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Discordance between high non-HDL cholesterol and high LDL-cholesterol among US adults

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BACKGROUND: Although low-density lipoprotein cholesterol (LDL-C) is recommended as the primary marker to guide lipid-lowering therapy, some data suggest non–high-density lipoprotein cholesterol (non–HDL-C) may better reflect coronary heart disease risk. Discordance between these measures has not been evaluated.

METHODS: We used data from the National Health and Nutrition Examination Surveys 2005–2010 (n = 4986) to examine the discordance between these lipid parameters. Elevated levels of non–HDL-C and LDL-C were defined by using the 2004 Adult Treatment Panel III guidelines.

RESULTS: The prevalence of high non–HDL-C and LDL-C was 22.7% and 24.5%, respectively. Of participants with high non–HDL-C, 9.7% had normal LDL-C, whereas 15.7% of participants with high LDL-C had normal non–HDL-C. We estimate 3.9 million US adults had high non–HDL-C and normal LDL-C, whereas 6.8 million US adults had high LDL-C and normal non–HDL-C. Persons with high non–HDL-C and normal LDL-C were older, more likely to be men, Hispanic, and have impaired fasting glucose, diabetes metabolic syndrome, and more risk factors for coronary heart disease.

CONCLUSIONS: Substantial discordance exists between high non–HDL-C and high LDL-C among US adults. Reliance on either single measure could result in failure to classify cardiovascular heart disease risks appropriately.

Guidelines for the detection and treatment of high cholesterol recommend using low-density lipoprotein cholesterol (LDL-C) as the primary marker to guide therapy.[1–4] The Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program advocates non–high density lipoprotein cholesterol (non–HDL-C) as a secondary target for lipid control. A growing body of literature suggests non–HDL-C may provide a more accurate measure of coronary heart disease (CHD) risk than LDL-C.[5–8] Moreover, non–HDL-C is readily calculated from standard lipid panels, does not require fasting, and is not subject to the limitations of the Friedewald formula for estimating LDL-C levels.[9,10] Therefore, non–HDL-C

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Table 1 Definitions of High Non-HDL-C and High LDL-C

	High Non–HDL-C	High LDL-C
History of CHD at very high risk*	Non-HDL-C ≥100 mg/dL	LDL-C ≥70 mg/dL
History of CHD or risk equivalent	Non-HDL-C ≥130 mg/dL	LDL-C ≥100 mg/dL
≥2 CHD risk factors and		
10-year Framingham risk of 10%–20%	Non-HDL-C ≥130 mg/dL	LDL-C ≥100 mg/dL
10-year Framingham risk <10%	Non-HDL-C ≥160 mg/dL	LDL-C ≥130 mg/dL
0–1 CHD risk factors	Non-HDL-C ≥190 mg/dL	LDL-C ≥160 mg/dL

CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; non–HDL-C, non–high-density lipoprotein cholesterol.

CHD risk equivalents included diabetes mellitus and stroke.

CHD risk factors include older age (≥55 years for women and ≥45 years for men), current cigarette smoking, hypertension, family history of CHD (history of myocardial infarction or angina before 50 years of age among first-degree relatives), and low HDL-C. HDL-C ≥ 60 mg/dL is considered protective and offsets the presence of one these risk factors.

*Very high risk is defined by having a history of CHD and diabetes mellitus, cigarette smoking, the metabolic syndrome or a combination.

may assume a larger role for identifying patients with hyperlipidemia and for assessing thresholds for therapy.

The ATP III guidelines define high non–HDL-C with the use of risk-specific cut points 30 mg/dL higher than those for LDL-C (Table 1). For example, among patients with diabetes, levels of LDL-C ≥100 mg/dL and non–HDL-C ≥130 mg/dL are considered high. Although the 2 measures often agree, some persons may have high LDL-C but normal non–HDL-C levels or normal LDL-C and high non–HDL-C.[8] However, few data are available on the number of US adults who are discordant for high non–HDL-C and high LDL-C. We used data from the National Health and Nutrition Examination Surveys (NHANESs) for 2005 through 2010 to compare the prevalence of high non–HDL-C and high LDL-C among US adults. We also assessed the prevalence of, and factors associated with, having high non–HDL-C and normal LDL-C and having high LDL-C and normal non–HDL-C.

Methods

A detailed description of NHANES is available.[11] Briefly, NHANES 2005–2006, 2007–2008, and 2009–2010 were conducted by the National Center for Health Statistics. Survey samples were identified through a stratified, multistage probability sampling of the noninstitutionalized US population and thus provide nationally representative prevalence estimates. The NHANES protocols were approved by the National Center for Health Statistics Ethics Review Board. Informed consent was obtained from all participants.

This analysis was limited to adult participants, 20 years of age and older, and attended a morning examination (n = 7825). We limited the analysis to participants who had fasted ≥9 hours before the study visit (n = 6914). We excluded participants with missing data on (n = 234), or were taking lipid-lowering therapy (n = 1207) and also participants missing total cholesterol, HDL-C, or triglyceride values (n = 36), or missing data needed to calculate their ATP III defined CHD risk (n = 362). Participants with triglycerides ≥ 400 mg/dL (n = 89) that prohibited LDL-C calculation were excluded, leaving an analysis cohort of 4986 (Fig. 1).

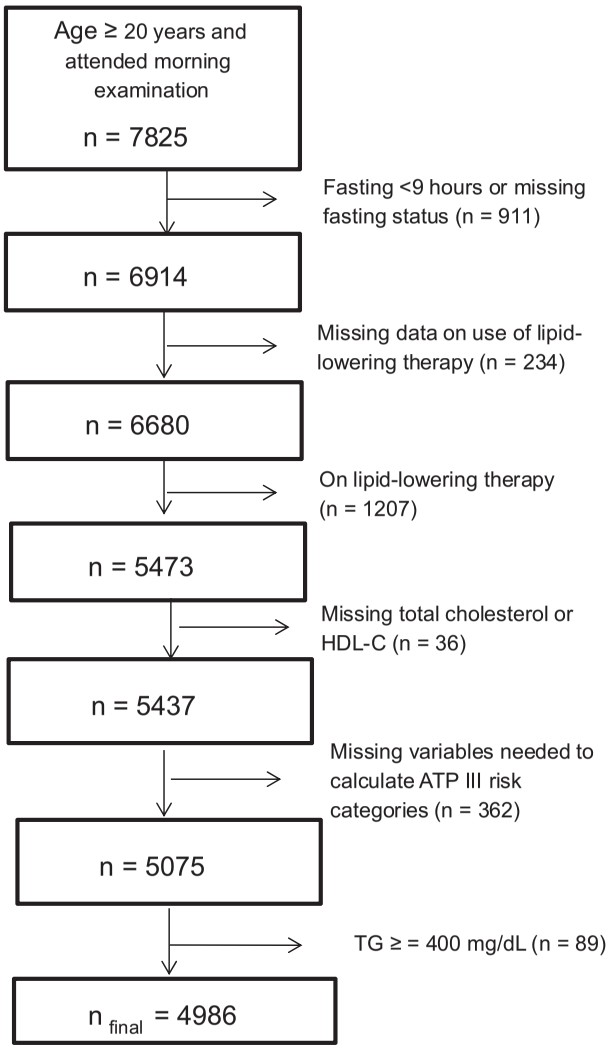

Figure 1 Exclusion criteria for National Health and Nutrition Examination Surveys (NHANES) 2005–2010 analyses. ATP III, Third Adult Treatment Panel; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.

Data collection

Information on age, race/ethnicity, sex, cigarette smoking, family history of CHD, and a personal history of CHD, myocardial infarction, stroke, or angina was collected by questionnaire. Blood pressure was measured 3 times, and height, weight, and waist circumference were measured during the medical examination. Hypertension was defined as systolic/diastolic blood pressure ≥140/90 mm Hg or the use of antihypertensive medication.

Details of the blood and urine collections and processing in NHANES are available.[11] With the use of a random spot collection, urinary albumin-to-creatinine ratio was computed, and albuminuria was defined as an albumin-to-creatinine ratio ≥30 mg/g. Estimated glomerular filtration rate (eGFR) was calculated using calibrated serum creatinine and the CKD-EPI equation and reduced eGFR was defined as levels <60 mL/min/1.73 m^2. Plasma glucose was measured enzymatically via a hexokinase reaction. Diabetes mellitus was defined as a fasting plasma glucose ≥126 mg/dL or self-report of a history of diabetes with concurrent antidiabetes medication use. Among persons without diabetes, impaired fasting glucose was defined as a fasting glucose of 100 to 125 mg/dL. Metabolic syndrome was defined with the harmonized definition.[12]

Total- and HDL-C and triglycerides were measured with the Hitachi 704 Analyzer, and reagents were purchased from Roche/Boehringer Mannheim Diagnostics, Indianapolis, IN. LDL-C was calculated with the Friedewald equation (LDL-C = total cholesterol–HDL-C–triglycerides/5). Non–HDL-C was calculated as total cholesterol–HDL-C.

We grouped participants into 4 mutually exclusive CHD risk categories by using 2004 ATP III guidelines as follows: (1) no CHD or CHD risk equivalents and 0 to 1 major CHD risk factors (0–1 risk factors), (2) no CHD or CHD risk equivalents and 2 or more major CHD risk factors (≥2 risk factors), (3) CHD not at very high risk or having CHD risk equivalents or both (CHD or risk equivalent), and (4) CHD at very high risk (CHD at very high risk).[1] CHD risk factors include older age (≥55 years for women and ≥45 years for men), current smoking, hypertension, family history of CHD, and low HDL-C (<40 mg/dL). HDL-C ≥60 mg/dL is considered protective and offsets the presence of one of the other CHD risk factors.

Participants who reported a prior diagnosis of CHD or myocardial infarction were defined as having a history of CHD. Risk equivalents included a history of stroke or

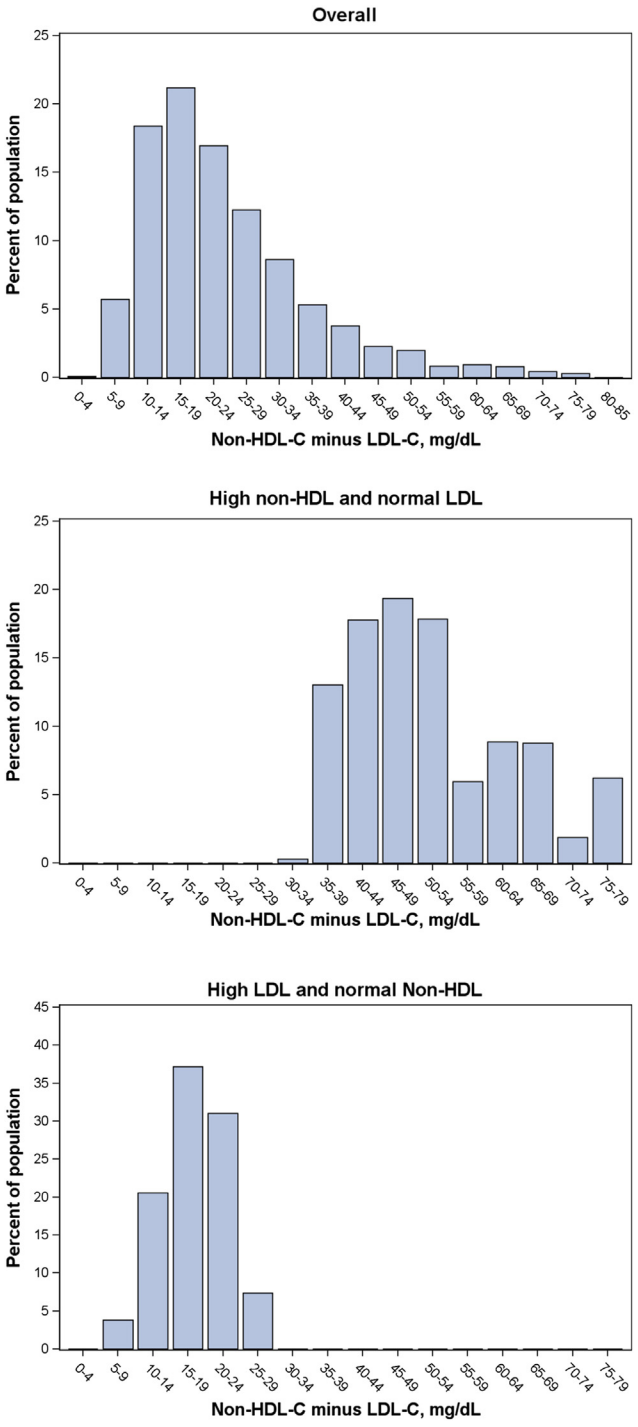

Figure 2 Differences in non–HDL-C and LDL-C, overall (top) and for persons with high non–HDL-C and normal LDL-C (middle) and for persons with high LDL-C and normal non–HDL-C (bottom). LDL-C, low-density lipoprotein cholesterol; non–HDL-C, non–high-density lipoprotein cholesterol.

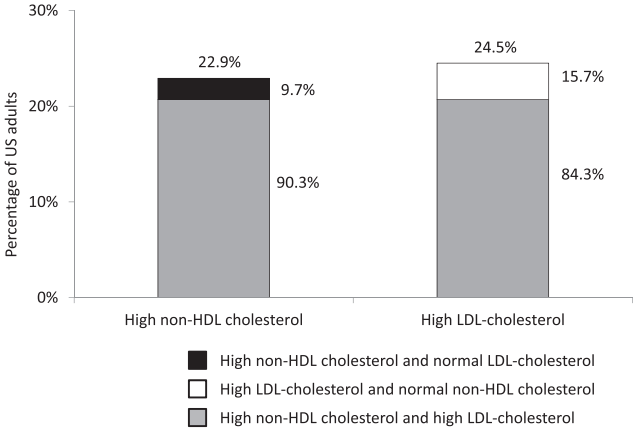

Figure 3 Prevalence of high non–HDL-C and high LDL-C among US adults. LDL-C, low-density lipoprotein cholesterol; non–HDL-C, non-high-density lipoprotein cholesterol.

diabetes mellitus. Data on other ATP III risk equivalents (eg, peripheral arterial disease, aortic aneurysm) are not available in NHANES 2005–2010. Among people with CHD, being a current smoker or having diabetes mellitus or metabolic syndrome placed them in the CHD at very high-risk category. Risk category specific cut points for defining high LDL-C and high non–HDL-C are provided in Table 1. For ease of description, we refer to participants with LDL-C or non–HDL-C levels below these cut points as having "normal" levels.

Statistical analysis

We plotted histograms of LDL-C and non–HDL-C and calculated mean and median levels. We calculated the mean differences (non–HDL-C−LDL-C), overall and for participants with high LDL-C and normal non–HDL-C and for participants with normal LDL-C and high non–HDL-C. We then calculated the prevalence of high non–HDL-C and high LDL-C. Among participants with high non–HDL-C, we calculated the percentage and number of US adults with and without high LDL-C. Among those with high LDL-C, we calculated the percentage and number of US adults with and without high non–HDL-C.

Participant characteristics were calculated for each of 4 groups as follows: (1) participants with normal non–HDL-C and normal LDL-C, (2) participants with high non–HDL-C and normal LDL-C, (3) participants with normal non–HDL-C and high LDL-C, and (4) participants with both high non–HDL-C and high LDL-C. Adjusted prevalence ratios for having high non–HDL-C and normal LDL-C and, separately, having high LDL-C and normal non–HDL-C, each vs having normal levels of non–HDL-C and LDL-C were derived with log binomial regression models, which are recommended for cross-sectional studies with common outcomes.[13] Prevalence ratios were calculated for age, sex, race/ethnicity, smoking status (current or former vs never), body mass index (BMI; calculated

Table 2 Characteristics of NHANES 2005–2010 Participants by Non–HDL-C and LDL-C Categories

	High Non–HDL-C and High LDL-C (n = 1189)	High Non–HDL-C and Normal LDL-C (n = 124)	High LDL-C and Normal Non–HDL-C (n = 196)	Normal LDL-C and Normal Non–HDL-C (n = 3477)
Age, years, mean (SE)	52.9 (0.6)	46.7 (1.7)	51.3 (1.1)	41.1 (0.4)
Male sex, % (SE)	56.1 (1.7)	56.5 (4.8)	57.1 (4.7)	44.1 (1.1)
Race/ethnicity, % (SE)				
NH white	72.5 (2.5)	70.3 (5.0)	64.3 (4.0)	67.5 (1.8)
NH black	10.0 (1.4)	5.1 (2.0)	15.2 (2.5)	12.0 (0.9)
Hispanic	12.4 (1.6)	21.9 (3.8)	11.6 (2.3)	14.0 (1.3)
Health insurance, % (SE)				
Private	47.8 (2.1)	64.2 (5.2)	52.5 (4.4)	61.3 (1.4)
Government	32.4 (1.8)	18.6 (3.4)	31.8 (3.3)	16.6 (1.0)
None	19.9 (1.5)	17.1 (4.2)	15.6 (3.1)	22.1 (1.1)
Smoking status, % (SE)				
Current	30.6 (1.7)	25.8 (5.4)	17.7 (2.7)	19.5 (0.9)
Former	27.8 (1.5)	21.7 (4.9)	25.7 (3.5)	21.8 (1.4)
Never	41.6 (1.8)	52.5 (5.7)	56.6 (3.5)	58.7 (1.4)
Body mass index, mean (SE)	29.8 (0.3)	31.6 (0.8)	29.2 (0.5)	27.7 (0.2)
Hypertension, % (SE)	42.9 (2.1)	29.7 (5.7)	38.0 (3.8)	16.0 (0.7)
Reduced eGFR, % (SE)	7.8 (1.0)	4.4 (2.2)	9.0 (2.1)	3.5 (0.3)
Albuminuria, % (SE)	10.0 (1.0)	12.4 (4.2)	9.6 (2.1)	6.6 (0.5)
Impaired fasting glucose, % (SE)	60.3 (2.0)	61.1 (6.5)	54.6 (4.8)	35.2 (1.4)
Diabetes, % (SE)	17.2 (1.4)	12.8 (4.3)	16.4 (3.3)	3.0 (0.3)
Metabolic syndrome, mean (SE)	52.5 (1.6)	74.5 (4.8)	22.3 (3.5)	18.5 (0.7)
CHD risk category, mean (SE)				
0–1 risk factors	29.4 (1.9)	46.5 (5.6)	39.6 (4.7)	84.3 (0.9)
≥2 risk factors	39.6 (1.5)	36.4 (6.1)	37.4 (4.6)	11.4 (0.7)
CHD or risk equivalent, mean (SE)	24.6 (1.3)	15.0 (4.5)	18.3 (3.8)	4.0 (0.4)
CHD at very high risk, mean (SE)	6.5 (0.8)	2.0 (1.7)	4.7 (1.6)	0.3 (0.1)
Total cholesterol, mg/dL, mean (SE)	237.1 (1.4)	218.2 (3.8)	208.4 (2.8)	184.5 (0.8)
HDL cholesterol, mg/dL, mean (SE)	49.9 (0.6)	41.7 (0.9)	55.7 (1.2)	57.3 (0.4)
Triglycerides, mg/dL, mean (SE)	156.5 (2.6)	255.2 (5.6)	90.3 (2.1)	106.2 (1.2)
LDL-C, mg/dL, mean (SE)	155.9 (1.4)	125.4 (2.8)	134.8 (2.3)	105.9 (0.6)
Non–HDL-C, mg/dL, mean (SE)	187.2 (1.4)	176.5 (3.2)	152.7 (2.3)	127.2 (0.6)

CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NH, non-Hispanic; non–HDL-C, non–high-density lipoprotein cholesterol.

Excludes people who were treated.

as weight divided by height squared; kg/m^2), reduced eGFR, albuminuria, impaired fasting glucose, diabetes, metabolic syndrome, and the 4 CHD risk categories defined earlier. All prevalence ratios were adjusted for age, sex, and race/ethnicity.

Two additional analyses were conducted. First, because persons with serum triglycerides ≥400 mg/dL may have high non–HDL-C, we calculated the percentage and number of US adults with triglycerides ≥400 mg/dL and, among those with triglycerides ≥400 mg/dL, the percentage with high non–HDL-C. Second, we examined alternate cut points for defining high non–HDL-C that would capture a larger percentage of people with high LDL-C. These cut points ranged from LDL-C + 30 mg/dL to LDL-C + 5 mg/dL in decrements of 5 mg/dL.

Data management was conducted with SAS version 9.2 (SAS Institute, Cary, NC), and analyses were performed with SUDAAN 10.1 (Research Triangle Institute, Research Triangle Park, NC), accounting for the complex sampling design of NHANES. Sampling weights were applied to all calculations to obtain US nationally representative prevalence estimates. NHANES sampling weights were recalibrated on the basis of the proportion of participants missing data by 10-year age group, sex, and race/ethnicity.

Results

The distributions for both LDL-C and non–HDL-C were roughly normal with some right skewness (Supplementary Fig. 1). The median (25th–75th percentiles) values were 115.2 (93.0–137.9) for LDL-C and 138.9 (113.2–164.8) for non–HDL-C. Non–HDL-C was 23.9 mg/dL (SE, 0.2 mg/dL) higher than LDL-C for the overall population, 51.0 mg/dL (SE, 1.1 mg/dL) higher among people with normal LDL-C and high non–HDL-C, and 18.0 mg/dL (SE, 0.4 mg/dL) higher among people with high LDL-C and normal non–HDL-C (Fig. 2).

Of US adults not on lipid-lowering therapy, 22.9% (40.4 million) had high non–HDL-C and 24.5% (43.2 million) had high LDL-C (Fig. 3). Among those with high non–HDL-C, 9.7% (3.9 million) had normal LDL-C and among those with high LDL-C, 15.7% (6.8 million) had normal non–HDL-C.

Table 2 provides characteristics of each of the 4 groups defined by non–HDL-C and LDL-C status (ie, both high; high non–HDL-C and normal LDL-C; normal non–HDL-C and high LDL-C; both normal). Compared with their counterparts with high LDL-C and normal non–HDL-C, participants who had high non–HDL-C and normal LDL-C were younger, more likely to be non-Hispanic white or Hispanic, have private health insurance, current smokers, have metabolic syndrome, and a higher mean BMI. In contrast, they were less likely to have hypertension or reduced eGFR.

After adjustment for sex and race/ethnicity, older age was associated with having high non–HDL-C and normal LDL-C and high LDL-C and normal non–HDL-C vs normal non–HDL-C and normal LDL-C (Table 3). After age and race/ethnicity adjustment, women were less likely to be discordant for non–HDL-C and LDL-C. After age and sex adjustment, non-Hispanic blacks were less likely to have high non–HDL-C and normal LDL-C and more likely to have high LDL-C and normal non–HDL-C, and Hispanics were more likely to have high non–HDL-C and normal high LDL-C, each compared with having normal non–HDL-C and normal LDL-C. After age, sex, and race/ethnicity adjustment, higher BMI, hypertension, impaired fasting glucose and diabetes, and higher CHD risk as indicated by risk categories were associated with having both high non–HDL-C and normal LDL-C and high LDL-C and normal non–HDL-C compared with normal non–HDL-C and normal LDL-C. Current smokers and persons

Table 3 Prevalence Ratios for High Non–HDL-C and Normal LDL-C and High LDL-C and Normal Non–HDL-C

	Prevalence Ratio (95% CI)	
	High Non–HDL-C and Normal LDL-C (n = 124)	High LDL-C and Normal Non–HDL-C (n = 196)
Age, per 10 years	1.25 (1.12–1.40)	1.45 (1.35–1.56)
Sex		
Male	1 (reference)	1 (reference)
Female	0.59 (0.40–0.87)	0.56 (0.39–0.81)
Race/ethnicity		
NH white	1 (reference)	1 (reference)
NH black	0.47 (0.20–1.08)	1.59 (1.13–2.23)
Hispanic	1.72 (1.14–2.59)	1.18 (0.77–1.81)
Smoking status		
Never	1 (reference)	1 (reference)
Former	0.88 (0.45–1.71)	0.87 (0.58–1.31)
Current	1.66 (0.93–2.98)	1.10 (0.79–1.55)
Body mass index, per 5 kg/m^2	1.23 (1.14–1.33)	1.13 (1.05–1.20)
Hypertension	1.86 (0.95–3.65)	1.78 (1.24–2.55)
Reduced eGFR	0.69 (0.23–2.06)	1.03 (0.59–1.80)
Albuminuria	1.69 (0.74–3.85)	1.01 (0.62–1.63)
Diabetes status		
Normal	1 (reference)	1 (reference)
Impaired fasting glucose	2.26 (1.31–3.89)	1.46 (0.96–2.22)
Diabetes mellitus	3.12 (1.22–7.95)	2.77 (1.66–4.63)
Metabolic syndrome	10.55 (6.1–18.1)	0.92 (0.61–1.40)
CHD risk category		
0–1 risk factors	1 (reference)	1 (reference)
≥2 risk factors	5.07 (2.84–9.04)	5.13 (3.26–8.07)
CHD or risk equivalent	5.33 (1.95–14.56)	5.07 (2.67–9.66)
CHD at very high risk	8.40 (1.96–36.06)	10.2 (5.79–17.9)

CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NH, non-Hispanic; non–HDL-C, non–high-density lipoprotein cholesterol.

Adjusted for age, race/ethnicity, sex (when appropriate) and weighted to reflect the national population.

Reference category is persons with normal non-HDL-C and normal LDL-C.

Table 4 Estimated Numbers of US Adults With High Non–HDL-C and Percentage With High LDL-C With High and Normal Non–HDL-C With the Use of Alternate Definitions for High Non–HDL-C

	High Non–HDL-C	High LDL-C		
Definition of High Non–HDL-C*	No., Millions	No., Millions	High Non–HDL-C, %	Normal Non–HDL-C, %
LDL-C + 30 mg/dL	40.4	43.2	84.3	15.7
LDL-C + 25 mg/dL	45.9	43.2	91.0	9.0
LDL-C + 20 mg/dL	51.3	43.2	96.5	3.5
LDL-C + 15 mg/dL	56.3	43.2	98.5	1.5
LDL-C + 10 mg/dL	61.9	43.2	99.9	0.1
LDL-C + 5 mg/dL	68.5	43.2	100.0	0.0

LDL-C, low-density lipoprotein cholesterol; non–HDL-C, non–high-density lipoprotein cholesterol.

*The definition of non-HDL-C varies from LDL-C + 30 mg/dL (eg, for very high risk persons; high LDL-C is defined as ≥70 mg/dL and high non–HDL-C is defined as ≥100 mg/dL) to LDL-C + 5 mg/dL (eg, for very high risk persons; high LDL-C is defined as ≥70 mg/dL and high non–HDL-C is defined as ≥75 mg/dL).

with the metabolic syndrome were more likely to have high non–HDL-C and normal LDL-C but not high LDL-C and normal non–HDL-C.

Serum triglycerides ≥ 400 mg/dL

The prevalence of serum triglycerides ≥400 mg/dL was 1.7%, which equates to 3.1 million US adults. The mean ± SE non–HDL-C for this population was 216.0 ± 5.6 mg/dL. Among the population with serum triglycerides ≥400 mg/dL, 77.3% had high non–HDL-C (2.4 million). Pooling together those with and without serum triglycerides ≥400 mg/dL, there are 6.3 million US adults with high non–HDL-C and with LDL-C levels that were normal or could not be accurately estimated.

Alternate cut points for defining high non–HDL-C

In our main analysis we used an LDL-C + 30 mg/dL cut point for defining high non–HDL-C, and 15.7% of the 43.2 million US adults with high LDL-C had normal non–HDL-C (Table 4). With the use of lower cut points, a smaller percentage of US adults with high LDL-C would be categorized as having normal non–HDL-C. For example, with the use of LDL-C + 15 mg/dL to define high non–HDL-C, only 1.5% of US adults with high LDL-C had normal non–HDL-C. However, with the use of this definition, 56.3 million US adults had high non–HDL-C compared with 40.4 million US adults with high non–HDL-C when defining high non–HDL-C by using the LDL-C + 30 mg/dL cut points. Finally, we produced a Supplementary Table that shows how the discordance of measures would vary if specific targets for LDL-C and non–HDL-C were set for everyone.

Discussion

We estimated that 3.9 million US adults had high non–HDL-C despite having an LDL-C below the cut point for which treatment initiation is recommended. An additional 2.4 million US adults with serum triglycerides ≥400 mg/dL, a population for which calculated LDL-C is not considered reliable, had high non–HDL-C. When designated as a "secondary" treatment target, non–HDL-C may not be routinely reported in laboratory results, and these persons may not be identified as candidates for therapeutic lifestyle changes or pharmacologic lipid-lowering therapy. These findings should be considered additional evidence of limitations related to a sole reliance on LDL-C for screening. Baruch et al[14] document discordance between calculated and directly measured LDL-C. In addition, 2 other studies have examined discordance between non–HDL-C and LDL-particle measurements.[15,16]

We found that persons with high non–HDL-C and normal LDL-C were more likely to have impaired fasting glucose, diabetes, the metabolic syndrome and to be at high risk for CHD events. Ignoring non–HDL-C may result in missed treatment opportunities for these persons with a high CHD risk. A stronger association for non–HDL-C vs LDL-C with CHD events has been reported in the literature.[8,17] For example, in a meta-analysis by Sniderman et al,[17] LDL-C was a less potent marker of cardiovascular risk (relative risk, 1.25; 95% CI, 1.18–1.33) compared with non–HDL-C (relative risk, 1.34; 95% CI, 1.24–1.49). In addition, the value of non–HDL-C independent of LDL-C was confirmed in an individual level meta-analysis of 38,153 patients randomly assigned to statin therapy in 8 trials.[8] Compared with patients with an LDL-C < 100 mg/dL and non–HDL-C <130 mg/dL, the adjusted hazard ratio for cardiovascular events was 1.02 (95% CI, 0.92–1.12) for LDL-C ≥100 mg/dL and non–HDL-C < 130 mg/dL and 1.32 (95% CI, 1.17–1.50) for non–HDL-C ≥130 mg/dL and LDL-C <100 mg/dL. The stronger association for non–HDL-C vs LDL-C on CHD risk has also been reported in other specific populations, including patients with diabetes, metabolic syndrome, and after bypass surgery.[18,19]

We also found that persons with high non–HDL-C and normal LDL-C were almost 11 times more likely to have metabolic syndrome than their counterparts with normal levels for each. Impaired fasting glucose and diabetes were

associated with higher adjusted prevalence ratios for high non–HDL-C and normal LDL-C vs high LDL-C and normal non–HDL-C each compared with persons with both normal non–HDL-C and normal LDL-C. This is not surprising because states of insulin resistance are characterized by atherogenic dyslipidemia rather than high LDL-C levels. Given the increasing prevalence of obesity, metabolic syndrome, and diabetes among US adults, the utility of using non–HDL-C may become more important.[20,21]

Our study estimates that a strategy focused on non–HDL-C, rather than LDL-C, for detection of hyperlipidemia has the potential to result in 6.7 million US adults with high LDL-C not being identified or not getting risk reduction therapy. Notably, non-Hispanic blacks were more likely to have high LDL-C and normal non–HDL-C than other race/ethnicity groups; they are at increased risk of cardiovascular disease, and the use of non–HDL-C rather than LDL-C may result in a missed opportunity to deliver appropriate risk reduction therapies. Our findings do tend to support the American Heart Association guidelines for CHD prevention in women, which recommend a non–HDL target of <130 mg/dl.[22]

The percentage of persons with high LDL-C that may be missed by using non–HDL-C as a primary lipid marker for initiating therapy can be substantially reduced through lowering the threshold for defining non–HDL-C from LDL-C + 30 mg/dL to LDL-C + 15 mg/dL. Future studies are needed to identify the optimal cut points for defining high non–HDL-C on the basis of the risk of cardiovascular disease events.

There are additional reasons why non–HDL-C may be useful for screening purposes. Non–HDL-C is easy to calculate and subject to less variance than calculated LDL-C. Patients do not need to be fasting for non–HDL-C measures to be valid, facilitating screening. Finally, interventions to reduce CHD risk among persons with high non–HDL-C may be similar to those applied for their counterparts with high LDL-C. Specifically, lifestyle interventions remain the first line of intervention, and statin therapy has proven beneficial in the management of non–HDL-C.[10] Some may argue guidelines should focus on LDL-C to align with prior randomized trials. We posit that these trials have only used LDL-C as an inclusion criterion and did not randomly assigned persons to achieve certain LDL-C goals. Furthermore, randomization to statins has resulted in substantial reductions in non–HDL-C.[23–26]

Certain limitations should be kept in mind in considering our findings. Non–HDL-C and LDL-C were based on a single measurement; day-to-day variability exists in non–HDL-C and LDL-C which may have resulted in misclassification of some participants. However, the mean difference between non–HDL-C and LDL-C among persons with high non–HDL-C and normal LDL-C was large (51.0 mg/dL), suggesting the effect of day-to-day variability on our results may be relatively modest. Several variables, including the presence of CHD, relied on self-report. Although this may result in misclassification, there is no reason to believe that it would differ on the basis of levels of non–HDL-C or LDL-C. Despite having a large sample size, a relatively small number of NHANES participants had high non–HDL-C and normal LDL-C (n = 124) or high LDL-C and normal high non–HDL-C (n = 196). This resulted in wide confidence intervals for some of the prevalence ratios. Finally, the lipid profiles did not include detailed measures of subfractions such as very low density lipoprotein and other lipoproteins that contain apolipoprotein B that could be of interest. Despite these limitations, the NHANES sampling design permits calculation of nationally representative estimates and rigorous data collection that includes fasting blood samples that follow a study protocol, and the broad data collection allowed us to determine factors associated with high non–HDL-C.

Conclusion

In conclusion, results from this study suggest that a substantial number of US adults not taking statins have high non–HDL-C despite a normal LDL-C. Many of these persons have CHD risk factors, including the metabolic syndrome and diabetes, and not using non–HDL-C may represent a missed opportunity for risk reduction. Further research is needed on the trade-off between using non–HDL-C and LDL-C as the primary lipid marker for lipid-lowering therapy or broadening the definition of high cholesterol to be based on both LDL-C and non–HDL-C. Data from the present study suggest that such a change in the primary lipid parameter used to define high cholesterol may affect millions of Americans.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jacl.2013.11.001.

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