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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☆,☆☆,★

Rachel H. Mackey [a,*], Kathleen M. McTigue [a,b], Yuefang F. Chang [c], Emma Barinas-Mitchell [a], Rhobert W. Evans [a], Lesley F. Tinker [d], Cora E. Lewis [e], JoAnn E. Manson [f], Marcia L. Stefanick [g], Barbara V. Howard [h], Lawrence S. Phillips [i,j], Simin Liu [k], Doina Kulick [l], Lewis H. Kuller [a]

[a] Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, United States
[b] Department of Medicine, University of Pittsburgh, Pittsburgh, PA, United States
[c] Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, PA, United States
[d] Department of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, United States
[e] Department of Medicine, University of Alabama at Birmingham, United States
[f] Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States
[g] Stanford Prevention Research Center, Department of Medicine, Stanford University, Stanford, CA, United States
[h] Medstar Health Research Institute, Hyattsville, MD, United States
[i] Clinical Studies Center, Atlanta VA Medical Center, Decatur, GA, United States
[j] Division of Endocrinology, Emory University School of Medicine, Atlanta, GA, United States
[k] Department of Epidemiology, Brown University, Providence, RI, United States
[l] Mayo Clinic Arizona, Phoenix, AZ, United States

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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/m^2 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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★ *Clinical Trial Registration Number*: NCT00000611.
* Corresponding author at: University of Pittsburgh Graduate School of Public Health, 542 Bellefield Professional Building, 130 N. Bellefield Ave, Pittsburgh, PA 15213, United States. Tel.: +1 412 624 5948; fax: +1 412 383 5891.
E-mail address: mackey@edc.pitt.edu (R.H. Mackey).

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

1. Introduction

The prevalence of extreme, or severe, obesity (body mass index [BMI] ≥ 40 kg/m^2) [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 40 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/m^2 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

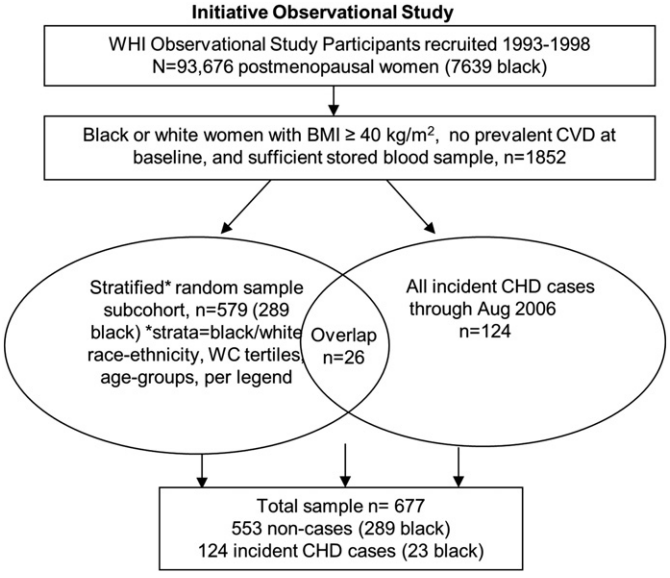

Fig. 1. Selection of case–cohort study participants from the Women's Health Initiative Observational Study (WHI-OS). The subcohort was selected without regard to incident CHD using stratified random sampling to obtain approximately equal numbers in strata defined by ethnicity, waist circumference tertiles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