Poor Performance of Body Mass Index as a Marker for Hypercholesterolemia in Children and Adolescents

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**Objective:** To evaluate the test performance of specific body mass index (BMI) percentile cutoffs for detecting children/adolescents with hypercholesterolemia.

**Design:** Cross-sectional analysis.

**Setting:** National Health and Nutrition Examination Survey 1999-2004.

**Participants:** Population-based sample of children (aged 3-18 years) with nonfasting total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol levels and adolescents (aged 12-18 years) with fasting low-density lipoprotein (LDL) cholesterol and triglyceride (TG) levels.

**Main Outcome Measures:** Individuals were classified as having hypercholesterolemia if they had a TC level greater than 200 mg/dL, HDL cholesterol level less than 35 mg/dL, LDL cholesterol level greater than 130 mg/dL, or TG level greater than 150 mg/dL, and sensitivity, specificity, and likelihood ratios were calculated for specific BMI percentiles. Receiver operating characteristic curves were constructed and area under the curve (AUC) was calculated.

**Results:** Receiver operating characteristic curves using BMI percentiles to predict abnormal levels of TC and LDL cholesterol had AUC values (0.60 for TC level and 0.63 for LDL cholesterol level) that were less than the threshold of acceptable discrimination (between 0.7-0.8). Body mass index percentiles provided better discrimination for detecting children with abnormal HDL cholesterol and TG levels, with AUC values approaching levels of acceptable discrimination (0.69 and 0.72, respectively), although there are no specific guidelines regarding management of children with these abnormalities.

**Conclusions:** According to the American Academy of Pediatrics guidelines, abnormal levels of LDL cholesterol are used to determine which children require nutritional and pharmacologic therapy. Because BMI percentiles did not adequately identify children and adolescents with abnormal TC and LDL cholesterol levels, the new recommendations for targeted screening of obese children and adolescents may require further consideration.

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In July 2008, the American Academy of Pediatrics (AAP) revised its cholesterol screening guidelines¹ to advocate that pediatric providers perform a fasting lipid profile in all children with cardiovascular risk factors. This group includes children with a family history of hypercholesterolemia or early cardiovascular disease (≥55 years for men and ≤65 years for women); children with hypertension, diabetes mellitus, or a smoking history; and children who are overweight (body mass index [BMI] [calculated as weight in kilograms divided by height in meters squared] ≥85th percentile and <95th percentile for age and sex) or obese (BMI ≥95th percentile for age and sex). Screening should ideally occur starting at 2 years of age and no later than 10 years of age, and if total cholesterol (TC) level is greater than 200 mg/dL (to convert to millimoles per liter, multiply by 0.0259) or low-density lipoprotein (LDL) cholesterol level is greater than 130 mg/dL (to convert to millimoles per liter, multiply by 0.0259), either dietary intervention or pharmacologic management is warranted.

Revision of these guidelines was prompted in part by the current epidemic of obesity among US children. The Centers for Disease Control and Prevention (CDC) now estimates that 31.9% of US children are overweight or obese, and 16.3% are obese.² Up to 25% of overweight children have abnormal TC and LDL cholesterol levels,³ and overweight and obese children have a higher likelihood of having lipid abnormalities compared with healthy-weight children.⁴ Given that a variety of longitudinal studies have demonstrated that elevated cholesterol levels during childhood often persist into...
adulthood, and are associated with an increased risk of atherosclerosis, there is an increasing focus on cholesterol screening and intervention.

Although the AAP designated a screening threshold of a BMI greater than or equal to the 85th percentile, it is unclear whether this represents an optimal threshold for case detection or test efficiency. Although 1 recent study examined the prevalence of cardiovascular risk factors at specific BMI percentiles based on data from the Bogalusa Heart Study, we are unaware of studies that have systematically assessed the trade-offs between sensitivity and specificity across a range of BMI percentile cutoffs for detecting children and adolescents with abnormal cholesterol levels. Therefore, the objective of our study was to evaluate test characteristics of BMI percentiles for detecting children with abnormalities of cholesterol levels, including TC, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, and triglycerides (TG) in a nationally representative, racially/ethnically diverse population-based sample of adolescents.

**DATA ANALYSIS**

Body mass index was adjusted for age and sex based on the 2000 CDC growth charts. Adolescents were classified as underweight if their BMI was less than the fifth percentile, normal weight if their BMI was between the fifth percentile or greater and less than the 85th percentile, overweight if their BMI was between the 85th percentile or greater and less than the 95th percentile, or obese if their BMI was in the 95th percentile or greater. Consistent with guidelines from the National Cholesterol Education Program, children were designated as having abnormal values if their levels were greater than 200 mg/dL for TC, less than 35 mg/dL (to convert to millimoles per liter, multiply by 0.0259) for HDL cholesterol, greater than 130 mg/dL for LDL cholesterol, or greater than 150 mg/dL for TG. Pearson correlation between TC and LDL cholesterol was calculated for adolescents aged 12 to 18 years.

For the overall population, we constructed receiver operating characteristic (ROC) curves to evaluate the performance of specific BMI percentile thresholds for predicting abnormal outcomes for each of the recommended screening measures. Receiver operating characteristic analysis is a formal technique for assessing the performance of various test cutoffs or thresholds. In an ROC curve, the “true-positive” rate (sensitivity) is plotted against the “false-positive” rate (1−specificity), which allows for consideration of the trade-offs between sensitivity and specificity at various test cutoffs or thresholds. The ROC curve also provides a measure of diagnostic accuracy, called the area under the curve (AUC). An ideal test with perfect discrimination would have an ROC curve close to the top left-hand corner of the graph and an AUC of 1.0, whereas a test with poor discrimination would have an ROC curve close to the diagonal line of no discrimination and an AUC of 0.5.

The ROC analyses were also performed separately for boys and girls and for specific age strata (3-11 years, 12-15 years, and 16-18 years for TC and HDL cholesterol levels and 12-15 years and 16-18 years for LDL cholesterol and TG levels). These age strata were selected so that age groups would be consistent across the fasting and nonfasting measures, with the 12 to 15 years age stratum representing the age at which most children are presumably experiencing puberty. We tested the equality of ROC areas for boys vs girls and the various age groups using Stata 9.0 (StataCorp, College Station, Texas). For the TC and HDL cholesterol outcome measures, we also compared ROC curves for those who were fasting vs those who were not fasting. Finally, for each of the specific BMI percentile thresholds, we also calculated positive predictive values (the proportion of true positives over the total number of positives) and negative predictive values (the proportion of true-negatives over the total number of negatives) and positive likelihood ratios (LRs), which are calculated by dividing sensitivity by 1−specificity.

All statistical analyses were performed using Stata 9.0, which applies appropriate sampling weights to adjust for the complex multicluster sample design. For description of the sample, χ² and t tests were performed (level of significance = .05), and laboratory sampling weights were used, which accounted for the additional sampling and nonresponse of the fasting subsample; hence, the laboratory subsample represents a nationally representative sample. Taylor series linearization was used for variance estimation.

**RESULTS**

Overall, there were 11,563 children aged 3 to 18 years in the NHANES survey. When we compared the 9338 children with BMI and TC measurements with those without available measurements, there were statistically significant differences by sex (girls, 49.4% vs 52.2%; P = .02), mean age (11.8 years vs 9.3 years; P < .01), and mean BMI (21.4 vs 19.5; P < .01). When we compared the 6317 chil-
Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>TC Level (n=9338)</th>
<th>HDL Cholesterol Level (n=6317)</th>
<th>LDL Cholesterol Level (n=2407)</th>
<th>TG Level (n=2416)</th>
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<tbody>
<tr>
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<tr>
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<td>11.1</td>
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<td>BMI, mean</td>
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<td>20.3</td>
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</tr>
<tr>
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<td>3186 (51.7)</td>
<td>1251 (51.1)</td>
<td>1257 (52.2)</td>
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<td>1159 (47.8)</td>
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<td>Normal, 5th percentile ≤ BMI &lt; 85th percentile</td>
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<td>1000 (14.9)</td>
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<td>Obese, BMI ≥ 95th percentile</td>
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<td>490 (10.2)</td>
<td>140 (5.4)</td>
<td>86 (7.0)</td>
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</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride.

The number of subjects is unweighted.

To our knowledge, this is the first study to systematically assess the test performance of specific BMI percentile thresholds for detecting abnormal cholesterol levels in a representative and diverse sample of US children. Generally, an AUC between 0.7 and 0.8 is considered accept-

comment

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able discrimination; our study found that AUC was less than this threshold for TC (0.60) and LDL cholesterol (0.63) levels, despite the fact that the AAP guidelines recommend dietary or pharmacologic intervention in children based solely on LDL cholesterol thresholds. For example, to detect abnormal TC or LDL cholesterol levels at the current recommended screening threshold of BMI in the 85th percentile or greater, sensitivity was 51% to 56% with a false-positive rate of 34%. Lowering the BMI threshold to the 75th percentile improved sensitivity (62%-66%) but resulted in even higher false-positive rates (46%). Likewise, increasing the BMI threshold to the 95th percentile improved the false-positive rate (18%-19%) but also led to substantive decreases in sensitivity (34%-35%). This pattern of findings was reflected in the low LRs, which were substantially lower than an LR greater than 10, the criterion used to determine that a test provides strong evidence for presence of disease.

Table 2. Test Characteristics of Specific BMI Percentile Thresholds for Predicting Abnormal TC, LDL and HDL Cholesterol, and TG Levels

<table>
<thead>
<tr>
<th>BMI Percentile Threshold</th>
<th>Sensitivity (True-Positive Rate)</th>
<th>Specificity (True-Negative Rate)</th>
<th>Positive Likelihood Ratio</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
<th>Sensitivity (True-Positive Rate)</th>
<th>Specificity (True-Negative Rate)</th>
<th>Positive Likelihood Ratio</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
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<td>TC Level, Ages 3-18 y</td>
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<td>LDL Cholesterol Level, Ages 12-18 y</td>
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<td>0-4</td>
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</table>

Abbreviations: See Table 1.

els of acceptable discrimination (0.69 and 0.72, respectively). However, the AAP guidelines do not make specific treatment recommendations for children with abnormal HDL cholesterol and TG levels and only recommend that overweight pediatric patients with abnormalities of HDL cholesterol and TG levels undergo weight management, such as lifestyle intervention. Because a child's overweight status would have prompted lifestyle management regardless of the HDL cholesterol and TG levels, this raises questions about the utility of abnormal HDL cholesterol and TG measurements in clinical practice.

In a recent population-based study from Canada, O'Loughlin et al evaluated the utility of screening in children and adolescents based on the AAP definition of a positive family history (positive history of premature cardiovascular disease) or a parent history of hypercholesterolemia (≥240 mg/dL). Consistent with the findings of other investigators, this study found that screening based on a positive family history was no better than a random screening strategy in the population, with a sen-
sensitivity of 40.7%, a false-positive rate of 24.9%, and an LR of 1.63. However, even after O’Loughlin et al included children with a BMI in the 85th percentile or greater to improve the test discrimination, there was minimal gain in the test performance characteristics, consistent with the findings of our study. The take-home message from all of these studies is that although children with elevated BMI are somewhat more likely to have abnormal TC and LDL cholesterol levels, this association may not be strong enough to make BMI a good discriminant for detecting which children have abnormal TC and LDL cholesterol values.

If neither BMI percentile nor a positive family history can accurately predict elevated cholesterol levels during childhood, this raises the question of how best to target individuals for cholesterol screening. It has been argued that cholesterol screening during childhood, whether targeted or universal, has little utility, based on the modest impact of a low-fat diet on LDL cholesterol levels (lowering of LDL cholesterol level by 3.23 mg/dL) among older children, and the lack of pharmacologic trials except among a high-risk subgroup of individuals with familial hypercholesterolemia. Furthermore, there are also concerns regarding the potential for “labeling” children with a disease for which there may not be adverse health consequences for decades and the potential difficulties that these children may face when applying for health insurance when they reach adulthood because of their “pre-existing” cholesterol condition.

On the other hand, studies have confirmed that elevated cholesterol levels during childhood are an impor-
tant risk factor for elevated cholesterol levels during adulthood, albeit with a modest sensitivity (about 43%-46%), and have demonstrated the presence of atherosclerotic lesions in young adulthood, suggesting that atherosclerosis is a process that begins in childhood. Further studies are certainly needed to link childhood hypercholesterolemia and its treatment to adult coronary heart disease outcomes.

Given the potential limitations of targeted cholesterol screening focused on “high-risk” groups, a general population-based preventive strategy may represent a useful alternative, with its focus on moving the entire population distribution to lower risk. With such a strategy, smaller changes in blood cholesterol level for the population at large could have a large public health impact. One recent randomized trial (Special Turku Coronary Risk Factor Intervention Project) demonstrated that low-saturated fat, low-cholesterol dietary counseling from infancy had beneficial effects on serum cholesterol values and endothelial function later in childhood without any negative consequences on growth or cognitive or pubertal development. The AAP could therefore consider general adoption of such an intervention for prevention of cardiovascular disease within the broader population, rather than a targeted cholesterol screening program focusing only on children with elevated BMI measures.

Given the current state of the evidence, it is not surprising that a variety of professional organizations differ with regard to their cholesterol screening recommendations. Although the American Heart Association also recommends lipid screening for children based on a positive family history and overweight status, similar to the AAP recommendations, the US Preventive Services Task Force, comprising primary care and prevention experts, recently concluded that there was insufficient evidence to recommend for or against screening in childhood, based on a systematic review of the evidence.

One critical issue that will need further assessment is the cost-effectiveness of screening and treatment of childhood hypercholesterolemia for primary prevention of coronary heart disease. Using the Coronary Heart Disease Policy Model, a validated simulation model of heart disease, Prosser et al estimated the cost-effectiveness of various cholesterol-lowering strategies (diet or statin) in adults aged 35 to 84 years, finding that for the youngest individuals aged 35 to 44 years without other cardiovascular risk factors, the ratios were well above the threshold that is deemed cost-effective ($50,000/QALY), ranging from $160,000/QALY to $1.4 million/QALY. Given that cost-effectiveness ratios of hypercholesterolemia treatment are likely to be even less favorable in the younger pediatric population, it is unlikely that even a targeted screening strategy among children would be judged acceptably cost-effective. Future studies are needed to assess the cost-effectiveness of cholesterol-lowering strategies among children.

Because of our large sample size, we were able to evaluate for age and sex differences. Our finding that AUC values for TC and TG levels were significantly lower for girls compared with boys suggests that a greater number of girls with lipid abnormalities may be missed in clinical practice. In addition, AUC values for TC and HDL cholesterol levels were significantly lower for the younger vs the older age groups, which would suggest that cholesterol screening focused on older age groups may have greater utility compared with screening for all children.

There were limitations to our study. We did not have measures of small, dense LDL cholesterol, which has been associated with various types of coronary heart disease. Our analysis was based on cross-sectional data, and therefore, we were unable to identify whether tracking of individuals at specific BMI percentile cutoffs during childhood was associated with elevated cholesterol levels during adulthood. We did not look at differences by race, given the small number of children with hypercholesterolemia at each of the BMI percentile cutoffs. We were also unable to look at differences by pubertal stage, as this information was not available in the data set. Although there were slight differences in the sex, age, and BMI distribution for those in our sample compared with those not in the sample for some of the outcome measures, we do not feel that this affected our results, as we constructed sex-specific ROC curves confirming that BMI was a poor predictor of abnormal TC and LDL cholesterol levels for both boys and girls. Although children included in our samples were generally older, we were able to control for this by constructing ROC curves for specific age strata.

We acknowledge that, aside from overweight, there are a variety of other risk factors that qualify a child for targeted cholesterol screening; however, not all measures are available in NHANES. We felt that including these other factors would distract from the main purpose of our study, which was primarily to look at the relationship between BMI percentiles and abnormal cholesterol levels.

We recognize that BMI percentiles were more predictive of HDL cholesterol and hypertriglyceridemia; however, as previously mentioned, no alternative dietary or

### Table 3. Comparisons of AUC for Specific Age Strata

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Aged 3–11 y</th>
<th>Aged 12–15 y</th>
<th>Aged 16–18 y</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC level</td>
<td>0.56</td>
<td>0.60</td>
<td>0.65</td>
<td>.001</td>
</tr>
<tr>
<td>HDL cholesterol level</td>
<td>0.62</td>
<td>0.71</td>
<td>0.72</td>
<td>.03</td>
</tr>
<tr>
<td>LDL cholesterol level</td>
<td>0.64</td>
<td>0.63</td>
<td>0.63</td>
<td>.92</td>
</tr>
<tr>
<td>Fasting TG level</td>
<td>0.73</td>
<td>0.71</td>
<td>0.71</td>
<td>.63</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride.
pharmacologic management is addressed by the AAP guidelines for these abnormalities. Misclassification of cholesterol levels is possible, given that we only had 1 measurement per individual and studies have shown that there can be variability of cholesterol measurements across time.42–45 Finally, 1 recent study developed age- and sex-specific standards for cholesterol based on NHANES data, to adjust for changes in cholesterol concentrations that occur during growth and maturation.46 However, we elected to use the thresholds that were recommended by the AAP in its 2008 guidelines, particularly given that another recent study found that age- and sex-specific standards were less predictive of TC and LDL cholesterol levels in adulthood than the National Cholesterol Education Program/AAP guidelines.47

The nationally representative data we present in this study indicate that BMI percentiles do not provide effective discrimination for distinguishing children with abnormal TC and LDL cholesterol levels, despite the fact that LDL cholesterol levels are the criterion by which the AAP recommends nutritional and pharmacologic therapy. These findings suggest that the new AAP recommendations for targeted screening of obese children and adolescents for abnormal cholesterol levels may require further consideration.

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**Announcement**

Submissions. The Editors welcome contributions to Picture of the Month. Submissions should describe common problems presenting uncommonly, rather than
total zebras. Cases should be of interest to practicing pediatricians, highlighting problems that they are likely to at least occasionally encounter in the office or hospita-
tal setting. High-quality clinical images (in either 35-mm slide or electronic format) along with parent or patient
permission to use these images must accompany the sub-
mission. The entire discussion should comprise no more
than 750 words. Articles and photographs accepted for
publication will bear the contributor’s name. There is no
charge for reproduction and printing of color illustrations.
For details regarding electronic submission, please see: http://archpedi.ama-assn.org.