Cholesterol Curves to Identify Population Norms by Age and Sex in Healthy Weight Children

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Abstract

Objective—Develop clinically applicable charts of lipid values illustrating fluctuations throughout childhood and by sex among healthy weight children.

Methods—The National Health and Nutrition Examination Survey (1999–2008) was used to estimate total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides by age and sex in healthy weight children age 3 to 17 years. Using LMS procedures, the authors created smoothed curves demonstrating population-based 50th percentile for age and the 75th and 95th percentiles.

Results—The curves were based on 7681 children meeting inclusion criteria. Total cholesterol, HDL, and LDL demonstrated peaks at approximately 8 to 12 years for boys. Similar peaks were evident for girls at slightly younger ages, approximately 7 to 11 years. Triglycerides showed peaks for girls, but values were similar across ages for boys.

Conclusions—The use of fixed lipid value cutoffs in established guidelines regardless of age or sex likely mislabels many children as abnormal. The authors' charts may allow for a more nuanced interpretation based on population norms.

Keywords

lipids; cholesterol; obesity; screening; preventive care

Introduction

Serum lipid values vary by age through childhood and are also affected by sex, race, and other factors.[1–4] Recently, Cook et al[1] published population-based lipid distributions with curves throughout childhood, which reinforced that there are variations in lipid values, particularly around ages 8 to 14. By tracking serum cholesterol values through childhood and graphing them, the charts clearly demonstrate that a static cutoff of normal and abnormal, as currently recommended,[2] is inappropriate based on the dynamic physiology of children at different ages. Currently, the American Academy of Pediatrics recommends screening for lipid abnormalities in all overweight children from after age 2 years to no later than 10 years of age and that those with abnormal values should be treated for hypercholesterolemia, initially with lifestyle changes, followed by statin treatment for those over age 8, should lifestyle changes fail.[2] These current definitions of normal are based on

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single cutoff values for children, regardless of age and gender. Thus, the use of sex-stratified "cholesterol curves" based on a population of healthy weight children and adolescents could enhance the interpretation of isolated total cholesterol (TC) or subcomponent values and help guide clinical decision-making.

Unfortunately, because of the known relationship between excess weight and hyperlipidemia, curves that include the full population of children including the obese, as previous reports have,[1,5] cannot necessarily be inferred as healthy standards or "normal" and therefore have limited applicability to clinical decision making. Since obesity is known to affect lipid values and obesity rates have increased over the years, population-based cholesterol curves may be inappropriately increased relative to what "normal" or "healthy" TC levels should be through the physiologic changes of childhood. Because of this and the fact that screening usually depends on comparison to a healthy population, curves that demonstrate lipid values in a healthy population could provide useful clinical information to aid in interpretation of cholesterol screening results. Therefore, we sought to develop clinically relevant lipid distribution charts by including only healthy weight children and excluding those with lipid values potentially indicative of familial hypercholesterolemia, which could provide a better understanding of healthy children's distributions of lipid values.

Methods

This study is based on the repeated cross sections of the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2008. NHANES is a stratified, multistage probability sample of the civilian, non-institutionalized population of the United States. It includes computer-based interviews, an in-home questionnaire on a variety of demographic and health topics, an examination including a thorough physical exam with measured heights and weights, and laboratory measures.[6]

Fasting

Previous work, including work using a population identical to ours, demonstrates very minimal differences in lipid values in children based on fasting time.[7] Adequate sample size is critical to the creation of population distribution curves, and limiting only fasting values left far too few children for reliable estimates, particularly for low-density lipoprotein (LDL) and triglycerides among young children. Therefore, we chose to include all children, regardless of fasting status, in our analyses. Examinations of curves limited to children who had fasted for at least 8 hours showed few differences in the patterns across age, but with greater instability in the estimates.

Sample

We included children ages 3 to 17 years, who had at least 1 of the 4 common lipid measurements available (TC, high-density lipoprotein [HDL], LDL, or triglycerides). We used height and weight as measured during the examination component to calculate body mass index (BMI) and determine percentile, using SAS code developed for that purpose.[8] Using standard definitions, we included only children who were of healthy weight (BMI 5th to 85th percentile for age and sex). We excluded children with very high values that could indicate familial hyperlipidemia (10 with cholesterol greater than 300 mg/dL, 4 with LDL greater than 200 mg/dL, and 3 with triglycerides greater than 350 mg/dL).

Laboratory Methods

Equipment for lipid analyses varied through the years. In 1999–2004, a Roche Hitachi 704 Analyzer was used, and a Roche Hitachi 717 was used in 2005. A Roche Hitachi 912 was

used in 2006, and a Roche Modular P in 2007–2008. No adjustments were needed for the changes in equipment.[9,10]

TC was measured enzymatically in serum or plasma for all years of data collection. HDL cholesterol in 1999–2002 was measured using a heparin-manganese precipitation, or direct measurement for children ages 3 to 5, because of small sample volumes. Beginning in 2003, all samples were tested using a direct immunoassay. Although changes in HDL values across time indicate possible laboratory method differences, our focus on age-based differences averaged over the period did not necessitate further adjustments. Triglycerides were measured enzymatically in serum for all years. LDL was calculated from total cholesterol, HDL, and triglycerides as follows: [LDL-cholesterol] = [total cholesterol] − [HDL-cholesterol] − [triglycerides/5].

Statistical Methods

We used Cole's LMS procedures to create population-based curves of lipid values throughout childhood,[11,12] which is similar but not identical to those used to create the CDC growth charts.[13] Although sample sizes of 100 at each age point have been recommended for growth curves, smaller sample sizes can be sufficient.[14] See Table 1 for the sample sizes at each age for each of the lipid measures. Sample sizes are small, particular among 3- to 5-year-old children. This suggests that some caution should be used when interpreting data at these young ages; however, we present data for all age groups. The exception is that we exclude 3-year-old children from our triglyceride analyses because of extreme standard errors in the values at this age.

As opposed to a prepackaged program, we used Stata 11.0 (College Station, TX) to calculate the L, M, and S parameters as described by Cole.[11,12] All analyses were adjusted for the complex survey design of NHANES and were performed using the survey estimation routines in Stata. This study was deemed exempt from institutional review board review under federal regulation 45 CFR §46.101(b) because it used only de-identified secondary data.

Results

The curves (see Figures 1–4) were based on 7681 children who met inclusion criteria. TC, HDL, and LDL demonstrated peaks at ~8 to 12 years for boys. Similar peaks were evident for girls, though at slightly younger ages, ~7 to 11 years. Triglycerides showed peaks for girls, but values were similar across ages for boys.

The curves demonstrate important differences from currently recommended cutoff values. Children around age 9 to 10 at the 95th percentile have total cholesterol values ~15 mg/dL higher than younger children or adolescents. Although the 95th percentile is similar to or lower than the static cutoff of 200 mg/dL for younger children and adolescents, it is clearly higher for children in middle childhood.

Discussion

Our findings confirm previous findings of differences in lipids throughout childhood.[1,4] We extend these findings by using a nationally representative sample of healthy weight children and excluding those with extremely elevated lipid values suggesting familial hyperlipidemia syndromes, to create curves that will help clinicians interpret lipid screening results.

Current established guidelines for lipid screening and treatment use fixed lipid value cutoffs regardless of age or sex and are based on population norms that include children who are

obese and may have familial hyperlipidemia. This likely mislabels many children as "abnormal" and leads to overtreatment of some children with lipid lowering medications as there are clear lipid variations based on age and sex.

The preadolescent peaks in HDL and LDL values for both girls and boys and for triglyceride values for girls could represent physiologic changes that cause lipid variations, and thus examining a patient's lipid values against these curves could be helpful in guiding lipid management. The differences in appearances between the boys' and girls' percentile values are a good reminder of sex-based differences. While there has been some adult literature examining cholesterol differences by sex[15] as well as variation during the menstrual cycle for women,[16] the pediatric differences may be even more stark.

There are several important limitations of this study. First, we use only cross-sectional data, so we are unable to demonstrate if individual children follow the patterns we show. However, we use a method comparable to those used to create the clinical growth charts, which also rely on cross-sectional data. Second, we were unable to look at variations by race/ethnicity. Sample size limited our ability to examine additional subpopulations in addition to sex. Although race is related to lipid values, patterns of lipid values may be similar throughout childhood.

Future research is needed to examine whether individual children follow these cholesterol curves over time and to determine appropriate abnormal cut-points for lipid values based on age, sex, and race/ethnicity. Additionally, there is a need to have increased sample size in very young children so we can obtain a better understanding about the distribution of lipid values in this group. Some previous studies have demonstrated that children with abnormal values in childhood often have normal values in adulthood[17] or even just 3 years later.[18] One possible explanation for this is the natural variations seen in the population norms we present in this study. It is not known whether these natural variations are detrimental to cardiovascular health, and future studies are needed to elucidate this relationship as well.

Conclusions

Although we do not delineate for a particular percentile to be defined as abnormal in this study, the ability for providers to clearly see how a child's lipid values compare to other children without known risk factors provides useful additional clinical information that can assist in the care of children after lipid screening. Thus, these charts may allow for a more nuanced interpretation based on population norms for healthy weight children.

Acknowledgments

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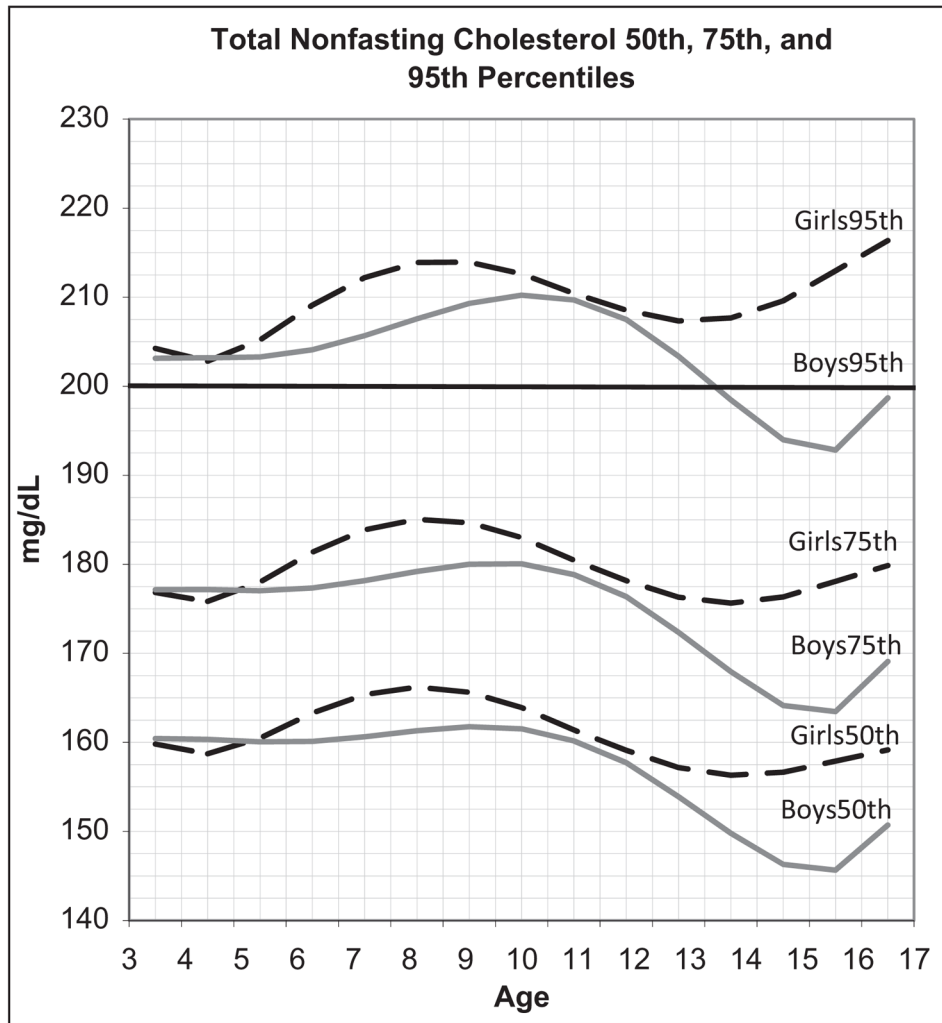
Figure 1.
Distribution of total cholesterol by age
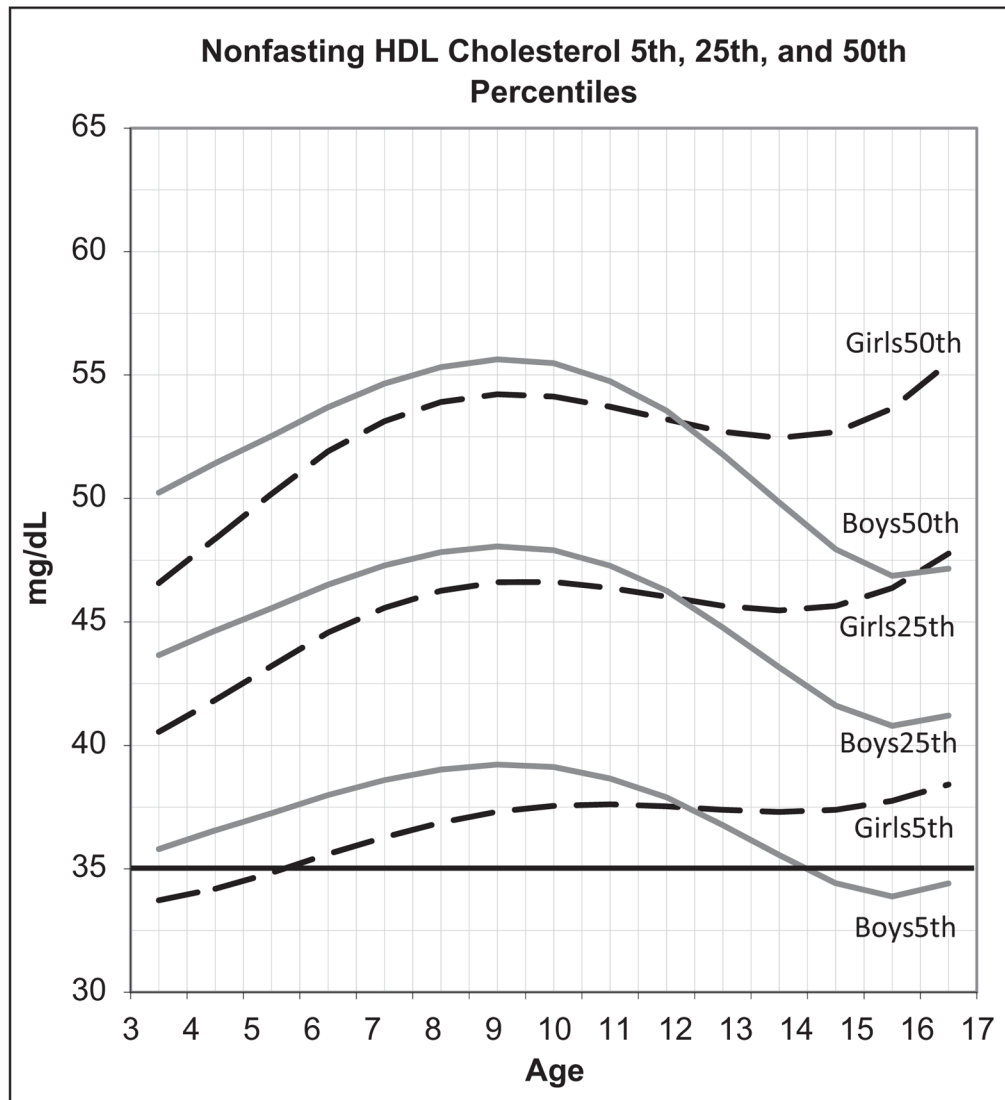Solid line indicates recommended static cutoff value.

Figure 2.
Distribution of HDL cholesterol by age
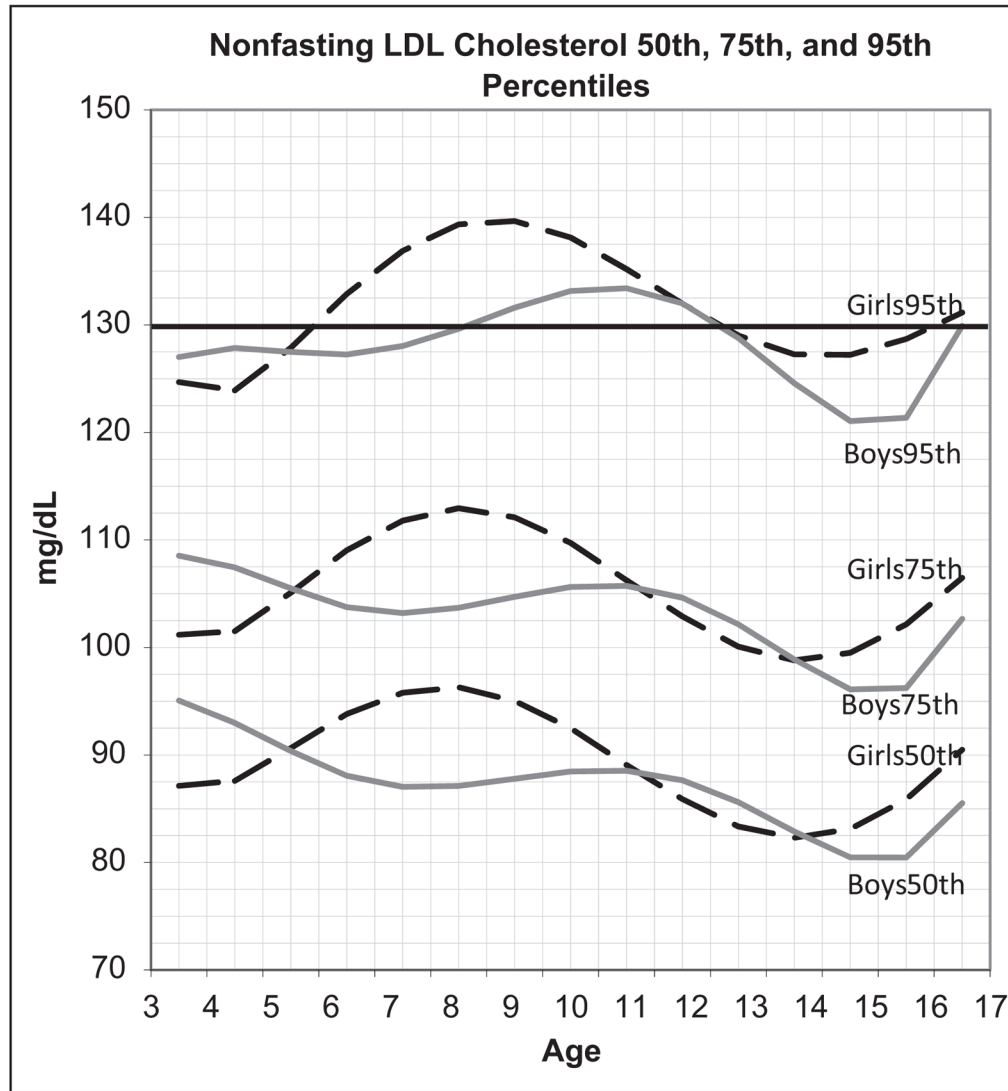Solid line indicates recommended static cutoff value.

Figure 3.
Distribution of LDL cholesterol by age
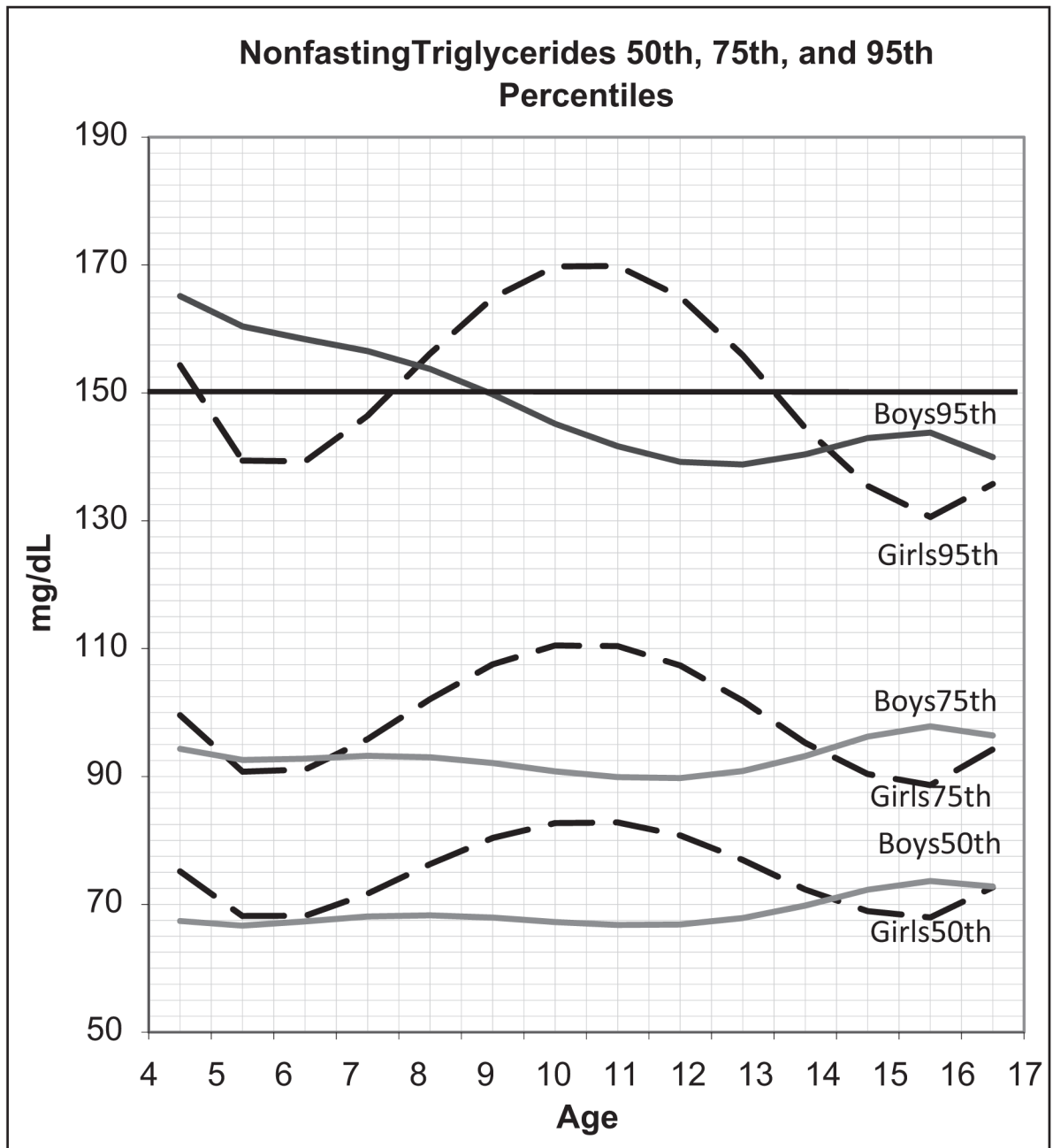Solid line indicates recommended static cutoff value.

Figure 4.
Distribution of triglycerides by age
Static cut off value is 150 mg/dL.

Table 1

Sample Size Distribution for Lipid Values at Each Age

Age	Cholesterol		HDL		LDL		Triglycerides	
	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys
3	94	131	94	132	39	48	39	48
4	144	144	145	144	55	57	55	57
5	136	120	136	120	44	52	44	53
6	226	205	226	205	71	55	71	55
7	244	246	246	246	67	69	69	69
8	238	235	238	235	55	60	55	60
9	227	232	228	232	53	55	53	55
10	205	222	205	222	51	53	51	53
11	226	224	227	225	53	50	54	51
12	326	320	326	320	153	160	158	163
13	354	340	354	340	150	163	157	166
14	371	343	371	343	162	161	167	164
15	316	342	316	343	133	159	141	167
16	367	375	368	374	163	174	170	182
17	349	370	349	371	164	175	171	183
Total	3823	3849	3829	3852	1413	1491	1455	1526

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.