Will Obesity Increase the Proportion of Children and Adolescents Recommended for a Statin? 

Brian W. McCrindle, MD, MPH; Pascal N. Tyrrell, PhD; Rae-Ellen W. Kavey, MD, MPH

New Expert Panel Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents commissioned by the National Heart, Lung and Blood Institute (NHLBI) recommend universal lipid screening at 9 to 11 years of age and provide a comprehensive algorithm for evaluation and management of identified dyslipidemia.1 The universal screening can be performed with the child either nonfasting (measure total cholesterol and high-density lipoprotein cholesterol [HDL-C] levels, and calculate non-HDL cholesterol level) or fasting (full lipid profile with low-density lipoprotein cholesterol [LDL-C] and triglycerides). Targeted screening with a fasting lipid profile is recommended outside of universal screening for those children and adolescents with a positive family history of premature cardiovascular disease or events, or hyperlipidemia. Further evaluation and confirmation with fasting lipid profiles leads to initial management aimed at achieving optimal lifestyle behaviors, primarily a fat- and cholesterol-restricted diet. For those with persistent and significant lipid abnormalities, moderate- and high-level risk factors and risk conditions, including obesity, contribute to decision-making regarding initiation of lipid-lowering drug therapy at defined LDL-cholesterol cut points (Tables 1 and 2). Recent (2009–2010) National Health and Nutrition Examination Survey (NHANES) data indicate that 16.9% of American children ages 2 through 19 years are obese.2 Will the new guidelines result in an increased proportion of children and adolescents recommended for a statin, particularly among those who are obese?

Methods

We performed a cross sectional analysis of U.S. children ages 12 to 17 years who had fasting or nonfasting lipid measurement performed through NHANES data from 1999 to 2010.3 The results also provide information on blood pressure, smoking status, and body mass index (BMI). Calculation of the proportion of individuals who would be recommended for drug therapy based on the Expert Panel guidelines1 was performed, with the following modifications based on limitations of the NHANES data: (1) all categorizations regarding need for drug therapy were based on the available single fasting lipid profile measurement (the guideline algorithm is based on the average of 2 measurements); (2) the impact of lifestyle management was unknown (in the guideline recommendations, lipid therapy is only considered after a 6-month trial of lifestyle change); (3) data regarding family history of cardiovascular events/death and all risk conditions specified in guidelines were not available and, hence, not considered in assessment of the algorithm; and (4) current smoking as a risk factor was defined as a serum cotinine level ≥10 ng/mL.4 For comparison, we calculated the proportion recommended for drug therapy based on the previous guidelines from the National Cholesterol Education Program (NCEP) and the American Academy of Pediatrics (AAP).5,6 SAS version 9.3 (SAS Institute, Cary, NC) was used for all analyses using SAS Survey procedures to adjust for the complex sampling design of NHANES.

Results

Screening

The unweighted response rate for NHANES participation over the surveys included ranged from 76% to 80%. The total population sample for children ages 12 to 17 years was 8861 participants for the 1999 through 2010 surveys. Of these, 692 participants were excluded from analysis by NHANES (nonresponse, ineligible). The primary lipid measure was a nonfasting lipid assessment, with a representative subsample requested for fasting lipid assessment (n=3505). Lipid data or height and weight were not available for 513 participants for the nonfasting group, leaving 4151 participants for analysis of nonfasting lipid values. Based on the screening recommendations from the Expert Panel guidelines to calculate non-HDL-C from non-fasting total cholesterol and HDL-C, 24.6% (95% confidence interval, 22.5–26.8%) of these participants would have been identified as having possible dyslipidemia (non–HDL-C ≥145 mg/dL or HDL-C <40 mg/dL) and required further evaluation with a fasting lipid profile.

The Expert Panel guidelines also recommend that screening may be performed with a fasting lipid profile. This analysis used 3315 of the 3505 participants who had fasting lipid assessment, with 190 participants (6%) missing data in order of exclusion regarding height and weight (n=28), cotinine (n=48), blood pressure (n=80), or specific lipid variables (n=34). Based on screening with a fasting sample, 20.3% (95% confidence interval, 18.3–22.3%) of these participants met the non–HDL-C and HDL-C cut points defining dyslipidemia, and 6.5% (95% confidence interval, 5.4–7.6%) met the LDL-C cut point of ≥130 mg/dL, hence meeting criteria for further evaluation.

Management

The algorithm for lipid management from the Expert Panel guidelines begins when a child or adolescent has an average

From the Department of Pediatrics, University of Toronto, Labatt Family Heart Centre, The Hospital for Sick Children, Toronto, Ontario, Canada (B.W.M., P.N.T.); and the Department of Pediatrics, University of Rochester Medical Center, Rochester, NY (R.-E.W.K.).

Correspondence to Brian W. McCrindle, MD, MPH, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8. E-mail brian.mccrindle@sickkids.ca

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Table 1. Risk Factor Definitions for the Expert Panel Guidelines Dyslipidemia Algorithm

Positive family history of premature cardiovascular disease: myocardial infarction, angina, coronary artery bypass graft/stent/angioplasty, sudden cardiac death; before age 55 years in a parent, grandparent, aunt, or uncle; males aged <55 years, females aged <65 years

High-level risk factors:
- Hypertension requiring drug therapy (systolic or diastolic blood pressure ≥ 99th percentile (%ile) ± 5 mm Hg)
- Current cigarette smoker
- Body mass index ≥ 97th percentile
- Presence of high-risk conditions

(Diabetes mellitus is also a high-level risk factor, but it is classified here as a high-risk condition to correspond with Adult Treatment Panel III recommendations for adults that diabetes mellitus be considered a cardiovascular disease equivalent.)

Moderate-level risk factors:
- Hypertension not requiring drug therapy
- Body mass index ≥ 95th percentile, < 97th percentile
- High density lipoprotein cholesterol (HDL-C) < 40 milligrams per deciliter
- Presence of moderate-risk conditions

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Data that were not available as part of the NHANES data collection.

LDL-C on ≥2 fasting lipid profiles of ≥130 mg/dL (95th percentile from normative data). Using the NHANES fasting subsample to represent this result, the weighted proportion of participants with a single fasting LDL-C ≥130 but <160 mg/dL was 5.2% (95% confidence interval, 4.2–6.1%), ≥160 but <190 mg/dL for 1.0% (0.5–1.4%) and ≥190 mg/dL for 0.4% (0.0–0.8%). For these participants, assuming no changes in the lipid profile on repeat fasting assessment, the algorithm would recommend a 6-month trial of lifestyle therapy using evidence-based recommendation specific to the pattern of dyslipidemia.

If fasting LDL-C levels remain ≥130 mg/dL after the trial of lifestyle therapy, identified risk factors and risk conditions (Table 1) are combined with LDL-C results to determine additional therapeutic steps (Table 2). In the NHANES fasting subsample, the weighted proportion of participants with high-level cardiovascular risk factors included 0.2% (95% confidence interval, 0.0–0.3%) with blood pressure level at stage 2 hypertension cut points, 9.6% (8.1–11.2%) with cotinine evidence for current smoking, and 12.1% (10.4–13.9%) with a BMI ≥97th percentile. The proportion with moderate-level risk factors included 2.5% (95% confidence interval, 1.8–3.2%) with blood pressure level at stage 1 hypertension cut points, 13.4% (11.8–15.9%) with HDL-C <40 mg/dL, and 5.1% (4.0–6.1%) with BMI ≥95th but <97th percentile. Information on risk conditions is not available. Combining the LDL-C results with identified risk factors, and assuming that none of these participants with initial high LDL-C responded to lifestyle therapy, 0.85% (95% confidence interval, 0.4–1.3%) of children ages 12 to 17 years would meet criteria for initiation of a hydroxymethylglutaryl coenzyme A reductase inhibitor, or statin, as specified by the Expert Panel guideline algorithm (Table 2).

For comparison, the NCEP 1992 guidelines recommended drug therapy after a trial of lifestyle therapy if the LDL-C remained ≥190 mg/dL, or if the LDL-C remained ≥160 mg/dL with either a positive family history of premature cardiovascular disease or the presence of ≥2 other cardiovascular disease risk factors (cigarette smoking, elevated blood pressure, HDL-C <35 mg/dL, weight for height ≥95th percentile, diabetes mellitus, physical inactivity). Applying these criteria to the current NHANES dataset with its limitations, 0.5% (95% confidence interval, 0.1–0.9%) would be recommended for drug therapy. The AAP 2008 guidelines recommended drug therapy after a trial of lifestyle therapy if the LDL-C remained ≥190 mg/dL, or if the LDL-C remained ≥160 mg/dL with either a positive family history of premature cardiovascular disease or the presence of any other cardiovascular disease risk factor (cigarette smoking, hypertension, obesity), or if the LDL-C remained ≥130 mg/dL for those with diabetes mellitus. Applying these criteria to the current NHANES dataset, 1.0% (95% confidence interval, 0.4–1.5%) would be recommended for drug therapy.
Stratified by BMI percentile category, statin therapy would be recommended for 0.6% (95% confidence interval, 0.1–1.1%) of those with BMI <95th percentile, none with BMI ≥95th but <97th percentile (this was a small stratum including only 176 participants; hence, this result, although counterintuitive, may have been influenced by low statistical power), and 3.1% (1.6–4.5%) of those with BMI ≥97th percentile. Among those with BMI ≥97th percentile, 60% (95% confidence interval, 35–84%) who might be recommended for statin therapy had an LDL-C level between 160 and 189 mg/dL, and 8% (0 to 19%) had an LDL-C level ≥190 mg/dL. Overall, statin therapy would be recommended for 3.6% (95% confidence interval, 0.4–6.7%) of obese children and 2.4% (0.1 to 4.7%) of obese girls. Higher proportions might be recommended for statin therapy for older obese adolescents, including 1.5% (95% confidence interval, 0.0–3.7%) of 12-year-olds, 0.5% (0–1.4%) of 13-year-olds, 1.1% (0–2.8%) of 14-year-olds, 2.2% (0–4.3%) of 15-year-olds, 6.0% (1.0–10.9%) of 16-year-olds, and 7.2% (0.1–14.3%) of 17-year-olds. Given small numbers regarding specific combinations of LDL-C categories and additional risk factors for obese participants recommended for statin therapy, further specification is precluded using NHANES data. Nonetheless, the great majority of these obese participants met criteria based on high LDL-C category, similar to nonobese participants. For those obese participants with LDL-C levels between 130 and 189 mg/dL recommended for statin therapy, current smoking was an additional risk factor in the majority.

Discussion
Based on analysis of the most recent NHANES data and assuming no response to lifestyle therapy, limited application of the new Expert Panel guideline algorithm for LDL-C management would specify a minimum of 0.85% of American children as being recommended for statin therapy. This represents 215,900 children 12–17 years of age (based on population projections from the 2009 U.S. Census Bureau data). This is an underestimate of a potential universal screening approach because family history and special risk conditions (integral parts of the algorithm) were not available for these calculations, but also potentially an overestimate because the guideline evidence review demonstrated a consistent, modest decrease in LDL-C in response to a low saturated fat and total fat diet. The estimate is also based on a single lipid assessment. Previous studies have highlighted relevant within-person variability and regression to the mean that may influence screening and assessment metrics.

A previously published analysis of NHANES data from 1999 to 2006 using the AAP 2008 guidelines estimated that 0.8% of participants aged 12 to 17 years would be recommended for drug therapy. This differs from 1.00% using the same guidelines but including NHANES data up to 2010, but is similar to 0.85% using the current Expert Panel guidelines. These guidelines use similar LDL-C cut points, but differ in the degree of specification as to how additional risk factors should contribute to decision-making. The Expert Panel guidelines provide the greatest degree of specification, for both the number and the level of risk factors.

Obese children with dyslipidemia were found to be recommended for statin therapy significantly more often than non-obese children, 3.1% vs 0.6%. This is explained by the association of obesity with multiple lipid abnormalities, insulin resistance, hypertension, and cardiometabolic disease. Clustering of risk factors in association with dyslipidemia exponentially increases the risk of accelerated atherosclerosis and provides the justification for initiation of statin therapy. Freedman et al used data from the Bogalusa Heart Study to analyze 6 cardiovascular risk factors (triglycerides, LDL-C, HDL-C, fasting insulin, and systolic and diastolic blood pressure) stratified by BMI percentile. They noted that 39% of children with BMI≥95th percentile and 59% of children with BMI≥99th percentile had ≥2 of the defined risk factors. Of children with BMI≥99th percentile, 65% went on to have an adult BMI>35 kg/m². In the longitudinal Cardiovascular Risk in Young Finns study, the presence of multiple cardiovascular risk factors in childhood and adolescence has been associated with multiple measures of subclinical atherosclerosis, independent of change in risk factor levels from adolescence to adulthood. These studies support the assertion that multiple risk factors present during youth greatly accelerate the atherosclerotic process.

If the current epidemic of obesity continues, complete implementation of the Expert Panel guidelines will potentially result in a greater number of children with dyslipidemia recommended for medical therapy in the years to come. This increase would not be as a result of higher levels of LDL-C, except in the scenario where obesity-related metabolic changes unmask an underlying genetic dyslipidemia, such as familial combined dyslipidemia. LDL-C levels are minimally affected in obesity, and few obese children will be expected to meet criteria for a statin based on associated increases in LDL-C alone. Rather, the association of obesity with low HDL-C, hypertension, and insulin resistance and type 2 diabetes mellitus will qualify dyslipidemic obese children for statin therapy. Even still, the proportion meeting criteria for statin therapy remains very low, both overall and in obese children, and the great majority are recommended based on high LDL-C category without multiple risk factors, and would likely be reflective of an underlying genetic dyslipidemia.

Universal screening would allow for earlier diagnosis and intervention for children with dyslipidemia secondary to lifestyle factors or genetics. Epidemiologic studies from the evidence review for the Expert Panel guidelines have suggested that low cardiovascular risk factor status entering adult life may be associated with significantly reduced cardiovascular mortality and increased longevity. Genetic natural history studies allow estimation of the effect of random allocation of alleles via Mendelian randomization. Since the Expert Panel guideline evidence review, several important studies of this kind have been published. In 2010, Cohen et al reported that for individuals with a PCSK9 nonsense mutation in whom LDL-C levels are a mean of 28% lower than the general population, the risk for coronary heart disease was reduced by >80%; this has been confirmed by others. In 2012, Ference et al reported a meta-analysis of >300,000 individuals with polymorphisms in 6 genes resulting in lower LDL-C. Naturally random allocation to long-term lower LDL-C...
exposure was associated with a 54.5% reduction in the risk of coronary heart disease for each mmol/L lower LDL-C. This represents a 3-fold greater reduction in the risk of coronary heart disease compared with statin treatment started later in life. These studies support the benefit of a lifetime of low risk related to lower LDL-C levels. It has been suggested that this benefit may also be achieved by the early identification and treatment of elevated LDL-C. Evidence to conclusively support this will be difficult to accrue whether this would be justified by savings in overall health care costs generated by a population of healthier adults.

Universal lipid screening and treatment of identified children with dyslipidemia using the risk-adjusted Expert Panel guidelines would result in a potentially important improvement in cardiovascular risk and a decrease in subsequent disease with a large cost to the health care system. It remains to be seen whether this would be justified by savings in overall health care costs generated by a population of healthier adults.

Disclosures

Brian McCrindle is a consultant for Bristol Myers Squibb, Merck, and Eli Lilly, is on the Data and Safety Monitoring Board of Medpace, and has received research support from Schering Plough and Astra Zeneca. The other authors report no conflicts. All of the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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