Non–High-Density Lipoprotein Cholesterol Concentration is Associated with the Metabolic Syndrome among US Youth Aged 12-19 Years

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Objective To test the hypothesis that the concentration of non–high-density lipoprotein cholesterol (non–HDL-C) is associated with the metabolic syndrome (MetS) in youth.

Study design Data on children and adolescents aged 12-19 years (n = 2734) from the cross-sectional National Health and Nutrition Examination Survey 1999-2004 were analyzed.

Results Depending on the definition of MetS used, the mean non–HDL-C concentration among youth with MetS ranged from 144.2 to 155.8 mg/dL, compared with 108.8-109.1 mg/dL in those without MetS (all $P < .001$). The MetS prevalence ranged from 6.9% to 11.7% in youth with a non–HDL-C concentration of 120–144 mg/dL and from 21.5% to 23.4% in those with a concentration ≥145 mg/dL—both significantly higher than the prevalence of 1.9%-3.4% in youth with a concentration <120 mg/dL (all $P < .001$). After adjustment for potential confounders, youth with a non–HDL-C concentration ≥120 mg/dL or ≥145 mg/dL were about 3 or 4 times more likely to have MetS compared with those with a non–HDL-C <120 mg/dL or <145 mg/dL (all $P < .001$).

Conclusions Fasting non–HDL-C concentration was strongly associated with MetS in US youth. Our results support the use of non–HDL-C thresholds of 120 mg/dL and 145 mg/dL to indicate borderline and high MetS risk, respectively. *(J Pediatr 2011;158:201-7)*.

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Non–high-density lipoprotein cholesterol (non–HDL-C) concentration is an important predictor of premature atherosclerosis[1] and first myocardial infarction,[2] and a reduction in non–HDL-C concentrations in adults has been associated with reduced risk for cardiovascular disease outcomes.[3] Non–HDL-C concentration is measured by subtracting the HDL-C concentration from total serum cholesterol concentration and can be accurately measured in nonfasting persons.[4] The result is a clinical value that reflects the concentration of many atherogenic lipoproteins, including low-density lipoprotein cholesterol (LDL-C), very–low-density lipoprotein cholesterol (VLDL-C), intermediate-density lipoprotein cholesterol (IDL-C), and lipoprotein(a), and is easy to use in clinical practice.

Non–HDL-C compared with LDL-C alone may have a stronger association with metabolic syndrome (MetS), a cluster of cardiovascular and metabolic abnormalities comprising abdominal obesity, dyslipidemia, impaired glucose regulation, and high blood pressure.[5] The cluster of risk factors that define MetS is on the increase in youth as well as adults in the United States; and the clustering of risk factors associated with MetS exponentially accelerates the atherosclerotic process in youth.[6] This study tested the hypothesis that non–HDL-C concentration is associated with MetS among US youth.

apo	Apolipoprotein
AUC	Area under the curve
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CRP	C-reactive protein
DBP	Diastolic blood pressure
IDF	International Diabetes Federation
IDL-C	Intermediate-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
MetS	Metabolic syndrome
NCEP/ ATP III	Third National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)
NHANES	National Health and Nutrition Examination Survey
Non–HDL-C	Non–high-density lipoprotein cholesterol
PDAY	Pathobiological Determinants of Atherosclerosis in Youth
ROC	Receiver operating curve
SBP	Systolic blood pressure
VLDL-C	Very–low-density lipoprotein cholesterol

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Methods

In the National Health and Nutrition Examination Surveys (NHANES) conducted during 1999-2004, a multistage, stratified sampling design was used to recruit a cross-sectional sample representative of the noninstitutionalized civilian US population.[7] Adolescents aged 12-19 years, non-Hispanic blacks, and Mexican Americans were oversampled to ensure accurate estimates in these subgroups. The NHANES 1999-2004 underwent ethical approval by the National Center for Health Statistics (NCHS) Institutional Review Board and Research Ethics Review Board (Protocol #98-12). Informed consent was obtained from participants aged 18-19 years. Consent from a parent or guardian and assent from the participant were obtained for participants aged 12-17 years. The response rates for participants attending the mobile examination center were 76% in 1999-2000, 80% in 2001-2002, and 76% in 2003-2004. Participants with missing data for non–HDL-C (n = 47) were excluded. We limited our analyses to boys and nonpregnant girls aged 12-19 years who attended a morning examination session after fasting between 8 and 24 hours and had valid data for non–HDL-C concentration (n = 2734). This was done to allow classification of all participants with regard to MetS.

Serum specimens were frozen at < -70°C, shipped on dry ice, and stored at < -70°C until analysis. Concentrations of total cholesterol and HDL-C were measured enzymatically on a Hitachi 704 Analyzer (Roche/Boehringer-Mannheim, Indianapolis, Indiana). HDL-C concentrations were measured directly after the precipitation of other lipoproteins with a heparin-manganese chloride mixture. Non–HDL-C concentration was computed by subtracting HDL-C concentration from total cholesterol concentration. Triglyceride concentration was measured enzymatically in serum after the specimen was hydrolyzed to glycerol through a series of coupled reactions. Lipid and lipoprotein measurements were made in the Johns Hopkins Analytical Laboratory, a Centers for Disease Control and Prevention (CDC)-certified laboratory.

Plasma glucose concentration was measured via an enzymatic reaction (Cobas Mira Chemistry System; Roche Diagnostic Systems, Montclair, New Jersey). Plasma insulin concentrations were measured with a Pharmacia insulin radioimmunoassay kit (Pharmacia Diagnostics AB, Uppsala, Sweden). C-reactive protein (CRP) concentrations were measured by latex-enhanced nephelometry (N high-sensitivity CRP assay) on a Behring Nephelometer II Analyzer System (Dade Behring Diagnostics Inc, Somerville, New Jersey). Serum cotinine concentration, a measure of tobacco exposure, was measured by isotope-dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry.

Participants' waist circumference was measured to the nearest 0.1 cm at the high point of the iliac crest at minimal respiration while in a standing position.[8] Body mass index (BMI; weight [kg]/height [m]^2) was calculated from weight and height measurements obtained following standard protocol and using standard instruments. Sex- and age-specific BMI percentile according to CDC growth charts was used to categorize participants' weight status as normal (<85th percentile), overweight (85th-94th percentile), or obese (≥95th percentile).[9] Up to 4 measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained. Blood pressure status was based on the average of the last two measurements for participants who had 3 or 4 measurements, on the last measurement for participants who had only 2 measurements, and on the sole measurement for participants who had one measurement.

Participants were divided into 3 age groups (12-15 years, 16-17 years, and 18-19 years) and 4 race/ethnicity groups (non-Hispanic white, non-Hispanic black, Mexican American, and other race/ethnicity). The poverty income ratio—a ratio of family income to the federal poverty threshold for that family[10]—was used to categorize participants by family income.

Because of the lack of an accepted pediatric definition of MetS in childhood, we used 4 definitions of MetS in this study: the definition for adults in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP/ATP III-adult),[11] the NCEP/ATP III definition adapted for children and adolescents (NCEP/ATP III-pediatric),[12] the International Diabetes Federation (IDF) definition for adults (IDF-adult),[13] and the IDF definition for children and adolescents (IDF-pediatric).[14] Adult definitions were included because of the lack of consensus on an accepted pediatric definition.

The NCEP/ATP III-adult definition includes the presence of 3 or more of the following:[11] (1) abdominal obesity (waist circumference ≥102 cm in males or ≥88 cm in females); (2) fasting triglyceride concentration ≥150 mg/dL (1.7 mmol/L); (3) HDL-C concentration <40 mg/dL (1.03 mmol/L) in males or <50 mg/dL (1.29 mmol/L) in females; (4) SBP ≥130 mm Hg or DBP 85 mm Hg; and (5) fasting glucose concentration ≥100 mg/dL (≥5.6 mmol/L). Participants who reported using antihypertensive medication were classified as having high blood pressure.

The NCEP/ATP III-pediatric definition includes the presence of 3 or more of the following:[12] (1) waist circumference ≥90th percentile for sex and age;[15] (2) fasting triglyceride concentration ≥110 mg/dL (1.25 mmol/L); (3) HDL-C concentration <40 mg/dL (1.03 mmol/L); (4) DBP or SBP ≥90th percentile for age, height, and sex;[16] and (5) fasting glucose concentration ≥100 mg/dL (≥5.6 mmol/L).

The IDF-adult definition is the presence of central adiposity (defined in the following paragraph) and two or more of the following:[13] (1) fasting triglyceride concentration ≥150 mg/dL (1.7 mmol/L) or current treatment for this lipid abnormality; (2) HDL-C concentration <40 mg/dL (1.03 mmol/L) in males or <50 mg/dL (1.29 mmol/L) in females or current treatment for this lipid abnormality; (3) SBP 130 mm Hg or DBP ≥85 mm Hg or current treatment for hypertension; and (4) fasting plasma glucose concentration

≥100 mg/dL (5.6 mmol/L) or previously diagnosis of type 2 diabetes.

The IDF uses the following sex- and race/ethnicity-specific cutoffs for waist circumference to define central adiposity: ≥94 cm for non-Hispanic white and black males, ≥90 cm for Mexican-American males, and ≥80 cm for non-Hispanic white, non-Hispanic black, and Mexican-American females.[13] For participants considered "other race, including multiracial," we used thresholds for South and Central Americans.

For children aged 10-15 years, the IDF-pediatric definition includes the presence of central adiposity (waist circumference ≥90th percentile for sex and age[15] or the adult cutoff if lower) and at least two of the following: (1) fasting triglyceride concentration ≥150 mg/dL (1.7 mmol/L); (2) HDL-C concentration ≤40 mg/dL (1.03 mmol/L); (3) SBP ≥130 mm Hg or DBP ≥85 mm Hg; and (4) fasting plasma glucose concentration ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.[14] For youth aged ≥16 years, MetS status was based on the IDF-adult definition of MetS.[13]

Statistical Analysis

We determined the distribution of non–HDL-C concentrations in the total sample and for subgroups defined by sex, race/ethnicity, age group, BMI percentile, and smoking status, and assessed associations between non–HDL-C concentrations and MetS according to each of the 4 definitions of MetS. We estimated the mean non-HDL-C concentration according to the number of MetS components.

We generated receiver operating characteristic (ROC) curves using a special SAS macro based on a bootstrap replication approach that takes the complex sampling design into account.[17] We estimated the area under the curve (AUC) and its 95% CI for the association between non–HDL-C concentration and MetS and its components by each of the 4 definitions of MetS. AUC is a measure of the discriminative power of a logistic regression model; possible AUC values range from 0.5 (indicating that the predictions of the model are no better than chance) to 1.0 (indicating a perfect prediction). We used the Youden Index (ie, sensitivity + specificity - 1) to establish optimal cutoff values for non–HDL-C concentrations in relation to MetS risk. The non–HDL-C concentration with the maximum value of the Youden Index was determined to be the optimal cutoff point.[18] We then determined the sensitivity and specificity of these cutoff points in identifying youth at risk for MetS.

In addition, we estimated the prevalence of MetS (and its standard error) by the 4 MetS definitions and 3 categories of non–HDL-C concentration (ie, <120 mg/dL, 120-144 mg/dL, and ≥145 mg/dL). These cutpoints were chosen according to the distribution of non–HDL-C in the population studied (about the 70th and 90th percentiles). We also used logistic regression analysis to estimate unadjusted MetS ORs and 95% CIs on the basis of the two non–HDL-C cutoff points (ie, <120 mg/dL vs ≥120 mg/dL and <145 mg/dL vs ≥145 mg/dL), as well as estimates adjusted for sex, age, race/ethnicity, poverty-to-income ratio, weight category, CRP concentration, and fasting insulin concentration.

We considered results with $P \leq .05$ in two-tailed tests to be statistically significant. SAS version 9.1 (SAS Institute, Cary, North Carolina), SAS macro[17] (SAS and SUDAAN release 9.0, (Research Triangle Institute, Research Triangle Park, North Carolina) were used to manage the data and obtain estimates that accounted for the survey's complex sampling design.

Results

Among youth with complete data for non–HDL-C (n = 2734), 52.8% were males; 50% were aged 12-15 years, 25.9% were aged 16-17 years, and 24.1% were aged 18-19 years. Race/ethnicity distribution was 27.0% non-Hispanic white, 31.4% non-Hispanic black, 34.7% Mexican American, and 6.9% other. The distribution of non–HDL-C concentrations in the total sample was approximately normal. Non–HDL-C concentration was highly correlated with total cholesterol concentration ($r = 0.93$; $P < .0001$) and LDL-C concentration ($r = 0.95$; $P < .0001$), moderately correlated with triglyceride concentration ($r = 0.49$; $P < .0001$), and inversely correlated with HDL-C concentration ($r = -0.25$; $P < .0001$).

The overall mean concentration of non–HDL-C was 111.7 mg/dL, and the median concentration was 107.8 mg/dL. The mean non–HDL-C concentration did not differ significantly by sex ($P = .47$); however, it was slightly lower in non-Hispanic blacks than in non-Hispanic whites ($P = .02$) and higher in youth aged 18-19 years than in those aged 12-15 years ($P < .01$). Regardless of the definition of MetS used, MetS prevalence was positively associated with non–HDL-C concentration ($P < .001$) and the number of MetS components was positively associated with non–HDL-C concentration (all $P < .001$ for linear trend). Among adolescents who met the various criteria for MetS, approximately 71% by NCEP/ATP III-pediatric, 77% by NCEP/ATP III-adult, 74% by IDF-pediatric, and 73% by IDF-adult had a non–HDL-C concentration ≥120 mg/dL, and about 54% by NCEP/ATP III-pediatric, 65% by NCEP/ATP III-adult, 60% by IDF-pediatric, and 57% by IDF-adult had a non–HDL-C concentration ≥145 mg/dL.

The AUC for the association between non-HDL-C concentration and MetS by the 4 definitions ranged from 0.77 for NCEP/ATP III-pediatric to 0.81 for NCEP/ATP III-adult (**Figure 1**). The AUC of non–HDL-C for the NCEP/ATP III-adult MetS definition was similar to that for the IDF-pediatric definition, but greater than that for the NCEP/ATP III-pediatric and IDF-adult definitions (**Table I**). The optimal non–HDL-C cutoff points were 120 mg/dL for the NCEP/ATP III-pediatric, NCEP/ATP III-adult, and IDF-pediatric MetS definitions and 125 mg/dL for the IDF-adult definition. The sensitivity of these cutoff points in identifying participants with MetS ranged from 67% to 75%, and the specificity ranged from 69% to 75%. Among

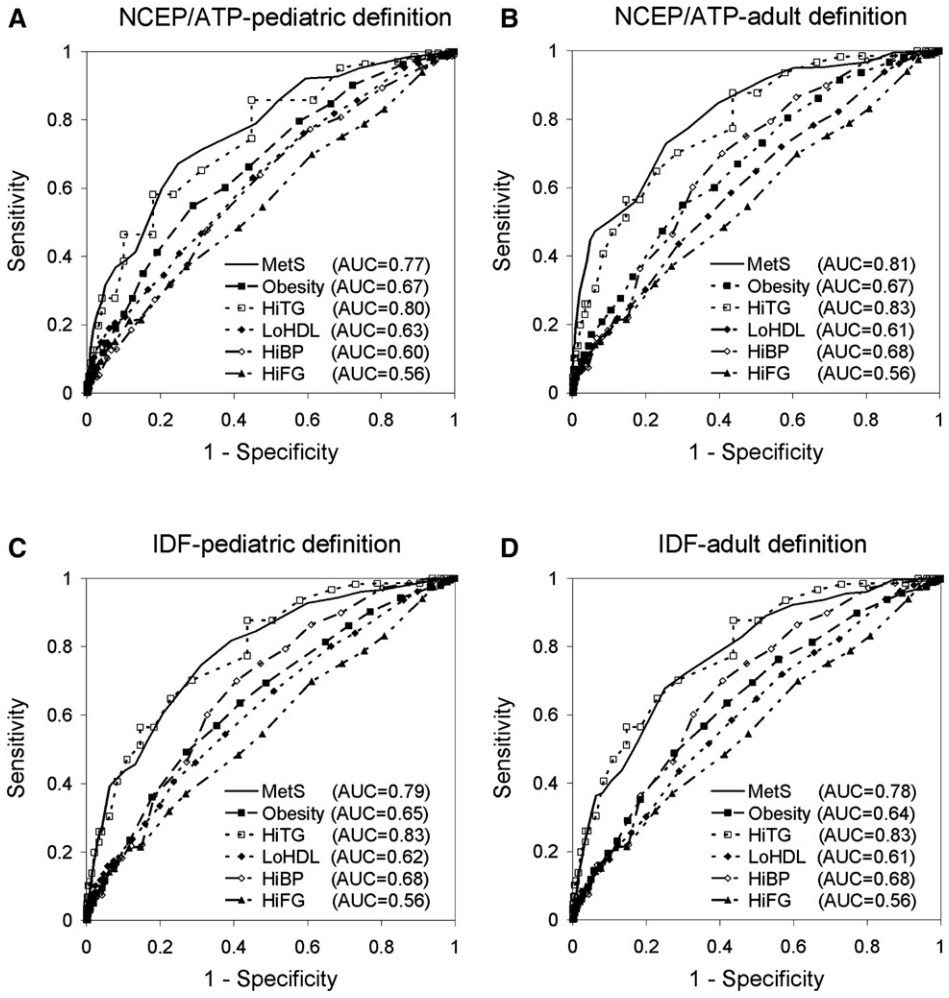

Figure 1. ROC curve and AUC of non–HDL-C for MetS and its 5 components among US youth aged 12-19 years, by 4 MetS definitions, NHANES 1999-2004. HiTG, high triglycerides; LoHDL, low HDL cholesterol; HiBP, high blood pressure; HiFG, high fasting glucose.

the 5 MetS components, triglycerides had the largest AUC and fasting glucose the smallest (Figure 1).

The prevalence of MetS was higher in youth with a non–HDL-C concentration ≥145 mg/dL ($P < .001$) or 120-144 mg/dL ($P < .001$) compared with those with a non–HDL-C concentration <120 mg/dL regardless of the MetS definition used (Figure 2). Unadjusted ORs for MetS in youth with non–HDL-C concentrations ≥120 mg/dL versus those with concentrations <120 mg/dL ranged from 5.5 (by the NCEP/ATP III-pediatric definition) to 7.5 (by the NCEP/ATP III-adult definition) (Table II). Unadjusted ORs for youth with non–HDL-C concentrations ≥145 mg/dL versus those with concentrations <145 mg/dL ranged from 8.6 (by the NCEP/ATP III-pediatric definition) to 13.4 (by the NCEP/ATP III-adult definition). After adjustments for the potentially confounding effects of sex, age, race/ethnicity, poverty-to-income ratio, cotinine concentration, CRP concentration, fasting insulin concentration, and weight status, the ORs based on the non–HDL-C cutoff point of 120 mg/dL ranged from 2.8 to 3.5, and the ORs based on the non–HDL-C cutoff point of 145 mg/dL ranged from 3.9 to 5.6.

Discussion

Atherosclerosis begins in childhood, and its development has been correlated with various cardiovascular disease risk factors, including lipoprotein disorders and MetS.[19,20] The presence of multiple cardiovascular risk factors, as in MetS, has been associated with early acceleration of atherosclerosis.[21] Results from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, which measured atherosclerosis in adolescents and young adults aged 15-30 years, showed that non–HDL-C concentration was highly correlated with coronary atherosclerosis measured at autopsy.[22] Elevated non–HDL-C concentration during childhood and adolescence also has been shown to predict high non–

Table I. ROC curve analysis of non–HDL-C for MetS among US youth aged 12-19 years, NHANES 1999-2004

	AUC	95% CI	Optimal cutoff point, mg/dL	Sensitivity, %	Specificity, %
NCEP/ATP III-pediatric	0.77*	0.73-0.81	120	75	69
NCEP/ATP III-adult	0.81	0.76-0.86	120	73	75
IDF-pediatric	0.79	0.74-0.84	120	68	75
IDF-adult	0.78*	0.73-0.83	125	67	75

*$P \leq .05$ in the two-tailed t test of 1000 replicates using the bootstrapping method compared with the AUC of MetS based on the NCEP/ATP III-adult definition.

HDL-C concentration during adulthood; for example, a non–HDL-C concentration above the 95th percentile during childhood was found to be 86%-96% sensitive and 96%-98% specific in predicting an elevated LDL-C concentration during adulthood.[23]

Screening for cardiovascular risk on the basis of non–HDL-C concentration has many advantages in the pediatric setting. For example, non–HDL-C concentration might be more reliable than calculated LDL-C concentration, because triglyceride variability contributes to significant variability in LDL-C assessment in children and adolescents.[24] The strong relationship of non–HDL-C concentration to both current MetS and future atherosclerosis suggests that non–HDL-C concentration might be extremely useful in both risk stratification and long-term management of cardiovascular risk in the clinical setting.

It is worth noting that there were no significant differences by sex and small differences by race/ethnicity in the distribution of non–HDL-C concentrations and by the 4 definitions of MetS in the association between non–HDL-C concentration and MetS. These findings imply that a universal cutoff value of non–HDL-C concentration potentially could be useful in the assessment of cardiovascular risk regardless of sex, race/ethnicity, and MetS definition. Furthermore, because fasting is not required before a measurement of non–HDL-C, the test can be performed at any time of the day. In adults, fasting has the advantage of also allowing assessment for impaired glucose tolerance, but the low prevalence of type II diabetes mellitus among adolescents (and the weak association that we found between non–HDL-C and blood glucose concentrations) suggests that fasting is not necessary for initial risk assessment. About one-third of the participants in our study had a non–HDL-C concentration ≥120 mg/dL, and this cutoff identified about 70% of those who met the various sets of MetS criteria.

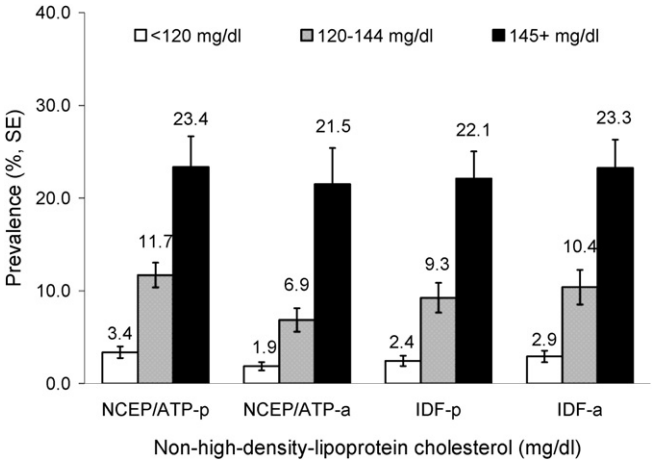

Figure 2. MetS prevalence among US youth aged 12-19 years, by 4 MetS definitions and 3 categories of non–HDL-C concentration, NHANES 1999-2004. a, adult; p, pediatric.

Table II. OR (95% CI) for MetS among US youth aged 12-19 years by cutoff point for non–HDL-C and definition of MetS, NHANES 1999-2004

MetS definition	Model	Non–HDL-C ≥120 mg/dL (vs <120 mg/dL)	Non-–HDL-C ≥145 mg/dL (vs <145 mg/dL)
NCEP/ATP III-pediatric			
	Model 1*	5.5 (3.9-7.8)	8.6 (5.9-12.3)
	Model 2†	5.6 (4.0-7.8)	8.4 (5.9-12.0)
	Model 3‡	5.4 (3.9-7.6)	7.8 (5.5-11.2)
	Model 4§	4.0 (2.5-6.5)	5.4 (3.3-8.8)
	Model 5¶	3.2 (2.1-4.6)	4.7 (2.8-7.7)
	Model 6**	2.8 (1.7-4.8)	4.0 (2.4-6.9)
NCEP/ATP III-adult			
	Model 1	7.5 (4.4-12.6)	13.4 (7.6-23.4)
	Model 2	7.1 (4.2-12.2)	11.9 (6.8-20.9)
	Model 3	6.8 (4.0-11.6)	10.9 (6.2-19.0)
	Model 4	4.9 (2.5-9.8)	7.5 (3.5-15.8)
	Model 5	3.9 (2.3-6.9)	6.6 (3.3-13.3)
	Model 6	3.5 (1.8-6.9)	5.6 (2.6-12.3)
IDF-pediatric			
	Model 1	6.5 (3.7-11.6)	10.8 (6.3-18.5)
	Model 2	6.4 (3.6-11.4)	9.6 (5.4-16.9)
	Model 3	6.1 (3.4-11.1)	8.9 (5.1-15.6)
	Model 4	4.5 (2.3-8.8)	5.8 (3.0-11.3)
	Model 5	3.7 (1.9-7.1)	5.5 (2.5-11.9)
	Model 6	3.2 (1.6-6.5)	4.5 (2.1-9.6)
IDF-adult			
	Model 1	5.9 (3.4-10.1)	9.1 (5.4-15.3)
	Model 2	5.7 (3.3-9.9)	8.3 (4.8-14.1)
	Model 3	5.5 (3.2-9.7)	7.7 (4.5-13.0)
	Model 4	4.1 (2.2-7.8)	5.0 (2.6-9.6)
	Model 5	3.3 (1.8-6.1)	4.7 (2.3-9.5)
	Model 6	3.0 (1.6-5.6)	3.9 (1.9-7.9)

*In model 1, ORs were unadjusted.
†In model 2, ORs were adjusted for sex, age, race/ethnicity, and poverty-to-income ratio.
‡In model 3, ORs were adjusted for covariates in model 2 plus cotinine and C-reactive protein.
§In model 4, ORs were adjusted for covariates in model 3 plus fasting insulin.
¶In model 5, ORs were adjusted for covariates in model 3 plus BMI.
**In model 6, ORs were adjusted for covariates in model 3 plus fasting insulin and BMI.

Among the 5 MetS components, non–HDL-C concentration was most strongly associated with elevated triglyceride concentration regardless of the definition of MetS. Because non–HDL-C is a combination of major apo-B–containing and potentially atherogenic lipoproteins, including LDL-C, VLDL-C, IDL-C, and lipoprotein(a), it might be associated with serum triglyceride concentration in 3 pathways.[25] First, serum triglycerides are carried primarily in lipid-rich particles, VLDL, in the fasting state; thus, fasting serum triglyceride concentration correlates highly with VLDL-C concentration. Second, elevated serum triglyceride

concentration often coexists with abnormal small particles of LDL and low HDL-C concentration, in the phenomenon of atherogenic lipoprotein phenotype or lipid triad.[26] Third, fasting serum triglyceride concentration and non–HDL-C concentration are associated with obesity, and both may serve as biomarkers of adiposity.[27] Growing evidence suggests that elevated non–HDL-C concentration and triglyceride concentration are associated with increased risk of cardiovascular disease.[28,29] Thus, an association between non–HDL-C concentration and MetS is not unexpected, although the strength of the association might be surprising, given the lack of a strong association between LDL-C and obesity. Along with its direct association with MetS, non–HDL-C also might be associated with MetS through the obesity–inflammation–insulin resistance linkage, as evidenced in our study. Nonetheless, non–HDL-C and triglycerides have appreciably different biochemical characteristics and metabolic mechanisms, such that non–HDL-C may be associated with cardiovascular risk mainly through atherogenic processes, and triglycerides may be associated with cardiovascular risk mainly through MetS, insulin resistance, and a procoagulant state.[25,30] In addition, we found a weak inverse association between non–HDL-C concentration and HDL-C concentration.

Insulin resistance, considered a key mechanism underlying MetS, has been associated with increased risk for cardiovascular disease.[31] Some of this increased risk may be traced through the development of diabetes. However, insulin resistance also has been linked to numerous cardiometabolic abnormalities, including dyslipidemia, elevated blood pressure, inflammation, microalbuminuria, and endothelial dysfunction, all of which can promote the development of cardiovascular disease. Dyslipidemia in MetS is characterized by elevated triglyceride concentrations, decreased HDL-C concentration, and increased particles of small LDL.[32] Furthermore, non–HDL-C concentration also has been shown to be elevated in individuals with MetS, whereas LDL-C concentration has not always been shown to be significantly different.[33] This suggests that the lipoprotein fractions other than LDL account for some increase in the risk for cardiovascular disease due to dyslipidemia in persons with MetS. Apo B (principally apo B-100) is a major glycoprotein of the lipoprotein fractions represented in non-HDL-C and is associated with increased risk for cardiovascular disease. Individuals with MetS have increased apo B-100 concentrations.[34] Apo B-48, which is associated with chylomicrons and chylomicron remnants, also has been linked to atherosclerosis and is elevated in individuals with MetS.[35] Thus, persons with MetS have at least two dyslipidemic mechanisms, represented by apo B-100 and apo B-48, that potentially increase the risk for cardiovascular disease. Although the underlying mechanisms linking non–HDL-C and MetS remain to be elucidated, non–HDL-C concentration might act as a composite marker of multiple interactive atherogenic and pathophysiologic effects of apo B–containing lipoproteins and triglyceride-rich lipoproteins. Future studies are warranted to identify the interrelations among non–HDL-C, apo B (apo B-48 and apo B-100), lipoprotein subfractions, and insulin resistance, as well as the effect of these interactions on the risk of cardiovascular events.

Strengths of the present study include the use of data from a nationally representative sample of US children and adolescents aged 12-19 years, the NHANES assessment of all biochemical markers in accordance with standard protocols and strict quality control procedures, and our careful accounting for potential confounders of the association between non–HDL-C concentration and MetS in our multivariable logistic regression analyses. A limitation of the study was that the cross-sectional design of the NHANES prevented us from drawing any causal inference concerning the association between non–HDL-C concentration and MetS. A second limitation is related to the lack of measured cardiovascular disease outcomes in children and adolescents in our data, preventing us from drawing inferences regarding the relationship between non–HDL-C and cardiovascular disease events. Nonetheless, the PDAY study suggests a very strong relationship of non–HDL-C to early atherosclerosis and the Bogalusa Heart Study suggests a strong relationship between non–HDL-C concentration measured in childhood and subclinical atherosclerosis evaluated in young adulthood.[1,21] Our results support the use of non–HDL-C threshold values of 120 or 125 mg/dL to indicate borderline risk and 145 mg/dL to indicate high risk because of an association with MetS. ■

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