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Combined hyperlipidemia in relation to race/ethnicity, obesity, and insulin resistance in the Multi-Ethnic Study of Atherosclerosis

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Abstract

We have asked whether the prevalence of combined hyperlipidemia (CHL) differs by race/ethnicity, obesity, and insulin resistance in a contemporary, multiethnic, US cohort. We determined the prevalence and adjusted odds of CHL in a cohort of 5923 men and women free of clinically recognized cardiovascular disease and diabetes according to race/ethnicity (white, Chinese, African American, and Hispanic), obesity, and insulin resistance. Untreated lipid values were imputed for those on lipid-lowering therapy. Combined hyperlipidemia was defined using age- and sex-specific greater than or equal to 75th percentile cut points for low-density lipoprotein cholesterol and triglycerides obtained from a predominantly white North American population study. Compared with whites, adjusted odds ratios for CHL were 0.48 in African Americans (95% confidence interval [CI], 0.30-0.75), 1.33 in Hispanics (95% CI, 0.93-1.91), and 1.06 in Asians (95% CI, 0.62-1.82). Within the entire population, the adjusted odds of CHL were over 2-fold higher in overweight and obese participants compared with normal-weight participants and more than 4-fold higher in quartiles 2 through 4 of insulin resistance compared with quartile 1. African Americans had lower odds for CHL than whites despite higher body mass index and abdominal adiposity. Hispanics had a nonsignificantly higher trend, and Asians had no significantly different odds than whites. Modest increases in weight and insulin resistance were associated with significantly higher odds of CHL in a multiethnic US population. Further research is needed to determine the most efficacious diet, exercise, and drug management to decrease the risk of CHL and coronary heart disease among racial/ethnic groups in the United States.

1. Introduction

Reference values for the definition of lipid abnormalities in the increasingly multiethnic US population are available from predominantly white North American population studies [1]. Despite the availability of these data, there has been no study of the prevalence of lipid abnormalities by racial-ethnic groupings in the United States. Effects of race and ethnicity on cardiovascular disease (CVD) risk factors have been conducted in 2 other multiethnic nations, Great Britain and Canada [2-4]. Differences in US ethnic populations are suggested by D'Agostino et al [5] who demonstrated that the sex-specific Framingham risk prediction score estimated coronary heart disease (CHD) risk well for whites and African Americans but not for Japanese, Hispanics, or Native Americans in the United States and Puerto Rico.

The strongest risk factor for first myocardial infarction worldwide is dyslipidemia [6] primarily consisting of simple hypercholesterolemia or combined hyperlipidemia (CHL). Beginning with the studies of Goldstein et al in 1973 [7], familial combined hyperlipidemia (FCHL) was more strongly associated with prevalent and incident CHD than simple hypercholesterolemia [7-10]. The diagnosis of FCHL requires elevations of cholesterol, triglycerides, or

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both, as well as these elevations in a first-degree relative [7-10]. Which lipid elevation predominates depends on cofactors such as body weight, abdominal adiposity, and diet. Overproduction of apolipoprotein B–containing lipoproteins (very low-density lipoprotein, intermediate-density lipoprotein, and low-density lipoprotein [LDL]) and small dense LDL particles is also a consistent feature of FCHL [11].

Family history of combined lipid elevations is often unavailable, in which case the condition is termed *combined hyperlipidemia* and not FCHL. Combined hyperlipidemia is usually diagnosed based simply on LDL and triglyceride elevations irrespective of family history. For the purpose of this investigation, we used a clinical trials definition of CHL: greater than or equal to 75th percentile for both LDL cholesterol (LDL-C) and triglycerides for age and sex based on a predominantly white population reference [1,12,13]. As an example, the 75th percentile for LDL in white men older than 45 years ranges from 163 to 170 mg/dL; and for triglyceride, between 150 and 178 mg/dL. These cut points are consistent with the National Cholesterol Education Program (NCEP)/Adult Treatment Panel III (ATP III) guidelines that suggest drug treatment for LDL-C of at least 160 mg/dL (2 or more risk factors but <10% 10-year risk of CVD) and define triglycerides of at least 50 mg/dL as abnormally elevated [14].

A strong relationship between FCHL and insulin resistance has been reported in predominantly people of European ancestry [15-20]. We studied the relationship of race/ethnicity, obesity, and insulin resistance with CHL in a contemporary, multiethnic, US population of men and women free of CVD and diabetes [21] to answer the following questions: (1) What are the prevalence and odds of CHL by ethnic group? (2) What are the independent associations of obesity and insulin resistance with CHL in this population?

2. Methods

The purpose of the Multi-Ethnic Study of Atherosclerosis (MESA) is to identify subclinical markers of CVD and measure progression of these subclinical markers over time [21]. The complete MESA cohort consists of 6814 men and women aged 45 to 84 years from 6 different US communities (Baltimore County, Maryland; Chicago, IL; Forsyth County, North Carolina; Los Angeles County, California; New York, NY; and St Paul, MN) representing 4 racial/ethnic categories including white, Chinese, African American, and Hispanic. Appropriate human subjects institutional review board approval was obtained for each field center and the MESA coordinating center. Race/ethnicity was self-reported and classified using standard National Institutes of Health race/ethnicity classification. Subjects could belong only to 1 category. All members of the cohort were free of clinically recognized CVD at baseline, 2000-2002. We excluded 13.2% (n = 897) with diabetes and 0.1% (n = 6) with missing glucose, insulin, or waist circumference data.

At baseline, several cardiovascular risk factors were directly measured or assessed via questionnaire including height, weight, blood pressure, waist circumference, medical history including presence of diabetes, hypertension, dyslipidemia, family history of MI, current medication use including lipid-lowering therapy, and assessment of personal habits such as tobacco and alcohol use. *Diabetes* was defined using the 2003 American Diabetes Association criteria of a fasting glucose of at least 126 mg/dL or taking medications for diabetes [22]. *Hypertension* was defined as systolic blood pressure of at least 140 mm Hg at baseline visit or diastolic blood pressure of at least 90 mm Hg, or by a history of physician-diagnosed hypertension [23].

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, and categorized according to the World Health Organization criteria as normal weight (BMI <25 kg/m^2), overweight (BMI = 25-30 kg/m^2), or obese (BMI ≥30 kg/m^2). Waist circumference was measured using a standardized protocol. Waist circumference was categorized (1) by the metabolic syndrome classification in whites of enlarged waist of at least 102 cm for men and at least 88 cm for women and (2) by ethnic-specific cut points for men and women from Alberti et al [14,24]. *Insulin resistance* was defined as quartiles of the homeostasis model assessment of insulin resistance (HOMA-IR) (glucose [in millimoles per liter]*insulin [in milliunits per liter]/22.5) [25]. Combined hyperlipidemia was defined as greater than or equal to the 75th percentile for both LDL-C and triglycerides for age and sex using the Lipid Clinics Prevalence Study data as a reference [1].

All lipids were measured at a central location, Collaborative Studies Clinical Laboratory at Fairview–University Medical Center (Minneapolis, MN), using standardized methods and reagents. Triglycerides were measured in plasma using a glycerol blanked enzymatic method (Trig/GB; Roche Diagnostics, 115 Hague Rd, Indianapolis, IN) on the Roche/Hitachi 911 Automatic Analyzer (Roche Diagnostics). Cholesterol was measured in plasma on the Hitachi 911 using a cholesterol esterase–cholesterol oxidase reaction (Chol R1, Roche Diagnostics). The same reaction was also used to measure high-density lipoprotein cholesterol (HDL-C) after precipitation of non–HDL-C with magnesium/dextran sulfate. The coefficient of variance was 4.0% for triglyceride measurements, 1.6% for total cholesterol, and 2.9% for HDL-C. Low-density lipoprotein cholesterol was calculated on specimens having a triglyceride of less than 400 mg/dL using the Friedewald formula [26]. Serum glucose was measured using the glucose oxidase method on the Vitros analyzer (Johnson & Johnson, Rochester, NY). Insulin was measured in serum by an immunoenzymatic sandwich assay using Access Ultrasensitive Insulin Reagent on the Access Immunoassay System (Beckman Instruments). Proton nuclear magnetic resonance (NMR) spectroscopy was used to determine HDL-C, LDL-

C, and very low-density lipoprotein C subclass size (Liposcience, Raleigh, NC).

For participants taking lipid-lowering medications at baseline (n = 855), we imputed the underlying untreated levels of total, LDL, and HDL cholesterol and triglycerides based upon their observed values under treatment and the observed changes in lipid levels associated with treatment among other MESA cohort members who started lipid-lowering therapy during cohort follow-up. A model relating untreated to treated lipid values (LDL-C, HDL-C, triglycerides, and total cholesterol) was created using a subset of participants who started taking lipid-lowering medications between baseline and examination 2. This model included terms for the untreated lipid value, an indicator regarding medication type, and an interaction between these 2 terms to allow the relationship between treated and untreated cholesterol to vary by drug type. This model was then used to estimate untreated values for the participants who were on treatment at baseline [27].

For 86 participants whose LDL-C was not able to be measured because triglycerides were greater than 400 mg/dL, we substituted LDL-C levels measured using recalibrated NMR measurements of LDL-C. A calibration equation was developed for this purpose, using participants who had both NMR and regular LDL measurements; and this was applied to the NMR values in cases of missing LDL. The NMR measurements were highly correlated to the regular LDL measurement (correlation, 0.86; r^2 for the calibration model, 0.73) [27].

2.1. Statistical analysis

We performed a cross-sectional analysis examining the association of race/ethnicity, obesity as defined by BMI categories, abdominal obesity as defined by waist circumference (in centimeters) categories, and insulin resistance as defined by quartiles of HOMA-IR, with the prevalence of CHL and with the odds of CHL after adjustment for appropriate cofactors. χ^2 Tests were used to compare categorical variables, and analysis of variance was used to compare means of continuous measurements across categories. Significance for comparisons of characteristics between pairs of race/ethnic groups was declared for P less than .01. Multivariate logistic regression was used to estimate the association of CHL with race/ethnicity (model 1), adiposity as defined by BMI (model 2), waist circumference using metabolic syndrome cutoffs (model 3), waist circumference using ethnic-specific cutoffs (model 4), and insulin resistance (model 5).

Important covariates (1) for the relationship between race/ethnicity and CHL included age, sex, and BMI; (2) for the relationship of adiposity with CHL included age, sex, and race/ethnicity; and (3) for the relationship of insulin resistance with CHL included age, sex, race/ethnicity, and BMI.

Three sensitivity analyses were performed. In one, the analysis was performed excluding those on lipid-lowering therapy and those with missing lipid values using only observed lipid values. In another sensitivity analysis, we redefined CHL using NCEP/ATP III cut points (LDL-C $\geq$160 mg/dL and triglycerides $\geq$150 mg/dL). Exogenous estrogen has known effects on LDL-C and triglycerides and could possibly be associated with adiposity. The final sensitivity analysis was performed by excluding women on estrogen (n = 901) to evaluate whether estrogen use confounded the associations examined. Statistical analyses were performed using Stata Statistical Software 9.0 (Stata, College Station, TX).

3. Results

After applying the exclusion criteria, there remained 5923 participants. Table 1 describes the baseline characteristics of the entire population and as classified by race/ethnicity. The mean age of the study population was 62 years (range, 44-84 years), 53% were women, and the mean BMI was 28.0 kg/ m^2 (range, 15.4-54.5 kg/m^2). The racial/ethnic breakdown of the 5923 participants was consistent with the entire MESA cohort: 41% white, 12% Asian, 26% African American, and 21% Hispanic. There were no significant differences observed in the number of women vs men among race/ethnicity categories. Whites were more likely to take lipid-lowering medications than the other race/ethnicity groups.

Compared with whites, African Americans had higher mean BMI, waist circumference, and HOMA-IR. Yet, their mean triglycerides and non–HDL-C were lower and LDL size was larger than those in whites. Compared with whites, Asians had lower mean BMI and waist circumference, LDL-C, and HDL-C. However, markers of insulin resistance such as HOMA-IR and triglycerides were not different between Asians and whites. Compared with whites, Hispanics had higher mean BMI, waist circumference, non–HDL-C, HOMA-IR, and triglycerides. Low-density lipoprotein cholesterol levels were not different but LDL size was significantly smaller for Hispanics compared with Whites.

Table 2 describes the prevalence of CHL and the characteristics of the subjects with and without CHL, including anthropometric, metabolic, and lipid parameters. Combined hyperlipidemia prevalence in the entire cohort was 2.9%. The CHL subjects were more likely to be women, be younger, be heavier, have larger waist circumference, and be more insulin resistant compared with the non-CHL subjects. The CHL subjects had higher mean total cholesterol, LDL-C, and triglycerides by definition compared with the non-CHL subjects. The CHL subjects also had lower mean HDL-C, higher non–HDL-C, smaller LDL size, and smaller HDL size compared with the non-CHL subjects.

Table 3 demonstrates the prevalence and adjusted odds of CHL by race/ethnicity. Hispanics had the highest prevalence of CHL at 4.6%. After adjusting for age and sex, the likelihood of CHL compared with whites was 47% lower for African Americans, 52% higher for Hispanics, and not

Table 1
Metabolic, anthropometric, and lipid parameters in all subjects and as classified by race/ethnicity

	All (N = 5923)	White (n = 2452)	Asian (Chinese) (n = 695)	African American (n = 1546)	Hispanic (n = 1230)
% Women	53	53	52	56	53
Age (y)*	61.8 (10.3)	62.4 (10.3)	61.8 (10.4)	61.7 (10.2)	60.6 (10.4)†
Hypertension (%)*	42	37	37	56†	37
Ever smoked (%)*	49	55	24†	54	45†
Current smokers (%)*	13	12	5.0†	18†	14
Education (%)*					
<High school education	16	5	23^	11†	42†
Completed high school	18	16	17	18	21†
>High school education	66	79	60†	71†	37†
Family history of myocardial infarction (%)*	43	51	20†	42†	40†
Lipid medication use (%)*	14	17	11†	14†	11†
Systolic blood pressure (mm Hg)*	127 (21)	124 (20)	125 (22)	132 (22)†	127 (22)†
BMI (kg/m^2)*	28.0 (5.4)	27.5 (5.0)	23.8 (3.3)†	29.9 (5.9)†	29.0 (4.8)†
Waist circumference (cm)*	97.2 (14.1)	97.3 (14.2)	86.6 (9.9)†	99.9 (14.5)†	99.4 (12.6)†
Glucose (mg/dL)*	89.6 (10.5)	87.9 (10.1)	91.6 (10.0)†	90.3 (10.8)†	90.9 (10.9)†
Insulin (mU/L)[a,*]	5.2 (3.4-8.0)	4.5 (3.1-7.2)	4.8 (3.5-7.3)	5.5 (3.6-8.6)†	6.1 (4.1-9.6)†
HOMA-IR[a,*]	1.1 (0.7-1.8)	1.0 (0.6-1.6)	1.1 (0.8-1.7)	1.2 (0.8-2.0)†	1.4 (0.9-2.2)†
Lipid, mean (SD) (mg/dL) (fasting)[b]					
Total cholesterol*	200.6 (34.4)	203.2 (33.0)	198.1 (31.5)†	195.8(36.3)†	203.1 (35.7)
LDL-C*	123.4 (30.6)	124.4 (29.4)	120.5 (28.4)†	121.9 (33.0)†	125.1 (30.9)
HDL-C*	51.3 (14.7)	52.3 (15.5)	50.0 (12.6)†	53.1 (15.3)	48.1 (12.8)†
Triglycerides[a,*]	112 (79-159)	112 (77-161)	119 (86-167)	88 (65-119)†	131 (94-184)†
Non–HDL-C*	149.2 (35.1)	150.9 (34.4)	148.0 (32.1)	142.6 (36.2)†	155.0 (35.8)†
LDL size (nm)*	20.8 (0.77)	20.9 (0.75)	20.7 (0.81)†	21.0 (0.77)†	20.7 (0.76)†
HDL size (nm)*	9.17 (0.41)	9.16 (0.42)	9.17 (0.37)	9.24 (0.43)†	9.09 (0.38)†

Data are mean (SD) or percentages, unless indicated otherwise.

[a] Median and interquartile range.

[b] Total cholesterol, LDL-C, HDL-C, non–HDL-C, and triglycerides are imputed values for those on lipid-lowering therapy; observed values were used for all others.

* $P < .001$ for race/ethnicity categories by χ^2 tests for categorical variables and by analysis of variance for continuous variables.

† $P < .01$ for analyses comparing Chinese, Hispanic, or African American to white.

significantly different for Asians. After further adjustment for BMI, the likelihood of CHL compared with whites remained lowest for African Americans (52% lower) and not significantly different for Hispanics or Asians.

Table 2
Characteristics of subjects by the absence or presence of CHL

	No CHL (n = 5749)	CHL (n = 174)
Women (%)†	53	63
Age (y)†	61.9 (10.3)	59.7 (10.2)
BMI (kg/m^2)*	28.0 (5.3)	29.4 (5.3)
Waist circumference (cm)†	97.1 (14.1)	99.9 (12.7)
HOMA-IR[a,†]	1.1 (0.7-1.8)	1.4 (1.0-2.0)
Total cholesterol (mg/dL)*	198.5 (32.2)	270.7 (32.5)
LDL-C (mg/dL)*	121.7 (29.1)	182.3 (21.8)
HDL-C (mg/dL)*	51.5 (14.8)	45.5 (9.1)
Triglycerides (mg/dL)[a,*]	109 (78-155)	189 (167-227)
Non–HDL-C (mg/dL)*	147.0 (32.6)	225.2 (31.7)
LDL size (nm)*	20.9 (0.77)	20.3 (0.61)
HDL size (nm)*	9.2 (0.41)	8.9 (0.35)

Data are mean (SD) or percentages, unless indicated otherwise.

[a] Median and interquartile range.

* $P < .001$ for not CHL vs CHL, † $P < .05$ for not CHL vs CHL using χ^2 tests for categorical variables and Student t tests for continuous variables.

Table 4 describes the prevalence and adjusted odds of CHL by BMI categories, waist circumference categories, and quartiles of insulin resistance. The likelihood of CHL was significantly greater with elevated BMI and enlarged waist circumference and demonstrated a threshold effect with increasing insulin resistance after adjustment for age and sex. Results for the association with BMI and waist circumference were similar after further adjustment for race/ethnicity, and results for insulin resistance were similar after further adjustment for race/ethnicity and BMI category. Combined hyperlipidemia was significantly associated with both the overweight and obese categories compared with the normal-weight group. Similarly, CHL was significantly associated with insulin resistance in quartiles 2, 3, and 4 of HOMA-IR compared with quartile 1.

In the sensitivity analysis excluding those on lipid-lowering therapies and those with missing values for lipid parameters, the overall prevalence of CHL was 3.4%, very similar to the primary analysis (2.9%). The odds ratios (ORs) for the relationship of race/ethnicity with CHL after adjusting for age, sex, and BMI categories were very similar to the primary analysis: Asians (OR, 1.26; 95% confidence interval [CI], 0.75-2.10), African Americans (OR, 0.36; 95%

Table 3
Prevalence and odds of CHL by race/ethnicity

	CHL (n = 174)	No CHL (n = 5749)	Prevalence of CHL (%)*	OR (95% CI)[a]	OR (95% CI)[b]
White	74	2379	3.0	1.0	1.0
Asian (Chinese)	18	677	2.6	0.84 (0.50, 1.42)	1.06 (0.62, 1.82)
African American	26	1520	1.7	0.53 (0.34, 0.84)	0.48 (0.30, 0.75)
Hispanic	56	1174	4.6	1.48 (1.04, 2.11)	1.33 (0.93, 1.91)

[a] Adjusted for age and sex.
[b] Adjusted for age, sex, and BMI categories.
* $P < .001$ by χ^2 test.

CI, 0.22-0.58), and Hispanics (OR, 1.31; 95% CI, 0.92-1.85). The ORs for the relationship of BMI categories, waist circumference, and insulin resistance with CHL were also very similar to the primary analysis.

In the sensitivity analysis using the NCEP/ATP III cut points to define CHL, the overall prevalence of CHL was 3.9%. The ORs for the relationship of race/ethnicity with CHL after adjusting for age, sex, and BMI categories were very similar to the primary analysis for Asians (OR, 1.16; 95%; CI, 0.73-1.85), African Americans (OR, 0.52; 95% CI, 0.35-0.77), and Hispanics (OR, 1.38; 95% CI, 1.00-1.89). The ORs for the relationship of BMI categories, waist circumference, and insulin resistance with CHL were very similar to those of the primary analysis. The threshold effect for odds of CHL based on quartile of HOMA-IR also remained. Finally, there were no important differences in the reported associations when women on estrogen were excluded from the analyses.

Table 4
Prevalence and odds of CHL by BMI, waist circumference, ethnic-specific waist circumference

	Prevalence of CHL (%)*	OR (95% CI)[a]	OR (95% CI)[b,c]
BMI categories			
Normal weight (n = 1808)	1.8	1.0	1.0
Overweight (n = 2355)	3.4	2.00 (1.32, 3.04)	2.05 (1.34, 3.16)
Obese (n = 1760)	3.6	1.97 (1.28, 3.03)	2.18 (1.38, 3.44)
WC[d]			
Normal WC (n = 2812)	2.0	1.0	1.0
Enlarged WC (n = 3111)	3.8	1.83 (1.30, 2.55)	1.87 (1.32, 2.65)
Ethnic-specific WC[e]			
Normal WC (n = 2238)	1.7	1.0	1.0
Enlarged WC (n = 3685)	3.7	2.05 (1.42, 2.96)	1.90 (1.29, 2.79)
HOMA-IR categories			
Quartile 1 (n = 1479)	0.7	1.0	1.0
Quartile 2 (n = 1480)	3.5	4.85 (2.51, 9.33)	4.50 (2.31, 8.76)
Quartile 3 (n = 1484)	3.9	5.51 (2.88, 10.6)	4.90 (2.49, 9.64)
Quartile 4 (n = 1480)	3.6	4.99 (2.60, 9.60)	4.40 (2.18, 8.90)

WC indicates waist circumference.
[a] Adjusted for age and sex.
[b] BMI and waist circumference analyses adjusted for age, sex, race/ethnicity.
[c] Insulin resistance analysis adjusted for age, sex, race/ethnicity, and BMI categories.
[d] NCEP/ATP III age and sex cutoff for metabolic syndrome definition for waist circumference [14].
[e] Age, sex, and race/ethnic cutoff for metabolic syndrome definition for waist circumference [24].
* $P < .01$ by χ^2 tests (prevalence of CHL).

4. Discussion

This is the first study, to our knowledge, to examine the association of race/ethnicity with the odds of CHL in the United States. In this cohort, African Americans were on average heavier, had larger waist circumference, and were more insulin resistant compared with whites. However, the odds of CHL were lower for African Americans compared with whites before and after adjustment for age, sex, and BMI categories. Lower triglyceride levels associated with increased levels of lipoprotein lipase activity have been previously observed in African Americans compared with whites [28]. Increased levels of lipoprotein lipase activity, however, do not explain the lower LDL levels seen in African Americans compared with whites. In our cohort, there was a small but statistically significant difference in LDL-C between African Americans (121.9 mg/dL) and whites (124.4 mg/dL) ($P < .01$). Increased body weight (BMI and waist circumference) predicts insulin resistance well in African Americans, but triglycerides do not [29]. These findings suggest the importance of other shared genetic and/or environmental factors among African Americans, such as a lower rate of lipoprotein entry into the circulation or a greater rate of LDL removal that protects them from the development of CHL even in a setting of obesity and insulin resistance.

In contrast, the odds of CHL were higher for Hispanics compared with whites after adjusting for age and sex. The association was no longer significant after also adjusting for BMI, indicating that a large proportion of the increased odds of CHL in Hispanics is explained by obesity. However, other shared genetic and/or environmental factors beyond obesity in Hispanics may also be present, as the point estimate for the OR remained greater than 1 after the full adjustment.

In Asians, the odds of CHL were not statistically different compared with whites, possibly because of a lack of power due to low numbers of Asians with CHL.

We have also established in this multiethnic cohort free of CVD that greater BMI was associated with higher odds of CHL after adjusting for age, sex, and race/ethnicity. The odds of CHL were approximately twice as high with abdominal adiposity, whether defined by traditional metabolic syndrome cutoffs or by ethnic-specific cutoffs for waist circumference, and remained so after adjusting for age, sex, and race/ethnicity. The odds of CHL were substantially higher with worsening insulin resistance but demonstrated a threshold effect, as the odds for quartiles 2 through 4 were similarly elevated compared with those for quartile 1. The mean BMI in the entire MESA population was rather high at 28.0 kg/m^2, and it is likely that CHL is expressed in an appropriate genetic background except in the context of very good insulin sensitivity.

The relationship of obesity and insulin resistance with FCHL has been previously described [15,17-20]. Our findings support a similar relationship with CHL. Although increasing obesity worsens insulin resistance, obesity is not necessarily always seen with FCHL [19]. However, insulin resistance as defined by various methods including HOMA-IR is a common concomitant finding with FCHL [15,30]. Our findings strongly support the same relationship of insulin resistance to CHL. Mechanistically, insulin resistance increases free fatty acid flux, causing hepatic overproduction of triglycerides and apolipoprotein B, key features of FCHL.

We demonstrated that the largest increment in CHL odds occurred in the transition between normal weight to overweight and between quartile 1 and quartile 2 of HOMA-IR. Current suggested obesity cutoffs using BMI of 30 appear to be less useful when considering increased cardiometabolic risk in a multiethnic population and especially populations of Asian origin [31,32]. This observation is supported by the Study of Health Assessment and Risk in Ethnic Groups and Risk Evaluation in Aboriginal Peoples groups' findings that a BMI much less than 30 is associated with increased cardiometabolic risk in various ethnic populations in Canada [4].

The present analysis is cross-sectional; and thus, a causal relationship cannot be directly inferred, especially because the temporal sequence between adiposity, insulin resistance, and CHL is unknown. However, the biological plausibility and magnitude of the association (for BMI categories, waist circumference categories, and HOMA-IR quartiles) are consistent with a causal association between obesity and CHL as well as insulin resistance and CHL independent of obesity in this multiethnic population. Furthermore, our findings are strengthened by very similar findings using only observed lipid values and excluding those on lipid-lowering therapies and with missing values for lipid values.

We have also demonstrated that CHL, as defined by greater than or equal to 75th percentile for both LDL cholesterol and triglycerides for age and sex based on a predominantly white population reference [1], is very consistent with current NCEP/ATP III cutoffs for consideration of treatment for LDL (≥160 mg/dL) and triglycerides (≥150 mg/dL) in terms of prevalence and associations with race/ethnicity, obesity, and insulin resistance. The benefit of identifying people based on age- and sex-standardized percentiles is that we can recognize dyslipidemia that is otherwise not obvious in younger people who traditionally are at lower Framingham/NCEP 10-year CHD risk. The percentile definitions allow young people to have enhanced recognition and screening for other cardiac risk factors, family history, and appropriate advice regarding diet, lifestyle, and when indicated pharmacologic intervention. Although the association between obesity and insulin resistance and FCHL has been clearly documented, we have demonstrated that CHL as defined by 75% cut points is strongly associated with only modest degrees of increasing weight and insulin resistance (second quartile and above) without the need of family history for lipid abnormalities. Thus, evaluating for CHL in overweight and/or insulin-resistant people may help practitioners better identify this dyslipidemia and propose appropriate treatment.

We acknowledge additional limitations. The HOMA-IR is a valid marker of insulin resistance in epidemiologic studies but is subject to misclassification [33]. The mean HOMA-IR was lower in this study than in previous population studies [34]. The difference may be due to differences in populations but also to differences in the method of measuring insulin. Nonetheless, the division of HOMA-IR into quartiles remained meaningful as demonstrated by the robust and significant association between insulin resistance and CHL beginning in the second quartile. Misclassification of abdominal obesity is also possible, using the traditional metabolic syndrome cutoffs of waist circumference in whites and probably African Americans. We analyzed the relationship of abdominal obesity using proposed ethnic-specific cutoffs to address this possible problem. The direction and magnitude of association of abdominal obesity and CHL were similar using traditional metabolic syndrome and ethnic-specific cutoffs for waist circumference.

Classification of race/ethnicity was self-reported and subject to misclassification. Many people may belong to multiple ethnic categories but could only be classified as 1 category in MESA. We may not presume race/ethnicity to represent common genetic traits and can only say that race/ethnicity as broadly classified could represent shared genetic and/or environmental influences that include social behaviors such as diet and activity.

5. Summary

Race/ethnicity had independent and important relationships with CHL, less severe in African Americans and more severe in Hispanics compared with whites. Modest degrees of obesity and worsening insulin resistance were associated

with a significant increased odds of CHL in a multiethnic US population of men and women free of clinically recognized baseline CVD. Future studies should examine (1) the relationship of CHL with subclinical markers of atherosclerosis and early atherosclerotic disease, (2) determine the risk of incident CVD in those with CHL, (3) determine if improving obesity and insulin resistance decreases the odds of CHL and CHD differentially among racial/ethnic groups, and (4) determine the best dietary and drug interventions for CHL among racial/ethnic groups.

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