Application of Pediatric and Adult Guidelines for Treatment of Lipid Levels Among US Adolescents Transitioning to Young Adulthood

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IMPORTANTCE
Health care practitioners who care for adolescents transitioning to adulthood often face incongruent recommendations from pediatric and adult guidelines for treatment of lipid levels.

OBJECTIVE
To compare the proportion of young people aged 17 to 21 years who meet criteria for pharmacologic treatment of elevated low-density lipoprotein cholesterol (LDL-C) levels under pediatric vs adult guidelines.

DESIGN, SETTING, AND PARTICIPANTS
We performed a cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES) population. Surveys were administered from January 1, 1999, through December 31, 2012, and the analysis was performed from June through December 2014. Participants included 6338 individuals aged 17 to 21 years in the United States.

MAIN OUTCOMES AND MEASURES
To estimate the number and proportion of individuals aged 17 to 21 years in the NHANES population who were eligible for statin therapy, we applied treatment algorithms from the 2011 Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents of the National Heart, Lung, and Blood Institute and the 2013 Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults from the American College of Cardiology and American Heart Association. After imputing missing data and applying NHANES sampling weights, we extrapolated the results to 20.4 million noninstitutionalized young people aged 17 to 21 years living in the United States.

RESULTS
Of the 6338 young people aged 17 to 21 years in the NHANES population, 2.5% (95% CI, 1.8%-3.2%) would qualify for statin treatment under the pediatric guidelines compared with 0.4% (95% CI, 0.1%-0.8%) under the adult guidelines. Participants who met pediatric criteria had lower mean (SD) LDL-C levels (167.3 [3.8] vs 210.0 [7.1] mg/dL) but higher proportions of other cardiovascular risk factors, including hypertension (10.8% vs 8.4%), smoking (55.0% vs 23.9%), and obesity (67.7% vs 18.2%) compared with those who met the adult guidelines. Extrapolating to the US population of individuals aged 17 to 21 years represented by the NHANES sample, 483 500 (95% CI, 482 100-484 800) young people would be eligible for treatment of LDL-C levels if the pediatric guidelines were applied compared with only 78 200 (95% CI, 77 600-78 700) if the adult guidelines were applied.

CONCLUSIONS AND RELEVANCE
Application of pediatric vs adult guidelines for lipid levels, which consider additional cardiovascular risk factors beyond age and LDL-C concentration, might result in statin treatment for more than 400 000 additional adolescents and young adults.

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A
dolescence is a common time for the emergence of risk
factors for cardiovascular disease (CVD), including
dyslipidemia.1 The 2011 National Heart, Lung, and
Blood Institute Integrated Guidelines for Cardiovascular Health
and Risk Reduction in Children and Adolescents7 recommend
universal screening of lipid levels for young people aged
17 to 21 years and pharmacologic treatment with statins for
those with low-density lipoprotein cholesterol (LDL-C) levels
of at least 190 mg/dL (to convert to millimoles per liter, mul-
tiply by 0.0259) without other risk factors or at least 130 or 160
mg/dL if additional risk factors are present. In contrast, the 2013
American College of Cardiology and American Heart Associa-
tion Guideline on the Treatment of Blood Cholesterol to Re-
duce Atherosclerotic Cardiovascular Risk in Adults3 recom-
mends medication for individuals younger than 40 years only
if their LDL-C level is at least 190 mg/dL. Because 17 to 21 years
is a typical age for transition from pediatric to adult-centered
care, these disparate approaches may lead to confusion in clin-
ical practice.

Despite their different approaches, both guidelines have
faced controversy because of concerns about overdiagnosis and
over treatment of individuals without known CVD.4,5 Previous
analyses using the National Health and Nutrition Examina-
tion Surveys (NHANES) demonstrate that compared with
prior guidelines, the 2011 pediatric guidelines and 2013 adult
guidelines expand the number of Americans eligible for phar-
macologic treatment of elevated LDL-C levels.6-7 However, no
study has reported on discrepancies that arise when applying
pediatric vs adult guidelines to adolescents transitioning to
young adulthood. The aim of this study was to determine the
proportion of young people aged 17 to 21 years who would meet
criteria for pharmacologic treatment with statins under the 2
guidelines.

Methods

We performed a cross-sectional analysis of participants in the
NHANES from January 1, 1999, through December 31, 2012,8
who were 17 to 21 years of age (n = 6338); the analysis was per-
formed from June through December 2014. NHANES is a pro-
gram that assesses the health status of the United States using
a nationally representative sampling strategy. Individuals 18
years or older provided written informed consent to collec-
tion of survey and biological data, and those younger than 18
years provided written assent along with parental written in-
formed consent.8 The analysis was deemed exempt by the in-
stitutional review board of the Tufts Health Sciences Cam-
pus. We excluded participants who were pregnant (1.8%) or
who reported taking medication to lower lipid levels at the time
of the examination (2.8%). NHANES investigators calculated
LDL-C levels from measured total cholesterol, triglyceride, and
high-density lipoprotein cholesterol (HDL-C) levels using the
Friedewald equation.7 We included the 2.2% of participants
with nonfasting cholesterol levels because a nonfasting LDL-C
level carries a prognosis similar to that of a fasting LDL-C level.7
We included data regarding family history of early atheroscle-
rotic CVD (ASCVD), defined as a first- or a second-degree rela-
tive with a heart attack or angina before age 50 years. This ques-
tion was asked of participants 20 years or older starting in 2005.
We included those answers and imputed answers for the re-
main ing population (see below). We included data on moder-
ate-level risk factors (stage I hypertension, class I obesity, and
HDL-C level <40 mg/dL) and high-level risk factors (stage II hy-
pertension, class II or III obesity, self-reported history of dia-
abetes mellitus, and self-reported use of tobacco cigarettes on
at least 20 days in the past month (individuals aged 17-19 years)
or on some or most days (individuals aged 20-21 years). Per-
sonal history of ASCVD was not considered because the esti-
imated prevalence was believed to be implausibly high and
likely related to inaccurate self-report. Data on rare high-risk
conditions, such as heart transplant and Kawasaki disease, for
which treatment at lower LDL-C levels is recommended in the
pediatric guidelines,2 were not available. Based on a Markov
chain Monte Carlo method,10 which assumes multivariate nor-
mality, we used multiple imputation (PROC MI, SAS, version
9.4; SAS Institute Inc) to estimate missing values for all other
variables included in the pediatric and adult guidelines, in-
cluding LDL-C levels, which were collected on only 2622 of 6338
participants (41.8%). Ten data sets were imputed.10

We applied treatment algorithms from the 2011 inte-
rated pediatric guidelines and the 2013 adult guidelines to the
sample of 6338 participants (Figure). We used software to
specify the subgroup variable (PROC SURVEYFREQ, SAS, ver-
sion 9.4) and the subgroup of interest (SURVEYMEANS, SAS,
version 9.4) on each imputed data set to incorporate NHANES
sampling weights for the complex sample design and to ac-
count for clusters and strata. We then used multiple imputa-
tion (PROC MIANALYZE; SAS, version 9.4) to combine results
performed on the 10 imputed data sets. To extrapolate the re-

At a Glance

- Physicians who care for adolescents transitioning to adulthood
  often face incongruent recommendations from pediatric and
  adult guidelines.
- Of the 6338 young people aged 17-21 years in NHANES, 2.5%
  would qualify for statin treatment under the pediatric guidelines
  compared with 0.4% under the adult guidelines.
- Participants who met pediatric criteria had lower mean LDL-C
  levels but higher proportions of other cardiovascular risk factors,
  including hypertension, smoking, and obesity.
- These differences translate into statin treatment for more than
  400 000 additional adolescents and young adults under the
  pediatric than the adult guidelines.
- Given the current uncertain state of knowledge and conflicting
  lipid treatment guidelines for youth aged 17-21 years, clinicians
  and patients should engage in shared decision making around
  potential benefit, harms, and patient preferences for treatment.
used serum cotinine values of greater than 10 ng/mL instead of self-report to classify participants as smokers. Third, to examine the effect of prior adult guidelines, we applied the third report of the National Cholesterol Education Program Guidelines in Adults (Adult Treatment Panel III [ATP III]), which recommended pharmacologic treatment for individuals with 2 or more risk factors and LDL-C levels of at least 160 mg/dL (or ≥130 mg/dL if the 10-year risk for ASCVD is 10%–20%). For determining statin therapy based on LDL-C level under the ATP III, we assumed that all individuals aged 17 to 21 years had a less than 10% chance of an ASCVD event within 10 years owing to their youth because the ATP III risk calculator extends only to 30 years of age. All analyses were performed using commercially available software (SAS, version 9.4).

Results

Demographic and clinical characteristics of the noninstitutionalized US population of young people aged 17 to 21 years represented by the NHANES population and the subset eligible for statin therapy by the pediatric and adult guidelines are shown in Table 1 and Table 2. We estimated 2.5% (95% CI, 1.8%–3.2%) and 0.4% (95% CI, 0.1%–0.8%) of young people aged...
17 to 21 years would be treated if the pediatric and adult guidelines, respectively, were fully applied. Participants who met pediatric criteria for treatment had lower mean total cholesterol and LDL-C levels but higher triglyceride levels than those meeting adult criteria (Table 1).

Extrapolating to the US population of 20.4 million young people aged 17 to 21 years, 483,500 (95% CI, 482,100-484,800) individuals would be eligible for statin treatment under the pediatric guidelines compared with 78,200 (95% CI, 77,600-78,700) under the adult guidelines. The most common major CVD risk factors (other than LDL-C level) among young people who would be candidates for pharmacologic therapy under the pediatric guidelines were smoking (55.0% [95% CI, 40.7%-69.3%]), obesity (67.7% [95% CI, 54.7%-80.7%]), and a low HDL-C level (47.8% [95% CI, 34.2%-61.4%]) (Table 2). The presence of these risk factors would increase the proportion of male individuals aged 17 to 21 years eligible for therapy 7.3-fold (from 0.4% with the adult guidelines to 2.9% with the pediatric guidelines) and increase the proportion of female individuals aged 17 to 21 years eligible for treatment by 5.3-fold (from 0.4% to 2.1%).

Compared with the current adult guidelines, application of the ATP III guideline increased the proportion of participants qualifying for treatment from 0.4% to 0.7% (95% CI, 0.3%-1.1%). Classifying smoking status based on cotinine levels slightly increased the proportion meeting the pediatric guidelines for statin therapy from 2.5% to 3.1% (95% CI, 2.3%-3.8%).

Discussion

Physicians who care for adolescents transitioning to adulthood often face incongruent recommendations from pediatric and adult guidelines. In this study, we focused on deciding whether to prescribe medication to lower lipid levels to people in this age group. Application of the pediatric guidelines resulted in recommendations for statin treatment for more young people overall and for young people with lower LDL-C levels but a higher prevalence of other CVD risk factors compared with the adult guidelines. These differences are not surprising given the current criteria considered in the 2 guidelines (Figure). However, direct application of the 2 guidelines in clinical practice has the potential to create confusion for patients and physicians. For example, if a pediatric cardiologist prescribes a statin for a 20-year-old obese male with an LDL-C level of 170 mg/dL who smokes cigarettes and has a family history of early ASCVD, should the patient continue taking the statin when he transitions to a physician who treats adults? Given that the underlying risk does not change when these pa-

### Table 1. Characteristics of US Adolescents and Young Adults Based on the NHANES Sample by Statin Eligibility According to the 2 Guidelines

<table>
<thead>
<tr>
<th>Variable</th>
<th>US Adolescents and Young Adults&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Eligible for Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (N = 20.4 Million)</td>
<td>NHLBI Pediatric Guidelines (n = 483 500)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACC-AHA Adult Guidelines (n = 78 200)</td>
</tr>
<tr>
<td>Age, mean (SE), y</td>
<td>19.0 (0.04)</td>
<td>19.3 (0.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19.2 (0.5)</td>
</tr>
<tr>
<td>Male sex, % (SE)</td>
<td>52.1 (0.9)</td>
<td>59.8 (7.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55.1 (17.7)</td>
</tr>
<tr>
<td>Race/ethnicity, % (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexican American</td>
<td>12.0 (0.9)</td>
<td>8.9 (2.6)</td>
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<tr>
<td></td>
<td></td>
<td>7.4 (5.3)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Other Hispanic</td>
<td>6.7 (0.7)</td>
<td>7.2 (3.7)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.3 (13.2)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>59.9 (1.6)</td>
<td>66.4 (6.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62.8 (15.3)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>14.6 (1.2)</td>
<td>12.2 (3.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.7 (5.4)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Other race/multiracial</td>
<td>6.9 (0.5)</td>
<td>5.3 (2.5)&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>4.8 (6.3)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma lipid concentrations, mg/dL</td>
<td></td>
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<tr>
<td>Total cholesterol</td>
<td>167.4 (0.7)</td>
<td>240.1 (4.8)</td>
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<td></td>
<td></td>
<td>285.4 (9.8)</td>
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<tr>
<td>Triglycerides</td>
<td>102.8 (2.3)</td>
<td>143.7 (16.7)</td>
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<td></td>
<td></td>
<td>125.8 (24.6)</td>
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<tr>
<td>HDL-C</td>
<td>50.8 (0.3)</td>
<td>44.1 (2.1)</td>
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<tr>
<td></td>
<td></td>
<td>50.2 (5.5)</td>
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<tr>
<td>LDL-C</td>
<td>96.0 (0.7)</td>
<td>167.3 (3.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>210.0 (7.1)</td>
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<tr>
<td>Other CVD risk factors</td>
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<tr>
<td>SBP, mm Hg</td>
<td>112.6 (0.3)</td>
<td>118.4 (1.7)</td>
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<tr>
<td></td>
<td></td>
<td>118.6 (4.5)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>63.7 (0.4)</td>
<td>66.4 (1.9)</td>
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<tr>
<td></td>
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<td>64.4 (4.5)</td>
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<tr>
<td>BMI</td>
<td>25.2 (0.1)</td>
<td>32.5 (1.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25.8 (3.6)</td>
</tr>
</tbody>
</table>

Abbreviations: ACC-AHA, American College of Cardiology and American Heart Association; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Surveys; NHLBI, National Heart, Lung, and Blood Institute; SBP, systolic blood pressure.

* May be unstable and should be interpreted with caution because the NHANES sample included fewer than 10 persons.

<sup>a</sup> Indicates aged 17 to 21 years. The NHANES data were collected from January 1, 1999, through December 31, 2010. Unless otherwise indicated, data are expressed as mean (SE).

<sup>b</sup> SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.
patients change physicians, starting the statin therapy in adolescence but stopping it in adulthood is counterintuitive.

Treatments decisions regarding individuals such as those with low short-term but high lifetime risks for ASCVD are hampered by the lack of randomized clinical trials in young adults. Such trials would require extensive follow-up to answer questions about the effect of statin therapy on the risk for CVD events. In their absence, policy makers and physicians often rely on data from genetic and epidemiologic studies that suggest that the lifetime risk for ASCVD in individuals with elevated LDL-C levels in conjunction with other CVD risk factors early in life is high. The 2011 pediatric guidelines are based on this type of extrapolated evidence for areas in which trial evidence was unavailable. In contrast, the 2013 adult guidelines were created using evidence from randomized clinical trials only, although they advocate for the physician’s judgment in areas where the evidence base is insufficient. In the future, policy makers should consider creating guidelines that can be applied more seamlessly across the life course.

Our study has important limitations. The analysis was based on measurements collected at a single point. In contrast, guidelines for the diagnosis and treatment of hyperlipidemia call for multiple measurements over time and for consideration of treatment after a trial of lifestyle changes. Second, very few participants had LDL-C levels of 190 mg/dL or greater; thus, estimates for treatment under the adult guidelines may be unstable owing to small sample sizes. Third, we chose not to consider individuals eligible based on self-report of ASCVD, an important eligibility criteria in both guidelines, because of concerns that these reports were implausible in this age group and hence inaccurate. Finally, family history of ASCVD was self-reported, not verified through clinical records, and only asked of participants 20 years or older. Although we attempted to address the high rate of missing data for a family history of ASCVD with multiple imputation, we still might have underestimated the number of young people who would qualify for statin treatment under the pediatric guidelines for individuals with LDL-C levels of 160 to 189 mg/dL and a family history of early ASCVD.

Conclusions

Our analysis suggests that for young people aged 17 to 21 years in the United States who have elevated LDL-C levels, direct application of the pediatric guidelines would result in statin treatment for more than 400,000 additional young people than the adult guidelines, a 6-fold difference. The actual number treated is likely to be much lower owing to less than universal screening in this age group, challenges with adherence to medication regimens, and physician or patient disagreement with the recommendations. Given the current uncertain state of knowledge and conflicting guidelines for treatment of lipid levels among youth aged 17 to 21 years, physicians and patients should engage in shared decision making around the potential benefits, harms, and patient preferences for treatment. The 2013 American College of Cardiology and American Heart Association guidelines recommend shared decision making with patients for whom data are inadequate, including young people with a high lifetime risk for ASCVD. Patients and cli-
nicians should clearly address other modifiable risk factors, including optimizing diet, exercise, and weight and promoting abstinence from tobacco, as strongly recommended by both the pediatric and adult guidelines.

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Disclaimer: All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute, its Board of Governors, or its Methodology Committee.

REFERENCES