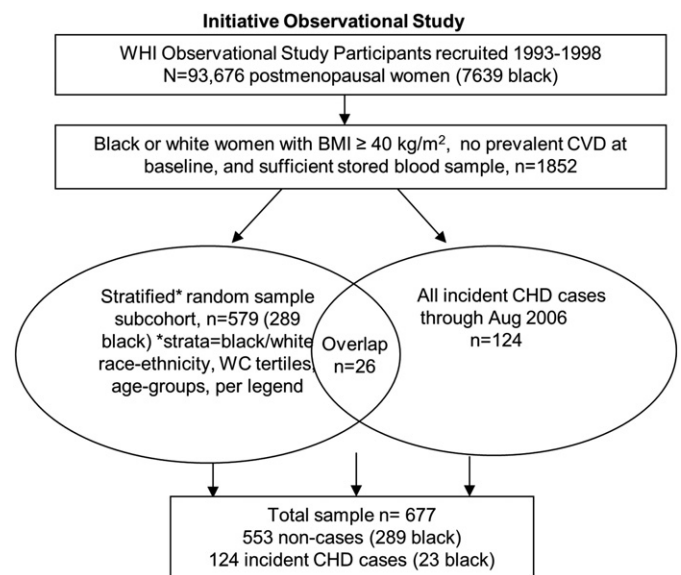


Fig. 1. Selection of case-cohort study participants from the Women's Health Initiative Observational Study (WHI-OS). The subcohort was selected without regard to incident CHD using stratified random sampling to obtain approximately equal numbers in strata defined by ethnicity, waist circumference tertiles (waist circumference [WC] < 111.6, 111.6–<121 and ≥ 121 cm), and age groups: 50–59, 60–69 and 70–79.

boards of collaborating institutions approved WHI and the current study. At baseline and 3 year follow-up clinic visits, data was collected on demographics, medical history, medications (including hormone therapy (HT)), measured height, weight and blood pressure. Blood was drawn after a minimum 10 h of fasting, and serum and plasma samples were frozen and stored at -70°C in a central repository [23]. Hypertension (systemic) was defined as SBP ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg or use of antihypertensive therapy [26]. Type 2 diabetes was defined as history of Type 2 diabetes, use of diabetic medications, or glucose ≥ 126 mg/dl [27]. Recreational physical activity was calculated from self-report based on a structured questionnaire, defined as expenditure of energy from recreational physical activity (includes walking, mild, moderate and strenuous physical activity) and expenditure of energy was estimated by total METs per week (kcal/week per kg), as previously described in detail [23].

2.2. Biomarker quantification

To conserve baseline samples, stored specimens from the year 3 follow-up visit were used, except for participants with inadequate specimen volume ($n = 70$), for whom baseline stored specimens were used. The visit concurrent with biospecimen collection was defined as baseline for case ascertainment and for other study data, except for time-independent variables (e.g., race), from WHI baseline. Under WHI coordinating center oversight, stored specimens were thawed, aliquoted (vials coded to blind study investigators/laboratories to participant identifiers), and shipped on dry ice to the Heinz Laboratory at the University of Pittsburgh Graduate School of Public Health, and to LipoScience, Inc., Raleigh, NC. The Heinz Laboratory assayed serum glucose by enzymatic methods; serum leptin, and insulin via standard radioimmunoassay (RIA) kits (Linco Research, Inc., St. Charles, MS); and total and HMW adiponectin via ELISA (ALPCO Diagnostics, Salem, NH). The intra- and inter-assay coefficients of variation were, respectively, 1.3% and 2.2% for glucose; 5.6% and 8.2% for insulin; 6.6% and 5.5% for leptin; 6.4% and 12.7% for total adiponectin; and 6.4% and 12.6% for HMW adiponectin. LipoScience, Inc. determined plasma lipoprotein subclasses using an automated nuclear magnetic resonance (NMR) spectroscopic assay (Lipoprofile III), as previously described in detail [28,29]. Particle concentrations of the different-sized lipoprotein subclasses were derived from the measured amplitudes of the characteristic lipid methyl group NMR signals they emit. Subclasses were summed to provide concentrations of total LDL-P, total HDL-P and total very large LDL particles (VLDL-P). Mean LDL-P and HDL-P sizes are weighted-averages (i.e., the diameter of each subclass multiplied by its relative concentration.) Inter-assay reproducibility (coefficient of variation), determined from 80 replicate analyses of 8 plasma pools over 20 days, was 8, 3, and 2% for total VLDL-P, LDL-P, and HDL-P; 0.7% for LDL and HDL size; 4% for VLDL size; 7, 13, and 22% for large, medium, and small VLDL-P; 43, 12, and 10% for IDL-P, large, and small LDL-P; and 9, 14, and 6% for large, medium, and small HDL-P, respectively.

2.3. Statistical analysis

Analyses were performed using SAS, version 9.2. A two-sided test with $p < 0.05$ was considered statistically significant. For testing multiplicative interaction between biomarkers and diabetes in relation to CHD risk, $p < 0.10$ was considered evidence of possible interaction, which was then evaluated by diabetes-stratified models. Total and HMW adiponectin, and physical activity were log-transformed for analysis. HRs were calculated with Cox proportional hazards regression weighted by the inverse of the sampling fractions to account for stratified sampling, and 95% confidence intervals were calculated using the robust variance estimator recommended for case-cohort analysis [24]. Each risk marker was modeled separately, sequentially adjusted for age and race, then BMI and WC, then smoking,

hypertension, lipid-lowering medication, hormone therapy use, and (log)physical activity. In the final model all variables were adjusted for each other and for the full covariate set. Sensitivity analyses included stratifying by race-ethnicity and excluding users of lipid-lowering medications and/or HT.

3. Results

Overall, at study baseline, the mean (SD) age of the study participants was 65.3 (6.9) years, 76.5% were hypertensive, 29.2% diabetic, 4.2% were current and 44% past smokers, 15.6% reported use of lipid-lowering medications, and 33.7% reported current hormone treatment. Mean (SD) follow-up time was 5.0 (1.8) years, 5.3 (1.5) for non-cases and 3.7 (2.2) for CHD cases. Women with CHD events during follow-up had similar mean age, BMI, WC, and prevalence of hypertension but higher prevalence of diabetes (42% vs. 29%), current smoking (8.3% vs. 3.9%) and lipid-lowering use (19.4% vs. 14.6%) compared to their counterparts without events during follow-up (Table 1).

Compared with no CHD, severely obese postmenopausal women with incident CHD had higher concentrations of total and small LDL-P, and small VLDL-P, lower concentrations of total, large, and medium HDL-P, smaller mean HDL-P size and LDL-P size, and lower mean levels of leptin, total and large HDL-P, and small VLDL-P (Table 2). For all, HRs for CHD per SD increase, were statistically significant in separate models, adjusted for age and race-ethnicity (Table 2). In contrast, women with incident CHD had similar mean levels of total and HMW adiponectin, large LDL-P and small HDL-P, compared with women with no CHD. Assessed by stratified models and interaction terms (not shown), biomarker associations with CHD risk were similar according to baseline diabetes status, except for total and HMW adiponectin, leptin, and large HDL-P, as described below.

Given evidence that associations of total and HMW adiponectin, leptin, and large HDL-P with CHD differed by baseline diabetes status ($p < 0.10$ for interaction terms) HRs adjusted for age, race-ethnicity, BMI and WC were calculated separately by baseline diabetes status. Among women without baseline diabetes (Table 3), levels of large HDL-P were significantly inversely related to CHD risk, but total and HMW adiponectin and leptin were not significantly related to CHD risk. In contrast, among women with baseline diabetes, higher total and HMW adiponectin and lower leptin were significantly associated with CHD risk, and large HDL-P was not. Results were similar when evaluated as CHD rates/1000 PYs (Fig. 2), but for women with diabetes, the increased risk of CHD was seen primarily in the highest quartiles of total and HMW adiponectin, and the lowest quartile of leptin.

For biomarkers with no interactions with diabetes, associations were further evaluated in separate models, first as quartiles, adjusted for age and race, and then as continuous variables (per SD or log-unit increase),

Table 1

Characteristics of 677 postmenopausal women with BMI ≥ 40 kg/m², by incident CHD.

Characteristic ^a	No CHD (n = 553)	Incident CHD (n = 124)
White/Black, n ^b	264/289	101/23
Age, years ^b	65.2 (6.9)	64.6 (6.9)
BMI, kg/m ²	44.4 (4.1)	44.4 (4.5)
Waist circumference, cm ^b	117.1 (10.7)	119.8 (10.1)
Physical activity, met/h/wk	6.2 (9.7)	5.3 (8.3)
Diabetes, %	28.6	42
Hypertension, %	76.1	76.0
Smoking, %		
Never	52.0	51.2
Prior	44.1	40.5
Current	3.9	8.3
Current hormone use, %	33.7	23.4
Lipid-lowering treatment, %	14.6	19.4

^a Values are mean (SD) unless indicated as %.

^b Subcohort sampling was stratified by race-ethnicity, age-group and waist circumference, accounted for in analyses by weighted regression analyses.

Table 2
Biomarkers in relation to incident CHD among 677 postmenopausal women with BMI \geq 40 kg/m².

Biomarker (SD)	No CHD (n = 553)	Incident CHD (n = 124)	CHD risk per SD
	Mean (SD)	Mean (SD)	HR (95% CI) ^a
Leptin, ng/ml (23.2)	61.6 (23.0)	57.1 (23.8)	0.80 (0.67, 0.96)^c
Total adiponectin, ^b μ g/ml	7.0 (3.9)	7.4 (5.2)	0.89 (0.66, 1.20) ^c
HMW adiponectin, ^b μ g/ml	2.8 (2.3)	3.2 (3.3)	0.93 (0.68, 1.27) ^c
Total LDL-P, nmol/l (377)	1363 (360)	1515 (425)	1.41 (1.21, 1.65)
Large LDL-P, nmol/l (283.7)	562 (285)	551 (281)	1.01 (0.87, 1.10)
Small LDL-P, nmol/l (390.5)	620 (376)	775 (430)	1.40 (1.21, 1.64)
LDL size, nm (0.6)	20.9 (0.6)	20.8 (0.6)	0.85 (0.74, 0.98)
Total HDL-P, μ mol/l (5.7)	33.6 (5.7)	32.1 (5.8)	0.69 (0.59, 0.81)
Large HDL-P, μ mol/l (2.6)	4.9 (2.6)	3.9 (2.2)	0.70 (0.59, 0.83)^c
Medium HDL-P, μ mol/l (3.6)	8.8 (3.6)	7.8 (3.6)	0.66 (0.56, 0.77)
Small HDL-P, μ mol/l (4.7)	20.0 (4.7)	20.4 (4.8)	1.05 (0.91, 1.20)
HDL size, nm (0.5)	9.0 (0.5)	8.9 (0.5)	0.74 (0.62, 0.87)
Total VLDL-P, nmol/l (33.3)	58 (32)	71 (37)	1.16 (0.99, 1.35)
Large VLDL-P, nmol/l (4.71)	5.0 (4.6)	6.5 (4.8)	1.02 (0.87, 1.20)
Medium VLDL-P, nmol/l (14)	18.7 (13.6)	23.1 (14.9)	1.06 (0.90, 1.25)
Small VLDL-P, nmol/l (20.9)	34.6 (20.0)	41.3 (23.7)	1.20 (1.02, 1.41)
VLDL Size, nm (7.2)	49.4 (7.1)	50.9 (7.3)	0.97 (0.82, 1.14)

^a Age and race-adjusted hazard ratios (HR) and 95% confidence intervals (CIs) calculated separately per 1 SD or 1 log-unit increase in each biomarker using Cox proportional hazard regression, weighted for sampling, with standard errors/confidence intervals calculated using robust estimator for case-cohort design. Significant results are in bold.

^b ln-transformed

^c $p < 0.10$ for interaction with diabetes.

adjusted for age, race, BMI and WC (Table 4). Higher levels of total and small LDL-P (but not mean LDL size), lower levels of total and medium HDL-P, and smaller mean HDL size each remained significantly associated with CHD risk in all models.

We also evaluated whether associations of small LDL, HDL subclasses or mean HDL particle size with CHD risk were independent of levels of total HDL-P and LDL-P, with which they are correlated (Table 5). Overall, HRs for total LDL-P and total HDL-P remained statistically significant and were relatively unchanged when adjusted for each other or for other lipoprotein parameters in multivariable-adjusted models. Inverse associations of medium HDL-P with CHD also remained significant when adjusted for both total LDL-P and total HDL-P. In contrast, the positive association of small LDL-P with CHD was completely attenuated when adjusted for total LDL-P. Likewise, the inverse association of mean HDL size with CHD was not significant if adjusted for total HDL-P or total LDL-P, and was abolished (HR = ~1.0) if adjusted for both HDL-P and LDL-P.

Finally, higher total LDL-P and lower total HDL-P independently predicted CHD, adjusted for each other, age, race-ethnicity, BMI, WC, physical activity, diabetes, smoking, hypertension, lipid-lowering medication and hormone therapy (Table 6), with similar results if medium HDL-P was substituted for total HDL-P. The risk of CHD was increased by 50% (HR \geq 1.50) for a 1 SD (377 nmol/l) increase in LDL-P, similar to the 64% increase (HR 1.64) for Q4 vs. Q1 of LDL-P (Table 4), but also close to the approximately 75% increase (HR 1.73) for diabetes vs. no

Table 3
CHD risk (HRs (95% CI)) in relation to baseline biomarkers that differ by diabetes, among 677 postmenopausal women with BMI \geq 40 kg/m².

Biomarker	No baseline diabetes	Baseline diabetes
	HR (95% CI)	HR (95% CI)
N cases/total	72/467	52/210
Total adiponectin, ^a μ g/ml	0.83 (0.55, 1.25)	1.79 (1.05, 3.07)
HMW adiponectin, ^a μ g/ml	0.88 (0.53, 1.45)	2.07 (1.19, 3.61)
Leptin, ng/ml (23.2)	0.94 (0.76, 1.18)	0.69 (0.50, 0.96)
Large HDL-P, μ mol/l (2.6)	0.69 (0.55, 0.86)	0.95 (0.66, 1.35)

HRs calculated separately for each biomarker adjusted for age, race-ethnicity, BMI and waist circumference using Cox proportional hazard regression, weighted for sampling, and with standard errors/confidence intervals calculated using robust estimator for case-cohort design. Results are reported for a 1 SD or 1 log-unit increase. Significant results are in bold.

^a ln-transformed.

diabetes. Higher SBP, current smoking and less physical activity were also significantly associated with incident CHD. In sensitivity analyses (not shown), restricted to those not using lipid-lowering medications or HT, or to white women only, results were similar, except for weaker associations of smaller LDL size with CHD risk when HT users were excluded. Among black women only, robust conclusions are precluded by the low number of CHD cases, but differences in mean levels of total and HMW adiponectin, leptin, total LDL-P, total and medium HDL-P by incident CHD are similar to our overall results (not shown.)

Total and HMW adiponectin were correlated (Spearman) with each other and various lipoproteins, as expected, e.g., associated with larger mean LDL-P size and HDL-P size, lower levels of small LDL-P and higher levels of large HDL-P (not shown). In contrast, leptin was uncorrelated with most risk factors. Correlations were similar when stratified by diabetes or when women using lipid-lowering medications were excluded (not shown). Evaluation of participant characteristics by adiponectin or leptin quartiles among women with diabetes also revealed no factors which explained the paradoxical associations with CHD risk.

4. Discussion

Among these severely obese postmenopausal women, higher concentrations of LDL-P and lower concentrations of HDL-P (total and medium) were the strongest determinants of CHD risk, independent of BMI, WC, diabetes, SBP, smoking, physical activity, and use of anti-hypertensive and lipid-lowering medications and HT. In contrast, associations of leptin, total and HMW adiponectin with CHD risk differed by baseline diabetes status. Among women without diabetes, leptin, total and HMW adiponectin were not significantly associated with CHD risk, whereas among women with diabetes, lower leptin and higher total and HMW adiponectin were paradoxically associated with CHD risk. These results are consistent with studies of average-weight adults, which show robust associations of atherosclerosis and CHD risk with higher concentrations of LDL-P [12,15–17,19,20,30] and lower concentrations of total HDL-P [11–14,18,21] and medium HDL-P [12,13]. These studies have also found that inverse associations of total and medium HDL-P with CHD, CVD, and atherosclerosis are relatively independent of atherogenic lipoprotein particles (LDL-P or apoB), and other lipids [11,12,18,21]. In contrast, associations of mean LDL size, HDL size, large HDL-P, and HDL-C with CHD are substantially attenuated when adjusted for concentrations of lipoproteins (LDL-P and HDL-P) or apolipoproteins (apoB and apoA-1) [11,12,14,18,19,21,22]. Our study also

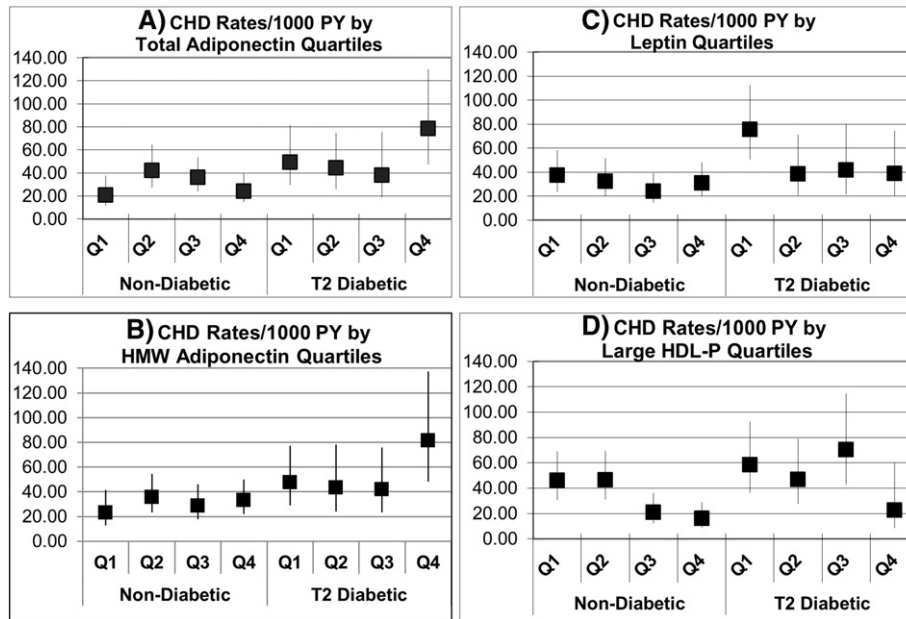


Fig. 2. Incident CHD rates per 1000 person-years (PY) by quartiles of total and HMW adiponectin, leptin and large HDL-P, stratified by baseline diabetes status. A. Total Adiponectin: quartiles are <4.3, 4.3–<6.2, 6.2–<8.6 and ≥ 8.6 µg/ml. B. HMW adiponectin; quartiles are <1.4, 1.4–<2.4, 2.4–>3.7 and ≥ 3.7 µg/ml; C. leptin: quartiles are <45.4, 45.4–<57, 57–<74.6 and ≥ 74.6 ng/ml; D. large HDL-P: quartiles are <2.8, 2.8–<4.2, 2.8–<6 and ≥ 6 µmol/l.

showed that inverse associations of large HDL-P with CHD risk were weaker for severely obese postmenopausal women with, than without, diabetes, consistent with evidence that larger HDL particles may be more susceptible to dysfunction in diabetes than smaller HDL particles [31,32].

Among severely obese postmenopausal women with diabetes only, higher total and HMW adiponectin and lower leptin were associated with CHD risk, whereas among women without diabetes, associations were weakly protective (adiponectin) or non-existent (leptin). Previous studies have reported similar null or paradoxical associations of higher total and HMW adiponectin with CHD and total mortality among older and high-risk adults [7–9,33–36]. As in studies of average-weight adults [35], associations of total and HMW adiponectin with lower WC, insulin resistance, and better lipoprotein levels did not explain their paradoxical associations with higher CHD risk among severely obese women with diabetes. These paradoxical associations with adiponectin may be due to increases in adiponectin in compensation for existing disease, rather than to adverse causal effects of higher adiponectin levels. Indeed, brain natriuretic peptide (BNP), which is increased in heart failure, is

also correlated with, and stimulates, adiponectin release [37], and adjusting for BNP partially attenuates the positive associations of adiponectin with CHD and CVD [34,36]. As noted, the complexities of adiponectin in relation to outcomes were also reported in the SOS Study, which found that baseline and 2 year changes in adiponectin were associated with incident MI and incident diabetes among the obese adults who did not receive bariatric surgery (control group), but not among those who received bariatric surgery [10].

Among the severely obese women in the current study, for those with diabetes, low leptin was associated with increased CHD rates, whereas most prior studies among average weight individuals have reported positive or null associations with CHD risk [6]. However, one study of overweight middle-aged women with a high prevalence of diabetes and impaired glucose tolerance found that low leptin was associated with CVD mortality [38]. Furthermore, in MESA, adjusted for weight and height, higher leptin was associated with smaller left ventricular mass and better left ventricular function [39]. We found no measured risk factors that explained our results, and additional studies are needed to verify whether the protective association of leptin with

Table 4
Incident CHD risk (HR (95% CI)) by baseline biomarkers, among 677 postmenopausal women with BMI ≥ 40 kg/m².

Predictor	Model 1: adjusted ^a HR (95% CI) by quartiles				Model 2: adjusted ^b HR (95% CI) per SD
	Q1	Q2	Q3	Q4	
Total LDL-P, nmol/l	<1129	1129–<1368	1368–<1598	>1598	1.41 (1.21–1.65)
HR (95% CI)	1.0	1.41 (0.91–2.18)	1.72 (1.08–2.73)	1.64 (1.05–2.55)	
Small LDL-P, nmol/l	<428	428–<634	634–<871	>871	1.34 (1.13–1.59)
HR (95% CI)	1.0	0.90 (0.59–1.35)	1.59 (1.03–2.46)	1.71 (1.15–2.53)	
LDL size, nm	<20.5	20.5–<21	21–<21.4	>21.4	0.92 (0.79–1.08)
HR (95% CI)	1.0	0.96 (0.64–1.43)	0.83 (0.55–1.25)	0.53 (0.34–0.83)	
Total HDL-P, µmol/l	<29.5	29.5–<33	33–<36.9	>36.9	0.73 (0.62–0.87)
HR (95% CI)	1.0	0.53 (0.35–0.80)	0.79 (0.52–1.18)	0.35 (0.23–0.53)	
Medium HDL-P, µmol/l	<6	6–<8.4	8.4–<11	>11	0.67 (0.57–0.79)
HR (95% CI)	1.0	0.61 (0.40–0.94)	0.61 (0.41–0.91)	0.40 (0.27–0.60)	
HDL size, nm (0.5)	<8.7	8.7–<9	8.7–<9.3	>9.3	0.80 (0.66–0.96)
HR (95% CI)	1.0	0.86 (0.59–1.28)	0.60 (0.41–0.89)	0.53 (0.35–0.81)	
Small VLDL-P, nmol/l	<20.3	20.3–<33.3	20.3–<48.2	>48.2	1.16 (0.98–1.37)
HR (95% CI)	1.0	0.35 (0.22–0.54)	0.64 (0.42–0.99)	0.99 (0.64–1.52)	

HRs from separate Cox models. Significant results are in bold.

^a Adjusted for age and race.

^b Adjusted for age, race, BMI and waist circumference.

Table 5
CHD risk (HR (95% CI)) per SD increase in lipoproteins modeled separately and jointly, among postmenopausal women with BMI ≥ 40 kg/m², n = 677.

Predictors	Total LDL-P	Small LDL-P	Mean HDL size	Med. HDL-P	Total HDL-P
Modeled separately	1.61 (1.35, 1.93)	1.45 (1.21, 1.75)	0.69 (0.55, 0.87)	0.66 (0.55, 0.80)	0.68 (0.56, 0.83)
Modeled jointly					
LDL-P + HDL-P	1.68 (1.39, 2.03)				0.72 (0.58, 0.91)
Small LDL-P + LDL-P	1.64 (1.25, 2.13)	1.04 (0.77, 1.39)			
HDL size + HDL-P			0.78 (0.59, 1.02)		0.75 (0.60, 0.95)
HDL size + LDL-P	1.63 (1.33, 2.00)		0.89 (0.66, 1.20)		
HDL size + HDL-P + LDL-P	1.67 (1.36, 2.05)		0.97 (0.71, 1.33)		0.73 (0.57, 0.93)
Med. HDL-P + total HDL-P				0.77 (0.64, 0.94)	0.84 (0.67, 1.05)
Med. HDL-P + total LDL-P	1.57 (1.30, 1.88)			0.72 (0.60, 0.87)	
Med. HDL-P + total HDL-P + Total LDL-P	1.57 (1.30, 1.88)			0.79 (0.64, 0.97)	0.84 (0.66, 1.07)

All models are adjusted for age, race-ethnicity, BMI, waist circumference, smoking, diabetes, hypertension, physical activity, lipid-lowering, hormone therapy. Significant results are in bold.

CHD among severely obese women with diabetes is real or due to unmeasured confounding or chance.

The results of this study should be interpreted in light of its strengths and limitations. The WHI-OS offers a rare opportunity to evaluate factors related to incident CHD among a large sample of severely obese women not selected for bariatric surgery, and with a relatively low prevalence of statin use at baseline. The biomarkers included have high potential clinical relevance and were measured in well-established laboratories blinded to study outcomes. However, as in all observational studies, our study is subject to potential unmeasured or residual confounding. Furthermore, of the 1852 WHI participants eligible for our study, only 371 (8%) were black, with 23 incident CHD cases, limiting the power for CHD analyses restricted to black women only. However, in sensitivity analyses (not shown), key predictors had similar direction of association with CHD when restricted to black women only, which agrees with a recent report showing that HDL-P was inversely associated with CHD risk among black and white adults, whereas HDL-C was associated with risk only among white adults [18]. Finally, due to cost and specimen volume limitations, the current study did not measure lipids or apolipoproteins, so it cannot compare the predictive ability of LDL-P and HDL-P with lipids (LDL-C, HDL-C, non-HDL-C, etc.) or apolipoproteins (apoB, apoA-1, etc.)

4.1. Clinical implications

Given the higher prevalence of severe obesity among women, severely obese women form one of the largest subgroups of women with high CVD risk, since we have previously shown that CHD, CVD and mortality rates among postmenopausal women with severe obesity are two-fold higher than women with normal BMI, and are even higher with concomitant diabetes, hypertension and/or smoking [3]. Hypertension and diabetes are both very common in severe obesity, with a prevalence of >60% and ~30%, respectively, in the current study, and among younger severely obese adults [40]. The current study adds that among severely obese postmenopausal women, regardless of diabetes and other CV risk factors, higher levels of LDL-P and lower levels of HDL-P are also strongly related to CHD risk, but levels of large LDL-P, which are strongly correlated with LDL-C (not measured in this study), are

Table 6
HRs (95% CIs) for the risk of incident CHD according to baseline biomarkers in multivariable-adjusted models, among 677 postmenopausal women with BMI ≥ 40 kg/m².

Predictor (SD)	Model 1	Model 2
Total LDL-P, nmol/l (377)	1.55 (1.28, 1.88)	1.50 (1.24, 1.82)
Total HDL-P, μ mol/l (5.7)	0.70 (0.57, 0.85)	–
Medium HDL-P, μ mol/l (4.0)	–	0.63 (0.51, 0.78)
Type 2 diabetes (vs. no)	1.73 (1.17, 2.56)	1.74 (1.18, 2.59)
Systolic blood pressure (17 mm Hg)	1.11 (1.02, 1.20)	1.09 (1.01, 1.19)
Current smoking (vs never)	2.99 (1.41, 5.97)	2.53 (1.23, 5.22)
(Log) physical activity, met/h/wk	0.85 (0.73, 0.99)	0.85 (0.72, 0.99)

Hazard ratios calculated per SD increase in biomarkers adjusted for each other and age, race-ethnicity, BMI, waist circumference, use of anti-hypertensive and lipid-lowering medications and hormone therapy. Significant results are in bold.

not significantly related to CHD risk. Mean LDL-P levels among severely obese postmenopausal women in our study were substantially higher than clinical recommendations (low risk <1000 nmol/l) [41], average-weight women [30], and adults in MESA [29]. In contrast, mean levels of large LDL-P (highly correlated with LDL-C) were lower among these severely obese women than among individuals in MESA [29], congruent with reports that hypercholesterolemia is not increased among severely obese postmenopausal women [40,42,43]. Furthermore, the Study of Women Across the Nation showed that although apoB, total cholesterol and LDL-C increase across the menopausal transition, the increase was substantially flattened for women in the heaviest tertile of weight [44]. Although we did not measure LDL-C in this study, these prior studies suggest that among severely obese postmenopausal women, levels of total or LDL cholesterol may not reliably indicate CHD risk related to LDL lipoproteins. However, the current study shows that higher levels of LDL measured by LDL-P are independently associated with incident CHD among severely obese postmenopausal women, as previously shown for average weight women [16].

An important issue is whether all individuals with severe (class III) obesity should be considered at high CHD risk and be offered statin drug therapy as well as treatment of hypertension and smoking cessation. We have also previously shown that among younger severely obese adults (predominantly middle-aged women) in a multicenter US bariatric surgery study, the majority of those without diabetes have low 10-year Framingham risk, but high lifetime predicted CVD risk [40]. Mean HDL-P levels in these severely obese postmenopausal women were also lower than levels reported in MESA [29]. Lifestyle intervention among overweight and obese postmenopausal women can decrease LDL-P [45], but effects are small relative to those of statins, which reduce LDL-P as well as LDL-C, and also raise HDL-P [14,46]. Clinical trial data demonstrate substantial reductions in CHD events with lipid-lowering therapy among women [47]. Bariatric surgery has been documented to successfully reduce body weight and diabetes mellitus, but in a non-randomized study, SOS, the incidence of CVD diverged only in very long-term follow-up, and incident MI and CVD were related to baseline total cholesterol, diabetes, and smoking rather than to baseline HDL-C, BMI, or 2 year weight change [4]. However, there are no randomized clinical trials that show that bariatric surgery reduces incidence of CHD or CHD mortality, especially in long term. It is very unlikely that such trials will be done in the foreseeable future.

5. Conclusions

In summary, postmenopausal women with severe obesity (BMI ≥ 40 kg/m²) have a high risk of CHD, driven by smoking, diabetes and hypertension [3], and as shown in this study, higher levels of LDL-P and lower levels of HDL-P, which are modifiable by statin use. The current study also suggests that among severely obese postmenopausal women, leptin and total and HMW adiponectin have complex relations to CHD risk that complicate use for risk assessment and as potential treatment targets. Prevention of CHD, as well as stroke and

heart failure in severe obesity is likely feasible and should be a very high priority in prevention therapy, especially among the increasing proportion of women with severe obesity.

Transparency documents

The Transparency documents associated with this article can be found in the online version.

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For a list of all the investigators who have contributed to WHI science, please visit: <https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf>.

References

- P. Poirier, M.A. Alpert, L.A. Fleisher, P.D. Thompson, H.J. Sugerman, L.E. Burke, et al., Cardiovascular evaluation and management of severely obese patients undergoing surgery: a science advisory from the American Heart Association, *Circulation* 120 (1) (2009) 86–95.
- K.M. Flegal, M.D. Carroll, B.K. Kit, C.L. Ogden, Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010, *JAMA* 307 (5) (2012) 491–497.
- K.M. McTigue, Y.F. Chang, C. Eaton, L. Garcia, K.C. Johnson, C.E. Lewis, et al., Severe obesity, heart disease, and death among white, African American, and Hispanic postmenopausal women, *Obesity (Silver Spring)* 22 (3) (2014) 801–810.
- L. Sjostrom, M. Peltonen, P. Jacobson, C.D. Sjostrom, K. Karason, H. Wedel, et al., Bariatric surgery and long-term cardiovascular events, *JAMA* 307 (1) (2012) 56–65.
- K.M. McTigue, R.H. Mackey, L.H. Kuller, Cardiovascular complications of extreme obesity in women, *Curr. Cardiovasc. Risk Rep.* 5 (2011) 246–252.
- N. Sattar, G. Wannamethee, N. Sarwar, J. Chernova, D.A. Lawlor, A. Kelly, et al., Leptin and coronary heart disease: prospective study and systematic review, *J. Am. Coll. Cardiol.* 53 (2) (2009) 167–175.
- E. Sook Lee, S.S. Park, E. Kim, Y. Sook Yoon, H.Y. Ahn, C.Y. Park, et al., Association between adiponectin levels and coronary heart disease and mortality: a systematic review and meta-analysis, *Int. J. Epidemiol.* 42 (4) (2013) 1029–1039.
- D.A. Lawlor, S.G. Davey, S. Ebrahim, C. Thompson, N. Sattar, Plasma adiponectin levels are associated with insulin resistance, but do not predict future risk of coronary heart disease in women, *J. Clin. Endocrinol. Metab.* 90 (10) (2005) 5677–5683.
- N. Sattar, P. Watt, L. Cherry, S. Ebrahim, S.G. Davey, D.A. Lawlor, High molecular weight adiponectin is not associated with incident coronary heart disease in older women: a nested prospective case-control study, *J. Clin. Endocrinol. Metab.* 93 (5) (2008) 1846–1849.
- C. Herder, M. Peltonen, P.A. Svensson, M. Carstensen, P. Jacobson, M. Roden, et al., Adiponectin and bariatric surgery: associations with diabetes and cardiovascular disease in the Swedish Obese Subjects Study, *Diabetes Care* 37 (5) (2014) 1401–1409.
- R.H. Mackey, P. Greenland, D.C. Goff Jr., D. Lloyd-Jones, C.T. Sibley, S. Mora, High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events: MESA (Multi-ethnic Study of Atherosclerosis), *J. Am. Coll. Cardiol.* 60 (6) (2012) 508–516.
- S. Parish, A. Offer, R. Clarke, J.C. Hopewell, M.R. Hill, J.D. Otvos, et al., Lipids and lipoproteins and risk of different vascular events in the MRC/BHF Heart Protection Study, *Circulation* 125 (20) (2012) 2469–2478.
- L.H. Kuller, G. Grandits, J.D. Cohen, J.D. Neaton, R. Prineas, Lipoprotein particles, insulin, adiponectin, C-reactive protein and risk of coronary heart disease among men with metabolic syndrome, *Atherosclerosis* 195 (1) (2007) 122–128.
- S. Mora, R.J. Glynn, P.M. Ridker, High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy, *Circulation* 128 (11) (2013) 1189–1197.
- J.D. Otvos, S. Mora, I. Shalaurova, P. Greenland, R.H. Mackey, D.C. Goff Jr., Clinical implications of discordance between low-density lipoprotein cholesterol and particle number, *J. Clin. Lipidol.* 5 (2) (2011) 105–113.
- S. Mora, J.E. Buring, P.M. Ridker, Discordance of low-density lipoprotein (LDL) cholesterol with alternative LDL-related measures and future coronary events, *Circulation* 129 (5) (2014) 553–561.
- R.H. Mackey, L.H. Kuller, K. Sutton-Tyrrell, R.W. Evans, R. Holubkov, K.A. Matthews, Hormone therapy, lipoprotein subclasses, and coronary calcification: the Healthy Women Study, *Arch. Intern. Med.* 165 (5) (2005) 510–515.
- A. Chandra, I.J. Neeland, S.R. Das, A. Khera, A.T. Turer, C.R. Ayers, et al., Relation of black race between high density lipoprotein cholesterol content, high density lipoprotein particles and coronary events (from the Dallas Heart Study), *Am. J. Cardiol.* 115 (7) (2015) 890–894.
- K. El Harchaoui, W.A. van der Steeg, E.S. Stroes, J.A. Kuivenhoven, J.D. Otvos, N.J. Wareham, et al., Value of low-density lipoprotein particle number and size as predictors of coronary artery disease in apparently healthy men and women: the EPIC-Norfolk Prospective Population Study, *J. Am. Coll. Cardiol.* 49 (5) (2007) 547–553.
- S. Mora, M. Szklo, J.D. Otvos, P. Greenland, B.M. Psaty, D.C. Goff Jr., et al., LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-ethnic Study of Atherosclerosis (MESA), *Atherosclerosis* 192 (1) (2007) 211–217.
- K. El Harchaoui, B.J. Arsenaault, R. Franssen, J.P. Despres, G.K. Hovingh, E.S. Stroes, et al., High-density lipoprotein particle size and concentration and coronary risk, *Ann. Intern. Med.* 150 (2) (2009) 84–93.
- W.A. van der Steeg, I. Holme, S.M. Boekholdt, M.L. Larsen, C. Lindahl, E.S. Stroes, et al., High-density lipoprotein cholesterol, high-density lipoprotein particle size, and apolipoprotein A-I: significance for cardiovascular risk: the IDEAL and EPIC-Norfolk studies, *J. Am. Coll. Cardiol.* 51 (6) (2008) 634–642.
- G.L. Anderson, J. Manson, R. Wallace, B. Lund, D. Hall, S. Davis, et al., Implementation of the Women's Health Initiative study design, *Ann. Epidemiol.* 13 (9 Suppl) (2003) S5–S17.
- W.E. Barlow, L. Ichikawa, D. Rosner, S. Izumi, Analysis of case-cohort designs, *J. Clin. Epidemiol.* 52 (12) (1999) 1165–1172.
- J.D. Curb, A. McTiernan, S.R. Heckbert, C. Kooperberg, J. Stanford, M. Nevitt, et al., Outcomes ascertainment and adjudication methods in the Women's Health Initiative, *Ann. Epidemiol.* 13 (9 Suppl) (2003) S122–S128.
- A.S. Go, M.A. Bauman, S.M. Coleman King, G.C. Fonarow, W. Lawrence, K.A. Williams, et al., An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention, *J. Am. Coll. Cardiol.* 63 (12) (2014) 1230–1238.
- American Diabetes A, (2) Classification and diagnosis of diabetes, *Diabetes Care* 38 (Suppl. (Supplement 1)) (2015) S8–S16.
- E.J. Jeyarajah, W.C. Cromwell, J.D. Otvos, Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy, *Clin. Lab. Med.* 26 (4) (2006) 847–870.
- R.H. Mackey, S. Mora, A.G. Bertoni, C.L. Wassel, M.R. Carnethon, C.T. Sibley, et al., Lipoprotein particles and incident type 2 diabetes in the Multi-ethnic Study of Atherosclerosis, *Diabetes Care* (2015) [Epub ahead of print].
- S. Mora, J.D. Otvos, N. Rifai, R.S. Rosenson, J.E. Buring, P.M. Ridker, Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women, *Circulation* 119 (7) (2009) 931–939.
- A. Kontush, M.J. Chapman, Why is HDL functionally deficient in type 2 diabetes? *Curr. Diab. Rep.* 8 (1) (2008) 51–59.
- L. Camont, M.J. Chapman, A. Kontush, Biological activities of HDL subpopulations and their relevance to cardiovascular disease, *Trends Mol. Med.* 17 (10) (2011) 594–603.
- M. von Eyndt, A. Hamann, D. Twardella, P.P. Nawroth, H. Brenner, D. Rothenbacher, Atherogenic dyslipidaemia but not total- and high-molecular weight adiponectin are associated with the prognostic outcome in patients with coronary heart disease, *Eur. Heart J.* 29 (10) (2008) 1307–1315.
- S.G. Wannamethee, P. Welsh, P.H. Whincup, N. Sattar, M.C. Thomas, V. Gudnarsson, et al., High adiponectin and increased risk of cardiovascular disease and mortality in asymptomatic older men: does NT-proBNP help to explain this association? *Eur. J. Cardiovasc. Prev. Rehabil.* 18 (1) (2011) 65–71.
- J.R. Kizer, D. Benkeser, A.M. Arnold, K.J. Mukamal, J.H. Ix, S.J. Zeman, et al., Associations of total and high-molecular-weight adiponectin with all-cause and cardiovascular mortality in older persons: the Cardiovascular Health Study, *Circulation* 126 (25) (2012) 2951–2961.
- J.R. Kizer, D. Benkeser, A.M. Arnold, L. Djousse, S.J. Zeman, K.J. Mukamal, et al., Total and high-molecular-weight adiponectin and risk of coronary heart disease and ischemic stroke in older adults, *J. Clin. Endocrinol. Metab.* 98 (1) (2013) 255–263.
- O. Tsukamoto, M. Fujita, M. Kato, S. Yamazaki, Y. Asano, A. Ogai, et al., Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure, *J. Am. Coll. Cardiol.* 53 (22) (2009) 2070–2077.
- L. Piemonti, G. Calori, A. Mercalli, G. Lattuada, P. Monti, M.P. Garancini, et al., Fasting plasma leptin, tumor necrosis factor- α receptor 2, and monocyte chemoattracting protein 1 concentration in a population of glucose-tolerant and glucose-intolerant women: impact on cardiovascular mortality, *Diabetes Care* 26 (10) (2003) 2883–2889.
- M.A. Allison, D.A. Bluemke, R. McClelland, M. Cushman, M.H. Criqui, J.F. Polak, et al., Relation of leptin to left ventricular hypertrophy (from the Multi-ethnic Study of Atherosclerosis), *Am. J. Cardiol.* 112 (5) (2013) 726–730.
- R.H. Mackey, S.H. Belle, A.P. Courcouas, G.F. Dakin, C.W. Deveney, D.R. Flum, et al., Distribution of 10-year and lifetime predicted risk for cardiovascular disease prior to surgery in the longitudinal assessment of bariatric surgery-2 study, *Am. J. Cardiol.* 60 (6) (2012) 508–516.
- M.H. Davidson, C.M. Ballantyne, T.A. Jacobson, V.A. Bittner, L.T. Braun, A.S. Brown, et al., Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an expert panel of lipid specialists, *J. Clin. Lipidol.* 5 (5) (2011) 338–367.
- K. McTigue, J.C. Larson, A. Valoski, G. Burke, J. Kotchen, C.E. Lewis, et al., Mortality and cardiac and vascular outcomes in extremely obese women, *JAMA* 296 (1) (2006) 79–86.
- E.H. Livingston, M. Chandalia, N. Abate, Do current body mass index criteria for obesity surgery reflect cardiovascular risk? *Surg. Obes. Relat. Dis.* 3 (6) (2007) 577–585.
- K.A. Matthews, S.L. Crawford, C.U. Chae, S.A. Everson-Rose, M.F. Sowers, B. Sternfeld, et al., Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? *J. Am. Coll. Cardiol.* 54 (25) (2009) 2366–2373.
- L.H. Kuller, K.K. Pettée Gabriel, L.S. Kinzel, D.A. Underwood, M.B. Conroy, Y. Chang, et al., The Women on the Move Through Activity and Nutrition (WOMAN) study: final 48-month results, *Obesity (Silver Spring)* 20 (3) (2012) 636–643.

- [46] R.S. Rosenson, J.D. Otvos, J. Hsia, Effects of rosuvastatin and atorvastatin on LDL and HDL particle concentrations in patients with metabolic syndrome: a randomized, double-blind, controlled study, *Diabetes Care* 32 (6) (2009) 1087–1091.
- [47] S. Mora, R.J. Glynn, J. Hsia, J.G. MacFadyen, J. Genest, P.M. Ridker, Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials, *Circulation* 121 (9) (2010) 1069–1077.