Guidelines for Lipid Screening in Children and Adolescents: Bringing Evidence to the Debate

AUTHORS: Brian W. McCrindle, MD, MPH; Peter O. Kwiterovich, MD; Patrick E. McBride, MD, MPH; Stephen R. Daniels, MD, PhD; and Rae-Ellen W. Kavey, MD, MPH

Department of Pediatrics, University of Toronto, Labatt Family Health Centre, The Hospital for Sick Children, Toronto, Canada; Johns Hopkins University School of Medicine, Baltimore, Maryland; University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; University of Colorado School of Medicine, Aurora, Colorado; and University of Rochester School of Medicine, Rochester, New York

KEY WORDS
- guidelines, hyperlipidemia, familial hypercholesterolemia

ABBRévIATiONS
- CV—cardiovascular
- FH—familial hypercholesterolemia
- IMT—intima media thickness
- LDL-C—low-density lipoprotein cholesterol

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Address correspondence to Brian McCrindle, MD, MPH, The Hospital for Sick Children, 555 University Ave, Toronto, ON, Canada M5G 1X8. E-mail: brian.mccrindle@sickkids.ca

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The commentary of Newman et al regarding recommendations for lipid screening in childhood from the expert panel guidelines commissioned by the National Heart Lung and Blood Institute misrepresents the evidence regarding screening and the specificity and rigor of the guideline development process. The expert panel developed comprehensive, integrated, and evidence-based guidelines for promotion of cardiovascular (CV) health and the identification and management of specific risk factors from infancy into young adulthood. The large, diverse, and complex evidence base that addresses CV risk beginning in childhood, and the absence of decades long event-driven clinical trials, required consideration of substantial and consistent evidence from observational studies, developing a chain of evidence. A priori, a systematic process was used to review and grade the evidence and develop the recommendations, which is explicitly described in the Full Summary Reports and the evidence tables are available on the National Heart Lung and Blood Institute web site.

Atherosclerosis is a lifelong process proven to begin and progress throughout childhood and adolescence. Childhood CV risk factors track into adulthood and have been shown in many autopsy and imaging studies in diverse populations to be strongly and consistently predictive of the extent of subclinical atherosclerosis in young adults. As an example, the Pathobiological Determinants of Atherosclerosis in Youth Study of individuals aged 15 to 30 years who had died traumatically showed that a 30 mg/dL incremental increase in non-high-density lipoprotein cholesterol was the equivalent of 2 years of vascular aging. The Bogalusa Heart Study showed that an increasing number of childhood CV risk factors exponentially increased the atherosclerotic burden noted at autopsy after accidental death. In the Cardiovascular Risk in Young Finns Study, higher low-density lipoprotein cholesterol (LDL-C) at ages 12 to 18 years was independently associated with greater carotid intima media thickness (IMT), a noninvasive indicator of atherosclerosis, measured later in adulthood, a finding confirmed when multiple cohorts were pooled. This large body of consistent and compelling evidence supports the imperative to screen lipids during childhood.

Familial hypercholesterolemia (FH) is an excellent biologic model demonstrating the link between childhood lipid levels and CV disease events because high levels of LDL-C are present from birth. Heterozygous FH is both prevalent, with a frequency of ~1:500, and important, with 51% of untreated affected men developing clinical CV disease by age 50 years (5% by 30 years of age). Rare homozygous FH patients have extremely high levels of LDL-C (from 500 to 1000 mg/dL) and develop clinical CV disease before adulthood.

Given the high prevalence and CV disease burden with FH, early identification and management is important, which was the primary focus for
the lipid-screening recommendations. A recent meta-analysis of published data on lipid values in FH individuals showed that LDL-C measured after 1 year of age and before puberty had better discrimination than at other ages, detecting 96% of those with FH at a false-positive rate of 1%. A study of 1034 children from FH kindreds showed that an LDL-C level >135 mg/dL predicted genetically confirmed FH with a 0.98 posttest probability. Previous guidelines used family history of premature CV disease as the entry point for screening, which misses a high proportion of individuals with lipid abnormalities, and cascade screening of relatives of an identified individual with FH is inadequate for population screening.

The rationale and justification for screening children must be linked to evidence supporting the need and safety for early treatment. Recent evidence suggests that ideal CV health in childhood predicts optimal cardiometabolic outcomes in adulthood, achieved through adoption of healthy lifestyle behaviors, as emphasized in the guidelines. The safety and efficacy of the recommended diet for the general population is supported by large randomized trials. However, for individuals with FH and high LDL-C levels, healthy lifestyle behaviors are rarely sufficient to achieve lipid targets, and the expert panel gave specific stepwise guidance for more intensive clinical management. Medical treatment recommendations are based on multiple randomized trials of statin therapy in children with FH demonstrating acceptable safety and efficacy over periods up to 2 years. Statin treatment of children and adolescents with FH normalizes endothelial function and regresses carotid IMT. Earlier treatment is associated with less progression in IMT at longer-term follow-up. Treatment of FH adults with statins for primary prevention reduces coronary heart disease mortality by 48%

There have been several studies exploring the cost-effectiveness of screening and management strategies for FH, including in young adults. An analysis of the genetic cascade screening program for FH in the Netherlands showed that new cases gained 3.3 years of life at an average lifetime cost of US$8700 per year gained, with 26 myocardial infarctions prevented for every 100 persons treated. More complex cost-effectiveness modeling of treatment of children and adolescents has not yet been performed.

Newman et al. raise concerns about “harms” that could be associated with screening and potential treatment, citing 2 small case series from the 1980s that involve parents making misinformed decisions about the diets for their children. A richer understanding of the impact of screening is now available. Among children with familial CV disease, including FH, an interview study showed positive future health perceptions and effective coping with their carrier status and prognosis. A health-related quality-of-life analysis showed no differences between the perceptions of carrier children and their normal peers. A study of universal CV risk screening in schools, accompanied by environmental change, showed improvements in healthy lifestyle behaviors and CV risk profiles.

Another concern is the perception that a large number of children without FH will be identified and started on medication, ignoring healthy lifestyle changes and the potential risk of serious adverse effects without clear benefit. In terms of numbers, application of American Academy of Pediatrics guideline thresholds for starting medication to NHANES data (1999–2006) in 12- to 17-year-old subjects showed that only 0.8% of adolescents would be eligible for medication. Similarly, a recent universal screening of fifth-grade children showed that 1.3% met criteria for medication.

The uncertainty regarding “harms” of statin use in children has been increasingly clarified and diminished. Long-term use in adults has shown insufficient risk to outweigh overwhelming benefit, and the mechanisms of adverse effects and intolerance are increasingly understood. A meta-analysis of clinical trials of statins in children and adolescents with FH over periods up to 2 years showed no adverse effects on growth, development, cognition, or sexual maturation. The expert panel guidelines include specific, evidence-based recommendations for initiation and monitoring of lipid-lowering medication while recognizing the importance of ongoing study and surveillance.

While the primary focus of screening in children is FH, the expert panel considered strong population-based evidence supporting the association of LDL-C (and other lipid parameters) with CV disease and events and clinical trial evidence of benefit with treatment in adults, regardless of the cause of LDL-C elevation. The evidence review identified specific risk conditions, including risk-factor clustering, associated with markedly accelerated atherosclerosis and manifest coronary artery disease events before 30 years of age. This evidence led to recommendations for management of dyslipidemia when a cluster of risk factors or conditions is present.

Newman et al. have asserted that the recommendations on lipid management are biased by expert panel members’ relationships with industry. They fail to acknowledge that the guideline development process was specified a priori and evidence based, and potential conflicts of interest were declared and vetted throughout the process. Declared relationships reflect participation as consultants in the design of studies relevant to lipids and children, service on data and safety monitoring boards, and participation in industry-funded trials. For children and adolescents,
evidence regarding the efficacy and safety of these medications would not be available without the academic partnership with industry. The remuneration received covered costs and time, without significant financial incentive. The lipid recommendations were approved by a strong consensus of the panel, the highest level of approval. To contest the integrity of panel members and their deliberations without evidence is unfair and uninformed.

Clinical practice guidelines should be strictly data driven and linked to a feedback loop that incorporates effective knowledge translation, stakeholder input, tracking of outcomes, and timely revision. The expert panel guidelines are one component in this process, combining the best available evidence with clinical expertise. They are appropriately and fairly calibrated to the benefits, risks, and evidence related to an important public health problem. To propose that this problem be ignored in the absence of decades-long clinical trials of screening and therapy starting in childhood and ending with CV events late in adulthood is unreasonable (even if one accepts the premise that they could be performed), especially when the important consequences of untreated FH is known.

In the guideline development by the expert panel, the accumulated evidence was extensively and objectively identified, reviewed, graded, weighed, and synthesized, being mindful of perceived conflicts of interest, and evidence gaps were identified and acknowledged. Newman et al.

offer only opinion and rhetoric and provide little evidence to inform an evidence-based discussion. The guidelines provide clinicians with the necessary evidence and the balanced perspective to make their own informed judgment as to the utility and role for these recommendations in the integrated identification and management of CV risk factors for children and adolescents.

REFERENCES

When it comes to age, the nose knows: When walking into my elderly grandparents’ home, an assisted living facility, or even some patients’ hospital rooms, I am often surprised to recognize a familiar scent. While I have wondered about the existence of a unique smell associated with older adults, it was not until recently that researchers started exploring the topic. A new study supports the idea that older people do have a different scent than younger ones, and that the human nose is quite attuned to this unique aroma. As reported by CNN (Health: May 30, 2012), researchers in Philadelphia conducted a study in which 41 men and women of varying ages wore shirts with nursing pads built into the garments’ underarms. Once the pads were removed from the shirts, 41 young adults, aged 20-30 years, were instructed to score the pleasantness and strength of pad smell as well as to identify the odor donor’s age group. At the study’s conclusion, the young adults were able to identify older individuals’ samples much more accurately than could be expected by chance. The young adults also rated older individuals’ odor as significantly less intense and less unpleasant when compared to samples from other age groups. Why the young adults were able to detect older individuals by scent is not known. Furthermore, little is known about the function or source of the odor. Researchers speculate that a natural age-associated increase in specific white blood cells may be responsible. Maybe it is a way to recognize maturity. Regardless of the scent’s specific source or purpose, it is fascinating that our senses can detect an aroma of age.

Noted by Leah H. Carr, BS, MS-III
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