Distribution and Correlates of Non–High-Density Lipoprotein Cholesterol in Children: The Bogalusa Heart Study

Sathanur R. Srinivasan, PhD*‡; Leann Myers, PhD§; and Gerald S. Berenson, MD*‡

ABSTRACT. *Objective.* Serum non–high-density lipoprotein (HDL) cholesterol (total cholesterol minus HDL cholesterol) is considered a better screening tool than low-density lipoprotein (LDL) cholesterol for the assessment of coronary artery disease (CAD) risk in adults because it includes all classes of atherogenic lipoproteins. Although population frequency distribution and clinically useful cutpoints for this variable in adults have been reported recently, such information is lacking in children. Therefore, this study sought to provide population-based data on the distribution and correlates of non-HDL cholesterol in biracial (black–white) children.

Methods. The study sample consisted of 2843 5- to 17-year-olds (57% white, 50% female) who participated in a cross-sectional screening of cardiovascular risk factors as part of the Bogalusa Heart Study.

Results. Non-HDL cholesterol levels were similar in black and white children, and higher in girls than in boys, especially among the younger (5–11 years) age group. Age was inversely related to both non-HDL cholesterol and LDL cholesterol. Body fatness as measured by body mass index and waist circumference was positively associated with non-HDL cholesterol. The magnitude of correlation with triglycerides was relatively higher for non-HDL cholesterol versus LDL cholesterol. Non-HDL cholesterol showed an inverse relation to HDL cholesterol. In a multivariate analysis, body mass index, age, gender, waist circumference, and cigarette smoking accounted for 7.7% of the variance in non-HDL cholesterol. Non-HDL cholesterol levels equivalent to currently recommended LDL cutpoints (110, 130, 160, and 190 mg/dL) for CAD risk assessment were 123, 144, 176, and 207 mg/dL.

Conclusion. Population-based data on non-HDL cholesterol are now available for children, which may help improve the CAD risk assessment and intervention. *Pediatrics* 2002;110(3). URL: http://www.pediatrics.org/cgi/content/full/110/3/e29; *non-HDL cholesterol, LDL cholesterol, children, coronary artery disease.*

ABBREVIATIONS. LDL, low-density lipoprotein; HDL, high-density lipoprotein; CAD, coronary artery disease; VLDL, very-low-density lipoprotein; BMI, body mass index.

Elevated levels of low-density lipoprotein (LDL) cholesterol and decreased levels of high-density lipoprotein (HDL) cholesterol have long been recognized as an important risk factor for coronary artery disease (CAD) in adults.[1] Although clinical manifestations of CAD do not usually emerge until middle age, the atherosclerotic process begins very early in life, and the childhood adverse lipoprotein levels are associated with coronary atherosclerosis in youth.[2–4] The National Cholesterol Education Program Pediatric Panel and the American Academy of Pediatrics Committee on Nutrition have provided guidelines to identify and treat children who are at risk for the development of accelerated atherosclerosis in early adult life.[5,6]

With respect to lipoprotein-related risk assessment and intervention, LDL cholesterol is widely considered as the "gold standard." However, the limitations of the use of LDL cholesterol measured as part of the lipid profile for screening of CAD risk was outlined recently by Havel and colleagues.[7,8] Estimation of LDL cholesterol by Friedewald equation,[9] which requires overnight fasting triglycerides measurement, becomes less accurate with increasing concentrations of triglycerides in serum. Furthermore, this calculated value also includes intermediate-density lipoproteins and lipoprotein (a) to varying degrees. For obviating these limitations, measurement of non-HDL cholesterol (total cholesterol minus HDL cholesterol) has been proposed as a better screening tool for CAD risk assessment and treatment, the rationale being that non-HDL cholesterol includes both cholesterol-rich and triglycerides-rich atherogenic apolipoprotein B–containing lipoproteins (very-low-density lipoprotein [VLDL], intermediate-density lipoproteins, LDL, and lipoprotein [a]), and the measurement does not require overnight fasting.

Because non-HDL cholesterol is increasingly being used in clinical research,[3,10–12] population frequency distribution and clinically useful cutpoints for this variable in the adult population of the Third National Health and Nutrition Examination Survey has been reported recently.[13] Although data on serum lipids and lipoproteins are available for US children,[14–20] population-based data on non-HDL cholesterol in this age group is scant. This report presents distribution and correlates of non-HDL cholesterol in children aged 5 to 17 years, using biracial (black–white) population-based data from the Bogalusa Heart Study.

METHODS

Study Population

The Bogalusa Heart Study is a long-term investigation of the early natural history of cardiovascular disease beginning in childhood in the biracial (65% white, 35% black) community of Bogalusa, LA.[21] The eligible population included all children and young adults living in Bogalusa (population approximately 22 000). Since 1973, cross-sectional studies of the school-age population have been conducted every 3 to 5 years; the current analysis consisted of 3262 children who participated in the examination conducted between October 1992 and June 1994. The participation rate was 80%. The study sample consisted of 2843 5- to 17-year-olds (57% white, 50% female) after exclusion of those who were outside the age range (n = 263), were neither white nor black (n = 7), were using oral contraceptives (n = 40 females), and had missing values for the study variables (n = 109).

General Examination

Standardized protocols were used by trained examiners.[21] Participants were instructed to fast for 12 hours before venipuncture, and compliance was determined by interview on the morning of the examination. Height, weight, and waist circumference were measured in triplicate, and the mean values were used in the analysis. As a measure of overall body fatness, the body mass index (BMI; weight in kilograms divided by the square of the height in meters) was used. Waist circumference was used as a measure of visceral adiposity. Information concerning cigarette smoking, alcohol intake, and oral contraceptive use was obtained by questionnaires. The reproducibility of anthropometric measurements was assessed in a 10% random sample, and the intraclass (within-observer) correlation coefficients were >0.99 for BMI and 0.97 for waist circumference.

Serum Lipids and Lipoproteins

Total cholesterol and triglycerides were determined enzymatically on an Abbott VP analyzer (Abbott Laboratories, North Chicago, IL). Lipoprotein cholesterols were measured by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis.[22] Measurement of total cholesterol, triglycerides, and HDL cholesterol are being monitored by a surveillance program of the Centers for Disease Control and Prevention (Atlanta, GA). On the basis of 10% blind duplicate determinations, intraclass coefficients of reliability were 0.99 for total cholesterol, 0.98 for LDL cholesterol and triglycerides, and 0.96 for HDL cholesterol.

Statistical Analyses

Non-HDL cholesterol was computed as the difference between total serum cholesterol and HDL cholesterol. Descriptive statistics (means, standard deviations, percentiles) were used to summarize non-HDL levels. Analysis of covariance methods were used to assess differences in mean non-HDL levels between gender and race groups. Spearman correlation coefficients were computed to determine the bivariate relationships between non-HDL and age, body fatness, and lipoprotein variables. Forward stepwise regression methods were used to determine which anthropometric, behavioral, and demographic factors correlate independently with non-HDL cholesterol; the criterion for entry into the model was $P < .05$. Simple regression models predicting non-HDL cholesterol from LDL cholesterol were also computed. All analyses were performed using SAS 8.0 (SAS, Inc, Cary, NC).

RESULTS

Mean and Selected Percentiles

Race- and gender-specific mean levels and selected percentiles of non-HDL cholesterol by age group and total sample are presented in Table 1. Levels were similar in black and white children, regardless of gender and age group. A significant male-female difference was seen in both races, with girls showing higher values than boys. However, the observed gender differential was significant in 5- to 11-year-olds but not in 12- to 17-year-olds.

Relation to Age, Body Fatness, and Lipoprotein Variables

The relation of non-HDL cholesterol to age, BMI, waist circumference, total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol are given in Table 2. Corresponding correlation data regarding LDL cholesterol are provided for comparison. Age was inversely correlated to both non-HDL cholesterol and LDL cholesterol. Both BMI and waist circumference were related positively to non-HDL cholesterol. As expected, both non-HDL cholesterol and LDL cholesterol associated strongly with each other and total cholesterol. Although both non-HDL cholesterol and LDL cholesterol were related positively to triglycerides, the magnitude of correlation was relatively higher for the former. Non-HDL cholesterol showed a significant inverse relation to HDL cholesterol.

Independent Correlates

The characteristics that were independently related to non-HDL cholesterol are presented in Table 3. General adiposity (BMI) and age, in that order,

TABLE 1. Mean and Selected Percentiles of Serum Non-HDL Cholesterol in Children by Age, Race, and Gender: The Bogalusa Heart Study

	n	Age (Years)	Mean ± SD (mg/dL)	Percentiles (mg/dL)						
				5	25	50	75	80	90	95
White male	348	5–11	114 ± 26	74	95	114	131	134	148	161
	472	12–17	113 ± 27	75	92	110	131	134	149	163
	820	5–17	113 ± 27	75	93	112	131	134	148	161
Black male	294	5–11	116 ± 29	74	97	113	137	140	152	164
	313	12–17	110 ± 28	71	89	107	127	131	149	159
	607	5–17	113 ± 18	73	93	109	131	137	150	160
White female	376	5–11	122 ± 29*	82	103	117	135	142	160	179
	415	12–17	114 ± 28	75	92	112	130	133	152	164
	791	5–17	118 ± 29*	77	98	115	131	137	157	172
Black female	298	5–11	123 ± 30*	82	106	120	138	142	156	174
	327	12–17	111 ± 28	72	92	107	128	133	149	163
	625	5–17	117 ± 29*	74	97	114	132	138	151	166
All	2843	5–17	115 ± 28	75	95	113	131	136	152	166

SD indicates standard deviation.

* Females > males ($P < .0001$), controlling for age, age^2, age^3, BMI, cigarette smoking (n/wk), and alcohol (mL/wk).

TABLE 2. Relation of Serum Non-HDL Cholesterol and LDL Cholesterol to Age, Obesity Measures, and Other Lipoprotein Variables: The Bogalusa Heart Study

	Spearman Correlation ($n = 2843$)	
	Non-HDL Cholesterol	LDL Cholesterol
Age	−0.11*	−0.17*
BMI	0.13*	0.03
Waist circumference	0.09*	−0.01
Total cholesterol	0.90*	0.90*
Triglycerides	0.42*	0.20*
LDL cholesterol	0.95*	-
HDL cholesterol	−0.12*	−0.01

* $P < .0001$.

TABLE 4. Serum Non-HDL Cholesterol Values Equivalent to National Cholesterol Education Program Pediatric Panel Cutpoints for LDL Cholesterol*: The Bogalusa Heart Study

LDL Cholesterol† (mg/dL)	Non-HDL Cholesterol† (95% Confidence Interval) (mg/dL)
110	123.2 (122.9–123.6)
130	144.3 (143.8–144.7)
160	175.8 (175.0–176.6)
190	207.3 (206.2–208.5)

* Sample size: 2843.
† Non-HDL cholesterol = $7.56 + 1.05 \times$ LDL cholesterol.

were the major factors that contributed to the explained variance of non-HDL cholesterol. Gender, visceral fatness (waist circumference), and cigarette smoking contributed to a lesser extent to the variance. Overall, the identified independent variables accounted for 7.7% of the variance in non-HDL cholesterol. It should be noted that the association of age with non-HDL cholesterol was nonlinear as indicated by the age^3 term in the model. The likelihood of underreporting among children on the self-report for cigarette smoking, alcohol intake, and oral contraceptive usage may potentially account for the attenuated R^2.

Levels by LDL Cholesterol Cutpoints

A regression of non-HDL cholesterol on LDL cholesterol was performed to provide non-HDL cholesterol levels corresponding to LDL cholesterol cutpoints (110, 130, 160, and 190 mg/dL) that determine the steps for risk assessment and treatment. As shown in Table 4, non-HDL cholesterol levels were 13.2 to 17.3 mg/dL higher than LDL cholesterol levels over the range of cutpoints used. Because age and gender were independent correlates of non-HDL cholesterol, the following regression equations are provided by age group and gender for non-HDL cholesterol:

5- to 11-year-olds: $5.68 + 1.05 \times$ LDL cholesterol
12- to 17-year-olds: $7.18 + 1.06 \times$ LDL cholesterol
Male: $8.48 + 1.04 \times$ LDL cholesterol
Female: $6.89 + 1.06 \times$ LDL cholesterol

The non-HDL cholesterol values corresponding to LDL cholesterol cutpoints by age group and gender varied by only 1 to 3 mg/dL from that of the total sample shown in Table 4.

TABLE 3. Characteristics Related to Serum Non-HDL Cholesterol in Children: The Bogalusa Heart Study

Independent Variable*	Regression Coefficient	Cumulative R^2
BMI	0.244	0.025
Age^3	−0.006	0.063
Gender (female > male)	5.195	0.067
Waist circumference	0.562	0.074
Cigarettes/wk	0.174	0.077
Intercept	80.657	

* Age, age^2, age^3, race, gender, waist circumference, BMI, cigarettes/wk, and alcohol (mL/wk). The variables listed in table entered the model in the order as shown at $P < .05$.

DISCUSSION

The present study provides distribution and correlates of non-HDL cholesterol in a population of children. The levels were higher in girls than in boys, especially among the younger (5–11 years) age group, and associated inversely with age. In addition, the levels were adversely associated with modifiable factors such as body fatness and cigarette smoking.

The observed female excess of non-HDL cholesterol in children is consistent with the previous data, including our own, showing higher LDL cholesterol and VLDL cholesterol and lower HDL cholesterol in girls compared with boys, especially among preadolescents.[15–19] Likewise, the relatively lower levels of non-HDL cholesterol in the older age group seen in this study may reflect the previously well-documented puberty-related decreases in total cholesterol, LDL cholesterol, and HDL cholesterol.[16–19,23] Of interest, as in an earlier report,[10] the current study found no black–white difference in non-HDL cholesterol. We and others have reported higher levels of total cholesterol, HDL cholesterol, and lipoprotein (a) and lower levels of VLDL cholesterol and triglycerides in black children than in white children.[15,16,19,20] It seems that the levels of cholesterol derived from atherogenic apolipoprotein B–containing lipoproteins are similar between black and white children, despite that black children have the advantage of higher HDL and lower VLDL (triglycerides).

The present data show that non-HDL cholesterol, unlike LDL cholesterol, was correlated better with triglycerides and associated inversely with HDL cholesterol. These findings are consistent in that non-HDL cholesterol includes the cholesterol component of triglyceride-rich lipoproteins, which are metabolically inversely related to HDL.[24–26] Furthermore, the current finding that non-HDL cholesterol, unlike LDL cholesterol, was associated better with measures of body fatness is consistent with the greater adverse impact of childhood overweight and obesity on triglycerides.[27–29] In this context, non-HDL cholesterol compared with LDL cholesterol may be a better parameter for monitoring the outcomes related to weight control, prudent diet, and physical activity.

The present study did not include measurement of apolipoprotein B, a better indicator of number of atherogenic particles and the attendant CAD risk than LDL cholesterol.[30–33] It was reported recently that non-HDL cholesterol is the best surrogate mea-

sure of apolipoprotein B, because it correlated better with apolipoprotein B than did LDL cholesterol across a wide range of triglyceride levels.[12]

Finally, the present report provides non-HDL cholesterol values equivalent to selected LDL cholesterol cutpoints recommended by National Cholesterol Education Program pediatric panel and the American Academy of Pediatrics.[5,6] Although LDL cholesterol is widely used as the standard for CAD risk assessment and intervention, non-HDL cholesterol may be even better in this regard for the reasons discussed earlier. However, studies are obviously needed to establish the utility of non-HDL cholesterol in the pediatric population.

REFERENCES

1. Kannel WB, Castelli WP, Gordon T. Cholesterol in the prediction of atherosclerotic disease: new perspectives based on the Framingham Study. *Ann Intern Med.* 1979;90:85–91
2. Newman WP 3rd, Freedman DS, Voors AW, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis: the Bogalusa Heart Study. *N Engl J Med.* 1986;314:138–144
3. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentration and smoking. *JAMA.* 1990;264:3018–3023
4. Mahoney LT, Burns TL, Stanford W. Coronary risk factors measured in childhood and young adult life are associated with coronary artery calcification in young adults: the Muscatine Study. *J Am Coll Cardiol.* 1996;27:277–284
5. National Cholesterol Education Program. Report of the expert panel on blood cholesterol levels in children and adolescents. *Pediatrics.* 1992;89:525–584
6. American Academy of Pediatrics, Committee on Nutrition. Cholesterol in childhood. *Pediatrics.* 1998;101:141–147
7. Havel RJ, Rappaport E. Management of primary hyperlipidemia. *N Engl J Med.* 1995;332:1491–1498
8. Frost PH, Havel RJ. Rationale for use of non-high-density lipoprotein cholesterol screening and assessment of risk and therapy. *Am J Cardiol.* 1998;81:26B–31B
9. Friedewald W, Levy R, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, with use of the preparative ultracentrifuge. *Clin Chem.* 1972;18:499–502
10. Winkleby MA, Robinson TN, Sundquist J, Kraemer HC. Ethnic variation in cardiovascular disease risk factors among children and young adults: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. *JAMA.* 1999;281:1006–1013
11. Frost PH, Davis BR, Burlando AJ, et al. Serum lipids and incidence of coronary heart disease. Findings from the Systolic Hypertension in the Elderly Program (SHEP). *Circulation.* 1996;94:2381–2388
12. Ballantyne CM, Andrews TC, Hsia JA, Kramer JH, Shear C for the ACCESS Study Group. Correlation of non-high-density lipoprotein cholesterol with apolipoprotein B: effect of 5 hydroxymethyl glutaryl coenzyme A reductase inhibitors on non-high-density lipoprotein cholesterol levels. *Am J Cardiol.* 2001;88:265–269
13. Gardner CD, Winkleby MA, Fortman SP. Population frequency distribution of non-high-density lipoprotein cholesterol (third National Health and Nutrition Examination Survey [NHANES III], 1988–1994). *Am J Cardiol.* 2000;86:299–304
14. Lauer RM, Connor WE, Leaverton PE, Reiter MA, Clarke WR. Coronary heart disease risk factors in school children: the Muscatine Study. *J Pediatr.* 1975;86:697–706
15. Srinivasan SR, Frerichs RR, Webber LS, Berenson GS. Serum lipoprotein profile in children from a biracial community. The Bogalusa Heart Study. *Circulation.* 1976;54:309–318
16. Srinivasan SR, Wattigney W, Webber LS, Berenson GS. Race and gender differences in serum lipoproteins of children, adolescents, and young adults—emergence of an adverse lipoprotein pattern in white males: the Bogalusa Heart Study. *Prev Med.* 1991;20:671–684
17. Tamir I, Heiss G, Glueck CJ, Christensen B, Kwiterovich P, Rifkind BM. Lipid and lipoprotein distributions in white children ages 6–19 years. The Lipid Research Clinics Program. Prevalence Study. *J Chron Dis.* 1981;34:27–39
18. Ellefson RD, Elveback LR, Hodgson PA, Weidman WH. Cholesterol and triglycerides in serum lipoproteins of young persons of Rochester, Minnesota. *Mayo Clin Proc.* 1978;53:307–320
19. Morrison JA, deGroot I, Edwards BK, et al. Lipids and lipoproteins in 927 school children, ages 6 to 17 years. *Pediatrics.* 1978;62:990–995
20. Srinivasan SR, Dahlen GH, Jarpa RA, Webber LS, Berenson GS. Racial (black-white) differences in serum lipoprotein (a) distribution and its relation to parental myocardial infarction in children. Bogalusa Heart Study. *Circulation.* 1991;84:160–167
21. Berenson GS, McMahan CA, Voors AW, et al. *Cardiovascular Risk Factors in Children: The Early National History of Atherosclerosis and Essential Hypertension.* New York, NY: Oxford University Press; 1980
22. Srinivasan SR, Berenson GS. Serum lipoprotein in children and methods for study. In: Lewis LA, ed. CRC *Handbook of Electrophoresis Vol III: Lipoprotein Methodology and Human Studies.* Boca Raton, FL: CRC Press; 1983:185–204
23. Berenson GS, Srinivasan SR, Cresanta JL, Foster TA, Webber LS. Dynamic changes of serum lipoproteins in children during adolescence and sexual maturation. *Am J Epidemiol.* 1981;113:157–170
24. Patsch JR, Prasad S, Gotto AM Jr, Patsch W. High density lipoprotein$_2$: relationship of the plasma levels of this lipoprotein species to its composition, to the magnitude of postprandial lipemia, and to the activities of lipoprotein lipase and hepatic lipase. *J Clin Invest.* 1987;80:341–347
25. Nikkilä EA, Taskinen MR, Sane T. Plasma high-density lipoprotein concentration and subfraction distribution in relation to triglyceride metabolism. *Am Heart J.* 1987;113:543–548
26. Tall AR. Plasma high density lipoproteins: metabolism and relationship to atherogenesis. *J Clin Invest.* 1990;86:379–384
27. Laskarzewski P, Morrison JA, Mellies MJ, et al. Relationships of measurements of body mass to plasma lipoprotein in school children and adults. *Am J Epidemiol.* 1980;111:395–406
28. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relationship of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. *Pediatrics.* 1999;103:1175–1182
29. Srinivasan SR, Myers L, Berenson GS. Rate of change in adiposity and its relationship to concomitant changes in cardiovascular risk variables among biracial (black-white) children and young adults: the Bogalusa Heart Study. *Metabolism.* 2001;50:299–305
30. Sniderman AD, Pedersen T, Kjekshus J. Putting low-density lipoproteins at center stage in atherogenesis. *Am J Cardiol.* 1997;79:66–67
31. Kwiterovich PO Jr, Coresh J, Smith HH, Bachonle PS, Derby CA, Pearson TA. Comparison of the plasma level of apolipoproteins B and A-I, and other risk factors in men and women with premature coronary artery disease. *Am J Cardiol.* 1992;69:1015–1021
32. Lamarche B, Moorjani S, Lupien PJ, Cantin B, Bernard PM, Dagenais GR, Despres JP. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Quebec Cardiovascular Study. *Circulation.* 1996;94:273–278
33. Gotto AM Jr, Whitney E, Stern EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS). *Circulation.* 2000;101:477–484

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/110/3/e29
References	This article cites 31 articles, 10 of which you can access for free at: http://pediatrics.aappublications.org/content/110/3/e29#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Cardiology** http://www.aappublications.org/cgi/collection/cardiology_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Distribution and Correlates of Non-High-Density Lipoprotein Cholesterol in Children: The Bogalusa Heart Study

Sathanur R. Srinivasan, Leann Myers and Gerald S. Berenson

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://pediatrics.aappublications.org/content/110/3/e29

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®