

Distribution of Lipoproteins by Age and Gender in Adolescents

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Background—The current National Cholesterol Education Program lipoprotein classification system for children and adolescents is recommended for use among 2- to 19-year-olds. This classification system does not take into account gender differences or the natural fluctuations in lipoprotein concentrations that occur with growth and maturation.

Methods and Results—Data from the National Health and Nutrition Examination Surveys were used to develop age- and gender-specific thresholds that can be used to denote abnormal levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Each curve was linked to the adult National Cholesterol Education Program Adult Treatment Panel III lipoprotein thresholds using LMS (Lambda-Mu-Sigma) growth curve regression methods. A series of growth curves and tables are presented that can be used to diagnose high-risk lipoprotein levels in the clinical and research settings. For example, in 1-year increments for males starting at age 12 and extending to age 19 years, the high-risk thresholds for total cholesterol were 6.03, 5.83, 5.70, 5.70, 5.77, 5.88, 6.02, and 6.16 mmol/L. The corresponding high-risk threshold for adults (≥ 20 years) is 6.22 mmol/L.

Conclusions—The present study is the first attempt at developing age- and gender-specific lipoprotein threshold concentrations for adolescents. This new classification system should provide a more accurate diagnosis of high-risk lipoprotein levels and associated cardiovascular risks in adolescents. (*Circulation*. 2006;114:1056-1062.)

Key Words: cholesterol ■ hypercholesterolemia ■ lipoproteins ■ adolescent

Although typically an adult disease, the progression of cardiovascular disease (CVD) begins in early childhood via the development of atherosclerosis, with the rate of progression being proportionate to plasma lipoprotein concentrations.¹⁻³ Abnormal lipoprotein concentrations in childhood and adolescence track into adulthood, providing further evidence that it is important to identify youth at increased CVD risk.⁴⁻⁷

underlie the pediatric NCEP classification system. First, lipoprotein concentrations change considerably with normal growth and maturation and vary by gender,¹⁰⁻¹² which is not reflected by these cutpoints. Second, the 75th and 95th percentiles (25th and 5th for HDL-C) were chosen arbitrarily and have no clinical or health meaning (ie, why not use the 90th percentile instead of the 95th?). Third, the NCEP cutpoints are based on the population distribution of the late 1980s, and the distribution of these lipoproteins, particularly TGs, has changed over time.^{13,14}

Given the concerns with the current pediatric NCEP classification system, the present study developed new age- and gender-specific lipoprotein cutpoints for adolescents 12 to 20 years of age. These cutpoints are linked to the adult health-based thresholds for abnormal lipoproteins (Table 2) and thus are indirectly linked to health risk.

Methods

Datasets

The newly developed age- and gender-specific lipoprotein cutpoints were based on lipoprotein measurements taken as part of the National Health and Nutrition Examination Surveys (NHANES) conducted between 1988 and 2002. NHANES are a series of nationally representative cross-sectional surveys. Each survey was

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The National Cholesterol Education Program (NCEP) has published cutpoints that can be used to identify youth with abnormal total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels, as shown in Table 1.⁸ The cutpoints for borderline-abnormal and abnormal lipoprotein concentrations are represented by the 75th and 95th percentiles (25th and 5th for HDL-C) of the population distribution and apply to all youth 2 to 19 years of age. Research indicates that these percentiles have a limited ability to predict the youth who, when adults, will have high-risk lipoprotein levels, as defined by the NCEP.⁹ Several other concerns

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TABLE 1. Classification of TC, LDL-C, HDL-C, and TG Concentrations in Children and Adolescents 2 to 19 Years of Age

	Normal	Borderline High	High
TC, mmol/L	<4.40	4.40–5.15	≥5.18
LDL-C, mmol/L	<2.85	2.85–3.34	≥3.37
HDL-C, mmol/L	>1.66	1.55–0.91 (Borderline-low)	≥0.91 (Low)
TG, mmol/L			
2–9 y	<0.85	0.85–1.12	≥1.13
10–19 y	<1.02	1.02–1.46	≥1.47

conducted with a stratified multistage probability design in which individuals 2 months of age or older were sampled in all 50 US states. The surveys used in the present study were collected in 1988 to 1994 (NHANES III), 1999 to 2000 (NHANES 1999–2000), and 2001 to 2002 (NHANES 2001–2002). Detailed descriptions of the plan and operations of each survey are found elsewhere.¹⁵ Data from the 3 surveys were combined to maximize the sample in the present study. NHANES III, NHANES 1999–2000, and NHANES 2001–2002 have undergone institutional review board approval by the National Center for Health Statistics and include written informed consent from all participants and their parents/guardian if they were under the age of majority. Secondary analysis of the NHANES dataset was approved by the Queen’s University Research Ethics Board.

Study Population

The NHANES surveys included a home interview and a standardized clinical examination performed in a mobile examination center. The analysis of the combined datasets was limited to adolescents aged 12 to 20 years who completed both the home interview and the mobile examination center examination and who had measurements of fasting (≥6 hours as per NHANES protocol) blood lipoproteins. Participants younger than 12 years of age were not requested to fast before blood sampling and therefore were not included in the

TABLE 2. NCEP ATP III Classification of TC, LDL-C, HDL-C, and TG for Adults Aged 20 Years and Older

Variable	Range
TC, mmol/L	
Desirable	<5.18
Borderline high	5.18–6.19
High	≥6.22
LDL-C, mmol/L	
Desirable	<2.59
Near or above desirable	2.59–3.34
Borderline high	3.37–4.12
High	4.14–4.90
Very high	≥4.92
HDL-C, mmol/L	
Low	<1.036
High	≥1.55
TG, mmol/L	
Normal	<1.70
Borderline high	1.70–2.25
High	2.26–5.64
Very high	≥5.65

analysis. This resulted in 6067 participants from all 3 surveys (2921 males and 3146 females).

Lipoprotein Measurements

Blood samples were collected during the mobile examination center examination according to standardized procedures. In each survey, lipoproteins were analyzed at the Johns Hopkins University Lipoprotein Analytical Laboratory. Details of the protocol are found in the NHANES laboratory procedures manuals.^{16–18} Briefly, lipoproteins were measured enzymatically in a series of coupled reactions in which cholesterol ester and triglyceride were hydrolyzed to cholesterol and glycerol, respectively. LDL-C was estimated from TC, HDL-C, and TG with the Friedewald formula.¹⁹ TC and HDL-C were measured in every subject who participated in a mobile examination center examination; however, TG was only measured in a morning subsample of the study population, ie, those who were examined before noon. Therefore, LDL-C was estimated only for those in the morning subsample.

Development of the Adolescent Lipoprotein Classification System

Age- and gender-specific growth curves were developed for TC, LDL-C, HDL-C, and TG, the 4 lipoproteins used in clinical practice, by the LMS method.²⁰ The distribution of each lipoprotein is summarized by 3 age-specific curves known as Lambda (L), Mu (M), and Sigma (S). The L curve accounts for the skewness in the distribution of the data, whereas the M and S curves represent the median and coefficient of variance, respectively, at each age. The values of L, M, and S can be computed for a series of ages and are used to plot the growth curves. The points on each growth curve are defined by the following formula:

$$M(1+LSz^2)^{1/L},$$

where L, M, and S are the values of the respective curves at each age, and z is the z score that corresponds to the percentile of the curve. The underlying assumption of the LMS method is that after a suitable power transformation, the distribution of the data at each age is normal.

The first step in creating the lipoprotein growth curves was to define the z score at age 20.0 years for each of the NCEP (Adult Treatment Panel III [ATP III]) adult lipoprotein cutpoints, as shown in Table 2.²¹ The evidence- and health-based adult cutpoints reflect the findings of prospective cohort studies and clinical trials.²¹ The cutpoints represent the point at which CVD risk increases (ie, risk is moderately increased within the borderline-high range and substantially increased within the high range). The z scores at age 20 were calculated with the following formula²²:

$$\frac{\left(\frac{Y}{M}\right)^L - 1}{LS},$$

where Y is the adult lipoprotein cutpoint and L, M, and S are the values at age 20.0 years. For example, the adult cutpoint for borderline-high TG is 1.695 mmol/L, which corresponds to a z score of 1.23 and is equivalent to the 89th percentile for males at exactly 20.0 years of age. This age was used to create the percentile for each growth curve because it is the age at which the adult lipoprotein cutpoints are initiated. By defining the percentile at age 20.0 years, the adolescent cutpoints are directly linked to the adult cutpoints, which in turn are linked to CVD risk.

In the second step, the age-specific curves were created by regressing the percentiles at age 20.0 years backward through the distributional growth curve of the respective lipoproteins. Each point on the curve was calculated using the predefined z score and the age-specific values of L, M, and S as defined in the first equation. Therefore, each percentile curve defines a series of age-specific cutpoints throughout adolescence that correspond to the adult cutpoint. For example, the percentile curve for borderline-high TG

TABLE 3. Mean Concentrations of TC, LDL-C, HDL-C, and TG for Males and Females

	No. of Subjects	Mean±SD
TC, mmol/L		
Males	2835	4.19±0.82
Females	3044	4.32±0.85
LDL-C, mmol/L		
Males	1382	2.46±0.69
Females	1467	2.49±0.73
HDL-C, mmol/L		
Males	3044	1.25±0.30
Females	2833	1.35±0.31
TG, mmol/L		
Males	1920	1.02±0.74
Females	2089	0.99±0.57

passes exactly through the adult cutpoint of 150 mg/dL at 20.0 years of age.

Although these percentile curves were derived from cross-sectional data, we propose that they will be useful for tracking changes in an adolescent's risk over time and not just for assessing risk at a given time point. This approach assumes that an adolescent's lipoprotein percentile will remain relatively constant as he or she ages (unless a lifestyle change occurs or other treatment is given), a position that is supported by many⁴⁻⁷ but not all²³ longitudinal studies that have tracked lipoproteins.

The NHANES surveys used a weighted sampling design, and the data were analyzed accordingly. Participants examined in the morning subsample were assigned a different weighting; thus, LDL-C and

TG had different weightings than did TC and HDL-C. The NHANES datasets were managed in SAS version 8.02 (SAS Institute, Cary, NC), and the percentile curves were developed with LMS Pro software, version 1.16 (Institute of Child Health, London, United Kingdom).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Table 3 lists the mean TC, LDL-C, HDL-C, and TG concentrations for both genders and the number of subjects that was used for each of the analyses. The growth curves corresponding to the increased risk values for TC, LDL-C, HDL-C, and TG are illustrated in Figures 1 and 2 for males and females, respectively (see online-only Data Supplement for Figures with data in milligrams per deciliter). As an alternative to the growth curves, Tables 4 and 5 list the age-specific cutpoints (in 1-year increments) that denote abnormal lipoprotein concentrations (see online Data Supplement for Tables with data in milligrams per deciliter). Each cutpoint reflects the midpoint of a given year (ie, the cutpoint for age 12 represents 12.5 years) and can be applied to all individuals within the 1-year age range (ie, 12.0 to 12.9 years). Furthermore, in the Data Supplement, the age- and gender-specific L, M, and S values are presented for each lipoprotein. These values can be used to calculate the z score for an individual based on his or her lipoprotein value.

The male (Figure 1A) and female (Figure 2A) growth curves for borderline-high and high TC concentrations fol-

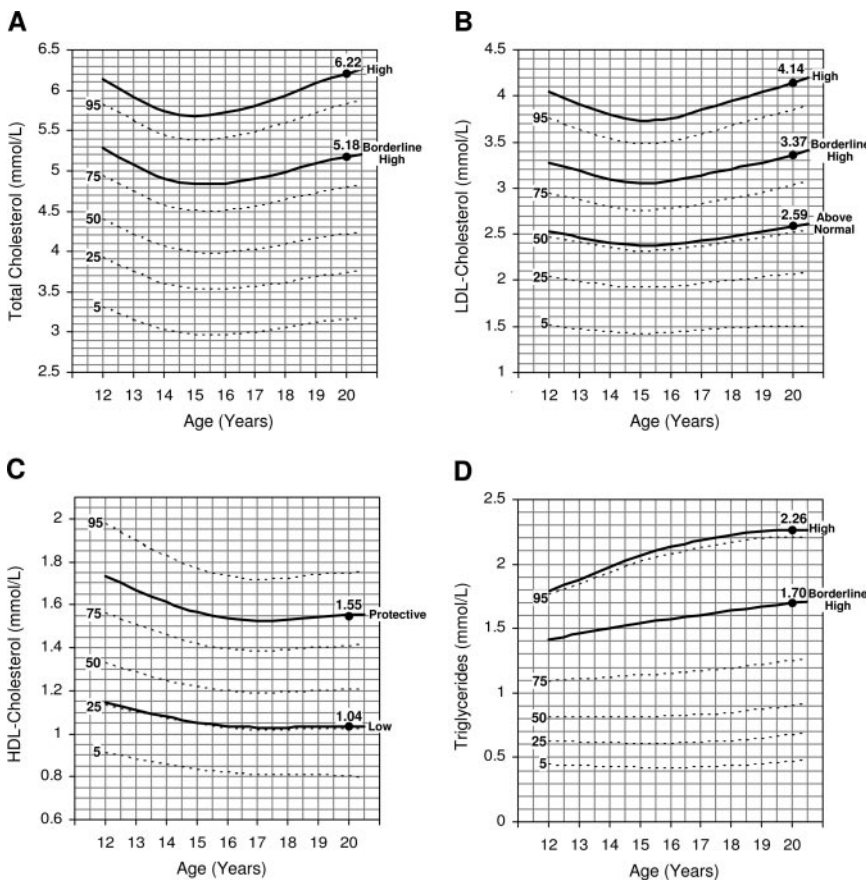


Figure 1. Age-specific cutpoints for (A) TC, (B) LDL-C, (C) HDL-C, and (D) TG for males 12 to 20 years of age. The curves corresponding to increased-risk values pass through the respective adult NCEP cutpoints at 20 years of age and are shown as solid lines. The other curves (dashed lines) represent the 5th, 25th, 50th, 75th, and 95th percentiles. To convert TC, LDL-C, and HDL-C in millimoles per liter to milligrams per deciliter, multiply by a factor of 38.67. To convert TG in millimoles per liter to milligrams per deciliter, multiply by a factor of 88.5. Figures in milligrams per deciliter units are shown in the online Data Supplement.

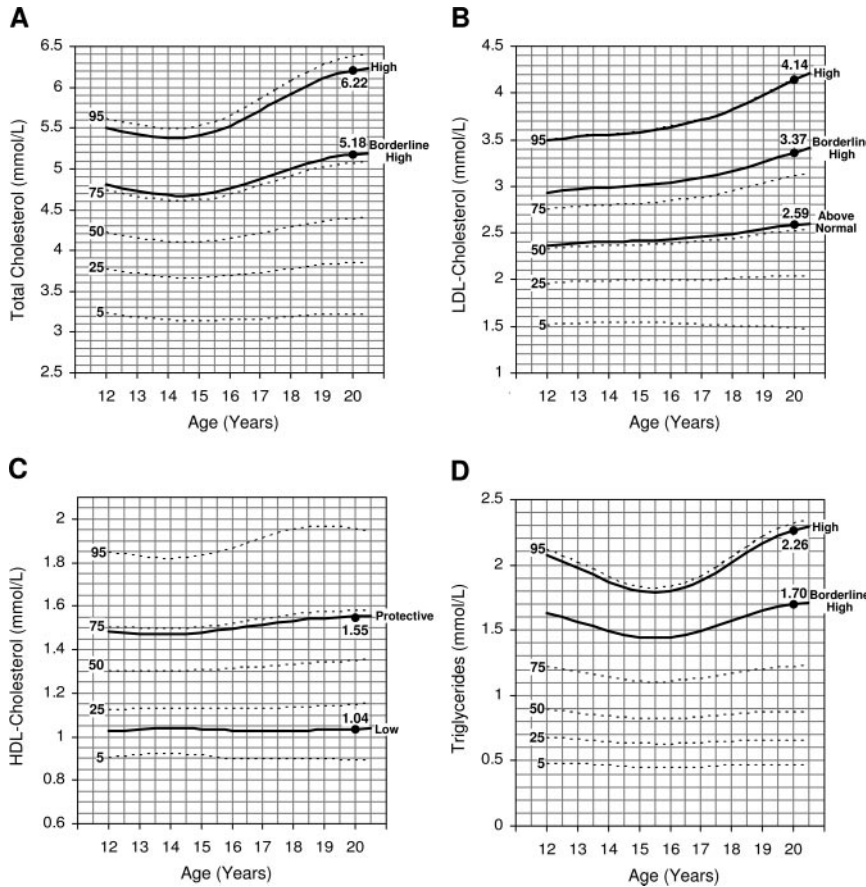


Figure 2. Age-specific cutpoints for (A) TC, (B) LDL-C, (C) HDL-C, and (D) TG for females 12 to 20 years of age. The curves corresponding to increased-risk values pass through the respective adult NCEP cutpoints at 20 years of age and are shown as solid lines. The other curves (dashed lines) represent the 5th, 25th, 50th, 75th, and 95th percentiles. To convert TC, LDL-C, and HDL-C in millimoles per liter to milligrams per deciliter, multiply by a factor of 38.67. To convert TG in millimoles per liter to milligrams per deciliter, multiply by a factor of 88.5. Figures in milligrams per deciliter units are shown in the online Data Supplement.

lowed a similar trajectory: TC concentrations declined during early adolescence and rose thereafter, approaching adult concentrations. Each curve was linked to the corresponding adult cutpoint such that the borderline-high-risk curve passes through 5.18 mmol/L and the high-risk curve passes through 6.22 mmol/L at 20.0 years of age. The borderline-high and high TC curves represent the 86th and 97th percentiles for males and the 78th and 94th percentiles for females, respectively.

Figures 1B and 2B represent the growth curves for near-borderline-high, borderline-high, and high LDL-C concentrations. Although the male and female LDL-C curves passed through the same adult cutpoints at 20.0 years of age, they did not follow similar trajectories. The male LDL-C risk curves decreased during early adolescence before increasing at ≈15.5 years of age, whereas those for females steadily increased from 12.0 to 20.0 years of age. The near-borderline-high, borderline-high, and high LDL-C growth curves repre-

TABLE 4. Age-Specific Lipoprotein Cutpoints (in Millimoles per Liter)* and Corresponding Percentiles for Males

Age, y†	TC			LDL-C		HDL-C		TG	
	Borderline-High (86th Percentile)	High (97th Percentile)	Above Normal (54th Percentile)	Borderline-High (86th Percentile)	High (98th Percentile)	Low (26th Percentile)	Protective (13th Percentile)	Borderline-High (89th Percentile)	High (95th Percentile)
12	5.18	6.03	2.50	3.24	3.98	1.13	1.70	1.44	1.84
13	4.99	5.83	2.44	3.15	3.86	1.10	1.64	1.48	1.93
14	4.86	5.70	2.39	3.08	3.76	1.07	1.59	1.52	2.02
15	4.84	5.70	2.38	3.06	3.74	1.04	1.55	1.56	2.10
16	4.88	5.77	2.41	3.11	3.81	1.03	1.53	1.59	2.16
17	4.95	5.88	2.46	3.18	3.91	1.03	1.53	1.62	2.20
18	5.05	6.02	2.51	3.25	4.00	1.03	1.54	1.65	2.24
19	5.14	6.16	2.56	3.32	4.09	1.04	1.55	1.68	2.26
20.0	5.18	6.22	2.59	3.37	4.14	1.04	1.55	1.70	2.26

*To convert TC, LDL-C, and HDL-C in millimoles per liter to milligrams per deciliter, multiply by a factor of 38.67. To convert TG in millimoles per liter to milligrams per deciliter, multiply by a factor of 88.5.

†Lipoprotein cutpoint concentrations represent the midpoint of a 1-year increment (ie, the values for age 12 years represent the values at 12.5 years) and can be used for individuals within the 1-year age range (ie, 12.0–12.9 years).

TABLE 5. Age-Specific Cutpoints (in Millimoles per Liter)* and Corresponding Percentiles for Females

Age, yr†	TC		LDL-C			HDL-C		TG	
	Borderline-High (78th Percentile)	High (94th Percentile)	Above Normal (53rd Percentile)	Borderline-High (83rd Percentile)	High (95th Percentile)	Low (26th Percentile)	Protective (13th Percentile)	Borderline-High (89th Percentile)	High (95th Percentile)
12	4.77	5.47	2.38	2.96	3.52	1.03	1.48	1.60	2.03
13	4.71	5.41	2.41	2.98	3.55	1.04	1.47	1.53	1.93
14	4.68	5.38	2.41	3.00	3.57	1.04	1.48	1.47	1.82
15	4.72	5.46	2.43	3.03	3.61	1.03	1.49	1.44	1.79
16	4.82	5.62	2.45	3.07	3.68	1.03	1.51	1.46	1.83
17	4.94	5.82	2.47	3.13	3.77	1.03	1.53	1.53	1.94
18	5.07	6.03	2.52	3.22	3.90	1.03	1.54	1.61	2.09
19	5.16	6.17	2.57	3.32	4.06	1.03	1.55	1.68	2.22
20.0	5.18	6.22	2.59	3.37	4.14	1.04	1.55	1.70	2.26

*To convert TC, LDL-C, and HDL-C in in millimoles per liter to milligrams per deciliter, multiply by a factor of 38.67. To convert TG in in millimoles per liter to milligrams per deciliter, multiply by a factor of 88.5.

†Lipoprotein cutpoint concentrations represent the midpoint of a 1-year increment (ie, the values for age 12 years represent the values at 12.5 years) and can be used for individuals within the 1-year age range (ie, 12.0–12.9 years).

sent the 54th, 86th, and 98th percentiles for males and the 53rd, 83rd, and 98th percentiles for females, respectively.

The growth curves for low and protective HDL-C concentrations are shown in Figures 1C and 2C for males and females, respectively. The low HDL-C curve for males declined slightly until 16 years of age, after which it did not change through young adulthood. On the other hand, the female curve for low HDL-C did not change with age during adolescence. The low and protective HDL-C growth curves were represented by the 26th and 87th percentiles in males and the 27th and 73rd percentiles in females, respectively.

The male (Figure 1D) and female (Figure 2D) growth curves for borderline-high and high TG did not follow similar trajectories: Whereas the male curves increased with age in a linear manner, the female curves declined during early adolescence before increasing to approach adult concentrations. The borderline-high and high TG curves represent the 88th and 95th percentiles for males and the 89th and 95th percentiles for females, respectively.

Discussion

The present study developed age- and gender-specific thresholds for high-risk TC, LDL-C, HDL-C, and TG concentrations for 12- to 19-year-olds. Most pediatricians will be familiar with the growth curve approach for identifying high-risk values, as illustrated in Figures 1 and 2, because this approach is similar to what is currently used to monitor height, weight, and body mass index growth patterns in children and adolescents.²⁴ Tables 4 and 5 present gender- and age-specific thresholds that can be used as an alternative to the growth curve approach.

In most clinical settings, not every adolescent is screened for high-risk lipoprotein values. The NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents recommends that selective screening take place among youth at high risk of dyslipidemia and CVD in adulthood⁸; that is, adolescents are screened on the basis of the presence of parental dyslipidemia or family history of premature CVD (any parent or grandparent diagnosed with CVD before the

age of 55 years).⁸ Initially, nonfasting TC should be measured. If nonfasting TC is within the borderline-high or high range, then a fasting lipoprotein analysis should be obtained.⁸ We recommend maintaining the current NCEP screening guidelines; however, we believe that the cutpoints developed in the present study will improve the identification of youth with high-risk values. Also, given the intrinsic variability of lipoprotein values, it is ideal to have multiple lipoprotein measurements over time to classify a patient into a risk category.^{8,21,23}

There are several benefits to the lipoprotein classification system developed in the present study compared with the NCEP system that is currently used for the pediatric population. First, the age- and gender-specific threshold values reflect the natural fluctuation in lipoprotein concentrations that occur with growth and maturation. Thus, adolescents should not be misdiagnosed simply because they are on a different part of the growth curve. Several hypotheses have been proposed to explain the changes in lipoprotein concentrations that occur during adolescence^{25–27}; more research, however, is warranted in this field.

A second advantage of the classification system developed in the present study is that the same proportion of at-risk adolescents will be identified at each age. For example, the borderline-high TC thresholds identify 14% of the male adolescent population irrespective of age. Conversely, using the existing NCEP classification system 50% of 10-year-olds compared with 25% of 13-year-olds would be diagnosed with borderline-high TC.¹⁰ Third, the new adolescent lipoprotein thresholds are linked to the adult NCEP ATP III values, which themselves are based on increased risk of CVD, as previously discussed in the Methods. This eliminates some of the arbitrariness inherent to the percentile approach used in the current NCEP guidelines for youth and should provide a more accurate assessment of CVD risk status among adolescents.

Several limitations of this study should be recognized. First, the development of the classification systems was limited to adolescents 12 to 20 years of age. Because

lipoprotein concentrations vary with age from birth through adulthood, lipoprotein cutpoints ideally would have been developed for all ages (2 to 20 years). However, to obtain accurate lipoprotein measurements, fasting blood samples must be collected. Requesting fasting blood samples from young children is rarely done in experimental settings and was not done in children under 12 years of age in the NHANES surveys.

Second, it is possible that race-specific lipoprotein thresholds would provide a more accurate assessment of risk status. Because the adult NCEP ATP III lipoprotein thresholds are not race specific, and because we wanted to link the adolescent cutpoints to those of the ATP III, we did not develop race-specific growth curves and thresholds. Another limitation to consider in the present study is that it would have been ideal to directly link the new adolescent lipoprotein thresholds to CVD risk. However, because CVD is a chronic disease of late onset, it is very difficult to establish a direct link between adolescent lipoprotein concentrations and CVD outcomes without having an exceptionally long follow-up period.

Lastly, the NHANES surveys are cross-sectional in design. A key assumption, therefore, is that the lipoprotein percentiles for an individual are maintained as he/she ages. Although it is well known that lipoprotein concentrations track well from adolescence into adulthood,⁵⁻⁷ the new lipoprotein classification systems need to be validated with longitudinal studies to establish whether they provide a more sensitive and specific assessment of CVD risk than the current NCEP adolescent guidelines.

The present study presents the first attempt to create age- and gender-specific lipoprotein thresholds for adolescents. It is only intuitive that lipoprotein risk curves be developed, given that pediatricians have used height, weight, body mass index, and blood pressure growth curves for years.^{24,28,29} We have developed 2 alternatives for clinical use, growth curves and tables, both of which are convenient and user friendly. We encourage clinicians and researchers to adopt this new classification system because it should provide a more accurate diagnosis of adolescents with high-risk lipoprotein values and associated cardiovascular health risks.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Atherosclerosis begins at a young age, and the rate of progression is related to plasma lipoprotein concentrations. Lipoprotein concentrations tend to persist from youth into adulthood, providing further evidence that it is imperative to identify and manage high-risk lipoprotein concentrations at an early age. The current pediatric National Cholesterol Education Program (NCEP) classification system recommends that the same thresholds be used to denote high-risk lipoprotein concentrations for all youth 2 to 19 years of age. Thus, the NCEP guidelines do not recognize that lipoprotein concentrations fluctuate naturally with growth and maturation. The purpose of this study was to develop age-specific lipoprotein classification systems for adolescents. The adolescent thresholds were anchored to the adult NCEP thresholds using growth curve modeling and were developed with nationally representative datasets. These adolescent lipoprotein classification systems are presented in a series of growth curves and tables that are practical for both clinical and research settings. It is hoped that the classification systems developed in the present study will better identify adolescents with high-risk lipoprotein concentrations; validation studies are needed, however.