Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents

Full Report

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Conflict of Interest Review/Financial and Other Disclosures

Expert panel members disclosed relevant financial interests to each other prior to discussions. The following financial interests are reported in the publication in the Journal of Pediatrics:

Dr. Benuck, Dr. Christakis, Dr. Dennison, Dr. O'Donnell , Dr. Rocchini, and Dr. Washington have declared no relevant relationships.

Dr. Daniels has served as a consultant for Abbott Laboratories and Merck, Schering-Plough. He has received funding/grant support for research from the NIH.

Dr. Gidding has served as a consultant for Merck, Schering-Plough. He has received funding/grant support for research from GlaxoSmithKline.

Dr. Gillman has given invited talks for Nestle Nutrition Institute and Danone. He has received funding /grant support for research from Mead Johnson, Sanofi-aventis and the NIH.

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Dr. McCrindle has been a consultant for Abbott, Bristol-Myers Squibb, Daichii Sankyo and Roche. He owns stock in CellAegis. He reports funding/grant support for research from Astra Zeneca, Sankyo, Merck, Schering-Plough and the NIH.

Dr. Urbina reports funding/grant support for research from Merck, Schering-Plough, Sankyo and the NIH.

Dr. Van Horn has provided advice to Chartwells School Food Service. She has received funding/grant support for research from General Mills and the NIH.

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1. BACKGROUND

In 2005, based on recommendations from experts convened in a national Thought Leaders Meeting, the National Heart, Lung, and Blood Institute (NHLBI), under the leadership of the Director Elizabeth G. Nabel, M.D., endorsed a new approach for guideline development. This new approach is characterized by a formal evidence review and an integrated format with the major cardiovascular (CV) risk factors addressed simultaneously in a single guideline document.

Atherosclerotic cardiovascular disease (CVD) remains the leading cause of death among North Americans. Although manifest disease in childhood and adolescence is rare, risk factors and risk behaviors that accelerate the development of atherosclerosis begin in childhood, and there is increasing evidence that risk reduction delays progression toward clinical disease. To address this health issue, the NHLBI appointed an Expert Panel to develop cardiovascular (CV) health and risk reduction guidelines for pediatric care providers based on the new approach, using a formal evidence review of this science with an integrated format addressing all the major CV risk factors simultaneously. This publication, *Full Report of the Expert Panel on Integrated Guidelines for Pediatric Cardiovascular Health and Risk Reduction*, is the result of the Expert Panel's work.

Chaired by Dr. Stephen R. Daniels, the Expert Panel's goal was development of evidence-based guidelines addressing all of the major risk factors to assist pediatric care providers—pediatricians, family practitioners, nurses and nurse practitioners, physician assistants, and registered dietitians—in both the promotion of CV health and the identification and management of specific risk factors from infancy to young adulthood. The Expert Panel determined that a focus on CV risk reduction in children and adolescents addresses a disease process—atherosclerosis—in which the clinical endpoint of manifest CVD is much later in life. Therefore, the recommendations would need to address both the prevention of risk factor development—

primordial prevention—and the prevention of future CVD by effective management of identified risk factors—primary prevention.

There have been no previous NHLBI-appointed expert panels that addressed multiple risk factors in children. Previous CV pediatric guidelines have addressed cholesterol (*National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents* (1992)) and blood pressure (*The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents* (2004)). The Expert Panel used these reports as a framework for development of the integrated format. A systematic review of the evidence was conducted to address a broad array of questions concerning the development, progression, and management of multiple CV risk factors extending from before birth to 21 years of age. This review required assessing all the evidence pertaining to the role of risk factors in childhood on the development and progression of atherosclerosis from childhood and adolescence to adulthood, as well as the body of evidence that addresses the impact of managing risk factors in childhood on the development and progression of atherosclerosis. Based on the assembled evidence, the Expert Panel developed graded, age-specific recommendations that are integrated across risk factors and across age groups.

In developing these comprehensive evidence-based Guidelines addressing all of the major risk factors, the panel has provided a practical approach to both the optimization of CV health and the management of identified risk factors throughout childhood and adolescence, a time when many health-behavior patterns develop and when risk reduction should have the greatest impact. These Guidelines should be of use to all those who provide health care to children to help them reduce future CV morbidity and mortality. By addressing the major population-based risk factors for CVD in children and adolescents, these guidelines will support pediatric care

providers in optimizing CV health in infancy, early childhood, and adolescence—developmental periods when many health behavior patterns develop, risk factors may become evident, and risk reduction should have the greatest impact.

This Full Report of the Guidelines and the evidence tables will be available on the NHLBI Web site under "Pediatric Cardiovascular Risk Reduction Initiative" at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. A Summary Report containing the conclusions of the evidence review and the recommendations has been prepared and is being published as a supplement in the December 2011 issue of the journal *Pediatrics*. The Summary Report is also available on the NHLBI Web site. Release of the Guidelines will be followed by dissemination and implementation activities.

1. INTRODUCTION

The Expert Panel's goal was development of comprehensive evidence-based guidelines addressing all of the major CV risk factors to assist pediatric care providers—pediatricians, family practitioners, nurses and nurse practitioners, physician assistants, and registered dietitians—in both the promotion of CV health and the identification and management of specific risk factors from infancy to young adulthood. An initial assessment indicated that an innovative approach would be needed to develop a comprehensive integrated product for the following reasons:

- A focus on CV risk reduction in children and adolescents addresses a disease process—atherosclerosis—in which the clinical end point of manifest cardiovascular disease (CVD) occurs much later in life. Therefore, the recommendations would need to address two different goals: the prevention of risk factor development—primordial prevention—and the prevention of future CVD by effective management of identified risk factors—primary prevention.

- Most systematic evidence reviews address one or, at most, a small number of finite questions addressing the impact of specific interventions on specific health outcomes. A rigorous literature search and review process involving explicit inclusion and exclusion criteria often results in only a handful of in-scope articles for inclusion in the review. These reviews seek direct, rigorous evidence of the causal effect of an intervention on the designated outcomes or indirect evidence in the form of a chain of causal evidence through surrogate or other intermediate outcomes linking the interventions to the outcomes of interest. Often, in-scope evidence is limited to randomized controlled trials (RCTs), systematic reviews, and meta-analyses published over a defined time period.

There is a defined format for abstracting studies, grading the evidence, and presenting the results. The level of evidence leads to the conclusions and recommendations.

- Because of the scope of the effort by the Expert Panel, this evidence review needed to address a broader array of questions concerning the development, progression, and management of multiple CV risk factors extending from before birth to 21 years of age, including studies with followup into later adulthood—a scope and breadth that had known gaps in the evidence base. In part, this task required assembling and appraising the body of evidence pertaining to the role of single risk factors and risk factor combinations in childhood in the development and progression of atherosclerosis from childhood and adolescence to adulthood. Rather than relying solely on RCTs, much of the evidence for guidelines in youth is available from epidemiologic observational studies, which must be included in the review. In addition, this review required critical appraisal of the body of evidence that addresses the impact of managing risk factors in childhood on the development and progression of atherosclerosis. Finally, because of known gaps in the evidence base relating risk factors and risk reduction in childhood to clinical events in adulthood, the review had to include the available evidence justifying the evaluation and treatment of risk factors in childhood. The process of identifying, assembling, and organizing the evidence was extensive; the review process was complex; and conclusions could be developed only by interpretation of the body of evidence. Thus, there was explicit Expert Panel involvement throughout the evidence review process.

The Expert Panel defined 14 critical questions for the literature search (Table 1–1) and the risk factors to be addressed (Table 1–2). The first phase of the evidence review focused on critical questions 1–9, which address the association between the development of atherosclerosis and

the presence and intensity of CVD risk factors in childhood and adolescence. The second phase of the evidence review addressed critical questions 10–14, which aim to assess the evidence for the safety and efficacy of reduction of each risk factor and the impact of risk factor change on the atherosclerotic process.

In addition to the typical RCTs, systematic reviews, and meta-analyses, two additional types of studies were considered to provide evidence pertaining to the development of atherosclerosis. Longitudinal observational studies were included to assess the tracking of risk factors from youth to adulthood and the relationship of risk factors in youth to the development of atherosclerosis. From the many available observational studies in the literature, the Panel identified the 12 listed in Table 1–3 for inclusion in the evidence review. The panel used several criteria to evaluate which studies should be in the evidence review, including sample size, and for longitudinal studies the length of followup. In general, the studies were large, averaging more than 1,000 subjects. Smaller studies that had long-term followup allowing evaluation of the relationship between risk factors identified in infancy and early childhood and adolescent and adult endpoints were also included. In addition, natural history studies of genetic disorders known to alter CV risk status were included to provide models of the consequences of prolonged risk exposure or risk protection.

The Expert Panel selected a literature search start date of January 1,1985, roughly 5 years before the previous expert panel process that had generated guidelines for the management of cholesterol in childhood, the National Cholesterol Education Program's *Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents*, which was published in 1992.[1] From an initial group of more than 1 million titles published between January 1, 1985, and June 30, 2007, the search was refined to ultimately include 648 studies: 50 systematic reviews, 33 meta-analyses, 293 RCTs, 194 observational studies, and, in addition, 78 sets of guidelines

relevant to pediatric CVD prevention, which were provided as reference material. Each of the first four listed types of studies underwent full text review and abstraction of critical information into evidence tables; each study was graded individually using a unique algorithm developed for these Guidelines. Details of the search methodology and the abstraction and individual study grading processes are provided in Appendix A. Methodology. The evidence tables are available electronically on the NHLBI Web site at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm.

Expert Panel members were grouped into subcommittees to focus on specific risk factors according to their respective areas of expertise, with many Expert Panel members participating on more than one subcommittee. In addition, two oversight committees were formed: (1) a Science Team to ensure high scientific quality of the entire evidence review and Guidelines development process and (2) a Clinical Team to maintain the relevance of the recommendations to clinical practice throughout Guidelines development. The Science Team, led by Samuel S. Gidding, M.D., addressed the first nine critical questions and summarized the evidence for the origins of atherosclerosis in childhood and the evidence for the role of risk factors in the atherosclerotic process in Section II. State of the Science: Cardiovascular Risk Factors and the Development of Atherosclerosis in Childhood. For each risk factor, the Expert Panel provided an overview of the evidence, focusing on those studies it believed provided the most important information. These summaries are provided in the risk factor-specific sections of this document. Because of the volume and complexity of the literature review, specific information on every study is provided only in the evidence tables. The risk factor subcommittees critically evaluated the body of evidence relative to each risk factor, using an evidence grading system from the American Academy of Pediatrics (AAP) (Table 1–4).[2] As shown in Table 1–4, the AAP evidence grading system was modified to incorporate genetic natural history studies in the Grade B evidence category. Each risk factor subcommittee then formulated age-specific recommendations with grade and strength of recommendation assigned

using the AAP grading system, based on consideration of the entire body of evidence used in developing each recommendation. The age categories corresponded with the system used by the AAP publication *Bright Futures: Guidelines for Health Supervision of Infants, Children and Adolescents*.[3] Each risk factor subcommittee reached internal consensus before presenting its recommendations to the full Expert Panel. The final recommendations were then reviewed and approved by the entire Expert Panel. Additional information on the Guidelines development process is provided in Appendix A. Methodology. A draft Guidelines document was reviewed by multiple professional societies and by many individuals within the National Institutes of Health, the Centers for Disease Control and Prevention, and relevant U.S. Department of Health and Human Services organizations. The Guidelines also underwent a 30-day public comment period. In total, individual responses were developed for more than 800 comments.

Section II. State of the Science: Cardiovascular Risk Factors and the Development of Atherosclerosis in Childhood summarizes all the evidence linking the presence of risk factors in childhood and adolescence to the presence and severity of the atherosclerotic process as assessed both pathologically and by imaging studies. An overview of the role of screening for CV risk factors in children is addressed in Section III. Screening for Cardiovascular Risk Factors. The next eight sections (IV–XI) address individual risk factors. Each risk factor section begins with a brief description of the current status of the risk factor in childhood and adolescence. Since this kind of information is often not available from studies that are included in evidence reviews, selected references are used to provide the context within which the recommendations were developed. This text is followed by the Expert Panel's written summary of the evidence review relative to the specific risk factor. As described above, Expert Panel members provided an overview of the evidence, focusing on those studies that in their expert opinions provide the most important information and identifying deficiencies in the evidence. Specific information on each study is provided in the evidence tables available through the

NHLBI Web site at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. The conclusions of the Expert Panel's review of the evidence are then summarized, accompanied by the evidence grades and the strength of the recommendation. Each risk factor section ends with the Expert Panel's age-specific recommendations, accompanied by supportive actions, which represent suggestions developed by Expert Panel consensus to support implementation of the recommendations. The recommendations are integrated across risk factors and developmentally across age groups into the Integrated Cardiovascular Health Schedule (Section XV), which summarizes the age-specific recommendations for all of the risk factors. To optimize accessibility, references are grouped by risk factor and are listed sequentially at the end of each section. References from the evidence review are identified by the unique PubMed identifier (PMID) number that appears in bold text. Additional references do not include the PMID number.

By addressing the major population-based risk factors for CVD in a single evidence-based set of Guidelines, the aim is to support pediatric care providers in optimizing CV health in infancy, early childhood, and adolescenceBy extending risk factor modification into childhood, our goal is to reduce the development of clinical CVD in the future lives of children.

Table 1–1. Development of the Evidence Base: Critical Questions

1. What is the evidence that atherosclerosis and atherosclerosis-related target organ damage begin in childhood?
2. What is the evidence that the presence of risk factors in childhood affects the development and progression of atherosclerosis and atherosclerosis-related target organ damage during childhood?
3. What is the evidence that the presence of risk factors in childhood affects the progression of atherosclerosis and atherosclerosis-related target organ damage in adulthood?
4. What is the evidence that indicates the relative importance of each risk factor in the development and progression of atherosclerosis and atherosclerosis-related target organ damage in childhood?
5. What is the evidence that racial or ethnic background, geographic region, or socioeconomic status affect cardiovascular (CV) risk factor status in childhood/adolescence?
6. What is the evidence that risk factors cluster in childhood?
7. What is the evidence that risk factor clustering is consistent in childhood?
8. What is the evidence that risk factors present in childhood persist (i.e., track) into adulthood?
9. What is the evidence that an increase in the number and/or intensity of risk factors in childhood alters (a) the development and progression of atherosclerosis and atherosclerosis-related target organ damage in childhood; (b) the development and progression of atherosclerosis and atherosclerosis-related target organ damage in adulthood; and/or (c) the development of clinical CV disease (CVD) in adulthood?
10. What is the evidence that risk factors in childhood can be decreased?
11. What is the evidence that a decrease in risk factors in childhood can be sustained?
12. What is the evidence that a decrease in risk factors in childhood alters (a) the development and progression of atherosclerosis and atherosclerosis-related target organ damage in childhood; (b) the development and progression of atherosclerosis and atherosclerosis-related target organ damage in adulthood; and (c) the development of clinical CVD in adulthood?
13. What is the evidence that acquisition of risk factors or risk behaviors can be prevented in childhood and adolescence?
14. What is the evidence that preservation of a low-risk state from childhood, adolescence, or young adulthood to later adult life is associated with (a) decreased development/progression of atherosclerosis and atherosclerosis-related target organ damage and/or (b) decreased incidence of clinical CVD?

Table 1–2. Evaluated Risk Factors

Family history
Age
Gender
Nutrition/diet
Physical inactivity
Tobacco exposure
High blood pressure
Blood lipids
Overweight/obesity
Diabetes mellitus and other predisposing conditions
Metabolic syndrome
Perinatal factors
Inflammatory markers

Table 1–3. Selected Observational Studies

Abbreviation	Full Title
NHANES	National Health and Nutrition Examination Survey
Bogalusa	Bogalusa Heart Study
PDAY	Pathobiological Determinants of Atherosclerosis in Youth
Muscatine	Muscatine Study
Princeton	Princeton Lipid Research Clinics Follow-Up Study
Young Finns	Cardiovascular Risk in Young Finns Study
NGHS	National Heart, Lung, and Blood Institute Growth and Health Study
STRIP	Special Turku Coronary Risk Factor Intervention Project (observational followup from this randomized controlled trial)
CARDIA	Coronary Artery Risk Development in Young Adults Study
Minnesota	Minnesota Children's Blood Pressure Study
Beaver County	Beaver County Lipid Study
Fels	Fels Longitudinal Study

Table 1–4. Evidence Grading System

EVIDENCE QUALITY GRADES FOR THE BODY OF EVIDENCE

Grade	Evidence
A	Well-designed randomized controlled trials (RCTs) or diagnostic studies performed on a population similar to the Guidelines' target population
B	RCTs or diagnostic studies with minor limitations; genetic natural history studies; overwhelmingly consistent evidence from observational studies
C	Observational studies (case-control and cohort design)
D	Expert opinion, case reports, or reasoning from first principles (bench research or nonhuman animal studies)

GUIDELINE DEFINITIONS FOR EVIDENCE-BASED STATEMENTS

Statement Type	Definition	Implication
Strong Recommendation	The Expert Panel believes that the benefits of the recommended approach clearly exceed the harms and that the quality of the supporting evidence is excellent (Grade A or B). In some clearly defined circumstances, strong recommendations may be made on the basis of lesser evidence (Grade C or D) when high-quality evidence is impossible to obtain and when the anticipated benefits clearly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	The Expert Panel believes that the benefits exceed the harms but that the quality of the evidence is not as strong (Grade B or C). In some clearly defined circumstances, recommendations may be made on the basis of lesser evidence (Grade D) when high-quality evidence is impossible to obtain and when the anticipated benefits clearly outweigh the harms.	Clinicians should generally follow a recommendation but remain alert to new information and sensitive to patient preferences.
Optional	Either the quality of the evidence that exists is suspect (Grade D), or well-performed studies (Grade A, B, or C) show little clear advantage to one approach versus another.	Clinicians should be flexible in their decisionmaking regarding appropriate practice, although they may set boundaries on alternatives; patient and family preferences should have a substantial influencing role.
No Recommendation	There is both a lack of pertinent evidence (Grade D) and an unclear balance between benefits and harms.	Clinicians should not be constrained in their decisionmaking and should be alert to newly published evidence that clarifies the balance of benefit versus harm; patient and family preferences should have a substantial influencing role.

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[1] NCEP Expert Panel of Blood Cholesterol Levels in Children and Adolescents. National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics 1992;89:495-501. **(PM:1741227)**

[2] American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. Pediatrics 2004;114:874-877.

[3] Hagan JF, Duncan PM, eds. 2008. Bright Futures: Guidelines for Health Supervision of Infants, Children and Adolescents, Third Edition. Elk Grove Village, IL: American Academy of Pediatrics.

2. STATE OF THE SCIENCE: CARDIOVASCULAR RISK FACTORS AND THE DEVELOPMENT OF ATHEROSCLEROSIS IN CHILDHOOD

This section presents the results of a critical review of the evidence that atherosclerosis begins in childhood and that this process, from its earliest phases, is related to the presence and intensity of known cardiovascular (CV) disease (CVD) risk factors (see Table 2–1). As described in Section I. Introduction, the literature search for these Guidelines addressed 14 critical questions (I. Introduction, Table 1–1). Of these, the first nine pertain to evidence that atherosclerosis begins in childhood and that early atherosclerosis is associated with the presence and intensity of identified risk factors; it is this evidence that is reviewed here. A conceptual model for CVD prevention by pediatric care providers beginning in childhood was developed based on the evidence review.

The risk factors considered in this analysis are listed in Table 2–1. Each risk factor exists within a behavioral, environmental, physiologic, and genetic context that provides the rationale for its consideration as a risk factor that could be used to identify persons who are at elevated risk or who may be the target of intervention. Included are conditions of life (family history, age, gender), measurable pathophysiologic risk factors (high blood pressure, lipids, overweight/obesity, diabetes mellitus), behavioral factors (tobacco exposure, nutrition/diet, physical inactivity), and emerging risk factors (metabolic syndrome, inflammatory markers, perinatal factors).

Table 2–1. Risk Factors for Cardiovascular Disease

Family history
Age
Gender
Nutrition/diet
Physical inactivity
Tobacco exposure
High blood pressure
Blood lipids
Overweight/obesity
Diabetes mellitus and other predisposing conditions
Metabolic syndrome
Perinatal factors
Inflammatory markers

Atherosclerotic vascular disease events—such as myocardial infarction, stroke, peripheral arterial disease, and ruptured aortic aneurysm—are the culmination of a lifelong disease process.[1,2] Pathologically, the process begins with the accumulation of abnormal lipid in the carotid intima, a reversible stage, progressing to an advanced stage in which a core of extracellular lipid is covered by a fibromuscular cap, culminating in thrombosis, vascular rupture, or acute ischemic syndromes.[1] Although the advanced stages of atherosclerosis and related clinical events are observed almost exclusively in adults, the initial phases of this chronic process are observed in childhood, with early changes identified even in the fetus (Figure 2-1).[2,3,4]

Figure 2–1. Atherosclerosis: A Progressive Process

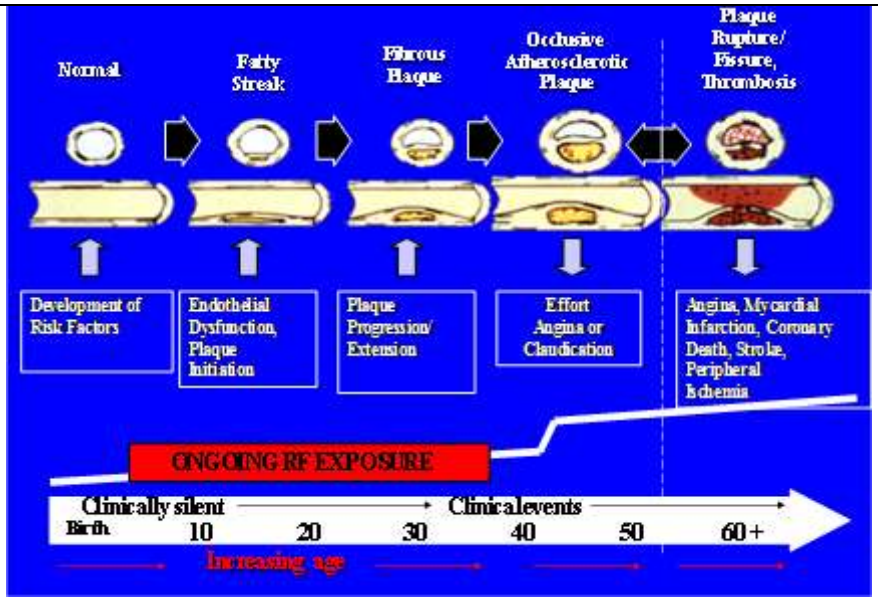


Figure 2–1 depicts the pathologic progression of atherosclerosis with aging, from no visible atherosclerosis at birth to the development of complex plaques with potential rupture and thrombosis in mid- to late adulthood. The process begins in the first decade of life when initial risk exposures occur. The progression of atherosclerosis is exacerbated and intensified by the presence of risk factors. The solid white line indicates clinical events as shown. Except in rare circumstances, atherosclerotic disease is subclinical for the first two to three decades of life.

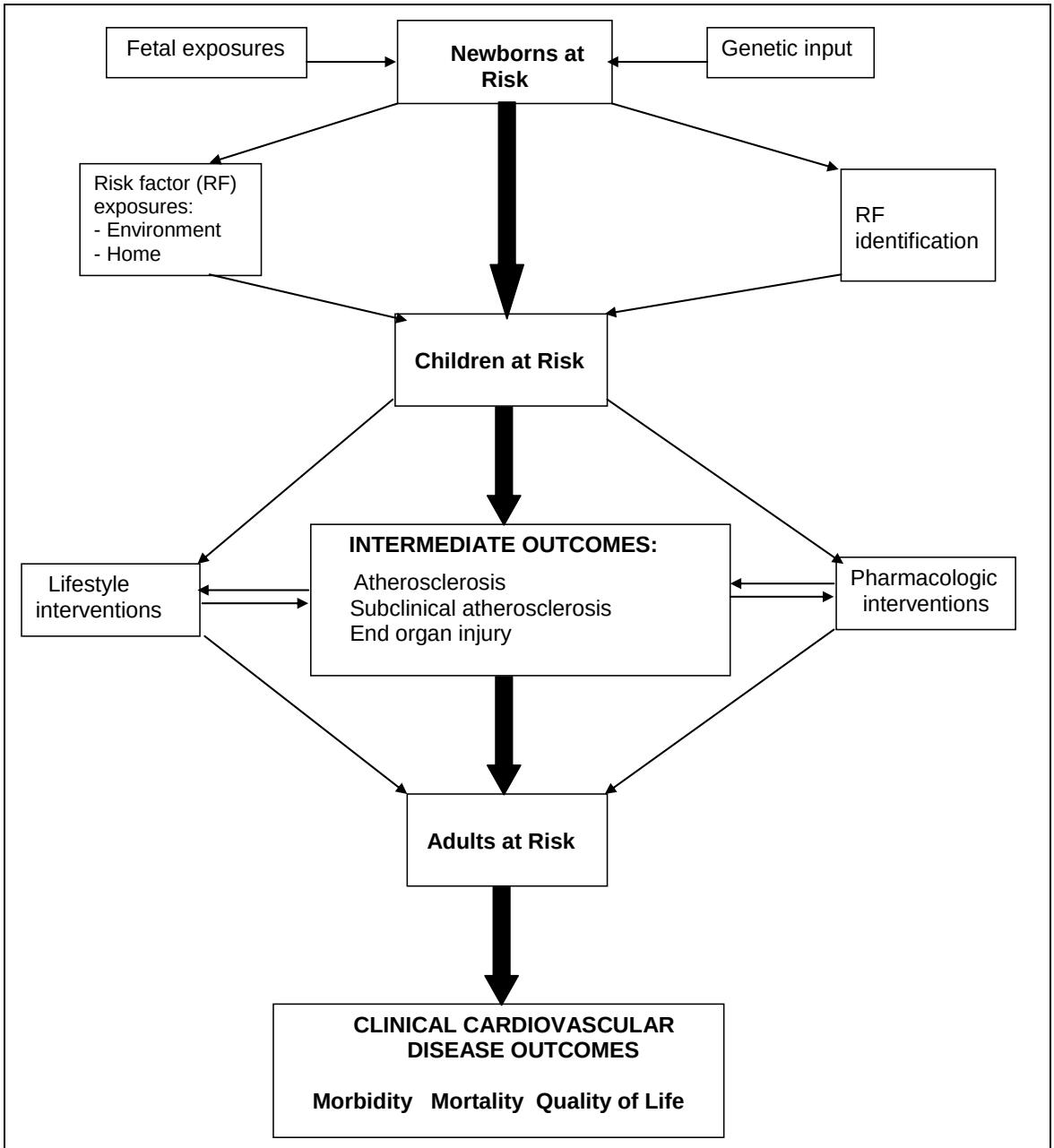
RELATIONSHIP OF RISK EXPOSURE TO ATHEROSCLEROSIS DEVELOPMENT AND CARDIOVASCULAR EVENTS

The most important evidence for the relationship of childhood risk factors to CVD is the establishment of a direct relationship between risk exposure and events. This evidence is best obtained from long-term observational studies beginning in childhood, with risk factors measured and related to CVD outcomes later in life. Because of the time course of atherosclerosis, studies of 50 to 60 years' duration linking early risk to CV events are impractical, although studies exist in which risk was measured in early adulthood and outcomes were measured much later in life. Clinical trials of voluntary risk exposure, in which children

would be randomized at birth to become, for example, chronic smokers, to determine the likelihood of future heart attack decades later, would be both impractical and unethical.

Thus, studies examining the clinical importance of CV risk in childhood must consider end points recognized as intermediate stages in the pathogenesis of CVD. This pathway is illustrated in Figure 2–2. Studies of this pathway include correlation analyses of risk factors measured either ante mortem or post mortem, with the extent of atherosclerosis at autopsy following accidental death early in life; longitudinal studies of individuals with specific genetic mutations that confer either lifelong risk exposure or protection; studies of individuals with risk assessed in childhood and subclinical measures of atherosclerosis (e.g., carotid intima media thickness (cIMT), coronary calcium measurements by computerized tomography assessed in young adulthood; studies of high-risk children who demonstrate cardiac or vascular end organ injury; and population-based studies demonstrating that the presence of risk factors in childhood predict risk in adulthood (tracking studies). Also relevant are studies of factors associated with the development of risk factors, such as a high-fat diet and a physically inactive lifestyle. The evidence review for these Guidelines includes examples of all of these study types.

Figure 2–2. Evidence Pathways Used in Developing Pediatric Cardiovascular Risk Reduction Guidelines



Legend to Figure 2–2: This flow diagram depicts the timeline for development of cardiovascular (CV) risk, atherosclerosis, and CV events along a continuum extending from before birth to adult life. The studies composing the evidence pathway are displayed relative to this process. Studies describing environmental or behavioral factors that affect the process are shown on the left side, and potential pathophysiologic or medical actions are shown on the right. The complexity of the evidence development process is apparent in the multiple interrelationships between risk factors that change and evolve throughout the history of each individual from childhood to adulthood. Atherosclerosis develops more rapidly as the number and the intensity of risk factors increase.

Considered collectively, these studies constitute an evidence chain, with the strength of the body of evidence represented in the evidence grades. Studies evaluated for the Guidelines may have examined single links in the chain of evidence, may have connected several links simultaneously, or may have evaluated the consequences of specific interventions for risk-benefit analysis. Although each study is graded individually in the evidence tables, the Expert Panel assigned summary grades for the body of evidence reviewed in developing each recommendation. The many evidence pathways pursued in preventive cardiology research and included in the evidence reviewed for the Guidelines are displayed in Figure 2–2. Some studies encompass the entire lifespan (e.g., natural history of familial hypercholesterolemia, relationship of low birth weight to CV mortality), whereas others examine the impact of interventions on intermediate outcomes (e.g., impact of cholesterol-lowering therapy on subclinical atherosclerosis, effect of exercise on CV risk factor development). The studies that make up the pathways in Figure 2–2 provide evidence addressing the key questions critical to this evidence review—including associations between exposures and outcomes, efficacy of screening for conditions of interest, the presence of adverse consequences of screening, the efficacy of interventions on outcomes, and the adverse consequences of interventions. This evidence inquiry is limited by the absence of reports of cost-effectiveness analyses of the screening and intervention strategies to lower CV risk in childhood. In contrast to adult guidelines, the challenge of preparing evidence-based guidelines for CV risk reduction in childhood is augmented by the scarcity of evidence pertaining to the impact of preventive interventions on mortality, morbidity, and quality of life.

Acute CV events in adults are the culmination of two processes: (1) the development and long-term progression of atherosclerosis and (2) a more acute thrombotic process associated with atherosclerotic plaque instability and rupture.[1] The pediatric component of this process is the development of atherosclerosis; thrombosis does not occur in the absence of the atherosclerotic

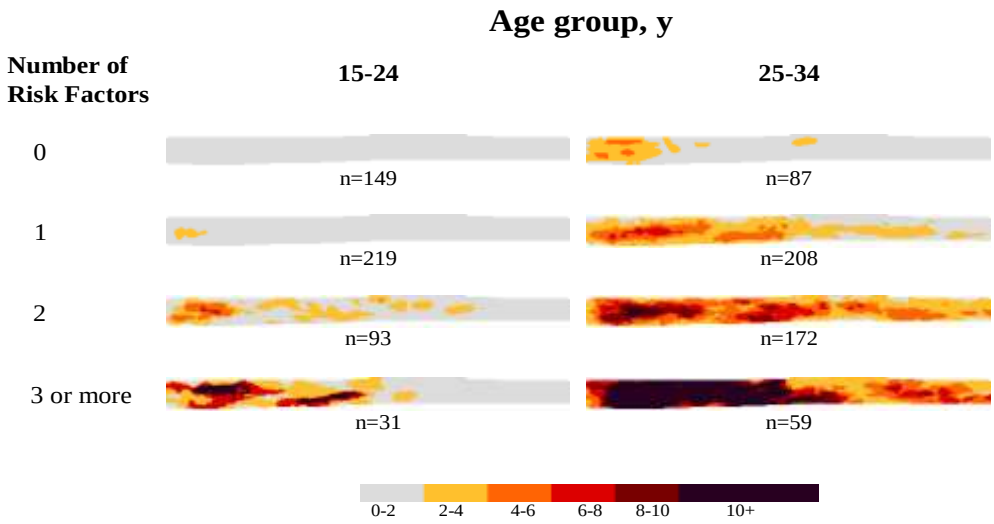
substrate. With aging, the role of risk assessment changes. Prevention of atherosclerosis development receives greater emphasis in children and young adults. In older adults, importance is placed on factors associated with the progression of atherosclerosis and factors associated with acute events, such as predisposition to thrombosis or plaque instability.

SUMMARY OF THE EVIDENCE REVIEW OF PATHOLOGIC STUDIES OF ATHEROSCLEROSIS IN CHILDHOOD

Atherosclerosis at a young age was first identified in Korean War and Vietnam War casualties.[5,6] Two major contemporary studies, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) and the Bogalusa Heart Study (Bogalusa), have subsequently demonstrated atherosclerosis, indicated by fatty streaks and more advanced lesions, in children, adolescents, and young adults who died as a result of unintentional injury. In the Bogalusa study, CV risk factors (lipids, blood pressure, body mass index (BMI), tobacco use) were measured as part of a comprehensive school-based epidemiologic study of a biracial community. Findings were related to atherosclerosis measured at autopsy after accidental death, and strong correlations were shown between the presence and intensity of risk factors and the extent and severity of atherosclerosis.[3,7] In the PDAY study, risk factors and surrogate measures of risk factors were measured post mortem in 15- to 34-year-olds who died accidentally of external causes. Strong relationships were demonstrated between atherosclerotic severity and extent and the presence and intensity of known risk factors, including higher age, higher non-high-density lipoprotein cholesterol (non-HDL–C), lower HDL cholesterol (HDL–C), hypertension (determined by renal artery thickness), tobacco use (thiocyanate concentration), diabetes mellitus (glycohemoglobin), and obesity in males. There was a strikingly higher atherosclerotic severity and extent as the number of risk factors increased.[8,9,10,11] An international study with more limited information on risk factors was consistent with these findings.[12]

Figure 2–3, from the PDAY study, shows the relationship between the number of identified CV risk factors and the pathologic lesions of atherosclerosis by age in the right coronary artery, using maps of arterial segments created by converting pathologically classified lesions to computerized images. These are displayed as prevalence maps of fatty streaks and raised lesions, with color intensity reflecting the density and grade of the lesions.[13] In 15- to 24-year-old subjects, the maps demonstrate the impact of increasing numbers of risk factors on both the presence and severity of the atherosclerotic process. Comparison with 25- to 34-year-olds shows the impact of both age and multiple risk factors. Risk, particularly the presence of multiple risk factors, accelerates the development of atherosclerosis. Finally, and most importantly, Figure 2–3 demonstrates that the absence of identified risk factors is associated with a virtual absence of advanced atherosclerotic lesions (American Heart Association Grades IV and V) in 15- to 34-year-olds.

Figure 2–3. Atherosclerosis Maps of the Right Coronary Artery



These computerized images from the Pathobiological Determinants of Atherosclerosis in Youth study are prevalence maps of fatty streaks and raised lesions, with color intensity reflecting the density and grade of the lesions for the two age groups and the number of risk factors.
SOURCE: Edward E. Herderick and C. Alex McMahan for the Pathobiological Determinants of Atherosclerosis in Youth Study Group, unpublished observation.

Comparison of the PDAY cohort to population-based data on CV risk factors obtained concurrent with acquisition of PDAY specimens suggests that risk distribution of the PDAY cohort mirrors the general population, after adjustment for factors associated with premature death.[14] This comparison to a living cohort also suggests that the PDAY risk relationships are conservative; measuring risk post mortem adds additional variability to the plasma- and serum-based risk measures.

SUMMARY OF THE EVIDENCE REVIEW ON MEASURES OF END ORGAN INJURY AND ATHEROSCLEROSIS IMAGING STUDIES

Measures of subclinical atherosclerosis and end organ injury include the presence of coronary calcium on electron beam computerized tomography (EBCT) imaging, increased medial thickness of the carotid artery assessed with ultrasound (cIMT), reduced endothelium-dependent dilation of the brachial artery with ultrasound imaging (flow-mediated dilation (FMD)), and increased left ventricular mass (LVM) by cardiac ultrasound. In adolescents with familial heterozygous hypercholesterolemia (FH), studies have shown abnormal levels of coronary calcium, increased cIMT, and impaired FMD.[15,16,17] Children with hypertension have increased cIMT, increased LVM, and eccentric left ventricular geometry.[18,19,20] Children with type 1 diabetes mellitus (T1DM) have significantly abnormal FMD and, in some studies, increased cIMT. In addition, adverse interactions with hypertension, obesity, and a high-fat diet have been observed in children with T1DM.[21,22,23,24,25] Children and young adults with a family history of myocardial infarction have increased cIMT, higher prevalence of coronary calcium, and impaired FMD.[26,27,28,29] Endothelial dysfunction has been demonstrated by ultrasound and plethysmography in association with cigarette smoking (passive and active) and obesity.[30, ,31,32,33] In several randomized controlled trials, a change in FMD has been used to assess the response to an exercise intervention.[34,35,36] Left ventricular hypertrophy at levels associated

with excess mortality in adults has been demonstrated in children with severe obesity and impaired glucose tolerance.[37]

Subclinical atherosclerosis imaging studies (coronary calcium by EBCT, cIMT) have been important in demonstrating the importance of childhood risk factors to future atherosclerosis. Four longitudinal studies have shown the relationships of risk factors measured in childhood and young adulthood—low-density lipoprotein cholesterol (LDL–C), non-HDL–C and serum apolipoproteins, obesity, hypertension, tobacco use, and diabetes—with measures of subclinical atherosclerosis in later adulthood.[38,39,40,41,42,43,44,45,46] In many of these studies, risk factors measured in childhood and adolescence were better predictors of adult atherosclerosis than were risk factors measured at the time of the subclinical atherosclerosis study.[38,41,42,43,45] In two of these cohorts, worsening risk status between the earliest and latest measurements was associated with increased evidence of the presence of atherosclerosis.[47,48]

SUMMARY OF THE EVIDENCE REVIEW LINKING RISK FACTORS IN CHILDHOOD TO CLINICAL CARDIOVASCULAR DISEASE

The most important evidence relating risk in childhood to clinical CVD is the observed association of risk factors for atherosclerosis to clinically manifest CV conditions. Genetic disorders related to high cholesterol are the biologic model for risk factor impact on the atherosclerotic process. In homozygous hypercholesterolemia, where LDL–C levels exceed 800 mg/dL beginning in infancy, coronary events begin in the first decade of life, and lifespan is severely shortened. In heterozygous hypercholesterolemia, in which LDL–C levels are minimally 160 mg/dL and typically higher than 200 mg/dL beginning in infancy, 50 percent of men and 25 percent of women experience clinical coronary events by age 50 years.[49,50] In contrast, genetic traits associated with low cholesterol are associated with longer life

expectancy.[51] In the PDAY study, every increase in non-HDL–C of 30 mg/dL was associated with incremental increases in the extent and severity of atherosclerosis, including the presence of advanced lesions associated with clinical myocardial ischemia.[52] In natural history studies of diabetes mellitus, early CVD mortality is so consistently observed that the presence of diabetes mellitus is considered evidence of vascular disease in adults.[53] Consonant with this, in 15- to 19-year-olds in the PDAY study, the presence of hyperglycemia was associated with advanced atherosclerosis of the coronary arteries.[54,55] In a 25-year followup, the presence of the metabolic syndrome risk factor cluster in children predicted clinical CVD in adults ages 30–48 years.[56] In the PDAY study, there is a strong relationship between abdominal aortic atherosclerosis and tobacco use.[12,52] This aligns with the epidemiologic evidence of an observed attributable risk of 80 percent for tobacco use with the incidence of abdominal aortic aneurysms.

As described above, there is evidence to indicate that hypertension, dyslipidemia, diabetes, obesity, and cigarette smoking—established risk factors for CVD in adults—contribute to the early development of atherosclerosis, with the exception of two risk factors. The first is physical fitness. Studies directly relating fitness levels in childhood to future atherosclerosis have not been performed. However, longitudinal studies have shown that optimal CV risk profiles are seen in individuals who are consistently physically active.[57,58,59] Tracking of both sedentary and active behaviors is moderately strong from childhood to young adulthood, with the most consistent tracking seen for higher levels of physical activity at 9–18 years of age, predicting higher levels of physical activity later in life.[60,61] The second risk factor is HDL–C. In adults, lower HDL levels are consistently shown to be associated with increased risk for CVD. In children, relationships between this risk factor and future atherosclerosis have been demonstrated, but the magnitude of the relationship is smaller than that shown in studies in adults.[38,42,52]

SUMMARY OF THE EVIDENCE REVIEW ON THE IMPACT OF RACIAL/ETHNIC BACKGROUND AND SOCIOECONOMIC STATUS IN CHILDHOOD ON THE DEVELOPMENT OF ATHEROSCLEROSIS

CVD has been observed in diverse geographic areas and in all racial and ethnic backgrounds. Cross-sectional research in children has shown differences by race and ethnicity and by geography for the prevalence of CV risk factors; these differences are often partially explained by differences in socioeconomic status (SES).[62,63,64,65,66,67,68,69,70,71,72] No group within the United States is without a significant prevalence of risk. Several longitudinal cohort studies referenced extensively in these Guidelines (Bogalusa, PDAY, Coronary Artery Risk Development in Young Adults (CARDIA)) examine biracial populations, although longitudinal data for Hispanic, Native American, and Asian children are lacking. Clinically important differences in the prevalence of risk factors exist by race and gender, particularly with regard to tobacco use rates, obesity prevalence, hypertension, and dyslipidemia. In adults, the influence of obesity on CV risk may vary by ethnicity.[73] Low SES in and of itself confers substantial risk. Evidence is not adequate for the recommendations provided in these Guidelines to be specific to racial or ethnic groups or to SES.

SUMMARY OF THE EVIDENCE REVIEW ON THE IMPACT OF MULTIPLE RISK FACTORS IN CHILDHOOD ON THE DEVELOPMENT OF ATHEROSCLEROSIS

Although genetic dyslipidemias and diabetes mellitus are recognized as high-risk states, from a population standpoint, it is the clustering of multiple risk factors that is most commonly associated with premature atherosclerosis. As demonstrated in the PDAY, CARDIA, Young Finns, and Bogalusa studies and as shown in Figure 2–3, the presence of multiple risk factors is associated with striking evidence of an accelerated atherosclerotic process. The two most

prevalent multiple risk combinations are tobacco use with one other risk factor[74] or the development of obesity, which often is associated with insulin resistance (as opposed to elevated blood sugar in adults), elevated triglycerides, reduced HDL–C, and elevated blood pressure. This latter combination, known as the metabolic syndrome in adults, has become increasingly prevalent in childhood.[67,75,76,77,78,79,80,81,82,83,84,85] Another risk factor that frequently occurs in combination is low cardiorespiratory fitness. This was identified in 33.6 percent of adolescents in the National Health and Nutrition Examination Survey from 1999 to 2002 and was inversely associated with overweight and obesity, elevated total cholesterol levels, higher systolic blood pressure, and reduced HDL–C.[86]

The relationship of the current obesity epidemic in children to future CVD and diabetes in adulthood is considered one of the most important public health challenges in the United States, particularly given the fact that more than 30 percent of the U.S. pediatric population is above the 85th percentile of the age- and gender-specific BMI for the generation of the 1970s and 1980s, with Native Americans, Hispanics, and African Americans disproportionately affected.[87] There is ample evidence from both cross-sectional and longitudinal studies that obesity-related risk factor clustering exists in childhood and continues into adulthood.[57,67,78,79,82,88,89,90,91]

SUMMARY OF THE EVIDENCE REVIEW ON RISK FACTOR TRACKING

Tracking studies from childhood to adulthood exist for all the major risk factors, including obesity, dyslipidemia, diabetes, cigarette smoking, and hypertension. Obesity tracks more strongly than any other risk factor. Among the many studies demonstrating this tracking,[72,92,93,94] one of the most recent is a report from the Bogalusa study, which followed more than 2,000 children from 5 to 14 years of age at initial evaluation to adult followup at a mean age of 27 years. Based on BMI percentiles derived from the study population, 84 percent of those with a

BMI in the 95th to 99th percentiles as children were obese as adults.[95] For obesity, increased correlation is seen with increasing age at which the elevated BMI is obtained. For cholesterol and blood pressure, tracking correlation coefficients in the range of 0.4 have been reported and are consistent across many studies, correlating these measures in children 5 to 10 years of age with results 20 to 30 years later.[96,97,98,99,100,101,102,103,104] These data suggest that having cholesterol or blood pressure levels in the upper portion of the pediatric distribution makes having these as risk factors as adults likely but not certain. Individuals who develop obesity have been shown to be more likely to develop hypertension or dyslipidemia as adults.[72,94] Tracking data on physical activity are more limited. Physical activity levels do track but not as strongly as the other risk factors.[60,61,105] Because of tobacco's addictive nature, its use often persists into adulthood, although approximately 50 percent of those who have ever smoked eventually quit.[106] T1DM is a lifelong condition. The insulin resistance of T2DM can be reduced by exercise, weight loss, and bariatric surgery, but the long-term outcome of T2DM diagnosed in childhood is not known.[107] As stated above, risk factor clusters, such as those seen with obesity and the metabolic syndrome, have been shown to track from childhood to adulthood.[67,78,79,82,88,89,90,91]

CARDIOVASCULAR DISEASE PREVENTION BEGINNING IN CHILDHOOD

The rationale for these Guidelines derives from several factors:

- Atherosclerosis, the precursor of CV morbidity in later life, originates in childhood.
- Risk factors for the development of atherosclerosis can be identified in childhood.
- To a greater or lesser extent, risk factors track from childhood to adulthood.
- Safe and effective interventions exist to manage identified risk factors.

It is important to distinguish between the goals of prevention at young ages and such goals at older ages when atherosclerosis is well-established, morbidity already may exist, and the process is only minimally reversible (Figure 2–2). At middle age and older, the goals are to prevent clinical events from occurring and to minimize the risk of future events in those with existing morbidity. At a young age, historically there have been two goals of prevention: (1) prevent the development of risk factors (primordial prevention) and (2) recognize and manage those children and adolescents at high risk due to the presence of one severe risk factor or multiple risk factors (primary prevention). With the development of measures of subclinical atherosclerosis, left ventricular hypertrophy, and endothelial function, the potential to assess a third goal has emerged: documentation of the prevention of the early stages of atherosclerosis and other forms of CV pathology. It is well-established that a population that enters adulthood with lower risk will have less atherosclerosis and will collectively have lower CVD rates.[1] This concept is supported by research showing that (1) populations with low levels of CV risk factors have low CVD rates and that changes in risk in those populations are associated with changes in CVD rates; (2) control of risk factors in those populations leads to declines in CVD morbidity and mortality; and (3) individuals in those populations without childhood risk have minimal atherosclerosis at ages 30–34 years, absence of subclinical atherosclerosis as young adults, extended life expectancy, and a better of quality of life free from CVD.[1,107,108,109,110,111,112]

Pediatric CVD prevention occurs in two settings: clinical practice and public health. These Guidelines focus on the clinical practice setting. That does not diminish the critical importance of public health measures to CVD prevention. For risk factors such as tobacco use and physical inactivity, public health measures are critical for risk reduction. For risk factors such as hypertension, diabetes mellitus, obesity, and dyslipidemia, public health measures will affect prevalence, but without medical recognition and treatment, effective risk reduction cannot occur.

THE PATHWAY TO RECOMMENDING CLINICAL PRACTICE-BASED PREVENTION

The most direct means of establishing evidence for active CVD prevention beginning at a young age would be to randomize young individuals with defined risks to treatment of CV risk factors or to no treatment and then to follow both groups over sufficient time to determine whether CV events are prevented without undue increase in morbidity arising from treatment. This direct approach is attractive because atherosclerosis prevention would begin at the earliest stage of the disease process, thereby maximizing benefit. Of course, this approach is as unachievable as it is attractive. Such a study would be extremely expensive and would require a high level of adherence and participant retention over several decades, during which time changes in environment and medical practice would diminish the relevance of the results. Many scenarios could arise in which the ethics of such a trial could be questioned, including undue exposure to risk in one of the trial arms, the discovery of novel treatments of improved efficacy during the conduct of the trial, environmental changes or shifts in priorities of the funding entity that complicate its completion, and the potential withholding of effective therapy to a generation of youths with identified risk who do not receive treatment.

The recognition that evidence from this direct pathway is unlikely to be obtained requires an alternate stepwise approach, linking segments of an evidence chain in a manner that serves as a sufficiently rigorous proxy for the causal inference of a clinical trial. Figure 2–2 demonstrates the components of this evidence chain, with links comprising a series of critical studies leading from risk beginning before birth, to risk acquisition during childhood, to risk modification by reduction strategies, and finally to clinical disease in adulthood. Studies evaluated for these Guidelines may examine single links in this evidence train, connect several links simultaneously, or evaluate the consequences of specific interventions to allow risk-benefit analysis. Some studies encompass the entire lifespan, whereas others examine the impact of interventions on

intermediate states. Many of these evidence links come from the epidemiologic studies described in this entire section and provide answers to the first nine critical questions of the evidence review: atherosclerosis begins in childhood, atherosclerosis is related to risk factors that can be identified in childhood, and the presence of these risk factors in a given child predicts an adult with risk factors.

The remaining evidence links pertain to the determination of whether interventions that aim to reduce risk factors will have a health benefit and whether the risk and cost of interventions to reduce risk are outweighed by the reduction in CVD morbidity and mortality. These issues are captured in the critical questions related to intervention (see I. Introduction, Table 1–1, questions 9–14), which are addressed subsequently in the evidence review of each risk factor. The best evidence for answering these questions derives from randomized trials showing event reduction in adults, randomized trials in children showing risk reduction with change in subclinical measures of atherosclerosis or target organ damage and patient safety, genetic studies that provide a model for the adverse effects of sustained exposure to risk, and long-term observational studies demonstrating the benefit of maintenance of low risk on health and all-cause mortality. Recommendations to intervene must consider not only the relationship of the risk factor to future disease but also whether reduction of that risk factor will result in an appreciable decline in subclinical disease or in adverse clinical events with an acceptable safety profile. The presence of a risk factor may confer a high relative risk of a future CV event, but intervention may not be warranted if actual event rates in the next several decades are low; conversely, a lower relative risk may be acceptable for intervention if the likelihood of an adverse event related to that risk factor is high. The timing and safety profile of pharmacologic interventions are important considerations for CVD prevention. The lifetime risk of disease associated with high risk in childhood may identify candidates for more aggressive intervention.

Intervention planning must consider that each risk factor exists within an individual's unique combination of environmental, behavioral, physiologic, and genetic characteristics. This context determines the timing and type of intervention under consideration. A family history showing multiple members affected by clinical CVD at a young age suggests the need to investigate both genetic risk and toxic environmental exposure and to consider early risk reduction. For example, tobacco use is a behavior with significant environmental predictors. That this behavior is highly addictive means that the use of tobacco alone is an indication for smoking cessation counseling. In contrast, recommendations to treat elevated blood pressure are based on multiple elevated measures over time because of the intrinsic variability of blood pressure and the possibility of significant modification through diet and exercise. However, the presence of elevated blood pressure and evidence of target organ damage (i.e., left ventricular hypertrophy) prompt more aggressive intervention. The presence of multiple risk factors represents a powerful stimulus for accelerated atherosclerosis, and knowledge of this situation affects treatment decisions. As described throughout these Guidelines, recommended strategies for intervention should consider environmental, behavioral, physiologic, and genetic attributes, as well as the efficacy and safety of potential treatment modalities, in selecting the type and timing of any intervention and in measuring outcomes.

For certain behavioral risk factors, limitations in measurement and data collection make the establishment of a causal pathway between the risk factor and disease impossible. There is unlikely to be a study comparing the effect of a lifetime of whole-milk consumption with fat-free milk consumption, or a study comparing daily physical training for decades with a lifetime of inactive television watching on the amount of atherosclerosis or rates of myocardial infarction. What is important about diet and exercise in childhood is the relationship of healthful behaviors to the development of future risk factors, including obesity, diabetes mellitus, hypertension, and dyslipidemia. Consequently, recommendations must include studies that examine the impact of

interventions on risk factor development and reduction rather than studies that only examine the effects on subclinical disease measures or clinical events.

Since risk levels in the preadolescent pediatric population with normal weight for height are generally below levels associated with CV events,[113] a critical component of pediatric CVD prevention is understanding those factors associated with the evolution from the low-risk state of childhood to the presence of risk in adulthood. The well-established factors on this environmental-behavioral axis are initiating tobacco use and becoming obese. Although the evidence for a heart healthy diet and physical activity in the treatment of established risk factors is strong, less strong but emerging evidence suggests that an energy-balanced, nutrient-dense diet and consistent routine levels of physical activity that promote physical fitness prevent risk factor acquisition over the course of decades. Given that at least 40 percent of the U.S. population currently experiences CVD and that maintaining a low-risk state prevents CVD most effectively, emphasis on healthful behaviors in children, in the absence of established risk factors, assumes added importance.[1,2]

A new consideration is the role of new noninvasive measures of cardiac and vascular injury in the evaluation of evidence. These include measurements of vascular functioning and arterial stiffness like FMD; noninvasive measures of atherosclerosis, such as cIMT and coronary artery calcium; and measures of cardiac characteristics, such as LVM by echocardiography. For adults, the primary use of these technologies has been in event prediction; that is, whether the presence of one of these markers increases the likelihood of a future CV event beyond that expected from conventional risk factor assessment. There remains considerable controversy over the clinical roles of these tests in adults. For children and adolescents, the role of these measurements may be different. Rather than predicting clinical events, future research may show that a positive test signals the transition to more advanced atherosclerosis or the

presence of CV target organ damage. Studies of subclinical atherosclerosis and LVM have been important in establishing the relationship of risk in childhood to evidence of CV injury. Monitoring of LVM has been incorporated into treatment algorithms for hypertension in childhood.[113] However, only a few studies in the pediatric age group have used these measures as clinical end points. It is expected that research using these intermediate end points will be used to clarify knowledge gaps identified in the evidence review for these Guidelines; the clinical importance of these new studies in adults and children remains to be fully established.

Thus, for each risk factor discussed in the sections below, recommendations reflect a complex decision process that integrates the strength of the evidence with knowledge of the natural history of atherosclerotic vascular disease, estimates of intervention efficacy and risk, and the physician's responsibility to provide both health education and effective disease prevention and treatment. These recommendations for providers of health care to children will be most effective when complemented by a broader public health strategy, as discussed in Section XVI. Implications of the Guidelines for Public Policy.

THE CHILDHOOD MEDICAL OFFICE VISIT: THE IDEAL SETTING FOR CARDIOVASCULAR HEALTH MANAGEMENT

In the beginning of this section, the differences in goals for CV risk management in children and in adults were presented, along with the dual pediatric focus on primordial prevention (i.e., the prevention of risk factor development) and primary prevention (i.e., the management of specific identified risk factors). One cornerstone of pediatric care is placing clinical recommendations in a developmental context. As opposed to virtually universal recommendations that apply to nearly all adults, pediatric recommendations must consider not only the relationship of age to disease expression but also the ability of the child and the family to understand and implement

medical advice and the safety of the intervention modality. For each risk factor, recommendations must be specific to age and developmental stage. Therefore, the *Bright Future*s concept of the American Academy of Pediatrics, in which age-specific prevention measures are embedded in routine pediatric care, is used to provide a framework for these Guidelines, with CV risk reduction recommendations specific for each age group.[114]

The concept of primordial prevention is a major theme in all pediatric care. Based on the results of the evidence review, the Guidelines provide recommendations for preventing the development of risk factors and optimizing CV health beginning in infancy. Pediatric care providers—pediatricians, family practitioners, nurses and nurse practitioners, physician assistants, and registered dietitians—are ideally positioned to reinforce these CV health behaviors as part of routine care. The Guidelines also offer specific guidance on primary prevention, with age-specific, evidence-based recommendations for individual risk factor detection. Management algorithms provide staged care recommendations for risk reduction within the pediatric care setting and identify risk factor levels requiring referral to a specialist. The Guidelines also identify specific medical conditions, such as diabetes and chronic kidney disease, which are associated with increased risk for accelerated atherosclerosis. Recommendations for ongoing CV health management for children and adolescents with these diagnoses are provided.

A second cornerstone of pediatric care is the provision of health education. In the U.S. health care delivery system, doctors and nurses are perceived as credible messengers for health information. Patients and families expect physicians, nurses, dietitians, and other health care providers and counselors to provide accurate health information. The childhood health maintenance visit provides a useful context for effective delivery of the CV health message. Providing health information alone is insufficient since reduction of CV risk typically requires

behavioral changes by the child and/or the family. The office of the pediatric care provider provides an effective setting for the health care team to engage children and families in the initiation of behavior change to reduce the risk of CVD and promote lifelong CV health.

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3. SCREENING FOR CARDIOVASCULAR RISK FACTORS

Reducing lifetime risk for cardiovascular (CV) disease (CVD) is the principle that underlies all CVD prevention strategies, including those beginning in childhood. Especially important is the prevention of CVD events occurring relatively early in life (e.g., before ages 50–60 years). In these Guidelines, the Expert Panel highlights two complementary prevention strategies: (1) primordial prevention, which seeks to prevent the development of risk factors in all children and (2) primary prevention, a high-risk strategy aimed at reducing risk in children with dyslipidemia, hypertension, obesity, diabetes mellitus, or other identified factors associated with accelerated development of atherosclerotic CVD. In contrast with primordial prevention, primary prevention requires knowledge of risk factor levels through the screening of individuals. This section focuses on the principles of screening within the context of the need for practical clinical recommendations even in the presence of insufficient evidence.

Screening is common practice in regular pediatric care with age-based recommendations designed to identify conditions at appropriate times relative to both the disease process and the stage of growth and development. For example, the American Academy of Pediatrics recommends universal newborn screening for metabolic conditions, hemoglobinopathy, and hearing loss, and selective screening for elevated levels of lead in infancy and early childhood.[1] Although many screening programs have been widely adopted, they are not always evidence based. This section reviews the criteria for an effective screening program and provides discussions of both scientific and practical considerations involved in screening for CV risk factors in childhood.

Empirically, a recommendation for universal screening requires a high burden of proof. First, by definition, screening is performed on asymptomatic individuals. Second, all of the downstream

consequences of screening, both beneficial and harmful, are important to consider; sometimes they are not obvious. Third, widespread screening programs are costly.

The highest quality evidence for establishing the utility of a screening program derives from randomized controlled trials (RCTs) of screening versus no screening. Such trials compare clinical outcomes among children randomly allocated to no screening with outcomes among children allocated to screening, followed by interventions among those with identified risk. For a CV risk factor screening trial, the children in both groups would be followed for decades to determine disease incidence, and the analysis would allow balancing of benefits, risks, and costs. For CV risk factors such as dyslipidemia, hypertension, and obesity, it is unlikely that such a large, long-term study will ever exist because of the time and costs involved, as well as the great degree of difficulty in achieving high levels of adherence and followup over decades. Furthermore, by the time substantial numbers of definitive end points occurred decades later, knowledge and technology most likely would have made the initial screening test obsolete. An RCT of CV risk factor screening with shorter term followup to examine change(s) in risk factor levels or surrogate outcomes (such as noninvasive measures of subclinical atherosclerosis) may be more feasible. However, like most surrogate measures and as described in the preceding Section II, subclinical measures of atherosclerosis do not perfectly predict clinical CVD outcomes.

One argument for screening is the knowledge that extreme elevations of risk factors are associated with early and severe clinical outcomes. For example, children with coarctation of the aorta have elevation of upper body blood pressure (BP) from infancy. When surgical repair of coarctation is delayed, early death from heart attack, stroke, and aortic rupture has been well-documented.[2] Similarly, in children with extreme elevations of low-density lipoprotein

cholesterol (LDL–C) levels due to the rare inherited homozygous form of familial hypercholesterolemia, clinical CVD events begin as early as the first decade of life.[3]

The question that the Expert Panel faced is whether childhood screening to identify less severe forms of these risk factors is a useful strategy to prevent CVD events from occurring in middle-aged adults. Without definitive evidence from RCTs of screening programs, the Expert Panel was left to determine the wisdom of recommending screening in the face of suboptimal evidence but with knowledge that the atherosclerotic process begins in childhood and that the long time period required between screening during youth and clinical end points makes the most rigorous test of a CV risk factor screening program infeasible. In this situation, assessing the usefulness of screening involves evaluating alternative criteria, including attributes of the test, outcomes of interventions among children with actionable levels of test results, and the program as a whole.

TEST CHARACTERISTICS

Reproducibility

Lipids, BP, height, and weight are measurements with intrinsic biologic and measurement variability. For BP and total cholesterol (TC), LDL–C, and high-density lipoprotein cholesterol (HDL–C) levels, two or three measurements, taken several days to weeks apart, appear necessary to place most children in the categories of normal, borderline, or high with reasonable confidence.[4,5] As described in Section X. Overweight and Obesity, height, weight, and body mass index (BMI) measurements are reliably reproducible, but measurements over time are needed to provide consistent information on growth trends and to determine whether there has been an inappropriate change in the BMI percentile relative to age- and gender-specific norms.

Validity/Accuracy

To be useful, a screening test must detect the condition of interest with sufficient reliability, sensitivity, and specificity to determine whether intervention is warranted or to mandate a second test to confirm the presence of the risk factor or disease. For most screening tests, the frequency of the screened condition is low, so even high sensitivity and specificity translate into a low positive predictive value—a consideration in screening for all rare conditions.[6] From a long-term perspective, this means that a majority of children with an identified CV risk factor in childhood will not develop premature CVD events (i.e., myocardial infarction, sudden cardiac death, or stroke by ages 50–60 years). Although counted statistically as false positives, pathology studies demonstrate that these individuals develop atherosclerosis faster than children with normal risk factor levels and are at increased risk for morbidity from a range of vascular complications (see Section II. State of the Science: Cardiovascular Risk Factors and the Development of Atherosclerosis in Childhood). The destructive effects of early heart attacks and strokes, the impact of multiple risk factors in increasing the risk for such events, and especially the potential to reduce the risk of sudden death as the first manifestation of early atherosclerotic CVD mean that decisionmakers might consider a lower positive predictive value for CV risk factor screening than for childhood screening for other disease processes. Specifically, because sudden cardiac death often occurs in asymptomatic individuals, the threshold for CV screening could be lower than that for diseases that always manifest with symptoms.

Risk factors that are considered to be most strongly associated with disease can nonetheless be suboptimal as screening tests. For example, adults with TC values in the highest fifth of the population distribution have approximately a threefold higher 10-year risk of fatal ischemic heart disease than adults in the bottom fifth of the distribution. Although this appears to be a strong association, assessing a screening test requires estimating the absolute risk for individuals

rather than the relative risk. If one assumes that 5 percent of unaffected individuals will have TC levels in the top fifth of the distribution, a relative risk of 3 means that among these individuals, the test will detect only 15 percent of those destined to die from ischemic heart disease.[7] In fact, even a relative risk of 200 would increase this detection rate (i.e., the sensitivity) to just over 50 percent. In the case of a 10-year death rate of 1 percent, for every 100 persons identified with high cholesterol levels, only 3 would die of ischemic heart disease and the other 97 would be false positives. This example is simplistic since it does not take into account other coexisting risk factors for heart disease, other manifestations of vascular disease, or the fact that lifetime CVD risk is higher than a 10-year risk; however, it does convey the point that relying on relative risk can lead to overestimation of screening test performance. These considerations also underscore that, for maximal benefit, a strong population approach should accompany any high-risk approach to CVD prevention beginning in childhood.

Role of Selective Screening

Updating recommendations for lipid screening was one of the most important tasks for the Expert Panel. The original 1992 National Cholesterol Education Program (NCEP) report *National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents* (*NCEP Pediatric Guidelines*) recommended screening for elevated cholesterol levels only among children with either a family history of early CVD or elevated TC levels.[8] The rationale was that, compared with universal screening, this selective approach would identify the majority of children with elevated LDL–C levels by screening fewer individuals with similar benefits at lower costs, because a group with higher prevalence was being screened. As outlined in Section IX. Lipids and Lipoproteins, the evidence review indicates that office-based, family history-directed CV risk factor screening identifies significantly fewer children with abnormal LDL–C levels than would universal screening. When this evidence is combined with the knowledge that a complete family history is unavailable for many children,

a family history-based screening approach for cholesterol does not appear to be effective. One caveat to this conclusion is that few data address whether family history-directed screening provides a useful approach for detecting extreme LDL–C levels (i.e., those high enough to warrant medication use). Also, as described in detail in Section IX. Lipids and Lipoproteins, most studies of medication use involve positive family history as an entry criterion, so that more research is needed about the efficacy of treatment among family history-negative children with elevated LDL–C.

The obesity epidemic makes more intensive lipid screening among overweight and obese children worthy of consideration, beyond the importance of identifying obesity as an independent risk factor for future CVD. As described in these Guidelines, particularly in Section X. Overweight and Obesity, evaluation of obese children will identify a large number with dyslipidemia, typically moderate to severe elevation of triglycerides (TG), mild elevation of LDL-C and reduced HDL–C, as well as elevated BP. A very small number also will have type 2 diabetes mellitus (T2DM). Primary treatment for any of these risk factors is weight control. TG levels in particular are very responsive to weight loss and to dietary change. HDL–C levels rise in response to regular exercise. As presented in Section IX. Lipids and Lipoproteins and in Section X. Overweight and Obesity, dietary change, exercise, and weight loss can contribute to normalization of lipid levels and BP and elimination of the metabolic abnormalities in T2DM. An unanswered question for both children and adults, however, is the extent to which treatment of the dominant lipid abnormalities associated with obesity will result in reduced risk of early CV events.

Acceptability

Obtaining risk factor measurements from children requires that testing be feasible and acceptable to parents and children. Measurement of length/height and weight are routine and

well-accepted in pediatric care from birth onward. Measurement of BP, recommended for all children beginning at 3 years of age,[9] is also routine in most practices. Lipid testing requires a blood test and in the past has required overnight fasting. As described in detail in Section IX. Lipids and Lipoproteins, measuring non-HDL–C, which is accurate in the nonfasting state,[10] as the first step in lipid screening should be a major improvement in feasibility for clinical practice and acceptability to parents and children. Additional blood draws in the fasting state are needed to confirm initially abnormal levels; their acceptability to children and parents is an open question. Some older research suggests low compliance by parents and children with followup screening recommendations in real-world practice, but current data are sparse.[11]

EVALUATION OF INTERVENTIONS AMONG CHILDREN WITH ABNORMAL RISK FACTORS

As reviewed throughout these Guidelines, the major rationale for CV risk factor screening in youth, followed by treatment of abnormal levels, derives from knowledge that atherosclerosis begins in childhood and that its severity is greater in children with a higher burden of atherogenic risk factors. However, these observations do not directly address interventions to reduce this burden. A sine qua non of useful screening programs is that interventions based on abnormal screening results must be not only efficacious but also more efficacious than interventions that occur later in the disease process. If earlier interventions are not more efficacious than those initiated later in life, they incur cost and potential risk with no benefit. Studies in adults indicate that treating prehypertension with medication or lifestyle change is associated with a lower subsequent incidence of hypertension.[12,13,14] In children with coarctation of the aorta, long-term followup studies demonstrate that early surgical repair is associated with reduced incidence of subsequent CVD.[15] The extent to which efficacy of intervention in youth extends to primary and less severe hypertension is not known. For obesity and lipids, no

studies directly address the benefits (or risks) of early childhood treatment over treatment later in life on clinical disease.

The case of heterozygous familial hypercholesterolemia (FH) provides partial proof of the concept that early reduction of risk factors may reduce future disease rates. Individuals with FH are at increased risk for early CVD because of elevated LDL–C levels from infancy. In natural history studies, 50 percent of males and 25 percent of females with FH develop clinical CVD by age 50 years.[16,17] In RCTs among older children and adolescents with FH, statin treatment substantially lowers LDL–C levels and slows progression of atherosclerosis as assessed by noninvasive testing.[18] Although pediatric medication trials are of relatively short duration, they suggest that sustained LDL–C-lowering therapy in children with FH will lower the risk of early clinical CVD. By extension and by analogy with adult treatment guidelines, the Expert Panel recommends treating less extreme elevations of LDL–C in childhood, especially in the setting of multiple CV risk factors. The extent to which either lifestyle change or medication treatment of lipids in youth reduces the atherosclerotic burden or risk of CV events is not yet known, nor is the long-term safety of treatment with statins beginning in childhood, although published trials do not show any adverse impact on growth, pubertal maturation, or hormonal metabolism over several years (see Section IX. Lipids and Lipoproteins).

It is vital to know how well primary care clinicians can incorporate recommended screening programs, including testing and interventions, into routine practice. Unfortunately, evidence is meager regarding repeated testing strategies or the effectiveness or sustainability of interventions in real-world practices. Thus, the evidence review almost exclusively identified studies that addressed intervention efficacy in a research setting. Nevertheless, the Expert Panel anticipates that practices will be better equipped to adopt its recommendations in the future than they are today. The recommendations may very well effect changes in policy and

systems, as well as additional research that will assist clinicians in overcoming current time, space, personnel, and reimbursement challenges.

Other Issues

A potential ancillary benefit of childhood CV risk factor screening is to alert older family members of the need to have their own risk factors checked, especially lipids. If they have not been screened previously, parents and grandparents of children with abnormal lipid values should have their own lipid levels checked by their primary care providers. Several studies have shown that first-degree relatives of children with elevated LDL–C levels have both higher LDL–C levels themselves and higher rates of CV events.[19,20,21]

It is also possible that knowledge of an abnormal risk factor in a child could spur lifestyle changes for the whole family. Many clinicians can cite anecdotes of families who made salutary changes after learning of a child's elevated cholesterol, BP, or BMI. However, the extent to which this phenomenon occurs is unclear, nor is it known whether this effect adds substantially to a concerted primordial prevention approach aimed at all children and families. Certainly, the literature is clear that, in general, knowledge alone is insufficient for effective behavior change.

FURTHER RESEARCH NEEDED

One of the most difficult issues to address in CV risk factor screening in childhood is the potential value of slowing or reversing atherosclerosis in its early stages. This issue is particularly important with respect to lipids. Statin treatment among high-risk adults reduces CV events within months of initiation.[22] However, statin therapy does not eliminate risk, and adult trials cannot include those who have already died of very early CV events, of which sudden

death is a particular concern. Thus, an RCT of childhood CV risk factor screening and treatment of elevated levels with a noninvasive measure of atherosclerosis as the primary outcome is an appealing study design. This study design could apply to any of the childhood CV risk factors, not just elevated LDL–C. As described in the previous section, one caveat of using measures of subclinical atherosclerosis as end points is that, whether invasive or noninvasive, all of those measures are surrogates for the true outcome of clinical CV events. Trials with surrogate end points have sometimes led to misleading recommendations and harmful clinical practices.[23]

Through the assessment of benefit, risk, and cost, the science of clinical decisionmaking offers an alternative to large long-term trials for the evaluation of CV risk factor screening in children. A decision analytic framework allows modeling of the immediate and downstream consequences of assessing childhood risk factors and intervening among those with abnormal results. As with any analytic method, decision analysis has strengths and weaknesses. The most important attribute of decision analysis is to ask the right questions. In the case of childhood CV risk factor screening, one strength of decision analysis is the ability to compare a number of strategies, including no screening or intervention, primordial prevention approaches only, universal or selective screening at specific ages, and the marginal benefit of screening at younger versus older ages. If a model contains appropriate decision points and outcomes, it can be a valuable method for assessing effects on long-term health outcomes without having to wait decades. In such a model, empirical evidence drives the quantitative comparison of one decision versus another. A good decision analysis not only will point out where data are lacking but also, through sensitivity analysis, will identify the most important new data to collect. The cost to society at large will likely be a major factor in decisions regarding screening. When added to a decision analytic model, the costs of screening, followup, and intervention can lead to estimation of the cost-effectiveness of various screening strategies, and sensitivity analysis

can show where variability in costs is meaningful or irrelevant. Cost-effectiveness can be a major driver of policy decisions to support prevention programs. For these reasons, well-considered cost-effectiveness analyses of childhood CV risk factor screening should be a priority for future research.

CONCLUSIONS

The Expert Panel recommends two complementary strategies to reduce future risk for clinical CVD. Primordial prevention seeks to prevent the acquisition of risk factors by optimizing CV health for all, beginning in infancy. Primary prevention requires screening to identify children at increased risk for CVD. This section focused on screening and reviewed the limitations of current knowledge within the requirements for a useful screening program. Taking these factors into account, the Expert Panel recommends routine measurement of length/height and weight beginning in infancy, with calculation of BMI annually beginning at age 2 years to identify growth trends; yearly assessment of BP from age 3 years; and universal screening for lipid abnormalities by a nonfasting non-HDL–C level at age 10 years. These screening strategies, described in detail in the respective risk factor sections of these Guidelines, will identify a relatively large number of children for whom the Expert Panel recommends intensified lifestyle intervention. Only a small number of children will require pharmacologic therapy. While they await the results of future research, the Expert Panel members conclude that recommending these assessments, followed by interventions as part of routine pediatric care, represents the best current primary prevention strategy to lower lifetime risk of atherosclerotic vascular disease.

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4. FAMILY HISTORY OF EARLY ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

INTRODUCTION

This section of the Guidelines provides recommendations to pediatric care providers on obtaining and using family histories for early cardiovascular (CV) disease (CVD) in managing CV health in their patients. The section begins with background information on the role of a positive family history of early atherosclerotic disease in evaluating risk for future heart disease. The evidence review and the development process for the Guidelines are outlined in Section I. Introduction and are described in detail in Appendix A. Methodology. As described, the evidence review augments a standard systematic review, where findings from the studies reviewed constitute the basis for recommendations, with each study described in detail. This evidence review combines a systematic review with an Expert Panel consensus process that incorporates and grades the quality of all relevant data based on preidentified criteria. Because of the large volume of included studies and the diverse nature of the evidence, the Expert Panel also provides a critical overview of the studies reviewed for each risk factor, highlighting those that, in its judgment, provide the most important information. Detailed information from every study has been extracted into the evidence tables, which will be available at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. The conclusions of the evidence review are summarized and graded, and the section ends with the Expert Panel's age-specific family history recommendations. Where evidence is inadequate, recommendations reflect a consensus of the Expert Panel. References are listed sequentially at the end of the section, with references from the evidence review identified by unique PubMed identifier (PMID) numbers in bold text. Additional references do not include the PMID number.

BACKGROUND

A family history of CVD represents the net effect of shared genetic, biochemical, behavioral, and environmental components. In adults, epidemiologic studies have demonstrated that a family history of premature coronary heart disease in a first-degree relative—heart attack, treated angina, percutaneous coronary catheter interventional procedure, or coronary artery bypass surgery, stroke or sudden cardiac death in a male parent or sibling before age 55 years or a female parent or sibling before age 65 years—is an important independent risk factor for future CVD. The process of atherosclerosis is complex and involves many genetic loci and multiple environmental and personal risk factors. Nonetheless, from a sentinel study in this area, the presence of a positive parental history doubled baseline risk for CVD.[1] Offspring risk was strongly inversely related to the age of the parent at the time of the index event. The association of a positive family history with increased CV risk has been confirmed for men, women, and siblings and for different racial and ethnic groups.[2,3,4,5,6,7,8]

OVERVIEW OF THE EVIDENCE FOR IMPACT OF FAMILY HISTORY OF CARDIOVASCULAR DISEASE ON ATHEROSCLEROSIS IN CHILDREN AND ADOLESCENTS

In young subjects, autopsy findings and vascular function abnormalities have been correlated with a family history of premature coronary disease. In infants with a positive family history of early coronary disease, relative luminal narrowing has been demonstrated in the left and right coronary arteries at post mortem compared with infants without such a history.[9] A series of vascular studies have demonstrated subclinical abnormalities: Carotid intima-media thickness (cIMT) assessed by ultrasound has been shown to be increased in children, adolescents, and young adults with a parental history of myocardial infarction.[10,11] Endothelium-dependent

dilation of the brachial artery (FMD) is impaired in young subjects with a family history of premature coronary heart disease.[12] In a combined study, cIMT was significantly increased and FMD was significantly reduced in young healthy teenagers whose parents had experienced a myocardial infarction compared with controls with a negative family history.[13] Two generations of the Framingham Heart Study were evaluated for the presence of coronary artery and abdominal aortic calcification (AAC). A history of premature parental CVD and/or coronary artery disease (CAD) was significantly associated with the presence of coronary artery calcium in young- to middle-aged third-generation cohort subjects; AAC was associated only with parental coronary heart disease.[14] Although it has not been shown how arterial wall changes early in life relate to adult clinical disease, the presence of both structural and functional abnormalities of arterial function, combined with the large body of epidemiologic data, supports the concept that a positive family history of early CAD is an important independent risk factor for accelerated atherosclerosis.

OVERVIEW OF THE EVIDENCE FOR ASSOCIATION OF FAMILY HISTORY OF CARDIOVASCULAR DISEASE WITH ABNORMAL CARDIOVASCULAR RISK PROFILES IN CHILDREN AND ADOLESCENTS

In addition to its strength as an independent risk factor, the presence of a positive family history is associated with an unfavorable CV risk profile in the family constellation. In offspring, a parental history of early CVD has been shown to be associated with an adverse CV risk factor profile.[4] The Muscatine Study and the Bogalusa Heart Study both demonstrate that a history of coronary heart disease in parents is associated with unfavorable CV risk profiles in their children. In the Muscatine Study, selecting children with total cholesterol (TC) above the 95th percentile, identified a family group with increased coronary mortality.[15] When index cases were children who were consistently obese on three successive Muscatine surveys, the relative risk

of dying from a CV cause was significantly increased for family members compared with lean and random group relatives.[16] From a cross-sectional analysis of more than 8,000 children in the Bogalusa study, offspring with a history of parental heart attack were significantly overweight after age 10 years and showed elevated levels of TC, low-density lipoprotein cholesterol (LDL–C), insulin, and glucose after age 17 years.[17] In a subsequent cohort study of children from the Bogalusa Study with a verified history of parental CAD, the adverse CV risk profile findings of the first study were confirmed: A positive family history was associated with obesity beginning in early childhood and with elevations of TC and LDL–C as well as glucose.[18] The association of a positive family history with an unfavorable CV risk profile suggests that both familial environmental influences and gene-environment interactions may underlie the increased risk associated with a positive family history.

OVERVIEW OF THE EVIDENCE FOR FAMILY HISTORY OF CARDIOVASCULAR DISEASE AND RISK REDUCTION IN CHILDREN AND ADOLESCENTS

The evidence review identified two randomized controlled trials in which the presence of familial CVD was a selection criterion. In a Norwegian study, young first-degree relatives of subjects with verified premature CAD were randomized to either a combined smoking cessation and low-fat diet modification or to usual care.[19] Outcome variables were smoking rates, lipid profiles, and a range of oxidative, inflammatory, and procoagulant markers. In the intervention group, there was a significant decrease in cholesterol and saturated fat intake with an associated decrease in LDL–C, oxidized LDL, and E-selectin, a vascular adhesion molecule. There was also a decrease in smoking in the intervention group, with an associated decrease in intercellular adhesion molecule-1. A second lifestyle intervention trial in Australian teenagers who were identified when a parent was hospitalized for treatment of angina or myocardial infarction showed minimal decreases in fat intake and serum cholesterol.[20]

If family history information is to be used to infer risk for CVD, reported information must be accurate. Unfortunately, even in subjects from established epidemiologic studies, the accuracy of reported family history for heart disease is variable. From the Framingham Heart Study, offspring reports of parental CVD and CV risk factors were compared with confirmed medical evidence of parental CV status.[21] Positive reports of high blood pressure, diabetes, and high cholesterol were accurate for mothers and fathers. By contrast, positive predictive values for a history of parental heart attack and stroke were low. Although this is partially due to the low prevalence of early onset heart disease in the Framingham population, it also reflects lack of awareness of parental disease. Since the Framingham cohort could be considered to represent a "best-case scenario" for the accuracy of parental CV history, inaccuracy is likely to be even more prevalent in the general population. One role for pediatric health care providers is to educate parents and families about the importance of complete and accurate family health history information. Life circumstances, such as divorce and geographic separation, can make learning about a family history difficult. Although there is nothing that can be done about missing family history information in adopted individuals, encouraging young parents to learn their own health history whenever possible, even when families are fragmented and family members are separated, should help improve future knowledge about this important risk factor.

CONCLUSIONS AND GRADING OF THE EVIDENCE REVIEW FOR THE ROLE OF FAMILY HISTORY IN CARDIOVASCULAR HEALTH

- Overwhelmingly consistent evidence from observational studies strongly supports inclusion of a positive family history of early coronary heart disease in identifying children at risk for accelerated atherosclerosis and for the presence of an abnormal risk profile (Grade B).
- For adults, a positive family history is defined as a parent and/or sibling with a history of treated angina, myocardial infarction, percutaneous coronary catheter interventional

procedure, coronary artery bypass grafting, stroke or sudden cardiac death before age 55 years in men or age 65 years in women. Because the parents and siblings of children and adolescents are usually young themselves, it was the Expert Panel's consensus that when evaluating family history in a child, history should also be ascertained for the occurrence of CVD in grandparents, aunts, and uncles, although the evidence supporting this is insufficient to date (Grade D).

- Overwhelmingly consistent evidence from observational studies shows that identification of a positive family history for CVD and/or CV risk factors should lead to evaluation of all family members, especially parents, for CV risk factors (Grade B).
- Family history evolves as a child matures, so regular updates are necessary as part of routine pediatric care (Grade D).
- Education about the importance of accurate and complete family health information should be part of routine care for children and adolescents. As genetic sophistication increases, linking family history to specific genetic abnormalities will provide important new knowledge about the atherosclerotic process (Grade D).

Table 4–1. Evidence-Based Recommendations for Use of Family History in Cardiovascular Health Care

Grades reflect the findings of the evidence review.
Recommendation levels reflect the consensus opinion of the Expert Panel.
Supportive actions represent expert consensus suggestions from the Expert Panel provided to support implementation of the recommendations.

Birth–18 years	Take detailed family history (FHx) of cardiovascular disease (CVD)***** at initial encounter and/or at ages 3, 9–11, and 18 years	Grade B *Recommend*
	If (+) FHx identified, evaluate patient for other CV risk factors, including dyslipidemia, hypertension, diabetes, obesity, history of smoking, and sedentary lifestyle	
	If (+) FHx and/or CV risk factors identified, evaluate family, especially parents, for CV risk factors	Grade B *Recommend*
	Update FHx at each nonurgent health encounter	Grade D *Recommend*
	Use FHx to stratify risk for CVD risk as risk profile evolves	Grade D *Recommend*
	Supportive actions: Educate parents about importance of FHx in estimating future health risks for all family members	
18–21 years	Review FHx of heart disease with young adult patients	Grade B *Strongly recommend*
	Supportive actions: Educate patient about family and personal risk for early heart disease, including need for evaluation for all CV risk factors	

* Parent, grandparent, aunt, uncle, or sibling with heart attack, treated angina, coronary artery bypass graft (CABG)/stent/angioplasty, stroke, or sudden cardiac death before age 55 years in men and 65 years in women.

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5. NUTRITION AND DIET

INTRODUCTION

This section of the Guidelines provides recommendations to pediatric care providers on nutrition and diet for the promotion of cardiovascular (CV) health for their pediatric patients and families. The section begins with important background information on nutrition and diet from the 2010 *Dietary Guidelines for Americans* (2010 *DGA*) for healthy people, including healthy children.[1] This is followed by the Expert Panel's summary of the evidence it reviewed relative to nutrition and diet for children, which collectively provides a rationale for initiating prevention efforts early in life. The evidence review and development processes for these Guidelines are described in detail in Section I. Introduction and in Appendix A. Methodology. More than the standard systematic review where findings from the included studies constitute the only basis for recommendations, these Guidelines combine the findings from a systematic review of the evidence with the Expert Panel's consensus process. The quality of all relevant data is incorporated and graded based on preidentified criteria. Because of the large number of included studies and the diverse nature of the evidence, the Expert Panel also provides a critical overview of the studies reviewed for this section, highlighting those that, in its judgment, provide the most important information. Detailed information from each study has been extracted into the evidence tables, which will be available at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. The conclusions of the Expert Panel's review of the evidence are then summarized and graded, followed by age-based recommendations for nutrition and diet in Table 5–2. Evidence-Based Dietary Recommendations for Patients of Pediatric Care Providers: Cardiovascular Health Integrated Lifestyle Diet (CHILD 1). The Expert Panel accepts the 2010 *DGA* as containing appropriate recommendations for diet and nutrition in children 2 years and older. The recommendations in these Guidelines are intended for pediatric care providers to use with their patients to address

CV risk reduction. Where evidence is inadequate, recommendations are based on a consensus of the Expert Panel. The recommendations therefore represent the best available evidence when that exists and expert consensus opinion when it does not. References are listed sequentially at the end of the section. References from the evidence review are identified by a unique PubMed identifier (PMID), which appears in bold font. Additional references do not include the PMID number. There is obvious overlap with the nutrition information contained in other sections of these Guidelines; additional specific dietary information relative to lipids, blood pressure (BP), and obesity is located in Section VIII. High Blood Pressure, Section IX. Lipids and Lipoproteins, and Section X. Overweight and Obesity.

BACKGROUND

These Guidelines provide evidence-based dietary recommendations to promote CV health and reduce CV risk that build on previous recommendations for adolescents and children 2 years and older that were established in the 2010 *DGA*.[1] The *DGA* provides science-based recommendations to promote health and reduce risk for chronic disease through diet and physical activity for members of the general public 2 years and older. The *DGA* is updated every 5 years: www.health.gov/dietaryguidelines. The recommendations in the *DGA* form the basis of Federal Government nutrition program and policy development. The 2010 *DGA* includes information from Dietary Reference Intake (DRI) reports of the Institute of Medicine (IOM); information from the DRIs also was accessed for this section. The 2010 *DGA* describe a healthy diet as one that:

- Emphasizes a variety of vegetables, fruit, whole grains, and low-fat dairy products
- Includes protein foods such as lean meats, poultry without skin, seafood, beans and peas, eggs, processed soy products, nuts, and seeds
- Is low in saturated fat and *trans* fat, cholesterol, sodium, and added sugar

- Stays within daily calorie limits

These new pediatric CV Guidelines not only build upon the recommendations for achieving nutrient adequacy in growing children as stated in the 2010 *DGA* but also add evidence regarding the efficacy of specific dietary changes to reduce CV risk from the current evidence review, for use by pediatric care providers in the care of their patients. Because the focus of these Guidelines is on CV risk reduction, the evidence review specifically evaluated dietary fatty acid and energy components as major contributors to hypercholesterolemia and obesity, as well as dietary composition and micronutrients as they affect hypertension. New evidence from multiple dietary trials addressing CV risk reduction in children provides important information for these recommendations.

ESTIMATED ENERGY REQUIREMENTS

The underlying premise of the 2010 *DGA* is that foods, not supplements, should constitute the primary basis of a recommended eating plan for children and adolescents. The dietary recommendations of the 2010 *DGA* included all of the nutrients required for growth and health, balanced with energy requirements. On average, children need greater energy intake per kilogram of body weight than adults to accommodate the body's demands for growth, and this must be balanced with physical activity needs. The increasing prevalence of obesity in children reflects a chronic imbalance between energy intake and expenditure, where calorie intake is in excess of what is needed for normal growth. An emphasis of the *DGA* is the importance of achieving the appropriate energy balance at all ages. Calculations for recommended daily Estimated Energy Requirements (EER) (contained in the *DRI*) for children aged 2 and older by gender and age are provided in Table 5–1 as taken from the *DGA*.[1] Because the calculations provide estimates only, monitoring weight status and stage of growth are important considerations in estimating energy needs.

Table 5–1. Estimated Calorie Needs per Day by Age, Gender, and Physical Activity Level[a]

Estimated amounts of calories needed to maintain caloric balance for various gender and age groups at three different levels of physical activity. The estimates are rounded to the nearest 200 calories. An individual's calorie needs may be higher or lower than these average estimates

		Calorie Requirements (kcals) by Activity Level[b]		
Gender	**Age (Years)**	**Sedentary**	**Moderately Active**	**Active**
Child	2–3	1,000–1,200	1,000–1,400[c]	1,000–1,400[c]
Female[d]	4–8	1,200–1,400	1,400–1,600	1,400–1,800
	9–13	1,400–1,600	1,600–2,000	1,800–2,200
	14–18	1,800	2,000	2,400
	19–30	1,800–2,000	2,000–2,200	2,400
Male	4–8	1,200–1,400	1,400–1,600	1,600–2,000
	9–13	1,600–2,000	1,800–2,200	2,000–2,600
	14–18	2,000–2,400	2,400–2,800	2,800–3,200
	19–30	2,400–2,600	2,600–2,800	3,000

a. Based on Estimated Energy Requirements (EER) equations, using reference heights (average) and reference weights (health) for each age/gender group. For children and adolescents, reference height and weight vary. For adults, the reference man is 5 feet 10 inches tall and weighs 154 pounds. The reference woman is 5 feet 4 inches tall and weighs 126 pounds. EER equations are from the Institute of Medicine. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington (DC): The National Academies Press; 2002.

b. Sedentary means a lifestyle that includes only the light physical activity associated with typical day-to-day life. Moderately active means a lifestyle that includes physical activity equivalent to walking about 1.5 to 3 miles per day at 3 to 4 miles per hour, in addition to the light physical activity associated with typical day-to-day life. Active means a lifestyle that includes physical activity equivalent to walking more than 3 miles per day at 3 to 4miles per hour, in addition to the light physical activity associated with typical day-to-day life.

c. The calorie ranges shown are to accommodate needs of different ages within the group. For children and adolescents, more calories are needed at older ages. For adults, fewer calories are needed at older ages.

d. Estimates for females do not include women who are pregnant or breastfeeding.

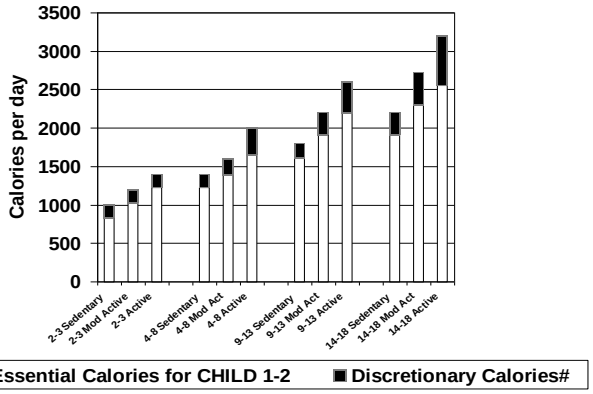
SOLID FATS AND ADDED SUGARS

Balancing energy intake with energy expenditure in a growing child is a complex process. Understanding the concepts of essential versus discretionary calories can assist pediatric care providers in guiding children and their families toward choosing nutrient-dense foods to maintain energy balance. Solid fats and added sugars (SOFAS) are always counted as "discretionary" or nonessential calories. Sources of SOFAS include "snack" foods, sugar-sweetened beverages, and desserts. Due to the sedentary behavior of most Americans, few such foods should be consumed, typically no more than 100–200 calories/day (kcal/d) as part of total energy intakefor the age group and physical activity level. To meet nutrient needs without overconsumption of calories (energy intake), meals and snacks need to be nutrient dense (high in nutrients) but as low as possible in saturated and *trans* fats and with little or no added sugars. Foods such as fat-free milk, fruits, vegetables, whole-grain breads, and low-sugar cereals exemplify this concept. Conversely, the sugar in sugar-sweetened beverages, the fat in whole milk (versus fat-free milk), the fat and added sugar in chocolate milk (versus fat-free unflavored milk), the fat in high-fat meats (versus lean meats), and the fat and sugar in cookies, cakes, pastries, granola bars, and sweetened cereals (versus unsweetened grain foods) are examples of sources of nonessential calories. Selecting nutrient-dense foods in each food group gives individuals an effective way to meet their nutrient needs without consuming excess calories. This approach can be adopted and maintained throughout life to prevent the development of overweight and obesity. Because the discretionary calorie concept is important but complex for most consumers, the Expert Panel emphasizes consuming mostly nutrient-dense foods for meals and snacks.

For growing children, the EER increases with age and with physical activity level, as do allowances for essential calories and discretionary calories, as shown in Figures 5–1 and 5–2.

However, due to the low levels of physical activity common among most American children, the nonessential, discretionary calorie allowance is no more than 100–400 kilocalories, based on age and activity level. This is not sufficient to accommodate daily (or regular) consumption of whole milk, high-calorie/low-nutrient-dense snacks, or desserts and/or sugar-sweetened beverages (see Figures 5–1 and 5–2). Sedentary children who regularly consume energy-dense, nutrient-poor foods are at risk of developing overweight and obesity and having inadequate nutrition, despite high calorie intake.

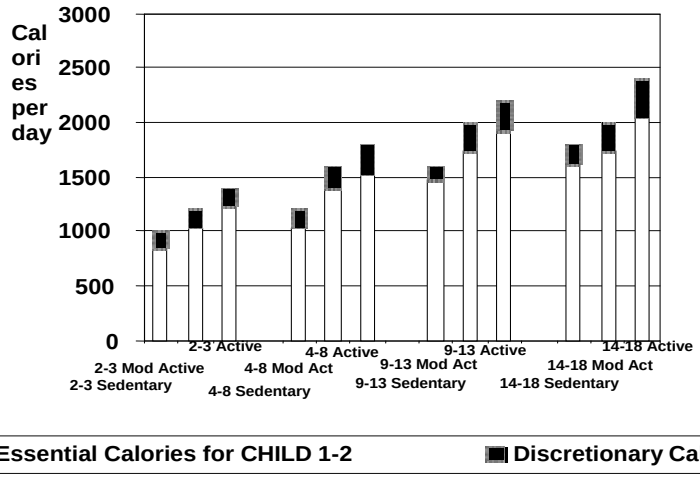
Figure 5-1. Estimated Energy Requirements (EER) and Discretionary Calorie Allowance by Level of Activity—Boys*



#Discretionary calories for children aged 4-8 are based on recommended 2 servings of dairy/day.
*Adapted from Gidding et al. *Circulation*.112(13), September 2005.

Figure 2

Estimated Energy Requirements (EER) and Discretionary Calorie Allowance by Level of Activity—Girls*



#Discretionary calories for children aged 4 -8 are based on recommended 2 servings of dairy/day.
*Adapted from Gidding et al. *Circulation* . 112(13), September 2005.

Figures 5–1 and 5–2**.** Concept of discretionary calories by gender. As daily physical activity increases, more energy is needed for normal growth, unless the child is overweight or obese and may benefit from limited additional calorie intake as determined by the health care provider. For sedentary children, only small amounts of discretionary calories can be consumed before caloric intake becomes excessive. Discretionary calories represent snacks, desserts, sugar-sweetened beverages, and other nutrient-poor, energy-dense foods whose intake should not exceed the indicated allowances according to level of activity. In Figures 5–1 and 5–2, the discretionary calorie allowance for children ages 4–8 years is based on 2 servings of dairy per day. Mod Act indicates moderately active. Information is based on estimated calorie requirements and discretionary calories published in the *Dietary Guidelines for Americans* (2005).

FORMAT OF THE EVIDENCE REVIEW FOR NUTRITION AND DIET

The results of the evidence review addressing the role of nutrition and diet in promoting CV health are summarized below. The review encompassed 30 systematic reviews, 12 meta-analyses, 121 randomized controlled trials (RCTs), and 47 observational studies. Because of the large volume of studies reviewed and the diverse nature of the evidence, the Expert Panel provides an overview of the studies reviewed, highlighting those that in its view provide the most important information. Detailed information from each study has been extracted into the evidence tables and will be available at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. Results are presented here by dietary component and by age group and are summarized after each dietary component review. Some studies were not specific to the age groups addressed in these Guidelines; the Expert Panel used clinical judgment in determining how best to apply results from those studies to age-specific recommendations. At the end of each dietary component review, the results are summarized. The conclusions of the entire evidence review for diet and nutrition, with grades and age-specific recommendations, appear at the end of this section.

CURRENT DIETARY INTAKE IN CHILDREN AND ADOLESCENTS

Four epidemiologic studies evaluated overall dietary content for children and adolescents. The Bogalusa Heart Study is a major community-based cohort of more than 1,655 Black and White children and young adults in Bogalusa, Louisiana, that began in 1973 and still continues. Participants were originally examined at ages 5–17 years and were 52 percent female and 44 percent Black. The Bogalusa investigators developed and applied a scoring system based on consumption of nutrient-dense foods. Repeated cross-sectional surveys between 1989 and 2004 showed an overall decline in dietary quality, with a decrease in the consumption of nutrient-dense foods with increasing age. This was accompanied by extensive development of

overweight and obesity in this cohort. At age 10 years, 50 percent of children had a good nutrient density score, but this dropped to only 19 percent by young adulthood.[2]

The Cardiovascular Risk in Young Finns study (Young Finns) is a multicenter longitudinal cohort study of CV risk from Finland, with 3,956 subjects enrolled at ages 3–18 years in 1980 and followed with serial lipid evaluation over time. Based on data from 21 years of followup, two major dietary patterns have been observed beginning in childhood: a "traditional" pattern characterized by high consumption of rye, potatoes, butter, sausages, milk, and coffee and a "health-conscious" diet that includes high consumption of vegetables, legumes and nuts, rye, cheese and other dairy products, and alcoholic beverages.[3] At the latest followup, with subjects now ages 24–39 years, the traditional diet was significantly and independently associated with higher total cholesterol (TC) and low-density lipoprotein cholesterol (LDL–C) concentrations, apolipoprotein B (apoB), and C-reactive protein (CRP) in both genders, and with systolic BP and insulin levels among females. The health-conscious diet was inversely but not significantly associated with the same CV risk factors.[3]

The National Heart, Lung, and Blood Institute National Growth and Health Study (NGHS) enrolled 2,379 Black and White girls in three different U.S. cities at age 9 years and followed their nutrition, growth, and development over the next decade. Among adolescent girls older than age 10 years, lower parental educational attainment was associated with increased total fat, saturated fat, and cholesterol intake and decreased carbohydrate intake.[4] Dietary total and saturated fat intake decreased with increasing age, but less than half of White girls and less than one-third of Black girls met the 1992 National Cholesterol Education Program (NCEP) expert panel's recommendations for dietary fat intake: less than 30 percent of calories from fat and less than 10 percent from saturated fat. Independent of parental education, living in a two-parent household was associated with decreased fat and cholesterol intake and increased

carbohydrate intake.[4] A dietary pattern characterized by high intake of fruits and vegetables, dairy products, and fiber-rich grains and low intake of sugar, fried foods, burgers, pizza, and total fat was associated with less adiposity (body mass index (BMI), percentage of body fat, and waist circumference) over 10-year followup; the difference was significant for White girls.[5]

A report from the Third National Health and Nutrition Examination Survey (NHANES III) (1988–1994) of more than 4,000 youths ages 8–18 years found that foods of low-nutrient density (snacks, desserts, etc.) contributed more than 30 percent of daily energy intake, with caloric sweeteners and desserts jointly contributing nearly 25 percent of daily caloric intake. Intake of food-based vitamins and minerals decreased as consumption of foods of low-nutrient density increased.[6]

OVERVIEW OF THE EVIDENCE BY DIETARY COMPONENT AND AGE GROUP

Milk and Other Beverage Intake

Age Birth to 12 Months: Human Milk

There is near universal agreement that human milk is the preferred complete nutrition source for healthy full-term newborns and infants for the first 6 months of life, with continued breastfeeding recommended until age 12 months. As recommended by the U.S. Surgeon General, World Health Organization (WHO), American Academy of Pediatrics (AAP), and American Academy of Family Practice (AAFP), human milk is the preferred primary source of nourishment in infancy. Human milk is a unique biological fluid that changes almost daily to meet the nutritional and immunologic needs of the growing infant. Human milk is high in fat (45–55 percent of total calories), saturated fat, and cholesterol. It provides a rich source of essential fatty acids linoleic acid (LA) and alpha linoleic acid (ALA) and long-chain polyunsaturated fatty acid (PUFA)

derivatives arachidonic acid (AA) and docosahexaenoic acid (DHA).[7] Human milk supplies the fat-soluble vitamins A, D, E, and K as well as carotenoids and bioactive components, with protective functions ranging from immunoglobulins to oligosaccharides, enzymes, antienzymes, and adrenal steroids, although vitamin D levels are often inadequate. To prevent vitamin D deficiency, the AAP recommends supplementation with 400 international units per day (IU/d) for all children.[8] The new RDA for Vitamin D for those 1-70 years old is 600 IU/day.[9]

The evidence review for these Guidelines identified studies that examined the long-term CV benefits of breastfeeding, including possibly but not conclusively protective effects against obesity,[10] lower serum TC levels and decreased carotid intima-media thickness (cIMT) in adulthood,[11,12] and a lower risk of type 2 diabetes mellitus (T2DM).[13] A meta-analysis of 37 studies compared the late effects of breastfeeding versus formula-feeding on TC levels in adolescents and adults.[11] In infancy, mean TC was higher in breast-fed versus formula-fed infants, but this difference disappeared in childhood and adolescence. Among adults, the TC level of those who had been breast-fed as infants was lower than the TC level of those who had been formula fed.

Ages Birth to 12 Months: Infant Formula

Infant formulas that meet regulatory requirements for quality and nutrient content are marketed in the United States and many other countries. These products are designed to support the normal growth and development of infants. Infant formula products currently marketed in the United States are iron fortified and contain mixtures of vegetable oils, including coconut, soy, high-oleic safflower, high-oleic sunflower, and/or palm olein, plus single-cell oils containing the two long-chain PUFAs DHA and AA. The *DRI* recommendations for nutrient intake by infants are based on the nutrient content of breast milk and include intake of essential fatty acids that

are unsaturated, specifically ALA omega-3 and LA omega-6 fatty acids. The fat and cholesterol contents of infant formula were varied in several small short-term RCTs, with subsequent significant differences in intervention infants, compared with controls for TC, LDL–C, triglycerides (TG), and high-density lipoprotein cholesterol (HDL–C); there were no differences between groups in lipoprotein profiles postweaning.[14,15,16,17]

Transition to Childhood: Ages 12 Months to 2 Years: Introduction of Cow's Milk

Vitamin-D-fortified cow's milk and other dairy products are excellent sources of calcium, magnesium, protein, and vitamin D. However, the dairy fat in whole cow's milk is a major source of atherogenic saturated fat, cholesterol, and calories and a poor source of the essential fatty acids LA and ALA.

Of particular relevance to the transition from breast milk or infant formula is the Special Turku Coronary Risk Factor Intervention Project (STRIP) in Finland. This important trial enrolled 1,062 healthy 7-month-old infants who were randomized to an intervention or a control group.[18] The intervention group families received repeated, individualized, nutritionist-delivered, low-saturated-fat counseling designed to achieve a diet with total fat of 30–35 percent of total kcal/d, a 1:1:1 intake ratio of saturated fatty acids (SFA)/monounsaturated fatty acids (MUFA)/PUFA/d, cholesterol intake of less than 200 milligrams per day (mg/d), protein 10–15 percent of total kcal/d, and carbohydrates 50–60 percent of total kcal/d. Until age 12 months, families were advised to continue with breast- or formula-feeding. After age 1 year, skim milk was recommended as the primary beverage; in the intervention group, parents were encouraged to supplement the diet as needed with soft margarines and vegetable oils until age 24 months to maintain adequate fat intake. The control group received basic health education and no instructions on the use of dietary fats.[18] The children then were followed with serial evaluations,

with the first at age 13 months, including dietary assessment with 4-day dietary records, to midadolescence, with reported findings to age 14 years. The children have been assessed for lipid results every 2 years and for other nutrition-related measures at irregular intervals. From the first intervention assessment at age 13 months onward until age 14 years, children in the intervention group consumed less total and saturated fat, less cholesterol, and more carbohydrates and polyunsaturated fat than controls. The percentage of calories in the intervention group from total fat (saturated fat in parentheses) was 26 percent (9 percent) at age 13 months, 30 percent (11 percent) at age 24 months, 30 percent (12 percent) at age 4 years, 30 percent (12 percent) at age 7 years, and 30 percent (11 percent) at age 10 years.[19,20,21,22,23] These dietary fat changes translated to significantly lower TC and LDL–C levels until age 7 years; after age 7 years, the latter difference was significant only for boys.[22,23] No harmful effects were reported on growth, micronutrient intake, development, or neurologic function.[24,25] In a subgroup of 78 intervention children and 89 control children assessed at age 9 years, the intervention children had significantly lower insulin levels and lower homeostatic model assessment of insulin resistance (HOMA–IR) than control children.[26] At age 10 years, followup included about half of the original cohort, as initially predicted and powered. Results showed that 10.2 percent of girls in the intervention group were overweight, compared with 18.8 percent of controls ($P = 0.04$); there was no difference in overweight prevalence between groups among boys. There was no significant difference between intervention and control groups in weight for height or obesity at any single age, thus illustrating energy adequacy despite recommended reduced fat intake.[27] For this study, overweight was defined as weight for height greater than 20 percent and obesity greater than 40 percent above the mean weight for height for Finnish children. In a subgroup assessed at ages 7 and 9 years, intervention children also had higher nutrition knowledge scores.[28]

Intake of Other Beverages

Infancy/Early Childhood

Consumption of fruit juices, representing a "naturally sweetened" beverage, has increased over the past 30 years due to increased availability, accessibility, marketing, and convenience.[29] Young children tend to be the highest consumers of fruit juices, and some studies have noted associations between high juice consumption and obesity.[30,31] Of note, juice intake was higher and the relationship between juice intake and obesity was strongest in low-income populations where children participated in public nutrition programs, such as the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) that provide vouchers for juice. Two longitudinal studies of children participating in the WIC Program found that the increased risk of obesity with increased juice intake was strongest among children who were already overweight.[30,31] The AAP recommends that a serving of natural, unsweetened fruit juice be limited to 4–6 fluid ounces and that infants can receive 1 serving per day after age 6 months as part of a meal or snack. After infancy, children ages 1–6 years should receive no more than 1 serving of unsweetened fruit juice per day, and children ages 7–18 years should limit juice consumption to no more than 2 servings per day.[32] This evidence review identified no additional studies in this subject area for these age groups.

Later Childhood and Adolescence

The Centers for Disease Control and Prevention's (CDC's) 2007 Youth Risk Behavior Surveillance report found that only 19 percent of male teens and 9 percent of female teens consumed at least 3 glasses of milk per day.[33] In contrast, 39 percent of males and 29 percent of females consumed at least one 12-ounce can of soda per day, not including diet soda. Soft drink consumption in the United States has increased more than 300 percent over the past two

decades; 56–85 percent of school-aged children consume at least one soft drink daily. The full impact on obesity and other CV risk factors from the displacement of calcium, vitamin D, protein, and other essential nutrients, combined with the increase in calories from sugar, is as yet unquantified. The NGHS (described previously) reported that higher consumption of sugar-sweetened beverages was associated with significantly lower milk consumption and that increased soda consumption predicted greater increases in BMI; BMI increased 0.01 unit for each 100 grams of soda consumed. Consumption of sugar-sweetened beverages was significantly associated with higher daily calorie intake. For every 100 grams of soda consumed, average daily calorie intake increased by about 82 calories.[34] A 2006 systematic review of sugar-sweetened beverage intake and weight gain included 21 (of 30) studies in children and adolescents.[35] The review concluded that greater consumption of sugar-sweetened beverages is significantly associated with both weight gain and obesity. Two RCTs reviewed in detail in Section X. Overweight and Obesity showed significant reductions in overweight and obesity when intake of sugar-sweetened beverages was limited.[36,37]

Sports drinks represent a relatively new beverage category. By design, they contain higher amounts of sodium, refined carbohydrates (sugar), and calories than does water. No studies in this evidence review dealt with sports drinks, but information is provided because of their increasing consumption as a sugar-sweetened beverage and thus their potential impact on children's caloric intake. Originally developed and marketed for use by trained athletes during competition, sports drinks have been marketed to the general public and "casual athletes" in recent years. Consumption by children and adolescents is increasingly common, with or without accompanying physical activity. In one review of adolescents ages 11–18 years, 56.4 percent reported having consumed a sports drink during the previous week.[38] Research in adult athletes evaluated under conditions of prolonged exercise with or without heat stress indicates that beverages containing electrolytes are effective in maintaining plasma volume and

preventing hyponatremia, compared with plain water.[39] Compared with water, drinks containing electrolytes and refined carbohydrates have been shown to improve performance in sustained exercise tasks lasting more than 45 minutes.[40] In studies of young adult competitive athletes, primarily males, sports drinks appear to be safe and effective during training and competition, especially in hot conditions.[41] Although it may be reasonable to extrapolate these benefits to adolescents exerting high levels of energy under similar conditions, the evidence review identified no research examining the effects of these drinks in children.

SUMMARY OF THE EVIDENCE REVIEW FOR MILK AND OTHER BEVERAGE INTAKE

- Human milk, as the primary source of nutrition in the first year of life, is associated with CV benefits on late followup in adult life.
- Results of the STRIP trial suggest that the fat content of cow's milk can be safely reduced in healthy infants when accompanied by counseling on nutrition quality and energy density, including attention to sufficient fat intake prior to age 2 years, with benefits on TC and LDL–C levels in boys and girls up to age 7 years and in boys through age 14 years, plus lower rates of obesity and insulin resistance.
- Increased sugar-sweetened beverage intake is associated with obesity in multiple reports.

OVERVIEW OF THE EVIDENCE FOR DIETARY FAT INTAKE

Background

The evidence that, in adults, a diet lower in fat is associated with reduced development of cardiovascular disease (CVD) originated with epidemiologic studies dating back half a century. Dietary fat intake (quantity) and fatty acid type regulate serum lipids in children as they do in adults, but fat intake may represent a major source of energy for children, especially infants and toddlers, whose volume capacity is limited. Energy density can be an important factor among finicky eaters whose total caloric needs may otherwise not be met. The original NCEP recommendations were published in 1992 and were based on evidence available at the time. The *National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents* recommended a diet with less than 30 percent of total calories from fat, less than 10 percent from saturated fat, and cholesterol intake <300 mg/d for all healthy U.S. children 2 years and older.[42] There is no biologic requirement for SFA, so the limits were intended to help reduce atherogenic risk without eliminating high-quality animal protein sources. The *DRI* recommendations promote the intake of essential fatty acids from unsaturated sources, specifically ALA and LA omega-6 fatty acids. The acceptable range for intake of LA is 5–10 percent of fat calories and for ALA is 0.6–1.2 percent of fat calories for children and adults. From the evidence review, dietary pattern studies in children and adolescents report that higher blood lipid levels are associated with higher total and saturated fat intake, just as in adults.[3,4,5,6] The evidence review for these Guidelines also identified a series of studies focused on evaluating the safety of lower dietary fat and saturated fat content as well as the efficacy of such diets in lowering serum lipid levels and reducing obesity. Most important among these studies for the youngest age range is the STRIP trial, now with 14 years of followup.[18,19,20,21,22,23] STRIP is the only trial examining and reporting health effects from a

reduced saturated fat diet in normal children from infancy through adolescence. The STRIP trial and each of the other dietary fat interventions identified by the evidence review are described by age group below.

Infancy

Despite recommendations advocating breast milk or formula in infancy, a 2002 survey reported that 20 percent of toddlers had been fed whole cow's milk on a daily basis before age 12 months.[43] The consequences of whole-milk consumption by infants, with its high protein and sodium content and reduced LA content, have not been reported. In several RCTs with small study groups, the fat and cholesterol contents of infant formulas varied, with subsequent short-term changes in levels of TC, LDL–C, and TG in infancy, but no long-term differences in lipoprotein profiles were demonstrated on followup.[14,14,15,16]

Infancy After Weaning

As described above, many of the data on the safety and efficacy of a diet low in saturated fat and cholesterol starting in infancy come from the STRIP study, in which 7-month-old Finnish infants were randomized into either (1) a group whose parents received counseling from a nutritionist for a diet with total fat of 30–35 percent of total kcal/d and with a 1:1:1 intake ratio of SFA/MUFA/PUFA per day, cholesterol intake <200 mg/d, protein 10–15 percent per day, and carbohydrates 50–60 percent per day or (2) a group whose parents received basic health education and no instructions on the use of fats.[18] From age 12 months onward, the primary beverage consumed by these children was skim milk. The children were followed with repeated dietary counseling and serial evaluations, including dietary assessment using 4-day diet records, the first at age 13 months and extending now into midadolescence.

Beginning at the age 13-month assessment and extending to age 14 years, children in the intervention group have consumed significantly less total and saturated fat and more carbohydrates and polyunsaturated fat, compared with children in the control group. The total fat content of the diet of the intervention children ranged from 26 to 30.5 percent throughout the 14-year followup period.[19,20,21,22,23] This compares with a significantly higher total fat intake of 28–33 percent in control subjects. Saturated fat intake among the intervention children was significantly lower, ranging from 9.5 percent to 11 percent, compared with 13–14 percent in control subjects. From age 13 months to age 14 years, those in the STRIP intervention group had lower TC and lower LDL–C than the control group; after age 7 years, the difference was only significant in males.[21,22,23] There were no differences in growth or in pubertal maturation between groups. In a substudy, serum stanol concentrations were measured to further assess the effect of replacing milk fat with vegetable fat. Campesterol and sitosterol levels were increased, but this was not associated with any change in the levels or production of cholesterol.[44] The lower total fat and saturated fat diet was associated with important CV health benefits, including the difference in serum lipids described above.[19,20,21,22] Assessed at age 9 years, a subgroup of STRIP intervention children also had significantly lower insulin levels and lower HOMA–IR than control children.[26] Assessed for obesity measures at age 10 years, there were significantly more overweight females in the control group than in the intervention group; only two intervention females and one male were obese, compared with eight control females and one male.[27] For this study, overweight was defined as weight for height greater than 20 percent and obesity as greater than 40 percent above the mean for Finnish children. In a subgroup assessed at ages 7–9 years, intervention children had higher nutrition knowledge scores.[28] No harmful effects on nutrient adequacy, physiologic development, or neurologic function were seen over 14 years of followup in those who continued to be followed, representing more than half the original cohort and adequately powered to assess the planned outcome measures.[23,24,25]

Childhood and Adolescence

The Dietary Intervention Study in Children (DISC)[45] assessed the safety and efficacy of a reduced-fat dietary intervention among children with moderately elevated LDL–C levels between the 80th and 98th percentiles at baseline. Prepubertal boys (N = 362) and girls (N = 301) (initially ages 8–10 years) and their parents were randomized to either an ongoing, nutritionist-driven, individual and group intervention or a usual-care group in a six-center clinical trial. A behavioral-based, nutritionist-tailored intervention with monthly nutritionist visits and telephone followup was used to promote adherence to a diet similar to the NCEP Step II diet, with 28 percent of energy from fat, <8 percent from saturated fat, ≤9 percent from polyunsaturated fat, and cholesterol intake <150 mg/d. The control group received dietary literature only. At the 3-year followup, dietary total fat intake averaged 28.6 percent of calories, with a saturated fat intake of 10.2 percent of calories in the intervention group, significantly lower than in the usual-care group. This change was accompanied by small but significant mean differences in LDL–C levels (reduction from baseline of 15.4 mg per deciliter (mg/dL) in the intervention group versus a reduction of 11.9 mg/dL in the control group). Greater sexual maturation and BMI were found to increase the normal fall in LDL–C levels in both groups, which occurs during adolescence.[46] At followup after a mean of 7.4 years, children in the intervention group maintained significantly lower dietary intakes of total fat, saturated fat, and cholesterol, compared with children in the control group, but there was no longer a significant difference in LDL–C between the two groups. There were no differences in any of the safety measures, including height or depression scores.[47,48]

A clinically initiated, home-based, parent-child autotutorial (PCAT) dietary education program directed at increasing dietary knowledge and reducing fat consumption and LDL–C levels was assessed in 174 boys and girls ages 4–10 years with borderline-high or high LDL–C.[49]

Intervention families received individualized dietary recommendations to maintain a total dietary fat intake of less than 30 percent of calories and a saturated fat intake of less than 10 percent of calories and used tape-recorded nutrition messages to support appropriate dietary decisions between clinical visits. After 3 months, the PCAT group had significantly lower intakes of total and saturated fat and calories and lower LDL–C levels than an at-risk control group that received no intervention; there were no significant differences in dietary intake or lipid levels between PCAT and traditional dietary counseling. Results were maintained at 1-year followup.[50] Another office-based, 16-week nutritional education program effectively decreased intake of total fat, saturated fat, and cholesterol and significantly lowered TC and LDL–C levels.[51]

In prepubertal children with heterozygous familial hypercholesterolemia (FH), an RCT of 96 children ages 6–11 years tested a fat-restricted diet with 23 percent ±5 percent of energy from total fat, 8 percent ±2 percent from saturated fat, 5 percent ±1 percent from polyunsaturated fat, 8 percent ±2 percent from monounsaturated fat, 15 percent ±2 percent from protein, and 62 percent ±5 percent from carbohydrates, with a cholesterol intake of 67 mg ±28 mg/1,000 kcal, for 1 year. TC and LDL–C levels were lowered by 4.4 percent and 5.5 percent, respectively. HDL–C, TG, apoB, ferritin, weight for height, and height velocity were unchanged.[52]

The Child and Adolescent Trial for Cardiovascular Health (CATCH) was an RCT to examine the outcomes of a multilevel school-based intervention, including health behavior education and school environmental changes, in 56 intervention schools compared with 40 control schools; effects in 5,106 initially third-grade students from ethnically diverse backgrounds in California, Louisiana, Minnesota, and Texas were assessed.[53] In intervention schools, there were school food service modifications to lower fat and sodium content plus enhanced physical education

and classroom health curricula, both with and without family education. Compared with control schools, children at intervention schools consumed significantly less total fat from cafeteria lunches (reduced from 38.9 percent to 31.9 percent of energy for the lunch meal only) and increased their amounts of vigorous physical activity. Due to limitations in the full collection of diet assessment methodology, whether total fat and saturated fat intakes per day were effectively reduced to NCEP guidelines levels of less than 30 percent and less than 10 percent of total calories, respectively, was only documented in a subsample.[54] However, after this 2.5-year intervention, there were no differences between the intervention and control schools regarding children's cholesterol levels, BP, or body size, nor were there any deleterious effects on growth or development.[55]

Of note, the evidence review for these Guidelines identified no RCT in which dietary fat intake of 30–35 percent was evaluated in children or adolescents. Even in the STRIP study, which focused on reducing saturated fat intake with dietary counseling for up to 30–35 percent of total calories from fat, total fat intake of the intervention group never exceeded 30.5 percent from ages 7 months to 14 years.[18,19,20,21,22,23] Lower total fat intake with nutritionist-tailored diet interventions was associated with no adverse events under the conditions specified for each trial.

SUMMARY OF THE EVIDENCE REVIEW FOR DIETARY FAT INTAKE

- A diet with total fat at less than 30 percent of calories, saturated fat less than 10 percent of calories, and cholesterol intake <300 mg/d, as recommended in the 1992 *National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents*, is safe for healthy children; in one large trial, this kind of diet was initiated in infancy through tailored, nutritionist-delivered

intervention and no harmful effects were reported throughout childhood into adolescence.

- Modifying the type and amount of fat intake in children's diets can be effectively accomplished by qualified ongoing nutritional guidance and behavioral counseling for parents and children, preferably along with environmental change.
- Dietary intervention studies in healthy children and in children with hypercholesterolemia using trained nutritionists safely achieved an average total fat intake of 28–30 percent of calories and an average saturated fat intake of 8–10 percent of calories.
- These levels of total fat and saturated fat intake were shown in RCTs to be associated with lower TC and LDL–C levels in intervention subjects, compared with control subjects.
- No harmful, adverse effects of restricting total or saturated fat intake at the levels described in the reviewed studies were demonstrated through several years of followup, with one RCT demonstrating no harm for as long as 14 years.

- This evidence review identified no studies evaluating *trans* fat intake in children.

OVERVIEW OF THE EVIDENCE FOR DIETARY CHOLESTEROL INTAKE

Cholesterol is found in the membranes of all cells and is the precursor of bile acids, sex hormones, vitamin D, and other essential biologic elements. Because of endogenous production, there is no dietary requirement for cholesterol.[56] However, dietary cholesterol is known to impact plasma lipids; it has been estimated that in adults on a 2,500 kcal/d diet, serum cholesterol will decrease by about 4 mg/dL for every 100 mg/d decrease in dietary cholesterol.[57] The 1992 *National Cholesterol Education Program: Report of the Expert Panel on Blood*

Cholesterol Levels in Children and Adolescents recommended that dietary cholesterol intake be limited to <300 mg/d in all children and to <200 mg/d in those with elevated LDL–C levels. From the NHANES surveys from the 1970s through 1994, mean dietary cholesterol intake in male and female children younger than age 13 years and in females through adolescence achieved the recommended level, averaging <300 mg/d. However, in males between ages 12 and 19 years, mean intake of cholesterol was 335 mg/d, exceeding the recommended 300 mg/d, regardless of racial/ethnic group.[58] This evidence review identified 15 RCTs that addressed dietary cholesterol in infancy, childhood, and adolescence. In several small short-term studies, the fat and cholesterol contents of infant formula varied, with subsequent changes in levels of TC, LDL–C, and TG in infancy, but there were no demonstrated long-term differences in lipoprotein profiles.[14,15,16,17] The STRIP trial, described in detail above, enrolled 1,062 healthy infants who were randomized to either intervention or control groups beginning at age 7 months. In addition to the low-saturated-fat diet described above, the intervention group received repeated, individualized, nutritionist-delivered counseling to maintain a dietary cholesterol intake of <200 mg/d.[18] The children were then followed with serial evaluations, including dietary assessment using 4-day food records, until early adolescence. Results demonstrate that from age 13 months onward, children in the intervention group consumed significantly less total fat, saturated fat, and cholesterol and had lower TC and LDL–C levels; after age 7 years, the difference in LDL–C levels was significant only among boys.[18,19,20,21,22,23] No harmful effects were detected on growth, micronutrient intake, development, or neurologic function.[23,24,25] Benefits on CV risk factors, especially lipids, described in detail in the preceding section, were seen, continuing into adolescence.[18,19,20,21,22,23,26,27]

The DISC trial[45] described in detail above, was an RCT to assess the safety and efficacy of a reduced-fat dietary intervention among children with elevated LDL–C levels (between the 80th and 98th percentiles) at baseline. The DISC trial used a behavioral-based, nutritionist-tailored intervention to promote adherence to a diet similar to the NCEP Step II diet, with 28 percent of

energy from fat, <8 percent from saturated fat, ≤9 percent from polyunsaturated fat, and cholesterol intake <75 mg/1,000 kcal/d, not to exceed 150 mg/d. Based on multiple 24-hour dietary recalls, cholesterol intake was shown to decrease from a mean of 118 mg/100 kcal to 90 mg/100 kcal at 1-year followup; this difference persisted at evaluation 5 years postinitiation. At 3-year evaluation, LDL–C levels were significantly lowered in the intervention group, compared with the control group (reduction from baseline of 15.4 mg/dL versus 11.9 mg/dL, respectively); this difference was not sustained at 7-year followup. There were no differences between groups in the prespecified safety measures of height and serum ferritin.[46,47]

In prepubertal children with heterozygous FH, an RCT of 96 children ages 6–11 years tested a fat- and cholesterol-restricted diet (23 percent ±5 percent of energy from total fat, 8 percent ±2 percent from saturated fat, 5 percent ±1 percent from polyunsaturated fat, 8 percent ±2 percent from monounsaturated fat,15 percent ±2 percent from protein, and 62 percent ±5 percent from carbohydrates with daily cholesterol intake of 67 ±28 mg/1,000 kcal).[52] After 1 year, TC and LDL–C levels decreased by 4.4 percent and 5.5 percent, respectively. HDL–C, TG, apoB, and ferritin levels, weight-for-height, and height velocity were unchanged.[52]

The PCAT dietary education program described previously was directed at increasing dietary knowledge, reducing fat consumption, and decreasing LDL–C levels in boys and girls ages 4–10 years with borderline-high or high LDL–C.[49] In addition to individualized dietary recommendations to maintain a total dietary fat intake at less than 30 percent of calories and saturated fat intake at less than 10 percent of calories, intervention families were trained to limit cholesterol intake to <300 mg/d. At baseline, cholesterol intake was well below the 300-mg goal in all subjects, averaging 156.5 ±6.6 mg/d in the intervention group and 178.4 ±7.7 mg/d in the control group. After 3 months, those in the PCAT intervention group had significantly lower intakes of total fat, saturated fat, cholesterol, and calories. Cholesterol intake averaged 133.2 ±8.0 mg/d in the intervention group but was unchanged at 173.1 ±8.2 mg/d in the control group.

LDL–C levels decreased 10 mg/dL in intervention subjects and 3.4 mg/dL in control subjects. These results were maintained at 1-year followup.[50] Another office-based, 16-week nutritional education program similarly decreased intakes of dietary total fat, saturated fat, and cholesterol—the latter to <200 mg/d—with significant decreases in TC and LDL–C levels and no reported adverse outcomes.[51]

SUMMARY OF THE EVIDENCE REVIEW FOR DIETARY CHOLESTEROL INTAKE

- Usual mean dietary cholesterol intake by children and adolescent females fall below the level of 300 mg/d previously recommended by the NCEP Pediatric Panel as reported in the 1992 *National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents*; in adolescent males, mean dietary cholesterol intake exceeds this level.
- In multiple RCTs in children with hypercholesterolemia, dietary cholesterol intake has been safely decreased with nutritional counseling to <200 mg/d, with one study of healthy children beginning in infancy and followed up through childhood into adolescence.
- Combined with lower total fat and saturated fat intake, lower cholesterol intake was associated with significant reductions in serum TC and LDL–C levels in the RCTs that were conducted in children ranging from age 7 months to early adolescence.

OVERVIEW OF THE EVIDENCE REVIEW FOR INTERVENTIONS TO INCREASE FRUIT AND VEGETABLE INTAKE

Background

Consumption of fruits and vegetables is advocated in the U.S. Department of Agriculture (USDA) MyPlate.[59] Most fruits and vegetables are plentiful in micronutrients and low in energy density. Because of their high fiber content, some studies suggest that fruits and vegetables can also contribute to feelings of satiety without excessive energy intake. As described in the section on dietary patterns, higher intake of fruits and vegetables in epidemiologic studies has been associated with less adiposity and lower BP and cholesterol levels.[4,5] The *DGA* concluded that some evidence exists to support the conclusion that there is an association between higher vegetable and fruit intake and less adiposity in children.[1] Despite the high nutrient value of fruits and vegetables, children have inadequate intake of fruits and vegetables. In a national survey from 1999 to 2002, only one-fourth of children ages 2–11 years were found to consume at least three servings per day of vegetables, and fewer than half consumed at least two fruit servings per day.[60] The Expert Panel focused its review on evidence supporting effective interventions to increase the intake of fruits and vegetables among children. None of the identified studies were interventions in children younger than age 4 years.

Childhood and Adolescence

Four systematic reviews and one meta-analysis addressed fruit and vegetable intake as primary outcome measures. The body of evidence presented here evaluates the effectiveness of various interventions on the consumption of fruits and vegetables, rather than evidence of the relationship between fruit and vegetable intake and CV risk factors. A 1998 meta-analysis[61] evaluated the results of 12 elementary-school-based studies (published between 1980 and 1996) on heart healthy eating behaviors, including fruit and vegetable intake. Three were

RCTs, which were included in this evidence review.[62,63,64] The results translated into a weighted standard effect size of 0.24, suggesting that school-based programs have a small but significant effect on fruit and vegetable intake as part of a heart healthy eating pattern. A systematic review published in 2002 evaluated the efficacy of behavioral interventions to modify dietary fat intake and fruit and vegetable intake in children and adults in studies published between 1975 and 1999.[65] That review included four studies from this evidence review[55,63,65,66,67] and concluded that more than three-fourths of all studies reported significant increases in fruit and vegetable intake, averaging 0.6 more servings per day; studies in children were not reported separately. Interventions were reported to be more successful in populations identified as being at risk for or diagnosed with disease, suggesting that results in the healthy pediatric population might have been less significant. A 2005 systematic review[68] focused on studies in children ages 6–12 years published between 1990 and March 2005 and included four studies from this evidence review.[55,66,67,69] The review concluded that availability, accessibility, and taste preferences were the determinants most consistently and positively related to higher consumption of fruits and vegetables. Among interventions, multicomponent school-based interventions were the most successful. The most recent systematic review from 2006 evaluated worldwide intervention studies (published any time before April 2004) designed to increase fruit and vegetable intake in children and adults.[70] A total of 15 studies focused on subjects ages 5–18 years; of these, 11 were RCTs, 10 of which were included in this evidence review.[55,63,65,67,71,72,73 74,75] Overall, 10 of the 15 studies showed a significant positive effect, ranging from an increase of 0.3 to 0.99 servings per day. The evidence was strongest for multicomponent interventions.

As indicated by the findings of the systematic reviews, most intervention studies addressing enhanced fruit and vegetable intake used multicomponent school-based strategies. The types of interventions varied and included such approaches as multimedia games, traditional

classroom instruction, reward systems, and computer-based education. Many studies focused on obesity and addressed lower fat intake, especially lower saturated fat intake, and/or increased physical activity in addition to increased intake of fruits and vegetables.[45,73,74,75] Several studies targeted parents, teachers, and food service workers as well as children.[53,67,72,74] Most demonstrated a modest, often short-term increase in fruit and vegetable intake. The most successful interventions provided fruits and vegetables free of charge, added them routinely to school meals or in supplemental food packages to families, and/or included children in preparing or taste-testing fruits and vegetables. Accessibility and availability were important aspects of successful interventions, compared with educational interventions alone[55,76,77]; the latter tended to result in an increase in knowledge but no increase in intake of fruits and vegetables.[28,72,75,78] A reward system in one study resulted in increased fruit and vegetable intake during the school lunch period.[79] However, these gains disappeared when the reward system was removed. A computer-game-based intervention was associated with better nutritional knowledge and better overall food choices than a conventional curriculum among students in the last three grades of primary school, but there was no significant impact on fruit and vegetable intake.[80]

SUMMARY OF THE EVIDENCE FOR INTERVENTIONS TO INCREASE FRUIT AND VEGETABLE INTAKE

- Intake of fruits and vegetables by children ages 5 years and older can be modestly increased through a variety of interventions, but almost all have been school based and have advocated a stronger parental component.
- Because most studies have addressed multiple aspects of dietary change and lifestyle modification, the independent effects of fruit and vegetable intake on child weight gain and BMI outcomes are often unclear.

- Providing more fruits and vegetables to children results in increased intake.
- Allowing children to prepare and taste fruits and vegetables enhances their acceptance of these foods.
- Interventions aimed at increasing children's nutritional knowledge less consistently result in an increase in children's intake of fruits and vegetables.
- Fruit and vegetable intake tends to decline as children reach the middle school and high school years.

OVERVIEW OF THE EVIDENCE FOR DIETARY FIBER INTAKE

Background

The *DGA* identified whole grains as an important source of fiber, which is a component of good nutrition.[1] Dietary fiber is the nondigestible carbohydrate component of plant foods that include fruits, vegetables, legumes, and nuts as well as whole grains. Functional or supplemental fiber refers to nondigestible, nonnutrient-contributing carbohydrate supplements, which have been shown to have some beneficial physiologic effects in adults but which are not required if dietary sources of fiber are adequate. Functional/supplemental fiber is addressed in the dietary supplements section below. The 2002/2005 IOM *DRI* report for residents of the United States and Canada specifically addressed dietary fiber intake as important for laxation, attenuation of blood glucose levels, and normalization of serum cholesterol levels in adults.[81] The *DRI* report includes specific recommendations for fiber intake in children beginning at age 12 months, extrapolated from adult levels. The evidence review for these Guidelines identified no studies of dietary fiber intake in young children.

Childhood and Adolescence

Past concerns that extreme high-fiber diets could cause excessive loss of calories, protein, and fat in growing children have been addressed in a series of reports demonstrating that high-fiber diets are associated with a more nutrient-dense eating pattern, whereas low-fiber diets are associated with lower nutrient density, higher calorie intake, and increased obesity.[82] From this evidence review, the Bogalusa Heart Study, described previously in this section, examined age and secular trends between 1976 and 1988 in dietary fiber intake by youths ages 10–17 years. Total dietary fiber intake, assessed by dietary recalls, was low, with a mean intake of 12 grams per day (g/d) or 5 g/1,000 kcal, with no change over the period of observation. When children were stratified by quartiles of fiber intake, the percentages of calories from dietary total fat and saturated fat were lower, and the percentage of calories from carbohydrates was higher in children with high fiber intakes.[83] The USDA Agricultural Research Service's Continuing Survey of Food Intake by Individuals (CFSII) (1994–1996, 1998) reported only slightly higher mean dietary fiber intakes for youths: 15.2 g/d and 17.7 g/d for males ages 9–13 and 14–18 years, respectively, and 12.9 g/d and 12.8 g/d for females ages 9–13 and 14–18 years, respectively.[84] A more recent report from the NHANES III of more than 4,000 youths ages 8–18 years found that dietary fiber intake was inversely related to low-nutrient-density food consumption: high dietary fiber intake was consistently associated with higher nutrient intake. Conversely, intake of vitamins and minerals decreased as consumption of low-nutrient-density foods increased.[6] In another analysis based on data from the CFSII, children ages 2–5 years with high fiber intake were found to consume diets with higher nutrient density, compared with those with low fiber intake.[85]

The Avon Longitudinal Study of Parents and Children found a relationship between lower dietary intake of fiber and higher fat mass as assessed by dual energy densitometry.[86] At age 9

years, a high-calorie, low-fiber, low-fat diet score was correlated with a significantly higher odds ratio for greater adiposity. Analysis of NHANES data from 1999 to 2000 used popcorn consumption as a proxy for fiber intake. Among individuals older than 4 years, popcorn consumers had a 25 percent higher intake of whole grains and a 25 percent higher daily fiber intake, compared with nonconsumers.[87]

In the *DRI*, the recommended average daily intake of total fiber for children and adolescents is based on data for adults reporting that a preponderance of the evidence indicated that 14 g/1,000 kcal reduced the risk of coronary heart disease.[81] Extrapolating from this, the *DRI* recommended total dietary fiber intakes for each age and gender group of children and adolescents as a product of the median energy intake and this recommended total fiber intake (14 g/1,000 kcal). Thus, for children ages 1–3 years and 4–8 years, a total fiber intake of 19 g/d and 25 g/d, respectively, is recommended. For males ages 9–13 years, a total fiber intake of 31 g/d is recommended, increasing to 38 g/d for males ages 14–30 years. For females ages 9–30 years, a total fiber intake of 25–26 g/d is recommended. The AAP recommends more moderate goals for fiber intake for children, age plus 5 g/d for young children, increasing to an adult goal of 22 g/d at around age 15 years.[87] Dietary fiber should come from foods such as fruits, vegetables, whole grains, nuts, and legumes rather than from fiber supplements.

SUMMARY OF THE EVIDENCE REVIEW FOR DIETARY FIBER INTAKE

- Higher dietary fiber intake is associated with high-nutrient-dense diets in children and adolescents.
- Existing recommendations for dietary fiber intake are extrapolated from those for adults.
- Dietary fiber should come from foods such as fruits, vegetables, whole grains, nuts, and legumes rather than from fiber supplements.

OVERVIEW OF THE EVIDENCE FOR MULTICOMPONENT DIETARY INTERVENTIONS

Many studies have evaluated dietary obesity prevention interventions that focus on lowering fat intake and increasing fruit and vegetable intake. Most of these were school based and were designed to both improve nutrition and increase physical activity; these studies are described in Section VI. Physical Activity and Section X. Overweight and Obesity in these Guidelines.[71,72,73,74,80,88,89,90,91,92] The age groups addressed ranged from preschoolers to teenagers and study sizes from 213 to more than 5,000 subjects. Most studies were successful in improving dietary quality, with small decreases in fat intake, small increases in fruit and vegetable intake, and small increases in physical activity; however, measures of obesity rarely changed. None of these studies focused on infancy or early childhood.

Later Childhood and Adolescence

The CATCH study described earlier in this section was the largest, most comprehensive, multicomponent CV health intervention ever conducted for middle-school-aged children. The 3-year study achieved significant improvement in diet (lower dietary saturated fat intake at the lunchtime meal) and physical activity (more time spent in vigorous physical activity) among children in intervention schools, compared with those in control schools.[53,54,55] These beneficial changes, however, were not associated with any difference in lipid levels, the study's primary outcome. The CATCH study was not focused on obesity, and the improvements noted in lunchtime dietary intake had no significant impact on BMI, further illustrating the potential value of more comprehensive, family-based recommendations.

SUMMARY OF THE EVIDENCE FOR MULTICOMPONENT DIETARY INTERVENTIONS

Many studies have evaluated dietary interventions designed to improve CV risk factors in children, with a focus on lowering fat intake, increasing fruit and vegetable intake, and increasing physical activity levels. Most were successful in improving dietary quality, with small decreases in fat intake, small increases in fruit and vegetable intake, and small increases in physical activity; however, measures of CV risk factors, including BMI, blood lipids, and BP, did not change.

OVERVIEW OF THE EVIDENCE FOR DIETARY PATTERNS

Background

Nutrients and food groups are not consumed in isolation but in combinations as part of a dietary pattern, a concept that has been shown to be useful in studying nutrition. From epidemiologic studies in adults, diets that are higher in fruits and vegetables and low-fat dairy foods and lower in prepared foods, salt/sodium, and saturated fat have been shown to be associated with reduced CV risk, including lower BP, optimal lipid profile patterns, and lower prevalence of obesity. Dietary pattern studies in adults have tested a Mediterranean-type diet and the Dietary Approaches to Stop Hypertension (DASH) diet. The former is a broadly defined diet that is high in fruits and vegetables, bread, potatoes, beans, nuts, and seeds, with olive oil and in some reports a high-linolenic-acid margarine as the primary fat sources, and low to moderate amounts of fish and poultry and little red meat. In adults, the Mediterranean diet has been shown to significantly decrease recurrent cardiac events when initiated after first myocardial infarction in adults.[93]

In the DASH intervention feeding trial in adults, a diet rich in fruits and vegetables, low-fat or fat-free dairy products, whole grains, fish, poultry, beans, seeds, and nuts substantially reduced

both systolic and diastolic BPs among adults with stage 1 hypertension or prehypertension.[94] The DASH diet is also lower in sweets and added sugars, fats, and red meat than the typical U.S. diet. Although originally tested for effects on BP, consumption of the DASH diet was also associated with reduced total and saturated fat intake and a significant decrease in LDL–C level.[95] Reduced dietary sodium in addition to following the DASH diet achieved the largest BP reductions.[96] In observational studies, sustained adherence to a DASH-style diet has been shown to be associated with lower risk of coronary heart disease and stroke in both men and women on long-term followup.[97,98] When tested in free-living conditions in adults, the Premier Research Group reported that a behavioral intervention, including the DASH dietary pattern along with other lifestyle changes to reduce BP—reduced dietary sodium, increased physical activity, and weight loss—resulted in increased intake of dietary fiber, weight loss, and reductions in BP and lipid levels among adults with prehypertension or hypertension.[99]

Childhood and Adolescence

The evidence review for these Guidelines identified no dietary pattern studies in infants, but such studies in older children have been emerging. As described previously, the Young Finns study, begun when subjects were ages 3–18 years, evaluated two major dietary patterns: a "traditional" pattern characterized by high consumption of rye, potatoes, butter, sausages, milk, and coffee and a "health-conscious" diet with high consumption of vegetables, legumes and nuts, cheese and other dairy products, and, in older subjects, alcoholic beverages.[3] At 21-year followup, with subjects then ages 24–39 years, the traditional diet was significantly and independently associated with higher TC and LDL–C levels, apo B, and CRP values in both genders and higher systolic BP and insulin levels among women; the health-conscious diet was associated with better CV risk status but the latter correlation did not achieve statistical significance.[3]

From the NGHS, a dietary pattern characterized by high intake of fruits and vegetables, low fat dairy products, and grains and low intakes of sugar, fried foods, burgers, and pizza was associated with less adiposity over 10-year followup.[5] From the Framingham Children's Study, data from 95 children ages 3–6 years at enrollment indicate that, in adolescence, those with consistently higher intakes of fruits and vegetables and dairy products had significantly lower systolic BP levels.[100]

An RCT of the DASH diet in 57 adolescents with prehypertension or hypertension found at 3-month followup that the DASH diet group had a significantly greater decrease in systolic BP associated with higher intakes of fruits, low-fat dairy products, potassium, and magnesium and a greater decrease in dietary total fat intake than the usual-care group.[101] There were no adverse effects.

SUMMARY OF THE EVIDENCE REVIEW FOR DIETARY PATTERNS

- There is emerging evidence in children and adolescents that a composite healthy eating pattern is feasible and is associated with reduced CV risk factors.
- The DASH dietary pattern was tested in only one RCT in adolescents, but the benefit may be extrapolated from studies in adults.

OVERVIEW OF THE EVIDENCE FOR INTAKE OF DIETARY SUPPLEMENTS

This evidence review identified several small studies that reported short-term effects of dietary supplements in children, often in the absence of dietary assessment data. Regardless, the findings are summarized below by age group for the purpose of providing available evidence on these topics as identified by the evidence review.

Infancy/Early Childhood

Fish Oil

To investigate whether maternal intake of n-3 long-chain PUFA during lactation or current macronutrient intake affects children's BP, mothers with low fish intake were randomized to receive fish oil or olive oil daily during the first 4 months of lactation.[102] At age 2.5 years, no significant effect of maternal fish oil intake on children's BP was detected.

Plant Sterols

The effect of replacing dietary fat with plant stanol ester was investigated in a subset of 6-year-old children from the STRIP study.[103,104] TC and LDL–C levels decreased 5.4 percent and 7.5 percent, respectively, among children who consumed a plant stanol-enriched margarine, compared with placebo. There were no effects on HDL–C or TG values. These changes were accompanied by decreased cholesterol absorption. Safety was judged to be excellent. The presence of the apoE–4 variant did not affect the response to plant stanols.[105] There was no significant difference in cholesterol absorption between boys and girls, but there was a greater decrease in the LDL–C level in boys (9.1 percent) than in girls (5.8 percent). The plant stanol results were confirmed in a short-term study of U.S. preschool children.[106]

Calcium

In a study designed to evaluate whether there is an association between calcium intake and change in body fat in children ages 3–5 years, calcium supplementation did not reduce gain in fat mass when baseline calcium intake was adequate.[107]

Adolescence

Fiber Supplements

Evidence of the use of fiber supplements in children is limited. In a small, 2-month RCT of 60 overweight adolescents, no significant difference was noted in weight change among subjects who received a fiber supplement (glucomannan), compared with placebo; dietary fiber intake was not assessed. At followup, the glucomannan group had lower HDL–C levels and higher very-low-density lipoprotein and TG levels, compared with lower TG and LDL–C values in the placebo group, suggesting no benefit and a potentially adverse impact of the supplement.[108]

SUMMARY OF THE EVIDENCE FOR INTAKE OF DIETARY SUPPLEMENTS

- Evidence on the health effects of dietary supplements in children is limited.
- Short-term replacement of dietary fat with plant stanol ester in healthy children ages 2–6 years was safe and was associated with significantly decreased TC and LDL–C levels.
- In children ages 3–5 years, supplemental calcium did not reduce gain in fat mass when baseline intake of calcium was adequate in one study.
- Maternal fish oil supplementation during lactation in healthy infants was not associated with any differences in children's BP at age 2.5 years in one study.

- Very limited evidence regarding use of fiber supplements in children suggests no benefit and possible adverse effects.

DEVELOPMENT OF FOOD PREFERENCES AND EATING BEHAVIORS

The development of food preferences in childhood is important because early preference patterns have a long-term influence on dietary intake later in life.[109,110] Research in this area generally does not include RCTs that address CV risk factors, and no studies were identified in this evidence review; however, because this is such an important precept, a brief review of knowledge in the area is provided below.

Children's food preferences develop from a complex interplay of innate, familial, and environmental factors. There are innate preferences for sweet and salty tastes demonstrated from early infancy, and genetic propensities toward certain food groups have been shown in twin studies.[111,112,113] One of the most important influences in the development of taste preferences is experience. Maternal diets have been shown to be experienced by the fetus and the breast-fed baby, and specific exposures have been shown to affect an infant's subsequent dietary preferences.[114] Repeated exposures to selected foods, including fruits and vegetables, in early infancy have been shown to be associated with acceptance and then preference for these foods. Between 5 and 14 exposures to a new food are needed to see increased preference in both infants and children.[115,116] Some research indicates that acceptance of textured foods is determined by earlier experience.[117] Early exposure to culture-specific foods and dietary styles gives rise to subsequent differences in food preferences, evident in the widely varying food preferences of children in different cultures.[118]

Parents powerfully shape children's early experiences with food, deciding what foods are made available and accessible and determining quantities provided and eating patterns. Parents and siblings model eating behavior from birth onward, and parent-child and sibling similarities in food preferences and eating behavior have been described.[119,120,121,122] In addition, parental feeding style, principally feeding restriction, has been suggested to enhance the appeal of energy-dense, nutrient-poor foods, leading to overeating of these foods when access is gained and potentially contributing to excess weight gain.[123,124] Finally, exposure to television and its associated child-oriented food commercials has been associated with food choices and higher food intake.[125,126]

In pediatric care, questions about feeding and diet are a dominant source of concern, especially in infancy. This period of opportunity allows pediatric care providers to introduce heart healthy, calorie-balanced eating patterns at a time when food preferences, eating patterns, and lifestyle behaviors are being formed. Routine, regularly scheduled well-child visits to the pediatric care provider allow for reinforcement of healthy eating patterns throughout childhood and into young adulthood.

HEALTHY EATING BEHAVIORS

Background

A number of eating behaviors in children and adolescents may promote or detract from a healthy nutrition pattern. These include eating breakfast (both frequency and quality); eating meals with family members ("family dinner"); eating away from home, especially fast food; eating school lunch; and both quality of snack foods and frequency of snacking. In addition, during early childhood, the quality of the mother-child feeding interaction may affect future

weight gain. The search strategy for the Expert Panel recommendations prioritized results from RCTs, but none were identified among children or adolescents for these eating behaviors. Thus, the Expert Panel carefully reviewed existing observational studies and extracted potentially useful findings. Limitations inherent in all observational studies include the inability to adequately control for confounding factors. Also, most of these studies are cross-sectional, thereby making it unclear whether an "exposure" causes an "outcome." The lack of high-quality evidence for these eating behaviors automatically requires that any resulting recommendations result from Expert Panel consensus, which is ranked lower than evidence-based recommendations. None of the reported studies addresses infancy or early childhood.

Childhood and Adolescence

Although the evidence in children is limited, eating breakfast may reduce excessive weight gain, hypothetically by enhancing satiety through high-fiber cereal and/or whole-grain intake, reducing hunger and overeating at lunchtime, and/or providing other foods as part of breakfast such as fruits or products that may contribute further to improved nutrition density while aiding appetite regulation. In adults, a small number of prospective observational studies and short-term RCTs suggest that eating breakfast may reduce weight or prevent weight gain.[127,128,129] In children and adolescents, prospective studies are few, and trials are lacking.[130,131] In the NGHS, 2,379 White and Black girls were followed annually from ages 9 to 19 years. Frequency of breakfast eating declined with age. The number of days per week when breakfast was eaten was associated with higher calcium and fiber intakes and was predictive of lower BMI, but the independent effect of eating breakfast on BMI was not significant after parental educational attainment, overall energy intake, and physical activity were included in the analysis.[132] Eating breakfast may have beneficial effects on cognition and school performance.[130]

In some observational, primarily cross-sectional, studies of children and adolescents, eating dinner or other meals with one's family has been associated with more healthful dietary patterns. The few existing prospective studies suggest that increased frequency of family meals is associated with less excessive weight gain, but confounding is possible, and mechanisms are unclear.[133,134,135] In preschool children, the association of healthful diets with the greater frequency of eating dinner as a family was counteracted by a higher frequency of watching television during the meal.[136]

The existing literature conflates eating away from home, eating certain foods or nutrients (such as fried foods) away from home, and fast-food consumption. Furthermore, the definition of "fast food" is not entirely clear. Nevertheless, several cross-sectional and a small number of prospective studies suggest that eating foods away from home, especially from fast-food establishments, may contribute to excessive weight gain.[137,138,139] In a study of preschool children, each 1 hour per day increase in television/video watching was significantly associated with greater consumption of fast food.[140]

A few, mostly cross-sectional, studies correlate the intake of snack foods, which tend to be relatively low in dietary quality, or snacking behavior with weight status. In the few longitudinal studies available, however, evidence argues against a substantial effect of snack food consumption.[134,141,142,143] In a study of children age 3 years, daily hours of television viewing were significantly associated with higher intakes of sugar-sweetened beverages, fast food, red and processed meats, total energy intake, and percentage of energy intake from *trans* fats and lower intakes of fruits and vegetables, calcium, and fiber.[144]

PUBLIC HEALTH APPROACHES

Clinicians should be cognizant of public health approaches, such as the WIC Program and other school- and community-based programs, that have the potential to significantly affect children's dietary intakes. For additional information about public health approaches, readers are encouraged to consult *The Guide to Community Preventive Services,* coordinated by the CDC, which provides evidence-based reviews of public health approaches (http://www.thecommunityguide.org/index.html). Because public health initiatives have the potential to affect the nutrition of children and adolescents, these approaches are an important avenue for advocacy by pediatric care providers. Key issues are summarized below.

Because many U.S. children obtain a large proportion of daily energy in the school setting, changing children's eating habits and dietary intakes at school could potentially influence both nutrition and weight status, as well as CV risk factors such as hypertension and dyslipidemia. Indeed, many of the intervention studies described in this section are school based. Although foods and beverages served as part of the USDA-reimbursable school breakfast or school lunch programs must meet dietary standards, foods sold in the cafeteria in competition with school lunch or school breakfast, sold in vending machines or school stores, or sold for fundraising events are not required to meet these standards. Some States and local school districts have been successful in changing the school food environment and, thus, children's eating habits.[145] Preliminary evidence suggests that improved nutrition standards, in conjunction with increases in physical activity and education, have increased awareness and may have begun to affect students' overweight rates.[146,147] A multicomponent school nutrition policy initiative randomized 10 schools in which at least 50 percent of students were eligible for free or reduced-price meals. After 2 years, among 1,349 initially fourth- through sixth-graders, there was a 50 percent reduction in the incidence of overweight, with significantly fewer children in the intervention

schools than in the control schools becoming overweight. The prevalence of overweight was also lower in the intervention schools. No differences, however, were observed in the incidence, prevalence, or remission of obesity at 2-year followup.[148] The findings suggest to the Expert Panel that public health approaches to overweight may have significant impact but that more intensive intervention may be needed for obese children. In addition, public health approaches can increase supportive environments for fruit and vegetable intake.[149],[150] (Story 2008; CDC Guide to F&V 2010). Because public health initiatives have the potential to affect the nutrition of children and adolescents, this is an important avenue for advocacy by pediatric care providers.

CONCLUSIONS AND GRADING OF THE EVIDENCE REVIEW FOR DIET AND NUTRITION IN CARDIOVASCULAR RISK REDUCTION

The Expert Panel concluded that there is strong and consistent evidence that good nutrition beginning at birth has profound health benefits, with the potential to decrease future risk for CVD. The Expert Panel accepts the 2010 *DGA* as containing appropriate recommendations for diet and nutrition in children 2 years and older. The recommendations in these Guidelines are intended for pediatric care providers to use with their patients to address CV risk reduction. The conclusions of the Expert Panel's review of the entire body of evidence in a specific nutrition area with grades are summarized below. The age- and evidence-based recommendations of the Expert Panel follow in Table 5–2. Where evidence is inadequate yet nutrition guidance is needed, recommendations for pediatric care providers are based on a consensus of the Expert Panel (Grade D).

In accordance with the Surgeon General's Office, the WHO, the AAP, and the AAFP, exclusive breast-feeding is recommended for the first 6 months of life. Continued breast-feeding is recommended to at least age 12 months, with the addition of complementary foods. If breast-feeding per se is not possible, feeding human milk by bottle is second best, with formula-feeding as the third choice.

- Long-term followup studies consistently demonstrate that infants who were breast-fed have sustained CV health benefits, including lower cholesterol levels, reduced prevalence of T2DM, lower measures of subclinical disease (e.g., cIMT), and possibly lower BMI in adulthood (Grade B).
- Ongoing nutrition counseling has been effective in helping children and families to adopt and sustain recommended diets for both nutrient adequacy and reducing CV risk (Grade A).
- Within appropriate age- and gender-based requirements for growth and nutrition, in normal children and in children with hypercholesterolemia, intake of total fat can be safely limited to 30 percent of total calories, saturated fat intake limited to 7–10 percent of calories, and dietary cholesterol limited to 300 mg/d. Under the guidance of qualified nutritionists, this dietary composition has been shown to result in lower TC and LDL–C levels, less obesity, and less insulin resistance (Grade A). Under similar conditions and with ongoing followup, these levels of fat intake may have similar effects starting in infancy (Grade B). Fats are important to infant diets due to their role in brain and cognitive development. Fat intake in infants younger than 12 months of age should not be restricted without medical indication.

- The remaining 20 percent of fat intake should comprise a combination of monosaturated and polyunsaturated fats (Grade D). Intake of *trans* fats should be limited as much as possible (Grade D).
- The current NCEP guidelines recommend that adults consume 25–35 percent of calories from fat. The 2010 *DGA* includes the IOM recommendation for 30–40 percent of calories from fat for ages 1–3 years, 25–35 percent of calories from fat for ages 4–18 years, and 20–35 percent of calories from fat for adults. For growing children, milk provides essential nutrients, including protein, calcium, magnesium, and vitamin D, that are not readily available elsewhere in the diet. Consumption of fat-free milk in childhood starting at age 2 years and through adolescence optimizes these benefits, without compromising nutrient quality while avoiding excess saturated fat and calorie intake (Grade A). Between ages 1 and 2 years, as children transition from breast milk or formula, milk reduced in fat (ranging from 2 percent milk to fat-free milk) can be used based on the child's growth, appetite, intake of other nutrient-dense foods, intake of other sources of fat, and risk for obesity and CVD. Milk with reduced fat should be used only in the context of an overall diet that supplies 30 percent of calories from fat. Dietary intervention should be tailored to each specific child's needs.
- Optimal intakes of total protein and total carbohydrates in children were not specifically addressed, but with a recommended total fat intake of 30 percent of energy, the Expert Panel recommends that the remaining 70 percent of calories include 15–20 percent from protein and 50–55 percent from carbohydrate sources (no grade). These recommended ranges fall within the acceptable macronutrient distribution range specified by the 2010 *DGA*: 10–30 percent of calories from protein and 45–65 percent of calories from carbohydrates for children ages 4–18 years.
- Sodium intake was not addressed by the evidence review for this section on nutrition and diet. From the evidence review for Section VIII. High Blood Pressure, lower sodium

intake is associated with lower systolic and diastolic BPs in infants, children, and adolescents.

- Plant-based foods are important low-calorie sources of nutrients, including vitamins and fiber, in the diets of children; increasing access to fruits and vegetables has been shown to increase their intake (Grade A). However, increasing fruit and vegetable intake is an ongoing challenge.
- Reduced intake of sugar-sweetened beverages is associated with decreased obesity measures (Grade B). Specific information about fruit juice intake is too limited for an evidence-based recommendation. Recommendations for intake of naturally sweetened fruit juice (without added sugar) in infants are a consensus of the Expert Panel (Grade D) and are in agreement with those of the AAP.
- Per the 2010 *DGA*, energy intake should not exceed energy needed for adequate growth and physical activity. Calorie intake needs to match growth demands and physical activity needs. Estimated calorie requirements by gender and age group at three levels of physical activity from the 2010 *DGA* are shown in Table 5–1. For children of normal weight whose activity is minimal, most calories are needed to meet nutritional requirements, leaving only about 10 percent of calorie intake from discretionary sources (e.g., foods with added fat and sugar) (Grade D).
- Dietary fiber intake is inversely associated with energy density and with increased levels of body fat and is positively associated with nutrient density (Grade B). A daily total dietary fiber intake from food sources of at least age plus 5 g for young children up to 14 g/1,000 kcal for older children and adolescents is recommended (Grade D).
- The Expert Panel supports the recommendation of the AAP for vitamin D supplementation with 400 IU/d for all infants and 600 IU/day for children over 1 years old. No other vitamin, mineral, or dietary supplements are recommended (Grade D).

- Use of dietary patterns modeled on those shown to be beneficial in adults (such as the DASH pattern) is a promising approach to improving nutrition and decreasing CV risk (Grade B).
- All dietary recommendations must be interpreted by the pediatric care provider for each child and family to address individual diet and growth patterns and patient sensitivities such as lactose intolerance and food allergies (Grade D).

As stated above, these dietary recommendations to promote CV health in children under the care of pediatric care providers are based on the results of the evidence review and the population recommendations are consistent with the *DGA*. Graded, age-specific recommendations for pediatric care providers to use in reducing CV risk in their patients are summarized in Table 5–2 (CHILD 1) and are designed to support implementation of the findings of the evidence review. CHILD 1 is the first stage in dietary change for children with identified dyslipidemia, overweight and obesity, risk factor clustering, and high-risk medical conditions who may ultimately require more intensive dietary change. More intensive recommendations to be implemented if needed for children with these conditions appear in the designated sections of these Guidelines. CHILD 1 is also the recommended diet for children with a positive family history of early CV disease, dyslipidemia, obesity, primary hypertension, diabetes, or children exposure to smoking in the home. Any dietary modification must provide nutrients and calories needed for optimal growth and development. Likewise, recommended intakes are adequately met by a DASH-style eating plan, which emphasizes fat-free/low-fat milk and dairy products and increased intake of fruits and vegetables. This pattern has been modified for use in children age 4 years and older based on daily energy needs and is shown in Table 5–3 as one example of a heart healthy eating plan using the CHILD 1 recommendations.

Table 5–2. Evidence-Based Dietary Recommendations for Patients of Pediatric Care Providers: Cardiovascular Health Integrated Lifestyle Diet (CHILD 1)

CHILD 1 is the recommended first step diet for all children and adolescents at elevated cardiovascular risk.

Grades reflect the findings of the evidence review.
Recommendation levels reflect the consensus opinion of the Expert Panel.
Supportive actions represent expert consensus suggestions from the Expert Panel provided to support implementation of the recommendations; they are not graded.

Birth–6 months	Infants should be exclusively breastfed (no supplemental formula or other foods) until age 6 months.*	Grade B *Strongly recommend*
	* Infants who cannot be fed directly at the breast should be fed expressed milk. Infants for whom expressed milk is not available should be fed iron-fortified infant formula.	
6–12 months	Continue breastfeeding* until at least age 12 months while gradually adding solids; transition to iron-fortified formula until 12 months if reducing breastfeeding	Grade B *Strongly recommend*
	Fat intake in infants younger than 12 months of age should not be restricted without medical indication	Grade D *Recommend*
	Limit other drinks to 100% fruit juice ≤4 oz/d; No sweetened beverages; encourage water	Grade D *Recommend*
	* Infants who cannot be fed directly at the breast should be fed expressed milk. Infants for whom expressed milk is not available should be fed iron-fortified infant formula.	

12–24 months	Transition to reduced-fat* (2% to fat-free) unflavored cow's milk** (see supportive actions bullet 1)	Grade B *Recommend*
	Limit/avoid sugar-sweetened beverage intake; encourage water	Grade B *Strongly recommend*
	Transition to table food with:	
	• Total fat 30% of daily kcal/EER***	Grade B *Recommend*
	• Saturated fat 8–10% of daily kcal/EER	Grade B *Recommend*
	• Avoid *trans* fat as much as possible	Grade D *Strongly recommend*
	• Monounsaturated and polyunsaturated fat up to 20% of daily kcal/EER	Grade D *Recommend*
	• Cholesterol <300 mg/d	Grade B *Strongly recommend*

Supportive actions:

- The fat content of cow's milk to introduce at ages 12–24 months should be decided together by parents and health care providers based on the child's growth, appetite, intake of other nutrient-dense foods, intake of other sources of fat, and potential risk for obesity and CVD.
- Limit 100% fruit juice (from a cup) to no more than 4 oz/d.
- Limit sodium intake.
- Consider DASH-type diet rich in fruits, vegetables, whole grains, low-fat/fat-free milk and milk products; lower in sugar (Table 5–3).

* Toddlers 12–24 months of age with a family history of obesity, heart disease, or high cholesterol should discuss transition to reduced-fat milk with pediatric care provider after 12 months of age.

****** Continued breastfeeding is still appropriate and nutritionally superior to cow's milk. Milk reduced in fat should be used only in the context of an overall diet that supplies 30% of calories from fat.

*** EER = Estimated Energy Requirements/d for age/gender (Table 5–1)

2–10 years

Primary beverage: Fat-free unflavored milk — Grade A *Strongly recommend*

Limit/avoid sugar-sweetened beverages; encourage water — Grade B *Recommend*

Fat content:

- Total fat 25–30% of daily kcal/EER — Grade A *Strongly recommend*
- Saturated fat 8–10% of daily kcal/EER — Grade A *Strongly recommend*
- Avoid *trans* fats as much as possible — Grade D *Recommend*
- Monounsaturated and polyunsaturated fat up to 20% of daily kcal/ EER — Grade D *Recommend*
- Cholesterol <300 mg/d — Grade A *Strongly recommend*

Encourage high dietary fiber intake from foods***** — Grade B *Recommend*

Supportive actions:

- Teach portions based on EER for age/gender/activity (Table 5–1).
- Encourage moderately increased energy intake during periods of rapid growth and/or regular moderate-to-vigorous physical activity.
- Encourage dietary fiber from foods: Age plus 5 g/d.[*]
- Limit naturally sweetened juice (no added sugar) to 4 oz/d.
- Limit sodium intake.
- Support DASH-style eating plan (Table 5–3).

***** Naturally fiber-rich foods are recommended (fruits, vegetables, whole grains); fiber supplements are not advised**.** Limit refined carbohydrates (sugars, white rice, white bread).

11–21 years	Primary beverage: Fat-free unflavored milk	Grade A *Strongly recommend*
	Limit/avoid sugar-sweetened beverages; encourage water	Grade B *Recommend*
	Fat content:	
	• Total fat 25–30% of daily kcal/EER	Grade A *Strongly recommend*
	• Saturated fat 8–10% of daily kcal/EER	Grade A *Strongly recommend*
	• Avoid *trans* fat as much as possible	Grade D *Strongly recommend*
	• Monounsaturated and polyunsaturated fat up to 20% of daily kcal/EER	Grade D *Recommend*
	• Cholesterol <300 mg/d	Grade A *Strongly recommend*
	Encourage high dietary fiber intake from foods*	Grade B *Recommend*

Supportive actions:

- Teach portions based on EER for age/gender/activity (Table 5–1).
- Encourage moderately increased energy intake during periods of rapid growth and/or regular moderate-to-vigorous physical activity.
- Advocate dietary fiber: Goal of 14 g/1,000 kcal.*
- Limit naturally sweetened juice (no added sugar) to 4–6 oz/d.
- Limit sodium intake.
- Encourage healthy eating habits: Breakfast every day, eating meals as a family, limiting fast-food meals.
- Support DASH-style eating plan as outlined in Table 5–3.

***** Naturally fiber-rich foods are recommended (fruits, vegetables, whole grains); fiber supplements are not advised**.** Limit refined carbohydrates (sugars, white rice, white bread).

Table 5–3. DASH-Style Eating Plan: Servings Per Day by Food Group and Total Energy Intake

(Table 5–1 provides Estimated Energy Requirements (EER) by age, gender, and activity level. EER and discretionary calorie allowance by age and level of activity for boys and girls are shown in Figures 5–1 and 5–2.)

Food Group	1,200 Calories	1,400 Calories	1,600 Calories	1,800 Calories	2,000 Calories	2,600 Calories	Serving Sizes	Examples and Notes	Significance of Food Group to DASH Eating Plan
Grains*	4–5	5–6	6	6	6–8	10–11	1 slice bread 1 oz dry cereal† ½ cup cooked rice, pasta, or cereal†	Whole- wheat bread and rolls, whole-wheat pasta, English muffin, pita bread, bagel, cereals, grits, oatmeal, brown rice, unsalted pretzels and popcorn	Major sources of energy and fiber
Vegetables	3–4	3–4	3–4	4–5	4–5	5–6	1 cup raw leafy vegetable ½ cup cut-up raw or cooked vegetable ½ cup vegetable juice	Broccoli, carrots, collards, green beans, green peas, kale, lima beans, potatoes, spinach, squash, sweet potatoes, tomatoes	Rich sources of potassium, magnesium, and fiber
Fruits	3–4	4	4	4–5	4–5	5–6	1 medium fruit ¼ cup dried fruit ½ cup fresh, frozen, or canned fruit ½ cup fruit juice	Apples, apricots, bananas, dates, grapes, oranges, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, raisins, straw-berries, tangerines	Important sources of potassium, magnesium, and fiber
Fat-free or low-fat milk and milk products	2–3	2–3	2–3	2–3	2–3	3	1 cup milk or yogurt 1½ oz cheese	Fat-free milk or buttermilk; fat-free, low-fat, or reduced-fat cheese; fat-free/low-fat regular or frozen yogurt	Major sources of calcium and protein

Food Group	1,200 Calories	1,400 Calories	1,600 Calories	1,800 Calories	2,000 Calories	2,600 Calories	Serving Sizes	Examples and Notes	Significance of Food Group to DASH Eating Plan
Lean meats, poultry, and fish	3 or less	3–4 or less	3–4 or less	6 or less	6 or less	6 or less	1 oz cooked meats, poultry, or fish 1 egg‡	Select only lean; trim away visible fats; broil, roast, or poach; remove skin from poultry	Rich sources of protein and magnesium
Nuts, seeds, and legumes	3 per week	3 per week	3–4 per week	4 per week	4–5 per week	1	1/3 cup or 1½ oz nuts 2 Tbsp peanut butter 2 Tbsp or ½ oz seeds ½ cup cooked legumes (dried beans, peas)	Almonds, filberts, mixed nuts, peanuts, walnuts, sunflower seeds, peanut butter, kidney beans, lentils, split peas	Rich sources of energy, magnesium, protein, and fiber
Fats and oils	1	1	2	2–3	2–3	3	1 tsp soft margarine 1 tsp vegetable oil 1 Tbsp mayonnaise 2 Tbsp salad dressing	Soft margarine, vegetable oil (canola, corn, olive, safflower), low-fat mayonnaise, light salad dressing	DASH study had 27% of calories as fat, including fat in or added to foods
Sweets and added sugars	3 or less per week	3 or less per week	3 or less per week	5 or less per week	5 or less per week	≤2	1 Tbsp sugar 1 Tbsp jelly or jam ½ cup sorbet, gelatin dessert 1 cup lemonade	Fruit-flavored gelatin, fruit punch, hard candy, jelly, maple syrup, sorbet and ices, sugar	Sweets should be low in fat

The Food and Drug Administration (FDA) and the Environmental Protection Agency advise women of childbearing age who may become pregnant, pregnant women, nursing mothers, and young children to avoid some types of fish and shellfish and eat fish and shellfish that are low in mercury. For more information, call the FDA's food information line toll free at 1–888–SAFEFOOD or visit http://www.cfsan.fda.gov/~dms/admehg3.html.

* Whole grains are recommended for most grain servings as a good source of fiber and nutrients.

† Serving sizes vary between 1/2 cup and 1¼ cups, depending on cereal type. Check the product's Nutrition Facts label.

‡ Because eggs are high in cholesterol, limit egg yolk intake to no more than four per week; two egg whites have the same protein content as 1 oz meat. Fat content changes serving amount for fats and oils. For example, 1 Tbsp regular salad dressing = 1 serving; 1 Tbsp low-fat dressing = 1/2 serving; 1 Tbsp fat-free dressing = zero servings.

Abbreviations: oz = ounce; Tbsp = tablespoon; tsp = teaspoon.

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6. PHYSICAL ACTIVITY

INTRODUCTION

This section of the Guidelines provides recommendations to pediatric care providers on physical activity relative to cardiovascular (CV) health in children and adolescents. The section begins with background information on the association between physical activity levels and cardiovascular disease. This is followed by the Expert Panel's summary of the evidence review of the association between physical activity and sedentary behavior and CV risk factors and the randomized controlled trials (RCTs) addressing behavior change relative to both physical activity and sedentary time. The evidence review and the Guidelines development processes are outlined in Section I. Introduction and are described in detail in Appendix A. Methodology. As described, the evidence review augments a standard systematic review where the findings from the studies reviewed constitute the only basis for recommendations, with each study described in detail. This evidence review combines a systematic review with an Expert Panel consensus process that incorporates and grades the quality of all relevant data based on preidentified criteria. Because of the large volume of included studies and the diverse nature of the evidence, the Expert Panel also provides a critical overview of the studies reviewed for each risk factor, highlighting those that, in its judgment, provide the most important information. Detailed information from each study has been extracted into the evidence tables and will be available at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. The conclusions of the Expert Panel's review of the evidence are summarized and graded, and the section ends with age-specific recommendations. Where evidence is inadequate, recommendations are a consensus of the Expert Panel. References are listed sequentially at the end of the section, with references from the evidence review identified by unique PubMed identifier (PMID) numbers in bold text. Additional references do not include the PMID number.

BACKGROUND

Physical activity is any bodily movement produced by contraction of skeletal muscle that increases energy expenditure above a basal level. Physical activity can be focused on strengthening muscles, bones, and/or joints, but because these Guidelines address CV health, the evidence review concentrated on aerobic activity. There is strong evidence for the beneficial effects of physical activity on the overall health of children and adolescents across a broad array of domains.[1] In the United States, 16.6 percent of total deaths have been attributed to the combination of a sedentary lifestyle and dietary factors.[2] The evidence review concentrated on the effects of physical activity on CV health where physical inactivity has been identified as an independent risk factor for coronary heart disease.[3,4] Research on physical activity in children has explored three interdependent but distinct constructs: fitness, physical activity, and sedentary behavior. A comprehensive review of the independent role of each of these in CV health is beyond the scope of these Guidelines; specifically, the Expert Panel reviewed studies on physical activity and sedentary behavior but did not address research on fitness.

OVERVIEW OF THE EVIDENCE OF THE ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR AND CARDIOVASCULAR RISK FACTORS

Over the past several decades, there has been a decrease in the amount of time that children spend being physically active and a steady increase in the amount of time spent in sedentary activities. A recent systematic review indicates that contemporary youths watch 1.8–2.8 hours/day (h/d) of television, with 28 percent watching more than 4 h/d; boys average 60 minutes/day (min/d) playing video games compared with 23 min/d for girls; computer use

increases with increasing age but averages 30 min/d across childhood. In this report, total screen time averaged 2.7–4.3 h/d.[5] From the current evidence review, multiple observational studies in children ages 4–18 years and young adults ages 19–21 years strongly link increased time spent in sedentary activities with reduced overall physical activity levels; disadvantageous lipid profile changes; higher systolic blood pressure (BP); increased levels of obesity and all of the obesity-related CV risk factors, including hypertension, insulin resistance, and type 2 diabetes mellitus, especially among male children and adolescents. Participation in routine physical activity, including team sports, is inversely associated with these same outcomes.[1,6,7,8,9,10,11,12]

Longitudinal studies show that the most optimal CV risk profiles are seen in individuals who are consistently physically active.[6,8,13] In diverse populations, the tracking of both sedentary and active behaviors is moderately strong from childhood to young adulthood, with the most consistent tracking seen for higher levels of physical activity at ages 9–18 years, predicting higher levels of adult physical activity.[6,9,14,15] Finally, health-enhancing and/or -compromising physical activity patterns, dietary choices, and smoking behaviors have consistently been shown to cluster together.[9,10]

OVERVIEW OF THE EVIDENCE FOR INTERVENTIONS TO INCREASE PHYSICAL ACTIVITY AND/OR DECREASE SEDENTARY TIME

The Guidelines evidence review identified 6 systematic reviews, 3 meta-analyses, and 46 RCTs addressing physical activity and/or sedentary behavior. Many studies simultaneously addressed increasing physical activity, decreasing sedentary behavior, and improving nutrition and measured fitness, obesity, lipid profile, BP, and/or insulin resistance as outcomes. More than a third of the identified RCTs were conducted in school settings and were designed as

multicomponent interventions addressing combinations of the physical activity regimen, time spent in physical activity, environmental factors, and/or training of supervisors. Of the school-based trials, most were successful in increasing time spent being physically active and/or in decreasing sedentary time during the intervention in either or both sexes.[16,17,18,19,20,21,22,23,24,25,26,27,28] Late followup after completion of an intervention is unusual, but when available, has not shown sustained physical activity change.[29] School-based physical activity interventions have been shown to lower BP in children and adolescents[19] and to decrease total cholesterol (TC).[17,27,28] Such interventions occasionally have resulted in decreased measures of overweight and obesity,[21,30] but more often, school-based physical activity trials that have been designed to address measures of obesity have been unsuccessful.[28,31,32]

Almost half of the physical activity RCTs have been relatively small studies in clinical research laboratory settings. Most were successful in increasing time spent being physically active and/or decreasing sedentary time during the intervention.[33,34,35,36,37,38,39,40,41,42,43,44,45,46,47] Several RCTs demonstrated that making a favored sedentary activity contingent on increased physical activity was successful in increasing time spent being physically active and decreasing sedentary time,[33,37,40,41,42,48] and one study applied this concept successfully in an Internet-based physical activity-contingent intervention.[49] Three of four studies set in daycare or community settings were successful in increasing physical activity and/or decreasing sedentary screen time.[50,51,52] Finally, one successful study was implemented through a primary care practitioner's office that used computerized telephone and mailed reminders.[53] Multiple physiologic outcomes were evaluated in these studies, many of which addressed prevention or treatment of obesity. The preponderance of the evidence indicates that increasing physical activity and decreasing sedentary time are associated with lower systolic and diastolic BP,[34,38,54,55,56] decreased measures of body fat,[21,33,34,35,36,37,42,45,46,54,55,57] decreased body mass index (BMI) or percentage

of overweight,[34,35,36,39,55,56] improved fitness measures,[21,35,38,39,43,44,45,47,54,55,56,58] lower TC,[36,55] lower low-density lipoprotein cholesterol (LDL–C),[34] lower triglycerides (TG),[21,34,38,55] higher high-density lipoprotein cholesterol (HDL–C),[44,55] and decreased insulin resistance.[21,34,46,54,57] Several studies in obese children have evaluated vascular function and have shown significant increases in flow-mediated dilation and reduced carotid intima-media thickness after exercise interventions.[34,43,44,47,56,58] No study reported any adverse CV outcome as a consequence of a physical activity intervention.

CONCLUSIONS AND GRADING OF THE EVIDENCE REVIEW FOR PHYSICAL ACTIVITY

Overall, the Expert Panel concluded that the evidence strongly supports the role of activity in optimizing CV health in children and adolescents.

- There is reasonably good evidence that physical activity patterns established in childhood are carried forward into adulthood (Grade C).
- There is strong evidence that increases in moderate to vigorous physical activity are associated with lower systolic and diastolic BPs, decreased measures of body fat, decreased BMI, improved fitness measures, lower TC, lower LDL–C, lower TG, higher HDL–C, and decreased insulin resistance in childhood and adolescence (Grade A).
- There is limited but strong and consistent evidence that physical exercise interventions improve subclinical measures of atherosclerosis (Grade B).
- Physical activity patterns, dietary choices, and smoking behaviors cluster together (Grade C).
- There is no evidence of harm associated with increased physical activity or limitation of sedentary activity in normal children (Grade A).
- There is strong evidence that physical activity should be promoted in schools (Grade A).

There is less specific information on the type and amount of physical exercise required for optimal CV health. Reported physical activity interventions from this evidence review ranged from 20 to 60 minutes, 2–5 times/week in children ages 3–17 years and included a wide variety of dynamic and isometric exercises. Extrapolating from these interventions which occurred in supervised settings to the real world of childhood and adolescence, the Expert Panel recommended at least 1 hour of moderate to vigorous physical activity every day of the week, with vigorous, intense physical activity on at least 3 of these days in agreement with the *2008 Physical Activity Guidelines for Americans* from the U.S. Department of Health and Human Services. In working with children and families, the Expert Panel suggested that moderate to vigorous activity could be compared with walking briskly or jogging and that vigorous physical activity could be compared with running, playing singles tennis, or playing soccer. Similarly, reducing sedentary time is convincingly associated with a favorable CV profile, and the Expert Panel agreed with the recommendation from the American Academy of Pediatrics for limiting leisure screen time to no more than 1 to 2 hours of quality programming per day. The *2008 Physical Activity Guidelines for Americans* was published after the evidence review for these Guidelines was completed and, therefore, cannot be formally included. However, the *2008 Physical Activity Guidelines* is recommended to pediatric care providers as an extensive resource on physical activity recommendations for their patients and is available at http://ww.health.gov/paguidelines.

Pediatric care providers represent an important source of accurate information about physical activity recommendations for children and adolescents. However, information about how to optimize the adoption of these recommendations in a practice setting remains limited. The supportive actions included in Table 6–1 represent expert consensus suggestions from the Expert Panel to support implementation of the recommendations.

Table 6–1. Evidence-Based Physical Activity Recommendations for Cardiovascular Health

Grades reflect the findings of the evidence review.
Recommendation levels reflect the consensus opinion of the Expert Panel.
Supportive actions represent expert consensus suggestions from the Expert Panel provided to support implementation of the recommendations.

0–12 months	Parents should create an environment promoting and modeling physical activity and limiting sedentary time *Supportive actions:* • Discourage television viewing altogether.	Grade D *Recommend*
1–4 years	Unlimited active playtime in a safe, supportive environment Limited sedentary time, especially TV/video *Supportive actions:* • Limit total media time to no more than 1-2 hours of quality programming per day. For children < 2 years of age, discourage television viewing altogether. • No TV in child's bedroom • Encourage family activity at least once a week • Counsel routine activity for parents as role models for children	Grade D *Recommend* Grade D *Recommend*
5–10 years	Moderate to physical activity* every day Limit daily leisure screen time (TV/video/computer)	Grade A *Strongly recommend* Grade B *Strongly recommend*

	Supportive actions: • Prescribe moderate to vigorous activity* 1 h/d, with vigorous intensity physical activity** on 3 d/w days • Limit total media time to no more than 1-2 hours of quality programming per day. • No TV in child's bedroom • Take activity and screen time history from child once a year • Match physical activity recommendations with energy intake (see Table 5–1 in Section V. Nutrition and Diet for Estimated Energy Requirements) by gender and age group at three levels of physical activity • Recommend appropriate safety equipment relative to each sport • Support recommendations for daily physical education in schools	
11–17 years	Moderate to vigorous physical activity* every day Limit leisure time TV/video/computer use *Supportive actions:* • Encourage adolescents to aim for 1 h/d of moderate to vigorous daily activity, with vigorous intense physical activity** on 3 d/w • Encourage no TV in bedroom • Limit total media time to no more than 1-2 hours of quality programming per day. • Match activity recommendations with energy intake • Take activity and screen time history from adolescent at health supervision visits • Encourage involvement in year-round, lifelong physical activities • Support continued family activity once a week and/or family support of adolescent's physical activity program • Endorse appropriate safety equipment relative to each sport	Grade A *Strongly recommend* Grade B *Strongly recommend*

18–21 years	Moderate to vigorous physical activity* every day	Grade A *Strongly recommend*
	Limit leisure time TV/video/computer use	Grade B *Strongly recommend*
	Supportive recommendations: • Support goal of 1 h/d of moderate to vigorous daily activity, with vigorous intense physical activity** on 3 d/w • Recommend that combined leisure screen time not exceed 2 h/d • Take activity and screen time history at health supervision visits • Encourage involvement in year-round, lifelong physical activities	
* Examples of moderate to vigorous physical activities are walking briskly or jogging. ** Examples of vigorous physical activities are running, playing singles tennis or soccer.		

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7. TOBACCO EXPOSURE

INTRODUCTION

This section of the Guidelines provides recommendations to pediatric care providers on limiting tobacco exposure in their child and adolescent patients. The section begins with background information on the importance of tobacco dependence as a risk factor for cardiovascular disease (CVD). This is followed by the Expert Panel's summary of the evidence review relative to tobacco exposure. The evidence review and the development process for the Guidelines are outlined in Section I. Introduction and are described in detail in Appendix A. Methodology. As described, the evidence review augments a standard systematic review where the findings from the studies reviewed constitute the only basis for recommendations with each study described in detail. This evidence review combines a systematic review with an Expert Panel consensus process that incorporates and grades the quality of all relevant data based on preidentified criteria. Because of the large volume of included studies and the diverse nature of the evidence, the Expert Panel also provides a critical overview of the studies reviewed for each risk factor, highlighting those that, in its judgment, provide the most important information. Detailed information from each study has been extracted into the evidence tables. The complete evidence tables will be available online at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. The conclusions of the Expert Panel's review of the evidence are then summarized and graded, and the section ends with age-based recommendations to prevent tobacco exposure. References are listed sequentially at the end of the section, with references from the evidence review identified by unique PubMed identifier (PMID) numbers in bold text. Additional references do not include the PMID number.

BACKGROUND

Tobacco dependence is responsible for approximately 4 million annual deaths worldwide. Moreover, in utero exposure to tobacco products, involuntary tobacco smoke exposure (secondhand smoke), and tobacco use directly impair the health of fetuses, infants, children, and adolescents. Based on an analysis of published causes of death, tobacco use is the leading actual cause of death in the United States.[1] The evidence that tobacco use is harmful and addictive is unequivocal.[2,3,4,5,6] In childhood, nicotine is highly addicting, with symptoms of tobacco dependence demonstrated after only brief intermittent use.[7] Current cigarette use among high school students declined from 1997 to 2003, but rates have been stable since, through 2007.[8] From a public health standpoint, the need to reduce tobacco exposure is sufficiently compelling that a role for pediatric health care providers is essential.

A clinical practice guideline update from the U.S. Public Health Service published in May 2008 systematically reviewed almost 9,000 publications and concluded that smoking prevention and cessation interventions are effective in adults.[9,10] However, different approaches may be needed for children and adolescents. Physicians who care for children are well-positioned to provide tobacco use prevention and treatment interventions for their patients. Youth interventions should target parents as well as their children, since parental smoking is both a risk factor for child smoking and a source of secondhand smoke exposure.

OVERVIEW OF THE EVIDENCE FOR PREVENTION OF TOBACCO EXPOSURE

From the evidence review relative to environmental smoke exposure, a moderate number of studies address the efficacy of physician-based interventions to alter parental smoking habits.[11] A 2003 systematic review included 19 studies published through October 2001 that tested interventions to reduce tobacco smoke exposure in children; 6 of these were part of the evidence review for these Guidelines.[12] Only four interventions were judged to be effective: Three involved intensive counseling in a clinical setting, and one used a curricular approach in a school setting. The reviewers concluded that there was good evidence that brief informational interventions were ineffective and found limited support for intensive counseling in primary care. The evidence review for these Guidelines identified eight randomized controlled trials (RCTs), three of which showed a significant decrease in children's smoke exposure.[13,14,15,16,17,18,19,20] An intervention in low-income families in a primary care setting used motivational interviewing with informational materials supplied to controls; at 6-month followup, household nicotine levels were significantly lower in the intervention group.[17] In low-income families, seven counseling sessions delivered over 3 months were effective in significantly decreasing maternal smoking rates by self-report and children's urine cotinine concentrations.[18] In a pediatric clinic setting, a brief motivational interview followed by up to three telephone counseling calls in the following 3 months showed significantly higher maternal abstinence rates at 3- and 12-month followups.[16] Studies with unsuccessful interventions used tobacco exposure demonstrations,[13] a home-based intervention by lay community health advisors,[15] and a physician-delivered report of infant urine cotinine results, with mailed information on decreasing smoke exposure.[13] The Special Turku Coronary Risk Factor Intervention Project, a Finnish study that successfully reduced

saturated fat intake beginning in infancy, with followup for more than a decade, showed no differences in parental smoking between the intervention and control groups despite repeated lifestyle counseling that included an antitobacco message.[14] Two pediatric care provider studies specifically addressed smoking cessation in mothers following the birth of a child.[16,19] As in the obstetrical literature, these were effective in achieving smoking cessation during pregnancy, but after 6–12 months, there was no evidence for postnatal effect. Overall, interventions to decrease environmental smoke exposure carried out in pediatric care settings have shown mixed results, with some evidence that intensive counseling can be effective.

Office-based counseling directed at children and adolescents for prevention of tobacco use has been a mainstay in pediatric preventive care. Although contact with preadolescents and adolescents in primary care is sporadic, pediatricians and family physicians retain a critical voice in conveying health information to children and their parents. Counseling with regard to the adverse effects of tobacco products does improve patient knowledge.[2,3,5] The evidence review identified two major systematic reviews for consideration. A 2003 systematic review of smoking prevention interventions delivered by health care providers included four studies, of which only one showed a significant effect on prevention of smoking initiation.[21] A 2007 systematic review of family-based programs for smoking prevention identified 14 RCTs for review.[22] Four of the nine that tested a family intervention against a control group had significant positive effects, whereas only one of the five that tested a family intervention against a school-based intervention had a significant positive outcome. None of the six that compared the incremental effects of a family plus a school program with a school program alone had significant positive effects. Overall, a significantly lower rate of smoking initiation was achieved in approximately 40 percent of interventions. The amount of implementer

training and the quality of the implementation were related to positive outcomes, but the number of sessions was not. Use of biomarkers of tobacco exposure in addition to self-report of tobacco use provided no consistent benefit. In an RCT, a pediatric practice-based smoking prevention and cessation program that used a combined provider- and peer-delivered intervention was effective in preventing initiation of smoking at 1-year evaluation.[23]

Studies of the benefits of office-based counseling on smoking reduction have yielded conflicting results. A 2006 Cochrane Collaboration review of the effectiveness of strategies to achieve smoking cessation in adolescents identified 15 trials for inclusion. The review found that interventions that used pharmacologic aids were ineffective, but those that used the stages of change approach and/or motivational interviewing did achieve statistically significant positive results at 6-month followup.[24] A randomized trial of more than 2,500 adolescents, both smokers and nonsmokers, in 7 large pediatric and family practice departments of a group health maintenance organization combined 30-second clinician advice, a 10-minute interactive computer program, a 5-minute motivational interview, and telephone booster sessions. At followup more than 6 months later, the abstinence rate was significantly higher in the intervention group compared to the control group.[25] In adolescent smokers, brief counseling by providers in an emergency department was associated with an increase in quit attempts by adolescent smokers.[26] A recent combined provider- and peer-delivered intervention set in pediatric practice settings increased abstinence rates among smokers at 6-month but not at 12-month followup.[23]

School-based smoking prevention programs have achieved modest success, although there, too, results have been inconsistent, and evidence of long-term benefits is often

unavailable.[27,28,29,30,31] Two systematic reviews provide important perspectives. A 2006 Cochrane review identified 23 high-quality RCTs of school-based programs to prevent smoking initiation.[32] The interventions included providing information, social influence approaches, social skills training, and community approaches. Information alone was ineffective, but the combined social influences and social skills interventions were moderately effective in approximately half of the trials. A 2005 systematic review focused on long-term followup of school-based smoking prevention. Of eight studies that were reviewed, only one showed decreased smoking prevalence in the intervention group at longer than 1-year followup.[33]

Pharmacotherapies (i.e., nicotine replacement and medication) have been proven to aid in smoking cessation in adults. Some RCTs have demonstrated the safety of the nicotine patch and nicotine gum, as well as bupropion in adolescent smokers, but cessation results are inconsistent.[34,35] Overall, such studies performed in young smokers have shown that pharmacotherapies were not successful.[24,36]

Public health measures have been the most effective methods to prevent and limit tobacco use. Successful strategies include taxation of tobacco products, clean indoor air legislation, and counteradvertising against tobacco products.[2] Regulatory efforts and activities as well as efforts to promote clean indoor air in homes, automobiles, and schools all have been shown to have positive effects on tobacco smoke exposure and tobacco use.[33,37]

CONCLUSIONS AND GRADING OF THE EVIDENCE REVIEW ON PREVENTION OF TOBACCO EXPOSURE

Among all the known risk factors for CVD, the dichotomy between known benefits of risk elimination and the paucity of evidence for effective interventions to achieve risk reduction in pediatric care provider settings is greatest for tobacco exposure. The quality of the evidence regarding the harm of smoking and the benefits of passive smoke exposure avoidance, smoking prevention, and smoking cessation is uniformly Grade A. The reason that evidence grades in the recommendations are less than Grade A reflects the lack of existing evidence on interventions impacting smoking behaviors in specific pediatric age groups as opposed to the collective evidence.

- Good-quality interventions in pediatric care settings to decrease children's environmental smoke exposure have shown mixed results (Grade B).
- Intervention studies to prevent smoking initiation have had moderate success, although long-term results are limited (Grade B).
- Practice-based interventions to achieve smoking cessation in adolescents have had moderate success with limited long-term followup (Grade B).
- School-based smoking prevention programs have been moderately successful, with limited long-term followup (Grade B).

Although the evidence base in support of an office-based approach to tobacco intervention is moderate and at times mixed, the evidence that cigarette use is harmful and addictive is unequivocal. From a public health standpoint, the need to reduce tobacco exposure is sufficiently compelling that a role for pediatric health care providers is essential. The lack of harm associated with such interventions and the importance of

communicating the message of risk associated with tobacco provide the rationale for supporting "*Strongly recommend*," despite the lack of conclusive evidence that office-based interventions reliably reduce tobacco initiation or smoking cessation. Physicians and nurses who care for children are well-positioned to provide intervention to patients who smoke. The Expert Panel believes that such providers should routinely identify patients who smoke using the medical history. Patients should be explicitly informed about the addictive and adverse health effects of tobacco use. By using the 5A questions (Ask, Advise, Assess, Assist, Arrange), providers can assess their patients' readiness to quit and assist in providing resources to support smoking cessation efforts. Information about telephone quit lines (e.g., 1–800–QUIT–NOW), community cessation programs, and pharmacotherapy should also be made available.

As described, practice-based interventions to decrease environmental smoke exposure have shown mixed results. Nonetheless, the Expert Panel believes that pediatric care providers should identify parents and other caregivers who smoke and explicitly recommend that children not be exposed to tobacco smoke in the home, in automobiles, and in any other space where exposure can occur. For the parent who smokes, information provided should include statements about health benefits to the individual, child, and/or fetus, as well as referral to smoking cessation care providers.

Prenatal tobacco exposure is addressed separately in Section XIII. Perinatal Factors. Pediatric care providers should identify mothers who use tobacco and should deliver explicit counseling to these mothers to quit smoking before pregnancy, not smoke during pregnancy, and remain smoke free after the baby's birth. Such counseling has been shown to be effective during pregnancy, but postpregnancy recidivism is high.

The Expert Panel strongly recommends that pediatric care providers deliver a clear and repeated antismoking and smoking cessation message. When possible, primary care providers should attempt to integrate more intensive approaches to tobacco use prevention and cessation in their practices. Only a small number of studies have demonstrated that pharmacotherapies (i.e., nicotine replacement and medication) have been effective in supporting smoking cessation efforts in adolescents. Nonetheless, pediatricians may wish to acquire experience using these therapies or identify another health care professional with such experience for referral.

Tobacco use is considered in risk stratification algorithms in individuals with hypercholesterolemia, hypertension, and diabetes mellitus. Treatment thresholds for pharmacologic treatment of elevated cholesterol and hypertension are lower with tobacco use, and treatment goals may be more aggressively pursued in active smokers.

Public health measures have been effective in preventing and limiting tobacco use. Pediatricians need to be involved in advocacy for such regulatory efforts, as well as in school- and community-based efforts to prevent the initiation of smoking and to promote effective cessation strategies.

Table 7–1. Evidence-Based Recommendations To Prevent Tobacco Exposure

Grades reflect the findings of the evidence review. **Recommendation levels** reflect the consensus opinion of the Expert Panel. **Supportive actions** represent expert consensus suggestions from the Expert Panel provided to support implementation of the recommendations.		
Prenatal	Obtain smoking history from mothers, then provide explicit smoking cessation message before and during pregnancy *Supportive actions:* • Identify resources to support maternal smoking cessation efforts • Advocate for school- and community-based smoke-free interventions • See Section XIII. Perinatal Factors	Grade A *Strongly recommend*
0–12 months; **1–4 years**	Promote a smoke-free home environment Reinforce this message at every encounter, including urgent visits for respiratory problems *Supportive actions:* • Provide information about health benefits of a smoke-free home to parents and children • Advocate for school- and community-based smoke-free interventions	Grade B *Strongly recommend* Grade C *Recommend*
5–10 years	Obtain smoke exposure history from child, including personal history of tobacco use Counsel patients strongly about not smoking, including providing explicit information about the addictive and adverse health effects of smoking	Grade C *Recommend* Grade C *Recommend*
11–17 years; **18–21 years**	Obtain personal smoking history at every nonurgent health encounter Explicitly recommend against smoking Provide specific smoking cessation guidance *Supportive actions:* • Use 5A questions to assess readiness to quit • Establish health care practice as a resource for smoking cessation: - Provide quit line number - Identify community cessation resources - Provide information about pharmacotherapy for cessation • Advocate for school- and community-based smoke-free interventions	Grade B *Strongly recommend* Grade B *Strongly recommend* Grade B *Strongly recommend*

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8. HIGH BLOOD PRESSURE

INTRODUCTION

This section of the Guidelines provides recommendations to pediatric care providers on the evaluation and treatment of high blood pressure (BP) in their child and adolescent patients. Because recent National Heart, Lung, and Blood Institute (NHLBI) guidelines address this subject,[1] this section differs from the rest of the sections in the Guidelines in that the evidence review was limited to the past 6 years, as described below. The results of this limited evidence review are summarized by the Expert Panel in this section, with detailed information from each study extracted into the evidence tables, which will be available at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. The conclusions of the Expert Panel's review of the evidence are summarized, and the section ends with age-specific recommendations for BP measurement and diagnosis and treatment of hypertension.

BACKGROUND

In 2004, an NHLBI Task Force published *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (Fourth Report)*.[1] This report was based on a complete review of the current evidence on BP management up to that time and included detailed recommendations for diagnosing and managing high BP throughout childhood. Those expert consensus recommendations were used as the basis for the recommendations for this section of these Guidelines. The review of the science was considered complete until 2003, when the review of the *Fourth Report* ended. Therefore, the evidence review on high BP for these Guidelines was limited to studies published between January 1, 2003, and June 30, 2007, with the addition of selected studies through June 30, 2008, identified by the Expert Panel that met all the criteria for inclusion. Repeating the review performed by the *Fourth Report* Task Force was not believed to be either necessary, given the relatively short time since publication of the *Fourth Report*, or to be a judicious use of the resources available for the development of these Guidelines. The randomized controlled trials (RCTs) identified from 2003 to 2008 for this evidence review were graded individually and can be viewed in the evidence tables, which will be available at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm.

OVERVIEW OF THE EVIDENCE ON TREATMENT OF HIGH BLOOD PRESSURE IN CHILDREN AND ADOLESCENTS

The evidence review for the defined period identified 9 observational studies, 13 RCTs, and 3 meta-analyses. Eight RCTs evaluated medications for hypertension control that had not previously been studied in childhood: amlodipine, felodipine, fosinopril, lisinopril, losartan, metoprolol, and valsartan.[2,3,4,5,6,7,8,9] Each of these medications was found to be well-tolerated

for relatively short periods in children from ages 6 to 17 years, but primarily in adolescents. Most of the trials lasted 3–8 weeks; 1 trial for adolescents lasted 52 weeks. One trial evaluated valsartan in children ages 1–5 years, but data on the use of other drugs in younger children are lacking. All studies tended to determine tolerability and efficacy on reducing BP levels. In one study, African American children were found to require greater doses of fosinopril to obtain the same BP control as Caucasian children.[4]

Several studies addressed the roles of diet and lifestyle as they relate to BP. A meta-analysis of RCTs testing reduction of salt intake on BP in children and adolescents found that a modest reduction in salt intake did decrease BP, with a significant effect size of -1.17 millimeters of mercury (mmHg) for systolic BP and -2.47 mmHg for diastolic BP in children ages 8–16 years who were normotensive or had high normal BP. The meta-analysis included three trials in infants; results for this age group indicated that salt reduction decreased systolic BP by 2.47 mmHg.[10] In the Coronary Artery Risk Development in Young Adults study, higher intake of plant foods (whole grains, fruits, vegetables) and lower intake of meat products were associated with lower BP on a population basis among individuals ages 18–30 years.[11] An RCT of the Dietary Approaches to Stop Hypertension (DASH) diet was conducted in 57 adolescents with prehypertension or hypertension. At 3-month follow up, the DASH group had a significantly greater decrease in systolic BP, associated with higher intake of fruits and vegetables and low-fat dairy products and lower intake of total fat, than did the usual-care group. In the intervention group, intake of potassium and magnesium was significantly higher than in usual-care controls, but there was no difference in sodium intake.[12] Another RCT found that a 4-month transcendental meditation intervention was effective in lowering BP assessed by ambulatory BP monitoring of African American adolescents with high-normal baseline BP measurements at 8-month followup.[13]

Four studies evaluated the late effects of feeding style in infants. A 6-year followup of an RCT in infants showed that increased intake of polyunsaturated fatty acids (PUFA) in infant formula was associated with a significantly lower BP than a standard formula-fed control group; in a breast-fed reference group, diastolic BP was significantly lower than in the nonsupplemented group but did not differ from the PUFA-supplemented group.[14] Maternal fish oil supplementation in lactating mothers was not associated with any difference in BP or pulse wave velocity at 2.5-year followup compared with either a control group whose mothers received olive oil or a breast-fed reference group.[15] In small-for-gestational-age babies, a nutrient-enriched diet that promoted more rapid weight gain in infancy was associated with higher BP in childhood 6–8 years later.[16] In a meta-analysis of 15 studies, breastfeeding in infancy was found to be associated with lower BP at followup 3–60 years later, with a small but significant effect size for both systolic and diastolic BP.[17]

A series of epidemiologic studies provide important information. Long-term followup studies suggest that low birth weight is inversely associated with BP later in adult life[18] and that differences in birth weight may explain the origin of "Black/White" differences in BP.[19] A weighted analysis of BP data from national surveys in 8- to 17-year-olds obtained from 1963 to 2002 demonstrated that BP, prehypertension, and hypertension trended downward from 1963 to 1988 but upward thereafter.[20] At least part of this increase was explained by the rise in obesity, with the upward shift in BP occurring approximately 10 years after the upward trend in the prevalence of obesity. There were racial/ethnic differences, with non-Hispanic Blacks and Mexican Americans showing a greater prevalence of hypertension and prehypertension than non-Hispanic Whites and males showing a greater prevalence than females. BP variability was assessed in an analysis of longitudinal data from the National Childhood Blood Pressure database.[21] Among subjects designated as having prehypertension at baseline, 14 percent of boys and 12 percent of girls had hypertension 2 years later. Among subjects classified as

hypertensive at baseline, 31 percent of boys and 26 percent of girls were still hypertensive after 2 years, and 47 percent of boys and 26 percent of girls were in the prehypertension category. Baseline BP z-score, baseline body mass index (BMI), and change in BMI were significant independent determinants of subsequent BP. Finally, a meta-analysis of 50 cohort studies confirmed that BP consistently tracks from childhood into adulthood, with the strength of tracking increasing with baseline age and decreasing with followup length.[22]

CONCLUSIONS OF THE EVIDENCE REVIEW UPDATE: 2003–2008

- The evidence review for the defined time period resulted in no major changes in the approach to BP evaluation and management.
- In epidemiologic surveys of children and adolescents over the past 20 years, BP levels are increasing, and the prevalences of hypertension and prehypertension are increasing; these findings are explained partially by the rise in obesity.
- Prehypertension progresses to hypertension at the rate of approximately 7 percent per year; hypertension persists in almost one-third of boys and one-fourth of girls on 2-year longitudinal followup.
- From the evidence review, both breastfeeding and supplementation of formula with PUFA in infancy are associated with lower BP at followup.
- A DASH-style diet—which is rich in fruits, vegetables, low-fat or fat-free dairy products, whole grains, fish, poultry, beans, seeds, and nuts and lower in sweets and added sugars, fats, and red meats than the typical American diet—is associated with lower BP, as in adults. The Cardiovascular Health Integrated Lifestyle Diet (CHILD 1) combined with the DASH eating plan (described in Section V. Nutrition and Diet) is an appropriate diet for children that meets the DASH study and *Dietary Guidelines for Americans 2010* (2010 *DGA*) nutrient goals.
- Lower dietary sodium intake is associated with lower BP levels in infants, children, and adolescents.
- Losartan, amlodipine, felodipine, fosinopril, lisinopril, metoprolol, and valsartan can be added to the list of medications that are tolerated over short periods, and can reduce BP in children from ages 6 to 17 years but predominantly is effective in adolescents. For African American children, greater doses of fosinopril may be needed for effective BP

control. Trial durations, however, were short, and long-term safety is still in question. Antihypertensive medications are shown in Table 8–5.

- In one study in small-for-gestational-age babies, a nutrient-enriched diet that promoted rapid weight gain was associated with higher BP on followup in late childhood. This potential risk should be considered when such diets are selected in the clinical setting.
- In one study, transcendental meditation has been shown to effectively lower BP in nonhypertensive adolescents.

RECOMMENDATIONS

Recommendations regarding BP are all graded as expert opinion (Grade D) since they are based on the expert consensus conclusions of the *Fourth Report*.

The current recommendations focus on a developmental approach to the prevention of cardiovascular disease (CVD) by appropriate identification and amelioration of risk factors during routine pediatric care. For BP, the *Fourth Report* provided an algorithm and flow diagram to assist clinicians in identifying hypertension in children.[1] For these Guidelines, these recommendations are stratified to provide age-appropriate approaches that are congruent with the risk factor recommendations in other sections; this is reflected in Table 8–1 and in revised algorithms (Figures 8–1 and 8–2). The BP norms for age, gender, and height are shown in Tables 8–3 and 8–4 and are taken directly from the *Fourth Report*.

For children from birth to age 3 years:

- Routine measurement of BP is not recommended. Blood pressure should be measured when there is a suspicion of renal disease, coarctation of the aorta, or other condition that may be associated with BP elevation. Conditions under which children younger than age 3 years should have BP measured are listed in Table 8–2.

- In these young patients, auscultation of BP is often quite difficult, so measurement with an oscillometric device using an appropriate size cuff is acceptable. The state of the infant or young child (e.g., sleeping, quiet, fussing, crying) is very important in the interpretation of BP measurement.
- For younger patients, treatment of high BP is often directed at the underlying cause, since primary hypertension is uncommon.

For children, ages 3–11 years:

- Routine measurement of BP during health care visits is recommended. This is true of visits for health maintenance and for visits when the child is ill.
- Auscultation should be the method of choice for confirmation of elevated BP measurements using an oscillometric device. The BP percentiles from the *Fourth Report* based on age, gender, and height percentiles should be used to categorize BP as prehypertension or Stage 1 or Stage 2 Hypertension (Tables 8–3 and 8–4). BP elevation must be persistent to be considered hypertension; the process for establishing the BP category is outlined in Table 8–1 and in Figures 8–1 and 8–2.
- In this age group, obesity is an increasingly important cause of BP elevation. When obesity is present, therapy should first be directed at improving diet and physical activity behaviors. This age group offers the opportunity to intervene early in the process of obesity development, allowing the clinician to focus on weight maintenance while the child grows, as opposed to weight loss. It also provides an important opportunity to introduce the DASH-style diet, which is described in Section V. Nutrition and Diet, as an example of CHILD 1. The DASH diet focuses on increased fruits and vegetables, low-fat dairy products, and whole-grain foods and meets all nutrient and energy requirements for children in this age range. Dietary sodium intake should also be limited.

- BP category-specific management is outlined in Table 8–1 and Figure 8–2.

For adolescents, ages 12–17 years:

- The approach to the evaluation of BP is similar to that of children ages 3 to younger than 12 years, but the prevalence of primary hypertension is much more common, and obesity is a major concern as an underlying factor. As shown in Tables 8–3 and 8–4, the percentiles of the *Fourth Report* should be used to evaluate BP.
- Adolescents with obesity are at risk of type 2 diabetes mellitus. Diabetes is a condition for which more aggressive BP lowering is recommended; this is described in Section XI. Diabetes Mellitus and Other Conditions Predisposing to the Development of Accelerated Atherosclerosis, which addresses the management of children with high-risk conditions.
- In this age group, the level of BP indicating prehypertension is at least 120/80, the same as that for adults. This is because the 90th percentile for adolescents is higher than 120/80 for most ages and height percentiles.
- For adolescents with increased BMI and elevated BP, weight loss is the cornerstone of therapy. Both dietary and physical activity behaviors should be addressed, aiming for appropriate energy balance, lower dietary sodium, and a DASH-like dietary pattern. Recommendations for the management of obesity are outlined in Section X. Overweight and Obesity.
- BP category-specific management is outlined in Figures 8–1 and 8–2 and in Table 8–1.

For young adults, ages 18–21 years:

- Adult cut points for BP in this age group are used to define hypertension, as per the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (*JNC 7*) guidelines.[23]
- In this age range, institution of the adult DASH diet is recommended for individuals with prehypertension or hypertension, as is reduction of dietary sodium. Overweight continues to be a major concern in this age group; weight reduction should be promoted through enhanced energy expenditure coupled with reduced energy intake. Physical activity should be promoted, since moderate-to-vigorous physical activity reduces BP levels in adults.
- The management of hypertension is as described in *JNC 7.*[23]

For all age groups, the assessment of left ventricular mass (LVM) by echocardiography is recommended as the best method to assess hypertensive target organ disease. Assessment should be done for patients with stage 2 hypertension and those with persistent stage 1 hypertension. Evaluation of LVM may be helpful in establishing the need for pharmacologic treatment of hypertension.

Table 8–5 shows medications that have been used to achieve BP control in children and adolescents. At present, no data support the use of specific antihypertensive agents for specific age groups, and long-term safety data are not available.

Table 8–1. Age-Specific Recommendations for Blood Pressure (BP) Measurement and Diagnosis of Hypertension

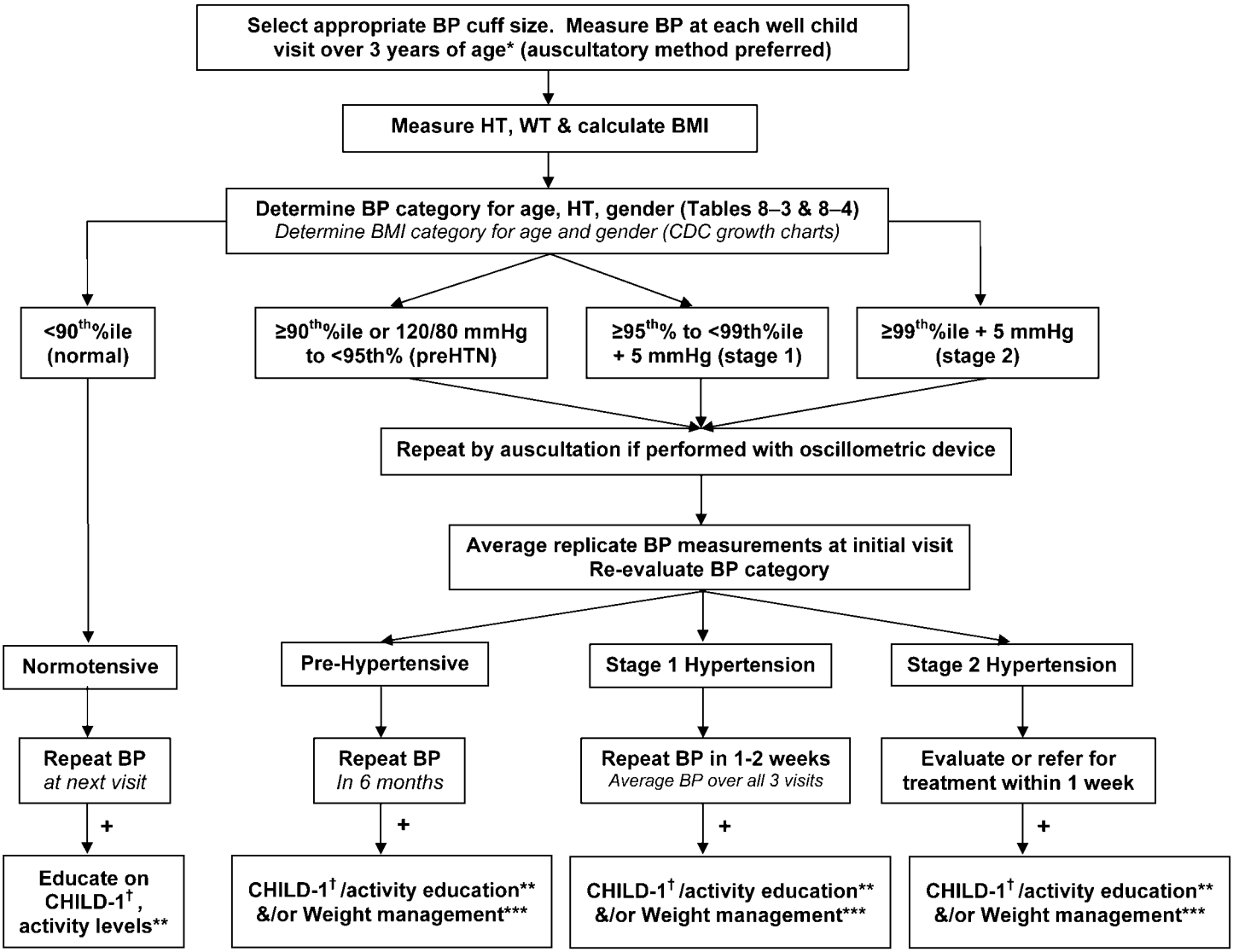
BP recommendations are based on *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (Fourth Report),* with the evidence review updated from 2003. *Recommendations are all graded as expert opinion (Grade D) as they are based on the expert consensus conclusions of the* Fourth Report*.*	
Birth–3 years	No routine BP measurement: • Measure BP if history (+) for neonatal complications, congenital heart disease, urinary/renal abnormality, solid-organ transplant, malignancy, drug prescription, or condition known to raise BP or increase intracranial pressure (see Table 8–2) ○ If BP at least 90th percentile by oscillometry, confirm by auscultation ○ If BP confirmed at least 90th percentile, initiate evaluation for etiology and treatment per algorithm
3–11 years	Annual BP measurement in all, interpreted for age/gender/height, per Tables 8–3 and 8–4: • BP less than 90th percentile, repeat in 1 year • BP at least 90th percentile: ○ Repeat BP × 2 by auscultation ○ Average replicate measurements, then reevaluate BP category ➔ If BP confirmed at least 90th percentile but less than 95th percentile = **prehypertension (preHTN):** • Recommend weight management if indicated • Repeat BP in 6 months ➔ If BP at least 95th percentile but less than 99th percentile + 5 mmHg: • Repeat BP in 1–2 weeks; average all BP measurements • Reevaluate BP category • BP confirmed at least 95th percentile but less than 99th percentile + 5 mmHg = **stage 1 HTN:** ○ Basic workup per Figure 8–2 ➔ If BP at least 99th percentile + 5 mmHg: • Repeat BP by auscultation × 3 <u>at that visit</u>; average all BP measurements • Reevaluate BP category • BP confirmed at least 99th percentile + 5 mmHg = **stage 2 HTN:** ○ Refer to pediatric HTN expert within 1 week <u>or</u> ○ Begin BP treatment and initiate basic workup per Figure 8–2
12–17 years	Annual BP measurement in all, interpreted for age/gender/height per Tables 8–3 and 8–4: • BP less than 90th percentile, counsel on CHILD 1 diet, activity recommendations, and repeat BP in 1 year • BP at least 90th percentile <u>or</u> at least 120/80:

	○ Repeat BP × 2 by auscultation ○ Average replicate measurements, then reevaluate BP category ➔ If BP confirmed at least 90th percentile but less than 95th percentile or at least 120/80 = **preHTN:** • CHILD 1 diet, activity recommendations, weight management if indicated • Repeat BP in 6 months ➔ If BP at least 95th percentile but less than 99th percentile + 5 mmHg: • Repeat BP in 1–2 weeks, average all BP measurements • Reevaluate BP category • BP confirmed at least 95th percentile but less than 99th percentile + 5 mmHg = **stage 1 HTN:** ○ Basic workup per Figure 8–2 ➔ If BP at least 99th percentile + 5 mmHg: • Repeat BP by auscultation × 3 at that visit; average all BP measurements • Reevaluate BP category • BP confirmed at least 99th percentile + 5 mmHg = **stage 2 HTN:** ○ Refer to pediatric HTN expert within 1 week or ○ Begin BP treatment and initiate workup per Figure 8–2
18–21 years	Measure BP at all health care visits: • BP at least 120/80 to 139/89 = preHTN • BP at least 140/90 to 159/99 = stage 1 HTN • BP at least 160/100 = stage 2 HTN Evaluation/treatment per *JNC7* recommendations.[23]

Table 8–2. Conditions Under Which Children Younger Than 3 Years Old Should Have Blood Pressure (BP) Measured

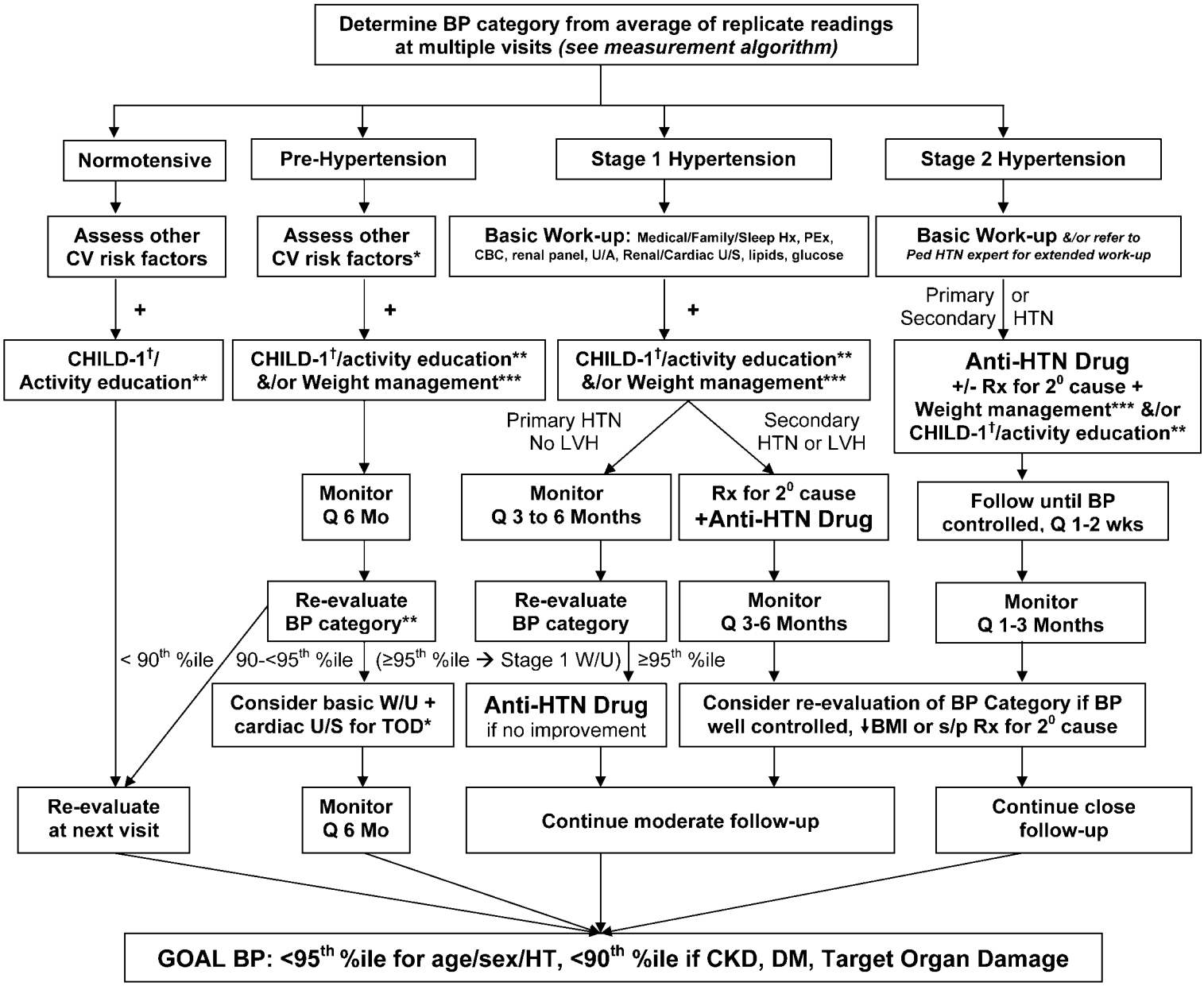
- History of prematurity, very low birth weight, or other neonatal complication requiring intensive care
- Congenital heart disease (repaired or unrepaired)
- Recurrent urinary tract infections, hematuria, or proteinuria
- Known renal disease or urologic malformations
- Family history of congenital renal disease
- Solid-organ transplant
- Malignancy or bone marrow transplant
- Treatment with drugs known to raise BP
- Other systemic illnesses associated with hypertension (neurofibromatosis, tuberous sclerosis, etc.)
- Evidence of increased intracranial pressure

Figure 8–1. Blood Pressure (BP) Measurement and Categorization



LEGEND: * See Table 1; †Cardiovascular Health Integrated Lifestyle Diet - Section V. Nutrition and Diet; **Section VI. Physical Activity; ***Section X. Overweight and Obesity

Figure 8–2. Blood Pressure (BP) Management by Category



LEGEND:
* Work up for target organ damage (TOD)/ LVH if obese or (+) for other CV risk factors;
† Cardiovascular Health Integrated Lifestyle Diet; See Section V. Nutrition and Diet;
** Activity Education. See Section VI. Physical Activity;
*** Weight management. See Section X. Overweight and Obesity.

Table 8–3. Blood Pressure (BP) Norms for Boys by Age and Height Percentiles (%iles)

Age (y)	BP %ile	Systolic BP (mm Hg) %ile of Height							Diastolic BP (mm Hg) %ile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82

	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	**50th**	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	**50th**	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	**50th**	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	**50th**	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	**50th**	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	**50th**	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	**50th**	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

SD = standard deviation.

The 90th percentile is 1.28 SD; 95th percentile is 1.645 SD; and 99th percentile is 2.326 SD over the mean.

Table 8–4. Blood Pressure (BP) Norms for Girls by Age and Height Percentiles (%iles)

Age (y)	BP %ile	Systolic BP (mm Hg) %ile of Height							Diastolic BP (mm Hg) %ile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	**50th**	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	**50th**	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	**50th**	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	**50th**	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	**50th**	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	**50th**	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	**50th**	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	**50th**	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	**50th**	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	**50th**	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80

	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	**50th**	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	**50th**	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	**50th**	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	**50th**	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	**50th**	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	**50th**	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	**50th**	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

SD = standard deviation.

The 90th %ile is 1.28 SD; 95th percentile is 1.645 SD; and 99th percentile is 2.326 SD over the mean.

1

Table 8–5. Antihypertensive Medications With Pediatric Experience

Class	Drug	Initial Dose*	Maximal Dose	Dosing Interval	Evidence†	FDA‡	Comments§
Angiotensin-converting enzyme (ACE) inhibitor	**Benazepril**	0.2 mg/kg/day up to 10 mg/day	0.6 mg/kg/day up to 40 mg/day	qd	RCT	Yes	1. All ACE inhibitors are contraindicated in pregnancy; females of childbearing age should use reliable contraception. 2. Check serum potassium and creatinine periodically to monitor for hyperkalemia and azotemia. 3. Cough and angioedema are reportedly less common with newer members of this class than with captopril. 4. Benezapril, and lisinopril labels contain information on the preparation of a suspension; captopril may also be compounded into a suspension. 5. FDA approval for ACE inhibitors with pediatric labeling is limited to children ≥6 years of age and to children with creatinine clearance ≥30 mL/min/1.73m^2. 6. Initial dose of fosinopril of 0.1 mg/kg/day may be effective, although African American patients may require a higher dose.
	Captopril	0.3–0.5 mg/kg/dose (>12 months)	6 mg/kg/day	tid	RCT, CS	No	
	Fosinopril**	Children >50 kg: 5–10 mg/day	40 mg/day	qd	RCT	Yes	
	Lisinopril**	0.07 mg/kg/day up to 5 mg/day	0.6 mg/kg/day up to 40 mg/day	qd	RCT	Yes	
	Quinapril	5–10 mg/day	80 mg/day	qd	RCT, EO	No	
Angiotensin-receptor blocker (ARB)	**Irbesartan**	6–12 years: 75–150 mg/day; ≥13 years: 150–300 mg/day	300 mg/day	qd	CS	Yes	1. All ARBs are contraindicated in pregnancy; females of childbearing age should use reliable contraception. 2. Check serum potassium and creatinine periodically to monitor for hyperkalemia and azotemia. 3. Losartan label contains information on the preparation of a suspension. 4. FDA approval for ARBs is limited to children ≥6 years of age and to children with creatinine clearance ≥30 mL/min/1.73m^2.
	Losartan**	0.7 mg/kg/day up to 50 mg/day	1.4 mg/kg/day up to 100 mg/day	qd-bid	RCT	Yes	
	Valsartan**	5–10 mg/day 0.4 mg/kg/day	40–80 mg/day 3.4 mg/kd/day	qd	RCT	No	
a- and b-antagonist	**Labetalol**	1–3 mg/kg/day	10–12 mg/kg/day up to 1,200 mg/day	bid	CS, EO	No	1. Asthma and overt heart failure are relative contraindications. 2. Heart rate is dose limiting. 3. May impair athletic performance in athletes. 4. Should not be used in insulin-dependent diabetics.
b-antagonist	**Atenolol**	0.5–1 mg/kg/day	2 mg/kg/day up to 100 mg/day	qd-bid	CS	No	1. Noncardioselective agents (propranolol) are contraindicated in asthma and heart failure. 2. Heart rate is dose limiting. 3. May impair athletic performance in athletes. 4. Should not be used in insulin-dependent diabetics. 5. A sustained-release, once-daily formulation of propranolol is available.
	Bisoprolol/ HCTZ	2.5–6.25 mg/day	10/6.25 mg/day	qd	RCT	No	
	Metoprolol**	Children >6 years: 1 mg/kg/day (12.5–50 mg/day)	2 mg/kg/day up to 200 mg/day	bid	CS	Yes***	
	Propranolol	1–2 mg/kg/day	4 mg/kg/day up to 640 mg/day	bid-tid	RCT, EO	Yes	

Class	Drug	Initial Dose*	Maximal Dose	Dosing Interval	Evidence†	FDA‡	Comments§
Calcium channel blocker	**Amlodipine****	Children 6–17 years: 2.5 mg/day	5 mg/day	qd	RCT	Yes	1. Amlodipine and isradipine can be compounded into stable extemporaneous suspensions. 2. Felodipine and extended-release nifedipine tablets must be swallowed whole. 3. Isradipine is available in both immediate-release and sustained-release formulations; sustained release form is dosed qd or bid. 4. May cause tachycardia. 5. Doses up to 10 mg of amlodipine have been evaluated in children. 6. Contraindicated for children <1 year of age.
	Felodipine	2.5 mg/day	10 mg/day	qd	RCT, EO	No	
	Isradipine	0.15–0.2 mg/kg/day	0.8 mg/kg/day up to 20 mg/day	tid-qid	CS, EO	No	
	Extended-release nifedipine	0.25–0.5 mg/kg/day	3 mg/kg/day up to 120 mg/day	qd-bid	CS, EO	No	
Central a-agonist	**Clonidine**	Children ≥12 years: 0.2 mg/day	2.4 mg/day	bid	EO	Yes	1. May cause dry mouth and/or sedation. 2. Transdermal preparation is available. 3. Sudden cessation of therapy can lead to severe rebound hypertension.
Diuretic	**HCTZ**	1 mg/kg/day	3 mg/kg/day up to 50 mg/day	qd	EO	Yes	1. All patients treated with diuretics should have electrolytes monitored shortly after initiating therapy and periodically thereafter. 2. Useful as add-on therapy in patients being treated with drugs from other drug classes. 3. Potassium-sparing diuretics (spironolactione, triamterene, amiloride) may cause severe hyperkalemia, especially if given with ACE inhibitor or ARB. 4. Furosemide is labeled only for treatment of edema but may be useful as add-on therapy in children with resistant hypertension, particularly in children with renal disease. 5. Chlorthalidone may precipitate azotemia in patients with renal diseases and should be used with caution in those with severe renal impairment.
	Chlorthalidone	0.3 mg/kg/day	2 mg/kg/day up to 50 mg/day	qd	EO	No	
	Furosemide	0.5–2.0 mg/kg/ dose	6 mg/kg/day	qd-bid	EO	`No	
	Spironolactone	1 mg/kg/day	3.3 mg/kg/day up to 100 mg/day	qd-bid	EO	No	
	Triamterene	1–2 mg/kg/day	3–4 mg/kg/day up to 300 mg/day	bid	EO	No	
	Amiloride	0.4–0.625 mg/kg/day	20 mg/day	qd	EO	No	
Peripheral a-antagonist	**Doxazosin**	1 mg/day	4 mg/day	qd	EO	No	1. May cause first-dose hypotension.
	Prazosin	0.05–0.1 mg/kg/day	0.5 mg/kg/day	tid	EO	No	
	Terazosin	1 mg/day	20 mg/day	qd	EO	No	
Vasodilator	**Hydralazine**	0.75 mg/kg/day	7.5 mg/kg/day up to 200 mg/day	qid	EO	Yes	1. Tachycardia and fluid retention are common side effects. 2. Hydralazine can cause a lupus-like syndrome in slow acetylators. 3. Prolonged use of minoxidil can cause hypertrichosis. 4. Minoxidil is usually reserved for patients with hypertension resistant to multiple drugs.
	Minoxidil	Children <12 years: 0.2 mg/kg/day; children ≥5 mg/day	Children <12 years: 50 mg/day; children ≥12 years: 100 mg/day	qd-tid	CS, EO	Yes	

RCT = randomized controlled trial
CS = case series
EO = expert opinion
***** The maximal recommended adult dose should not be exceeded in routine clinical practice.
† Level of evidence on which recommendations are based.

‡ U.S. Food and Drug Administration (FDA)-approved pediatric labeling information is available for treatment of hypertension. Recommended doses for agents with FDA-approved pediatric labels contained in this table are the doses contained in the approved labels. Even when pediatric labeling information is not available, the FDA-approved label should be consulted for additional safety information.
§ Comments apply to all members of each drug class except where otherwise stated.
****** Indicates drug added since *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents* (2004).
******* Study did not reach primary end point (dose response for reduction in systolic blood pressure). Some prespecified secondary end points demonstrated effectiveness.

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9. LIPIDS AND LIPOPROTEINS

INTRODUCTION

This section of the Guidelines provides recommendations to pediatric care providers on lipid management in their patients. The section begins with background information about the association between dyslipidemia and atherosclerosis and the changing clinical picture of dyslipidemia in childhood. This is followed by the Expert Panel's written synopses of the evidence review relative to lipids in five subsections:

1. Relationship between dyslipidemia and atherosclerosis
2. Lipid and lipoprotein assessment in childhood and adolescence
3. Overview of the dyslipidemias
4. Dietary treatment of dyslipidemias
5. Pharmacologic treatment of dyslipidemias

This evidence review and the development process for the Guidelines are outlined in Section I. Introduction and are described in detail in Appendix A. Methodology. As described, the evidence review here augments a standard systematic review where the findings from the studies reviewed constitute the only basis for recommendations with each study described in detail. This evidence review combines a systematic review with an Expert Panel consensus process that incorporates and grades the quality of all relevant data based on preidentified criteria. Because of the large volume constituted by the included studies and the diverse nature of the evidence, the Expert Panel also provides a critical overview of the studies reviewed for each of the five subsections, highlighting those that in its judgment provide the most important information. Detailed information from each study has been extracted into the evidence tables, which will be available at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. The conclusions of the Expert Panel's review of the evidence are summarized and graded at the end

of each subsection, followed by age-specific recommendations. Where evidence is inadequate, recommendations are a consensus of the Expert Panel. References are listed sequentially at the end of this section, with references from the evidence review identified by unique PubMed identifier (PMID) numbers in bold text. Additional references do not include the PMID number.

BACKGROUND

Since the previous guidelines for lipid management in children and adolescents from the National Cholesterol Education Program (NCEP) were published in 1992,[1] both the knowledge base surrounding dyslipidemia in childhood and the clinical picture have changed. A series of critical observational studies, which are summarized below, have demonstrated a clear correlation between lipoprotein disorders and the onset and severity of atherosclerosis in children, adolescents, and young adults.[2,3,4] Over that time period, a major increase in the prevalence of obesity has led to a much larger population of children with dyslipidemia. At the time of the original guidelines, the focus was almost exclusively on identification of children with elevated low-density lipoprotein cholesterol (LDL–C). Since then, the predominant dyslipidemic pattern in childhood is a combined pattern associated with obesity, with moderate to severe elevation in triglycerides (TG), normal to mild elevation in LDL–C, and reduced high-density lipoprotein cholesterol (HDL–C). Both dyslipidemic patterns have been shown to be associated with initiation and progression of atherosclerotic lesions in children and adolescents, as demonstrated by pathology and imaging studies.[2,3,4,5,6,7,8,9,10,11,12,13,14,15] Identification of children with dyslipidemias, which place them at increased risk for accelerated early atherosclerosis, must include a comprehensive assessment of serum lipids and lipoproteins.

OVERVIEW OF THE EVIDENCE FOR A RELATIONSHIP BETWEEN DYSLIPIDEMIA AND ATHEROSCLEROSIS

Postmortem pathology studies of atherosclerosis in children, adolescents, and young adults demonstrate that early atherosclerotic lesions of fatty streaks and fibrous plaques are significantly related to elevations in total cholesterol (TC), LDL–C, and non-HDL–C; lower levels of HDL–C; and the presence and intensity of other risk factors.[2,3,4,5,6,7] The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, described in detail in Section II. State of the Science, evaluated the presence of atherosclerosis at postmortem in adolescents and young adults ages 15–34 years who died accidentally.[3,4,5] The extent of atherosclerosis in the aorta and coronary arteries was correlated with the presence of abnormal lipid levels, obesity, a measure of hypertension, and evidence of cigarette smoking. Using a risk score derived from these results, non-HDL–C was shown to be the major correlate of coronary atherosclerosis in this age group, with a 30 milligram per deciliter (mg/dL) increase in non-HDL–C equivalent to 2 years of vascular aging.[6,7] Based on imaging studies assessing subclinical atherosclerosis, abnormal levels of lipids and lipoproteins are associated with endothelial dysfunction assessed by flow-mediated dilation (FMD) in the brachial artery, coronary artery calcium (CAC), and increased carotid intima-media thickness (cIMT)—all of which are considered precursors of advanced atherosclerosis.[8,9,10,11,12,13,14,15] Childhood levels of TC/HDL–C, LDL–C, HDL–C, and TG are each predictors of CAC and cIMT.[9,11,12] Overall risk factor scores, lipids, and increased body mass index (BMI) have been shown to be significant longitudinal predictors of CAC and increased cIMT.[16] In subjects from the Cardiovascular Risk in Young Finns (Young Finns) Study, the baseline cardiovascular (CV) risk profile predicted both CAC and cIMT from adolescence through young adulthood. The Young Finns study also found that dyslipidemia in childhood with elevated LDL–C and TG levels predicted increased cIMT independently and synergistically with other CV disease (CVD) risk factors and the metabolic syndrome. Young

adults with a TC level >200 mg/dL had five times the risk of developing CVD events 40 years later compared with those who had a TC level <172 mg/dL.[16] As part of the metabolic syndrome, childhood dyslipidemia has been shown to predict development of the metabolic syndrome, type 2 diabetes and adult CV disease at 25 year follow-up.[17,18] The effects of risk factors, including dyslipidemia, on coronary lesion severity are multiplicative rather than simply additive.[2]

In adults with elevated LDL–C but without CVD, convincing evidence suggests that lipid-lowering therapy with statins significantly decreases the incidence of major coronary and cerebrovascular events.[19] In children, no randomized clinical trials (RCTs) address whether treating dyslipidemias in children and adolescents will reduce CVD events in later life. However, increasing evidence indicates that lipid-lowering interventions in childhood delay the atherosclerotic process. In one trial, healthy male children treated with a low saturated fat, low cholesterol diet from infancy had enhanced vascular endothelial function at age 11 years compared with controls; this effect was not seen in females.[20] In a separate 2-year study, lowering TC and LDL–C levels with a low-fat diet and statin therapy in children and adolescents with heterozygous familial hypercholesterolemia (FH) was associated with a significantly smaller increase in cIMT than that seen in children treated with diet and placebo.[21] Followup of participants in this trial who continued on statin therapy for a mean of 4.5 years revealed that younger age at initiation was associated with subsequently smaller cIMT, suggesting that earlier initiation of statin therapy delays progression of the atherosclerotic process in children with FH assessed noninvasively.[22] In another RCT, impaired endothelial function in FH children, as judged by FMD, improved significantly in those with LDL–C lowered by simvastatin therapy versus those on placebo to a level similar to that in normal non-FH controls.[23]

OVERVIEW OF THE EVIDENCE FOR LIPID AND LIPOPROTEIN ASSESSMENT IN CHILDHOOD AND ADOLESCENCE

In the past, NCEP guidelines were based on standard serum measures of TC, very low-density lipoprotein cholesterol (VLDL–C), HDL–C, LDL–C, and TG, with recommendations focused on TC and LDL–C. Since that time, knowledge about lipoprotein heterogeneity and apolipoproteins as predictors of CVD has increased significantly. This evidence review assessed whether measures of any of these in youths are better predictors of subclinical atherosclerosis in adults.

Apolipoproteins B and A–1

In adults, apolipoprotein B (apoB), the major apolipoprotein of LDL–C, and apolipoprotein A–I (apoA–1), the major apolipoprotein of HDL–C, are predictors of the development of CVD and response to treatment to prevent CVD.[24] The level of total apoB includes all the apoB-containing lipoproteins, chylomicrons, and VLDL–C and their remnants: intermediate-density lipoprotein cholesterol (IDL–C), LDL–C, and lipoprotein(a) (Lp(a)). When present in increased amounts, all the apoB-containing lipoproteins are considered atherogenic. Since there is one molecule of apoB on each apoB-containing lipoprotein particle, apoB provides the most accurate assessment of the total number of LDL–C particles. ApoB and apoA–1 are determined using well-standardized immunochemical methods.[24,25] These apolipoproteins have been studied in children and adolescents; cut points for apoB and apoA–1—empirically derived from the Third National Health and Nutrition Examination Survey (1988–1994) (NHANES III)—are shown in Table 9–1.[25]

In the Bogalusa Heart Study, tracking of apoB and apoA–1 over 4 years was compared with tracking for LDL–C and HDL–C. The correlations for apoB and apoA–1 were significant but of

somewhat lower magnitude than those for LDL–C and HDL–C.[26] Thus, on a population basis, there was no clear advantage of using apoB and apoA–1 over LDL–C and HDL–C to assess tracking. Measurement of apoB and apoA–1 and the ratio of apoB to apoA–1 might provide additional useful information for selective screening, particularly in youths with a family history of premature CVD in parents.[27,28] This may be related to the fact that elevated apoB is often the first expression of familial combined hyperlipidemia (FCHL) in adolescents and young adults, before the onset of overt combined dyslipidemia.[29] In the Bogalusa study, no improved prediction of cIMT over that obtained with LDL–C and TC/HDL–C was observed when apoB, apoA–1, or the apoB/apoA–1 ratios were used.[8] However, the latest report from the Young Finns study indicates that apoB and apoA–1 levels in childhood were both better predictors of cIMT and brachial endothelial function in adult life than were LDL–C or HDL–C levels.[14]

Non-HDL–C

Non-HDL–C has emerged as a useful combined measure of the cholesterol content of all the atherogenic apoB-containing lipoproteins. TC and HDL–C can be measured accurately in plasma from nonfasting patients with non-HDL–C calculated by subtracting HDL–C from TC. The coefficient of variability for non-HDL–C thus reflects the variability of measuring both TC and HDL–C. This variability is theoretically less than that for estimated LDL–C, which includes the variability from the measurement of TC, HDL–C, and TG. Percentiles and NCEP-equivalent cut points for non-HDL–C have been determined in children from the Bogalusa study and are shown in Table 9–1.[30]

In adults, non-HDL–C has been shown to be a better independent predictor of CVD than LDL–C.[31] In a longitudinal cohort of subjects (N = 1,163) from the Bogalusa study, studied as both children ages 4–5 years old and adults 27 years later, non-HDL–C ($p = 0.52$) and LDL–C ($p =$

0.58) were the best predictors of adult levels.[32] The odds ratios (ORs) of developing dyslipidemia in adulthood, on the basis of childhood levels of non-HDL–C and LDL–C, were 4.49 and 3.46, respectively, independent of baseline BMI and BMI change over 27 years. At equivalent cut points, childhood high-risk non-HDL–C and LDL–C levels were significantly associated with increased obesity, high LDL–C, and high TG in adulthood. However, only childhood high-risk non-HDL–C status was associated with low HDL–C, hyperinsulinemia, and, marginally, hyperglycemia. Thus, childhood non-HDL–C appears to predict adult dyslipidemia, as well as nonlipid CVD risk factors, better than LDL–C.[32]

In the pathology studies reported in the PDAY study, non HDL–C and HDL–C levels were the best lipid predictors of pathologic atherosclerotic lesions, both significantly associated with fatty streaks in the thoracic aorta and abdominal aorta and in the right coronary artery and with raised lesions in all three sites;[33] non-HDL–C and HDL–C levels were more strongly associated with pathologic lesions than either apoB or apoA–1.

In the Bogalusa study, levels of non-HDL–C, LDL–C, TC/HDL–C, apoB, and apoB/apoA–1 in childhood emerged as significant predictors of subclinical atherosclerosis assessed by higher cIMT measurements in adulthood, but ORs were highest for LDL–C and non-HDL–C.[15] Overall, childhood non-HDL–C was as good as, or better than, other lipoprotein measures in predicting cIMT in adulthood.

Apolipoprotein E Polymorphism

Apolipoprotein E (apoE) binds to receptors on the surface of liver cells, promoting the hepatic uptake of remnant lipoproteins of both dietary and hepatic origins. Human apoE exists as three major isoforms—E_2, E_3, and E_4—each of which is specified by an independent allele at the locus for the apoE gene. Children with the rarest allele, apoE–2, generally have lower levels of TC and LDL–C, lower BMI and percentage of body fat, and lower insulin but higher HDL–C levels than those with apoE–3 or apoE–4.[34,35,36] Tracking of plasma lipid and lipoprotein is influenced to some degree by the apoE polymorphism. Children with apoE–4 have the highest LDL–C levels, but apoE–4 does not appear to influence the response to a low-cholesterol, low-fat diet[36] or to the addition of plant stanols.[37]

Lp(a) Lipoprotein

Lp(a) consists of a molecule of LDL–C in which its apoB moiety is connected through a disulfide bond to apo(a), a glycoprotein homologous to plasminogen. When present in elevated amounts, Lp(a) appears to be atherogenic because of its high cholesterol content and thrombogenic by virtue of the inhibition of the conversion of plasminogen to plasmin at the surface of endothelial cells.[38] Lp(a) is most accurately measured by an enzyme-linked immunosorbent assay (or ELISA) that is independent of apo(a) size differences, with the upper limit of normal by this method being 75 nanomoles per liter.

In adults, higher Lp(a) levels may be an independent risk factor for coronary artery disease (CAD), pulmonary vascular disease, ischemic stroke, and aortic aneurysm.[39] Elevated Lp(a) levels appear to particularly contribute to risk when combined with high LDL–C levels. In some families, isolated elevated Lp(a) levels have been seen with premature CAD and normal lipid and lipoprotein levels. In the Bogalusa study, Lp(a) was measured in 2,438 children.[40] Mean

Lp(a) levels were 1.7 times higher in Blacks than in Whites. White children with a history of parental myocardial infarction had significantly higher Lp(a) levels than did those with a negative family history, but there was no such association in Black children. Nowak-Gottl studied 1,002 household members of 282 White pediatric patients with a first acute ischemic stroke. Significant heritability estimates (but not environmental estimates) were found for Lp(a).[41] In children with stroke, Lp(a) levels are significantly elevated in about half of cases with either ischemic or hemorrhagic stroke.[42]

Advanced Lipoprotein Testing

The plasma levels of VLDL–C, LDL–C, and HDL–C subclasses and their sizes have been determined in children and adolescents by nuclear magnetic resonance spectroscopy[43,44,45] and by vertical-spin density-gradient ultracentrifugation[46] in research studies, but cut points derived from these methods for the diagnosis and treatment of dyslipidemia in youths are not currently available.

OVERVIEW OF THE EVIDENCE FOR NORMAL DISTRIBUTION PATTERNS OF LIPIDS AND LIPOPROTEINS

The Lipid Research Clinics (LRC) Prevalence Study collected lipid and lipoprotein values in children and adolescents from ages 0 to 19 years at multiple centers in the United States and Canada from 1970 to 1976. In that study, the mean TC level was approximately 160 mg/dL, and the mean LDL–C level was 100 mg/dL. The 95th percentiles for these two measures were 200 mg/dL for TC and 130 mg/dL for LDL–C.[47] These values were used in developing recommendations in *National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents*, which was published in 1992.[1]

The NHANES III collected cholesterol levels in more than 7,000 U.S. children ages 0–19 years from 1988 to 1994.[48] Over the intervening time period following the LRC study—just over a decade—lipid levels in the pediatric population had increased significantly. The mean TC level was 171 mg/dL, and the 95th percentile was 216 mg/dL; the 95th percentile for LDL–C was 152 mg/dL. This evaluation included significant numbers of African American, Hispanic American, and Mexican American subjects. African American children and adolescents were shown to have significantly higher TC and HDL–C levels and lower TG levels compared with the other racial/ethnic groups of children in the survey.[48] Although the percentiles of lipid levels varied by race, the risk of atherosclerosis (as measured by cIMT) was equally related to lipid levels and risk factors in African Americans and Whites, so results were not reported separately.[10]

Lipid levels change with normal growth and maturation. Lipoproteins are very low in cord blood at birth and rise slowly in the first 2 years of life.[49,50] After age 2 years, lipid and lipoprotein levels are relatively stable until adolescence. During puberty, TC and LDL–C levels decrease with increasing age before rising in the late-teen years and again in the third decade of life.[51] HDL–C levels decrease during puberty in males but not in females. From the Bogalusa study, there are differences in lipoprotein levels between Blacks and Whites during childhood, with higher levels of TC and HDL–C and lower levels of VLDL–C and TG in Black children and adolescents.[52] Recent evaluations have developed age- and gender-specific distribution curves for lipoproteins from the NHANES III data linked to CVD risk.[53,54] The distribution curves reflect the changes noted with normal growth and maturation. It has been suggested that these lipid curves, similar to growth curves, be used to account for normal maturational changes and to allow accurate selection of high-risk thresholds. Alternatively, designating the 50th percentile of the pooled NHANES results as “borderline high” and the 75th percentile as “high,” results in thresholds similar to these derived values. The cut points for plasma lipid, lipoprotein, and

apolipoprotein levels in children and adolescents are shown in Table 9–1 and for young adults in Table 9–2.

Table 9–1. Acceptable, Borderline High, and High Plasma Lipid, Lipoprotein, and Apolipoprotein Concentrations (mg/dL) for Children and Adolescents*

NOTE: Values given are in mg/dL. To convert to SI units, divide the results for total cholesterol (TC), low-density lipoprotein cholesterol (LDL–C), high-density lipoprotein cholesterol (HDL–C), and non-HDL–C by 38.6; for triglycerides (TG), divide by 88.6.

Category	Acceptable	Borderline High	High†
TC	<170	170–199	≥200
LDL–C	<110	110–129	≥130
Non-HDL–C	<120	120–144	≥145
Apolipoprotein B (ApoB)	<90	90–109	≥110
TG			
0–9 years	<75	75–99	≥100
10–19 years	<90	90–129	≥130

Category	Acceptable	Borderline High	Low†
HDL–C	>45	40–45	<40
Apolipoprotein A–1 (ApoA–1)	>120	115–120	<115

* Values for plasma lipid and lipoprotein levels are from the National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol Levels in Children.[1] Non-HDL–C values from the Bogalusa Heart Study are equivalent to the NCEP Pediatric Panel cut points for LDL–C.[30] Values for plasma apoB and apoA–1 are from the National Health and Nutrition Examination Survey III.

† The cut points for high and borderline high represent approximately the 95th and 75th percentiles, respectively.[1,25,30] Low cut points for HDL–C and apoA–1 represent approximately the 10th percentile.[25]

Table 9–2. Recommended Cut Points for Lipid and Lipoprotein Levels (mg/dL) in Young Adults*

NOTE: Values given are in mg/dL. To convert to SI units, divide the results for total cholesterol (TC), low-density lipoprotein cholesterol (LDL–C), high-density lipoprotein cholesterol (HDL–C), and non-HDL–C by 38.6; for triglycerides (TG), divide by 88.6.

Category	**Acceptable**	**Borderline High**	**High**
TC	<190	190–224	≥225
LDL–C	<120	120–159	≥160
Non-HDL–C	<150	150–189	≥190
TG	<115	115–149	≥150
Category	**Acceptable**	**Borderline Low**	**Low**
HDL–C	>45	40–45	<40

***** Values provided are from the Lipid Research Clinics Prevalence Study.[47] The cut points for TC, LDL–C, and non-HDL–C represent the 95th percentile for subjects ages 20–24 years and are not identical with the cut points used in the most recent National Cholesterol Education Program's Adult Treatment Panel III,[55] which are derived from combined data on adults of all ages. The age-specific cut points given here are provided for pediatric care providers to use in managing this young adult age group. For TC, LDL–C, and non-HDL–C, borderline high values are between the 75th and 94th percentiles, whereas acceptable values are <75th percentile. The high TG cut point represents approximately the 90th percentile, with borderline high between the 75th and 89th percentiles; acceptable is <75th percentile. The low HDL–C cut point represents roughly the 25th percentile, with borderline low between the 26th and 50th percentiles; acceptable is >50th percentile.

OVERVIEW OF THE EVIDENCE FOR TRACKING OF LIPID AND LIPOPROTEIN LEVELS FROM CHILDHOOD INTO ADULT LIFE

An important factor in considering lipid assessment in childhood is the accuracy of childhood lipid levels in predicting adult results. This evidence review identified 13 prospective screening cohort studies that assessed tracking of elevated lipid and lipoprotien levels from childhood into adulthood, with significant tracking identified in 12 of the 13 studies. From the Bogalusa study, more than 3,000 children ages 5–14 years at baseline were followed for 12 years. Lipid and lipoprotein levels tracked well statistically, with the best correlations for TC and LDL–C levels after age 12 years. Children with TC levels above the 75th percentile had approximately a 50 percent rate of falling into a similar percentile as adults, which was more than twice that predicted by chance alone.[51,56] The best predictors of elevated TC and LDL–C levels in adults were childhood elevations in TC and LDL–C levels.[56] In a stepwise multiple logistic regression, incremental increases in TC and BMI independently predicted incremental increases in adult TC.[53] Similarly, in a later report from the Bogalusa study, obesity, insulin level, and TC level were highly correlated, and increasing levels of obesity predicted elevated lipid levels.[57]

The 16-year experience of the Beaver County Lipid Study also demonstrated that the overall correlation (r = 0.44) between baseline and followup TC levels was significant; females had a higher correlation than males (0.51).[58] In an RCT of dietary intervention in children ages 7 months through 5 years, tracking of TC levels was significant for both the diet group and the control group, and the only gender effect was stronger HDL–C tracking for boys.[34] In an epidemiologic study of Finnish children followed for more than 12 years, all lipid and lipoprotein levels had significant tracking, with correlations ranging from 0.48 to 0.59 for TC, LDL–C, and HDL–C.[59]

In the LRC study,[47] more than 1,700 subjects had their initial TC levels drawn in grades 1–12 and then again 30 years later. Sensitivities for elevated TC and LDL–C levels were 44 percent and 43 percent, respectively, and specificities were 85 percent and 86 percent, respectively. Sensitivity and specificity were not improved by selecting children with a positive family history of early CVD or high cholesterol level.[60] Pubertal changes caused sensitivities and specificities to be lowest at ages 14–16 years regardless of lipid status. CVD events were too infrequent to allow testing of the ability of childhood cholesterol levels to predict future CVD in a still relatively young adult cohort.

The Muscatine Study followed more than 14,000 children with two measures of TC levels and other risk factors, the first between ages 8 and 18 years and the followup between 20 and 30 years later. Although TC tracked well from adolescence to adulthood, many adolescents identified as high risk would not be considered high risk in adulthood.[61] For children with TC levels above the 75th percentile on two occasions, 75 percent of females and 56 percent of males would not qualify for treatment as adults. For children with TC levels above the 90th percentile on two occasions, 43 percent of females and 70 percent of males had lipid levels above the 75th percentile as adults—that is, the level designated as requiring intervention in adults.[61]

In summary, the vast majority of epidemiologic studies indicate that there is strong statistical tracking of TC and LDL–C levels from childhood to adulthood. Clinically, this means that approximately half of children with lipid levels above the 75th percentile in childhood will have elevated lipid levels as adults.[62] In general, the higher the childhood result and the older the postpubertal age at which the value is obtained, the better the correlation with results in adult life: A TC level above 200 mg/dL will identify children at risk for more marked hypercholesterolemia with 90 percent confidence.[63]

OVERVIEW OF THE EVIDENCE FOR DYSLIPIDEMIAS IN CHILDHOOD AND ADOLESCENCE

Dyslipidemias are abnormalities in lipoprotein metabolism associated with any abnormal level of lipoproteins. There are many different types of dyslipidemias, which are influenced by genetics and environmental factors, including nutrition, physical inactivity, smoking, social factors, etc. Dyslipidemia also can be secondary to other specific causes that affect lipoprotein metabolism; these are listed in Table 9–3. The presence of dyslipidemia is an established risk factor for the development of atherosclerosis in both children and adults, but the incidence of CV clinical events due to atherosclerosis is extremely rare in children.

Table 9–3. Causes of Secondary Dyslipidemia

EXOGENOUS
Alcohol
Drug therapy: Corticosteroids
Isoretinoin
Beta-blockers
Some oral contraceptives
Select chemotherapeutic agents
Select antiretroviral agents

ENDOCRINE/METABOLIC
Hypothyroidism/hypopituitarism
Diabetes mellitus types 1 and 2
Pregnancy
Polycystic ovary syndrome
Lipodystrophy
Acute intermittent porphyria

RENAL
Chronic renal disease
Hemolytic uremic syndrome
Nephrotic syndrome

INFECTIOUS
Acute viral/bacterial infection*
Human immunodeficiency virus (HIV) infection
Hepatitis

HEPATIC
Obstructive liver disease/cholestatic conditions
Biliary cirrhosis
Alagille syndrome

INFLAMMATORY DISEASE
Systemic lupus erythematosis
Juvenile rheumatoid arthritis

STORAGE DISEASE
Glycogen storage disease
Gaucher's disease
Cystine storage disease
Juvenile Tay-Sachs disease
Niemann-Pick disease

OTHER
Kawasaki disease
Anorexia nervosa
Post solid organ transplantation
Childhood cancer survivor
Progeria
Idiopathic hypercalcemia
Klinefelter syndrome
Werner's syndrome

* Delay measurement until ≥3 weeks postinfection.

The known dyslipidemias are defined by age, gender, and racial cutoffs based on population distributions and known genetic disorders and are outlined in Table 9–4. Genetic lipid disorders include FH, FCHL, familial defective apoB (FDB), familial hypertriglyceridemias, and hypoalphalipoproteinemia. The genetic disorders may be the result of a single-gene defect but more commonly are due to oligogenic defects involving several more genes, which lead to abnormal lipoprotein metabolism.[16]

Table 9–4. Summary of Major Lipid Disorders in Children and Adolescents

Primary Lipid Disorders	Lipid/Lipoprotein Abnormality
Familial hypercholesterolemia	Homozygous: ↑↑ LDL–C Heterozygous: ↑ LDL–C*
Familial defective apolipoprotein B	↑ LDL–C
Familial combined hyperlipidemia*	Type IIa: ↑ LDL–C Type IV: ↑ VLDL–C, ↑ TG Type IIb: ↑ LDL–C, ↑ VLDL–C, ↑ TG Types IIb and IV often with ↓ HDL–C
Polygenic hypercholesterolemia	↑ LDL–C
Familial hypertriglyceridemia (200–1,000 mg/dL)	↑ VLDL–C, ↑ TG
Severe hypertriglyceridemia (≥1,000 mg/dL)	↑ Chylomicrons, ↑ VLDL–C, ↑↑ TG
Familial hypoalphalipoproteinemia	↓ HDL–C
Dysbetalipoproteinemia (TC: 250–500 mg/dL; TG: 250–600 mg/dL)	↑ IDL–C, ↑ chylomicron remnants

* These are the two lipid and lipoprotein disorders seen most frequently in childhood and adolescence; familial combined hyperlipidemia most often manifests with obesity.

HDL–C = high-density lipoprotein cholesterol; IDL–C = intermediate-density lipoprotein cholesterol; LDL–C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VLDL–C = very low-density lipoprotein cholesterol.

Disorders Affecting LDL Receptors

There are five known genetic disorders causing elevated LDL–C that are expressed in children and that cause early atherosclerosis and premature CVD; they include FH, FDB, autosomal recessive hypercholesterolemia, sitosterolemia, and mutations in proprotein convertase subtilisin-like kexin type 9. These disorders arise from either gene mutations that affect LDL receptor activity or abnormalities in the LDL receptor itself. The presence of these disorders indicates a significantly elevated risk for premature atherosclerosis and CVD events in adulthood.[16] Of these genetic disorders affecting LDL receptor activity, only FH occurs commonly enough to be a concern for pediatric care providers.

FH is an autosomal dominant disorder that causes isolated LDL–C elevation due to gene mutations in the LDL receptor. Homozygous FH (hoFH) is very rare, with a prevalence of approximately 1:1 million children and is associated with extremely high LDL–C levels (four to eight times higher than normal). Children with hoFH usually develop CVD by the second decade of life.[16] Heterozygous FH has a prevalence of approximately 1:500 children in the United States. In families with known FH, children with LDL–C levels above 160 mg/dL are likely to have FH.[16] Untreated FH is associated with premature atherosclerosis and CVD events, with 25 percent of females and 50 percent of males experiencing clinical CVD by age 50 years.

Combined Dyslipidemia

Multiple phenotypes of VLDL–C overproduction and associated TG and LDL–C elevations have been described. These include FCHL, familial dyslipidemic hypertension, hyperapoB, and LDL subclass pattern B. VLDL–C overproduction presents with the lipid pattern of normal to modest elevation of TC and LDL–C, moderate to moderately severe elevation of TG, and reduced HDL–C, with increased numbers of small, dense LDL–C particles.[16] Roughly 20–30 percent of obese

children have evidence of this dyslipidemic pattern.[64,65,66,67,68,69] Since publication of the 1992 *NCEP Pediatric Guidelines*, the presence of elevated TG-rich remnants, often reflected as elevated total TG or non-HDL–C, has become a recognized risk factor for CVD.[70]

From the standpoint of lipoprotein metabolism, elevated TG in the fasting state most often reflects increased levels of VLDL–C production from the liver as a consequence of metabolic alterations associated with obesity. As the TG in VLDL–C are hydrolyzed by lipoprotein lipase (LPL) and its cofactor apolipoprotein C–II (apoC–II), a series of VLDL–C remnants of different sizes is produced, ending with IDL–C. IDL–C can be removed directly from plasma by the interaction of apoE with the LDL receptor, or the TG on IDL–C can be hydrolyzed by LPL and hepatic lipase (HL), producing LDL–C. Elevated IDL–C may promote atherosclerosis by its conversion to LDL–C. As well, IDL–C can be small enough to cross the endothelial barrier and enter the vascular wall, where its cholesterol component is atherogenic. In the nonfasting state, patients with elevated VLDL–C often have delayed removal of TG-enriched chylomicrons and chylomicron remnants because both VLDL–C and chylomicrons are competing for LPL. This further accentuates postprandial hypertriglyceridemia.[71] Finally, elevated TG levels are usually accompanied by low HDL–C levels, further providing an atherosclerotic milieu, and are commonly associated with nonlipid risk factors, such as obesity, hypertension, insulin resistance, and enhanced thrombogenesis.[16,67]

Elevated TG may be due to enhanced production of VLDL–C, decreased hydrolysis, or a combination of both. The most common cause of elevated TG is increased VLDL–C synthesis. This leads to an enhanced transfer of TG from VLDL to both LDL and HDL in exchange for cholesteryl esters (CEs) via the CE transfer protein. As the TG on LDL–C and HDL–C are hydrolyzed, smaller cholesterol-depleted particles are produced. Overproduction of VLDL–C leads to an increased number of atherogenic small, dense LDL–C particles and low HDL–C.

Small HDL–C particles are more avidly removed by the kidney, reducing the number of HDL–C particles available for reverse cholesterol transport. Increased VLDL–C production most often results from enhanced hepatic uptake of free fatty acid (FFA) from plasma, leading to overproduction of TG and apoB. The elevated FFA is derived from adipose tissue due to insulin resistance and the decreased inhibition of hormone-sensitive lipase by insulin.

High TG in combination with elevated LDL–C and reduced HDL–C is the dyslipidemia seen as one of the components of the metabolic syndrome.[72] Elevated non-HDL–C also will be present in this dyslipidemic phenotype. The presence of this cluster of findings in childhood predicts the development of type 2 diabetes mellitus (T2DM), the metabolic syndrome, and premature clinical CVD in adulthood.[17,18] The pediatric aspects of the metabolic syndrome cluster are addressed separately later in Section XII. Risk Factor Clustering and the Metabolic Syndrome.

No single gene defect has been identified with the combined dyslipidemia disorders, which appear to be oligogenic in origin, with expression exacerbated due to lifestyle factors, especially obesity. In pediatric lipid clinics to which children are referred because of dyslipidemia, combined hyperlipidemia is seen about three times as often as FH and is usually associated with obesity.[73] In families identified because of an adult proband with clinical CVD and a lipid abnormality (types IIa, IIb, IV), the expression of combined hyperlipidemia often is delayed until the third decade of life. However, combined hyperlipidemia appears to be expressed in adolescents as an elevated apoB level.[29] A recent report from the longitudinal Young Finns study revealed that, at 21-year followup, subjects with the combined dyslipidemia pattern beginning in childhood had significantly increased cIMT compared with normolipidemic controls, even after adjustment for other risk factors; cIMT was further increased when the dyslipidemia occurred in the context of the metabolic syndrome.[9]

Given the association with obesity, combined dyslipidemia is an increasingly common problem.[65] In a recent study of overweight children, TG levels were significantly elevated in 18 percent of boys and 29 percent of girls, with the degree of elevation directly correlated with the severity of insulin resistance.[74,75] The combined dyslipidemia pattern is now the most common form of dyslipidemia seen in childhood, and in longitudinal studies, it has been shown to persist into adulthood.[67,76] Normal values for TG are <100 mg/dL in children younger than age 10 years and <130 mg/dL at ages 10–18 years (see Table 9–1). Obesity and insulin resistance are usually associated with TG levels between 100 and 400 mg/dL.[77] TG values >500 mg/dL usually identify an underlying rare genetic abnormality and are addressed below. Acute conditions associated with severe inflammation and/or endothelial injury and chronic conditions, such as human immunodeficiency virus (HIV) infection and cancer chemotherapy, can be associated with marked TG elevation. Profound hypertriglyceridemia also may occur transiently with ketoacidosis in type 1 diabetes mellitus (T1DM).

Severe Hypertriglyceridemia

Severe elevation in TG to ≥500 mg/dL is rare in childhood and is usually associated with genetically based recessive metabolic defects, including defects in LPL and apoC–II. Severe elevations in TG to >1,000 mg/dL are associated with increased risk for pancreatitis. With LPL and apoC–II deficiency, massive increases in chylomicrons and VLDL–C can occur, producing TG ≥1,000 mg/dL and as high as 5,000–10,000 mg/dL. Such profound increases in TG can produce pancreatitis and eruptive xanthomas but are not associated with premature atherosclerosis because the TG-enriched particles are too large to enter the vascular wall. Finally, TG ≥500 mg/dL can be seen in HL deficiency.[16] In this condition, HDL–C levels are actually elevated. However, so are the TG-enriched remnants, and premature atherosclerosis can occur in adulthood.

A fasting TG level of ≥ 500 mg/dL often indicates postprandial elevations to >1,000 mg/dL; children with this degree of hypertriglyceridemia present a special clinical problem that requires treatment by a lipid specialist to prevent pancreatitis. These children require a very low-fat diet (<10 percent fat) undertaken with a nutritionist to ensure adequate intake of essential fatty acids. Medium-chain TG, which are absorbed directly into the portal system and do not require chylomicrons for transport to the liver, can have a significant effect on TG, especially in the LPL defect. Neither LPL nor apoC–II deficiency responds to lipid-altering medications. Patients with HL deficiency will respond to lipid-lowering medication; this is addressed below in the subsection about pharmacologic therapy.

Low HDL–C Disorders

HDL–C varies inversely with the risk for CVD, and low HDL–C is an independent predictor of increased risk. In childhood, low HDL–C is usually expressed as part of combined dyslipidemia accompanied by obesity, as described previously. It can also be reduced significantly due to the presence of sedentary lifestyle, cigarette smoke exposure, inherited defects of low HDL–C production, or increased catabolism. Rare genetic forms of low HDL–C include familial hypoalphalipoproteinemia, apoA–1 mutations, Tangier disease, and lecithin cholesterol acyltransferase deficiency. Some, but not all, forms of low HDL–C disorders are associated with premature CVD.[16]

OVERVIEW OF THE EVIDENCE FOR SCREENING FOR LIPID DISORDERS IN CHILDHOOD AND ADOLESCENCE

Screening for dyslipidemia in childhood is based on the concept that early identification and control of dyslipidemia throughout youth and into adulthood will substantially reduce clinical CVD risk beginning in young adult life. The primary objectives of screening for dyslipidemia are the identification of children and adolescents who are (1) at the highest risk for premature CVD because of extreme lipid abnormalities secondary to inherited or acquired cholesterol disorders and (2) at increased risk because of dyslipidemia that is often associated with other risk factors, such as a family history of CVD or obesity. As described previously, the evidence that children with dyslipidemia are at significant risk for becoming adults with dyslipidemia with an increased risk for early CVD is strong. Accurate identification allows early treatment efforts to focus on children and adolescents at defined risk for accelerated atherosclerosis.

In 2007, the U.S. Preventive Services Task Force (USPSTF) published a major systematic review on screening and treatment for lipid disorders in children.[62] The review noted that in the included studies, family history questions were not standardized and had limited diagnostic accuracy. In addition, with the dispersion of families, knowledge of family history for medical problems was often incomplete. The reviewers concluded that the evidence demonstrated that using family history as a primary factor to identify children for screening would miss the majority of children with inherited dyslipidemias, including approximately 50 percent of those with FH. Although overweight has been shown to be the best of the known risk factors for predicting combined dyslipidemia, the review concluded that the use of other risk factors, alone or in combination, had not been evaluated adequately to assess their ability to identify children with dyslipidemia. The review noted that currently recommended screening strategies had low

adherence rates by pediatric health care providers and parents of children at risk. In addition, studies did not adequately identify the optimal age and frequency of testing.[62]

In Section IV. Family History of Early Atherosclerotic Cardiovascular Disease of these Guidelines, a positive family history of early CVD was identified as important information implying increased risk for future CVD in offspring. In the previous NCEP Pediatric Panel guidelines, family history of early CVD was used as the screening tool to define the need for lipid assessment.[1] Since that time, a number of studies have evaluated the limitations of this approach. There is no standardized methodology to assess the family history of CVD, and family histories are often inaccurate and/or incomplete. Using the recommendations from the NCEP Pediatric Panel,[1] the proportion of children who have a family history of premature CVD that will support lipid screening is between 25 and 55 percent. Those studies that used a family history measure to screen for elevated TC levels found that this method for screening misses between 30 and 60 percent of children with high TC levels. From the Bogalusa study, when a positive family history of premature CVD was present, there was a higher risk that the progeny would have abnormal LDL–C levels, but the additional sensitivity gained was minimal.[78,79] Late in adolescence, children with a family history of CVD have been shown to have higher TC, LDL–C, TG, and blood glucose levels and higher body weight.[80] However, a negative family history does not rule out dyslipidemia in children. As noted in the USPSTF systematic review, although a positive family history of early coronary heart disease has been shown to predict increased risk for future CVD, inaccurate and incomplete family history reporting make it neither sensitive nor specific enough to use as a predictive screening tool for childhood dyslipidemia.[62] Overweight in children is associated with significant adverse effects on risk factors, primarily combined dyslipidemia with elevated TG and low HDL–C levels; these abnormalities track into adulthood.[67,76] Although overweight is the risk factor most predictive of dyslipidemia, the magnitude of the effect is variable.[64,65,66,67]

In the past, fasting TC levels have been chosen as the initial screening test by most health care organizations and guidelines. Using the 95th percentile as abnormal, TC levels in the LRC study have 69 percent sensitivity and 98 percent specificity in accurately assessing LDL–C elevations.[47] Using NHANES data, TC levels had 50 percent sensitivity and 90 percent specificity in detecting elevated LDL–C levels. As described previously, correlations for TC, LDL–C, and HDL–C levels with future measures range from approximately 0.4 to 0.6.[62] Approximately half of those with TC levels above the 75th percentile in childhood will have elevated TC levels in adulthood.

The issue of appropriate cutoffs for children screened for lipid disorders was addressed in analyses by both the NCEP Pediatric Panel[1] and the NHANES III.[48] In a more recent analysis,[53] TC, LDL–C, HDL–C, and TG levels from more than 1,700 participants in three population-based prospective cohort studies were used to compare the ability of single NCEP cut points with multiple NHANES cut points in adolescence to predict abnormal levels in adulthood. NCEP cut points were found to be more predictive of adult high TC, LDL–C, and TG levels than NHANES results but were less predictive of low HDL–C levels. The likelihood of an adult having abnormal lipids was significantly higher in those adolescents with borderline or high lipoprotein levels compared with those with normal levels, and the increase in risk for adult levels was directly correlated and graded according to adolescent levels. Acceptable, borderline, and elevated lipid levels in childhood and young adulthood are shown in Tables 9–1 and 9–2.

Race and gender have both been shown to affect lipid results. Analysis of more than 4,000 children and adolescents from the Bogalusa study revealed that after controlling for overweight, White males had significant adverse changes in TC, LDL–C, VLDL–C, and HDL–C levels on entering adulthood, with less significant changes for White and Black females and Black

males.[52] By age 26 years, 9 percent of White males, 8 percent of White females, 2 percent of Black males, and 6 percent of Black females had abnormal lipid profiles, with White males having a dramatic worsening of the TC/HDL–C ratio.[52] Also from the Bogalusa study, there were racial differences in TG and VLDL–C levels between Blacks and Whites, with higher VLDL–C and TG levels in Whites and a modest difference related to higher HDL–C levels in Blacks.[45,81] White female children and Black males had higher HDL–C levels than White males, although the absolute differences are modest.[45,81] Differing distributions of individual risk factors in different groups is not in itself a reason for different standards for evaluation and/or management. Race and/or ethnic group-specific recommendations would be indicated only if there were evidence of a different relationship between risk factor level and future risk of CVD. At this time, there is insufficient evidence linking lipid levels to atherosclerosis by race or ethnic group, so similar cut points are recommended for determining risk status.

The number of children with dyslipidemia continues to increase along with population increases in overweight and decreases in insulin sensitivity. Cardiovascular risk factors cluster in children and are strongly correlated with body fatness.[82,83] Childhood overweight is clearly correlated with abnormal lipid levels.[69,77,83,84,85] Other conditions—such as diabetes, nephrotic syndrome, chronic renal disease, inflammatory disease, hypothyroidism, and other secondary causes of dyslipidemia, known to be associated with accelerated atherosclerosis—should indicate a higher frequency of testing (see Table 9–3 and Section XI. Diabetes Mellitus and Other Conditions Predisposing to the Development of Accelerated Atherosclerosis).[86] Children with these conditions need to be evaluated for dyslipidemia when the diagnosis of the primary condition is made.

As described previously, non-HDL–C is now increasingly used in evaluating adults for dyslipidemia. In analyses of two large pediatric cohorts from the Bogalusa study, non-HDL–C

was shown to be both sensitive and specific for identifying those who will have elevated LDL–C levels and other dyslipidemias as adults. Children in the top quartile of non-HDL–C were approximately four times more likely to have dyslipidemia as adults.[15,32] A non-HDL–C level above the 95th percentile was 86–96 percent sensitive and 96–98 percent specific for detecting an elevated LDL–C level in both African American and Hispanic children.[62] In a separate study, the top quartile of non-HDL–C levels correlated with the top decile of cIMT, as well as did any other lipoprotein measure.[15] Non-HDL–C levels appear to be a sensitive test for screening, with the additional advantage of being readily available in the nonfasting state.[32] As with TC and LDL–C, levels at which risk are identified could be defined by the 75th and 95th percentiles, as shown in Tables 9–1 and 9–2. A recent observational study found that non-HDL–C was as powerful as any other lipoprotein measure for predicting the presence of atherosclerosis in children and adolescents.[15] For both children and adults, non-HDL–C levels appear to be more predictive of persistent dyslipidemia, and therefore atherosclerosis and future events, than TC, LDL–C, or HDL–C levels alone.[32]

Risks/Harms Associated With Lipid Screening

No studies have identified any consistent harm from screening for cholesterol in children and adolescents. A concern is whether screening abnormalities may cause labeling of children, although the evidence is not sufficient to demonstrate any adverse effects. Although one small nonrandomized study showed some possible behavior changes in children identified with dyslipidemia, this has not been substantiated in any of the many other screening studies, observational trials, or clinical trials.[62]

There is a significant rate of lack of compliance with screening and followup recommendations by both clinicians and parents of children with abnormal levels. A number of factors have been

suggested, including inconvenience, discomfort with the screening tests, refusal by the child or parent, concerns about upsetting the child, resistance regarding dietary and lifestyle changes, and other unidentified factors.

CONCLUSIONS AND GRADING OF THE EVIDENCE REVIEW FOR LIPID ASSESSMENT IN CHILDHOOD AND ADOLESCENCE

- Combined evidence from autopsy studies, vascular studies, and cohort studies strongly indicates that abnormal lipid levels in childhood are associated with increased evidence of atherosclerosis (Grade B).
- The evidence review supports the concept that early identification and control of dyslipidemia throughout youth and into adulthood will substantially reduce clinical CVD risk beginning in young adult life. Preliminary evidence in children with heterozygous FH with markedly elevated LDL–C indicates that earlier treatment is associated with reduced subclinical evidence of atherosclerosis (Grade B).
- Multiple prospective screening cohort studies have demonstrated the normal lipid and lipoprotein distributions in childhood, adolescence, and young adult life (Tables 9–1 and 9–2) (Grade B). Cohort studies have also demonstrated significant tracking of elevated lipid levels from childhood to adulthood, with lipid and lipoprotein results in childhood predictive of future adult lipoprotein profiles; the strongest statistical correlation occurs between results in late childhood and the third and fourth decades of life (Grade B).
- TC and LDL–C levels fall as much as10–20 percent or more during puberty (Grade B). Based on this normal pattern of change in lipid and lipoprotein levels with growth and maturation, age 10 years (age range 9–11 years) is a stable time for lipid assessment in children (Grade D). For most children, this age range will precede onset of puberty.

- Significant evidence exists that using family history of premature CVD or of cholesterol disorders as the primary factor in determining lipid screening for children misses approximately 30–60 percent of children with dyslipidemias, and accurate and reliable measures of family history are not available (Grade B). In the absence of a clinical or historic marker, identification of children with lipid disorders that predispose them to accelerated atherosclerosis requires universal lipid assessment (Grade D).
- Non-HDL–C has been identified as a significant predictor of the presence of atherosclerosis, as powerful as any other lipoprotein cholesterol measure in children and adolescents. For both children and adults, non-HDL–C appears to be more predictive of persistent dyslipidemia, and therefore atherosclerosis and future events, than TC, LDL–C, or HDL–C alone. A major advantage of non-HDL–C is that it can be accurately calculated in a nonfasting state and is therefore very practical to obtain in clinical practice. The evidence supports use of non-HDL–C as a screening tool for identification of a dyslipidemic state in childhood (Grade B).
- In terms of other lipid measurements: (1) at this time, most but not all studies indicate that measurement of apoB and apoA–1 for universal screening provides no additional advantage over measuring non-HDL–C, LDL–C, and HDL–C; (2) measurement of Lp(a) is useful in the assessment of children with both hemorrhagic and ischemic stroke; (3) in offspring of a parent with premature CVD and no other identifiable risk factors, elevations of apoB, apoA–1, and Lp(a) have been noted; and (4) measurement of lipoprotein subclasses and their sizes by advanced lipoprotein testing has not been shown to have sufficient clinical utility in children at this time (Grade B).
- Obesity is commonly associated with a combined dyslipidemia pattern, with mild elevations in TC and LDL–C, moderate to severe elevation in TG, and low HDL–C. This is the most common dyslipidemic pattern seen in childhood, and lipid assessment of

overweight and obese children identifies an important proportion with significant lipid abnormalities (Grade B).

- Dyslipidemias can be acquired genetically but also secondary to specific conditions, such as diabetes, nephrotic syndrome, chronic renal disease, postorthotopic heart transplant, history of Kawasaki disease with persistent coronary involvement, chronic inflammatory disease, hypothyroidism, and other causes, as outlined in Table 9–3. There is impressive evidence for accelerated atherosclerosis both clinically and as assessed with noninvasive methods in some of these conditions, which accordingly have been designated as special risk diagnoses for accelerated atherosclerosis (Table 9–7); management of these is described in Section XI. Diabetes Mellitus and Other Conditions Predisposing to the Development of Accelerated Atherosclerosis. Lipid evaluation of these patients contributes to risk assessment and identifies an important proportion with dyslipidemia (Grade B).

- The complete phenotypic expression of some inherited disorders, such as FCHL, may be delayed until adulthood. Evaluation in children and adolescents from high-risk families with FCHL that begins in childhood and continues through adulthood (per NCEP adult treatment guidelines) will lead to early detection of those with abnormalities (Grade B).

Age-specific recommendations for lipid assessment are outlined in Table 9–5. Specific management for children with identified dyslipidemia is outlined in the algorithms in Figures 9–1 and 9–2. Definitions of the risk factors and special risk conditions for use with the recommendations and in the algorithms appear in Tables 9–6 and 9–7. The advantages of identifying dyslipidemia and initiating treatment in childhood are the potential for increased reversibility or slowing of the disease process, the knowledge that lifestyle change and attention

to risk are more readily accomplished than with individuals in their twenties and thirties, and the fact that regular contact with the health care system is routine in this age group. Late adolescence is often the last time for many years that young adults will routinely undergo health assessment, at the precollege or preemployment physical. It therefore represents an opportunity to diagnose lipid disorders and to advise the young adult about his or her CV risk profile and a healthy lifestyle pattern. When medication is recommended, the decision occurs in the context of the complete CV risk profile of the patient and the sociocultural milieu of the family.

The first step proposed for management of children with identified lipid abnormalities is a focused intervention to improve diet and physical activity. Conclusions of the evidence review and recommendations for dietary management of dyslipidemias are provided in the next subsection.

Table 9–5. Evidence-Based Recommendations for Lipid Assessment

Grades reflect the findings of the evidence review. **Recommendation levels** reflect the consensus opinion of the Expert Panel.		
NOTE: Values given are in mg/dL. To convert to SI units, divide the results for total cholesterol (TC), low-density lipoprotein cholesterol (LDL–C), high-density lipoprotein cholesterol (HDL–C), and non-HDL–C by 38.6; for triglycerides (TG), divide by 88.6.		
Birth–2 years	No lipid screening	Grade C Recommend
2–8 years	No routine lipid screening	Grade B Recommend
	Measure fasting lipid profile (FLP) × 2*; average results** if: • Parent, grandparent, aunt/uncle, or sibling with myocardial infarction (MI), angina, stroke, coronary artery bypass graft (CABG)/stent/angioplasty at <55 years in males, <65 years in females	Grade B Strongly recommend
	• Parent with TC ≥240 mg/dL or known dyslipidemia	Grade B Strongly recommend
	• Child has diabetes, hypertension, BMI ≥95th percentile or smokes cigarettes	Grade B Strongly recommend
	• Child has a moderate- or high-risk medical condition (Table 9–7)	Grade B Strongly recommend
	* Interval between FLP measurements: after 2 weeks but within 3 months. ** Use Table 9–1 for interpretation of results; use lipid algorithms in Figures 9–1 and 9–2 for management of results.	
9–11 years	Universal Screening • Non-FLP: Calculate non-HDL–C: Non-HDL-C = TC – HDL-C* Non-HDL ≥145 mg/dL, HDL< 40 mg/dL --> FLP × 2, lipid algorithms below** OR • FLP: LDL–C ≥130 mg/dL, non-HDL–C ≥145 mg/dL HDL–C <40 mg/dL, TG ≥100 mg/dL if < 10 years; ≥130 mg/dL if ≥10 years --> Repeat FLP after 2 weeks but within 3 months → lipid algorithms below** * Disregard TG and LDL–C in nonfasting sample. ** Use Table 9–1 for interpretation of results; use lipid algorithms in Figures 9–1 and 9–2 for management of results.	Grade B Strongly recommend

12–16 years	No routine screening*	Grade B Recommend
	Measure FLP × 2**, average results, if new knowledge of:	
	• Parent, grandparent, aunt/uncle or sibling with MI, angina, stroke, CABG/ stent/angioplasty, sudden death at < 55 years in males, < 65 years in females	Grade B Strongly recommend
	• Parent with TC ≥240 mg/dL or known dyslipidemia	Grade B Strongly recommend
	• Patient has diabetes, hypertension, BMI ≥85th percentile or smokes cigarettes	Grade B Strongly recommend
	• Patient has a moderate- or high-risk medical condition (Table 9–7)	Grade B Strongly recommend
	* Lipid screening is not recommended for those ages 12–16 years because of significantly decreased sensitivity and specificity for predicting adult LDL–C levels and significantly increased false-negative results in this age group. Selective screening is recommended for those with the clinical indications outlined. ** Interval between FLP measurements: after 2 weeks but within 3 months.	

17–21 years	Universal screening once in this time period: Non-FLP: Calculate non-HDL–C: Non-HDL–C = TC – HDL–C* 17–19 years: Non-HDL–C ≥145 mg/dL, HDL–C<40 mg/dL → FLP × 2, lipid algorithm below (Figure 9–1) OR FLP: LDL–C ≥130 mg/dL, non-HDL–C ≥145 mg/dL HDL–C < 40 mg/dL, TG ≥130 mg/dL → Repeat FLP after 2 weeks but within 3 months → lipid algorithms in Figures 9–1 and 9–2.	Grade B Recommend
20–21 years:	Non-HDL–C ≥190 mg/dL, HDL–C < 40 mg/dL** → FLP × 2***, average results → *Adult Treatment Panel III* (*ATP III*) management algorithm OR FLP: LDL–C ≥160 mg/dL, non-HDL–C ≥190 mg/dL HDL–C <40 mg/dL, TG ≥150 mg/dL → Repeat FLP after 2 weeks but within 3 months, average results → *ATP III* management algorithm	

* Use Table 9–1 for interpretation of results of 7- to 19-year-olds and lipid algorithms in Figures 9–1 and 9–2 for management. Use Table 9–2 for interpretation of results of 20- to 21-year-olds and *ATP III* algorithms for management

** Disregard TG and LDL–C in nonfasting sample.

*** Interval between FLP measurements: after 2 weeks but within 3 months

Table 9–6. Risk Factor (RF) Definitions for Dyslipidemia Algorithms

(+) Family history: myocardial infarction, angina, coronary artery bypass graft/stent/angioplasty, sudden cardiac death in parent, grandparent, aunt, or uncle, male <55 years, female <65 years

High-Level RFs:

- Hypertension requiring drug therapy (BP ≥99th percentile + 5 mmHg)
- Current cigarette smoker
- BMI ≥97th percentile
- Presence of high-risk conditions (Table 9–7)

(Diabetes mellitus (DM) 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 DM be considered a CVD equivalent.)

Moderate-Level RFs:

- Hypertension not requiring drug therapy
- BMI ≥95th percentile but <97th percentile
- HDL–C <40 mg/dL
- Presence of moderate-risk conditions (Table 9–7)

Table 9–7. Special Risk Conditions

High Risk:

- Diabetes mellitus, type 1 and type 2
- Chronic renal disease/end-stage renal disease/postrenal transplant
- Postorthotopic heart transplant
- Kawasaki disease with current aneurysms

Moderate Risk:

- Kawasaki disease with regressed coronary aneurysms
- Chronic inflammatory disease (systemic lupus erythematosus, juvenile rheumatoid arthritis)
- Human immunodeficiency virus (HIV) infection
- Nephrotic syndrome

OVERVIEW OF THE EVIDENCE FOR DIETARY TREATMENT OF DYSLIPIDEMIA

BACKGROUND

In the first NCEP guidelines addressing lipids in children published in 1992, the NCEP Pediatric Panel recommended a prudent diet (the NCEP Step I diet), with no more than 30 percent of calories from fat, less than 10 percent of calories from saturated fat, and cholesterol intake less than 300 milligrams per day (mg/d) for all healthy U.S. children older than age 2 years.[1] Children with dyslipidemias, primarily those with elevated LDL–C levels, were to be treated first with the Step I diet; then, if after 3 months they failed to achieve therapeutic goals, with a more stringent diet (NCEP Step II diet). The NCEP Step II diet recommended no more than 30 percent of calories from fat, less than 7 percent of calories from saturated fat, and less than 200 mg/d of dietary cholesterol. Calories were to be sufficient to maintain normal growth and development. These recommendations were based primarily on epidemiologic and clinical studies. At that time, few RCTs addressed the effects of diet modification in children, particularly during infancy and adolescence, the periods of most rapid growth and development. The increasing prevalence of obesity in childhood has led to a large population of children with combined dyslipidemia who also need dietary management. The evidence review for these Guidelines identified a large number of observational studies and RCTs that, when combined, provide a substantial body of information on which to base new recommendations.

EVIDENCE FOR DIETARY TREATMENT OF HYPERCHOLESTEROLEMIA BY AGE GROUP

Infant Feeding

A meta-analysis of 37 observational cohort and cross-sectional studies compared the effect of breast-feeding versus formula-feeding on TC levels in adolescents and adults.[87] Although the mean TC level was higher in breast-fed versus formula-fed infants, this difference did not persist into childhood or adolescence. In adults, the TC levels of those who were breast fed as infants

were lower than in those who were formula fed. Short-term feeding studies, all RCTs with small sample sizes, varied the fat and cholesterol contents of infant formula, with subsequent changes in levels of TC, LDL–C, TG, and HDL–C in infancy; there were no differences in lipoprotein profiles postweaning.[87,88,89,90]

Infancy Feeding Beyond Weaning

Many of the data on the safety and efficacy of a diet low in saturated fat and cholesterol starting in infancy come from the Special Turku Coronary Risk Factor Intervention Project (STRIP), in which 7-month-old Finnish infants (N = 1,062) were randomized into either a group receiving intensive counseling from a nutritionist for a diet with total fat at 30–35 percent of calories, a 1:1:1 intake ratio of saturated fatty acid/monounsaturated fatty acid/polyunsaturated fatty acid (PUFA), cholesterol <200 mg/d, protein (10–15 percent), and carbohydrate 50–60 percent or into a group receiving basic health education and no instructions on the use of fats.[91,92,93,94] Breastfeeding or formula feeding was advised until age 12 months; after age 12 months, the recommended beverage was fat-free milk supplemented with vegetable fat to maintain total fat intake at the recommended level until age 2 years. The children were followed with serial evaluations, including dietary assessment using 4-day food records, to early adolescence. At baseline, there was no difference in total fat or saturated fat consumption between the groups. At the first postrandomization lipid evaluation at age 13 months, the diets of intervention subjects contained a mean of 26 percent of calories from fat, with 9 percent from saturated fat compared with 28 percent and 13 percent, respectively, in the diets of control subjects, a significant difference between groups. This change was associated with significantly lower TC and LDL–C levels in the intervention group, with no differences in measures of growth and development.[91,92]

A short-term study varied the fat content of cow's milk in toddlers between ages 12 months and 2 years. Increasing the vegetable fat content increased plasma linoleic acid and alpha linoleic acid concentrations with no change in long-chain PUFA, arachidonic acid, or docosahexaenoic acid (DHA).[95]

Infancy to Ages 5, 7, and 11 Years

When assessed at ages 3 and 5 years, the STRIP intervention group consistently had lower intakes of total fat and cholesterol, higher ratios of polyunsaturated to saturated fat and unsaturated to saturated fat, and higher intakes of protein and carbohydrate than the control group.[92] These dietary differences were associated with significantly lower levels of TC, LDL–C, HDL–C, apoB, and apoA–1 in the intervention group. There were no differences between the groups in mean energy intake, relative weight, relative height, or neurologic development.[93] The dietary differences between the intervention and control groups were maintained at age 7 years.[94] However, only the boys had significantly lower levels of TC, LDL–C, apoB, and TG. At age 11 years, with a 55 percent followup rate, intervention boys and girls again had significantly lower intake of saturated fat and higher polyunsaturated fat to saturated fat ratios than controls.[20] There were no differences in weight, BMI, or physical activity. In intervention males, TC levels were 4.6 percent lower, and LDL–C levels were 9.6 percent lower than control males, but again, there were no significant lipid differences between groups for females. Of note, intervention boys had significantly greater endothelial function, as judged by FMD, than control boys, even after adjusting for differences in LDL–C levels.[20]

A clinically initiated, home-based, parent-child autotutorial (PCAT) dietary education program directed at increasing dietary knowledge and reducing fat consumption and LDL–C levels was assessed in an RCT of 4- to 10-year-old boys and girls with borderline high or high LDL–C

levels.[96] Intervention families received either individualized diet counseling or use of tape-recorded nutrition messages aimed at achieving a total dietary fat of less than 30 percent of calories, saturated fat less than 10 percent of calories, and cholesterol less than 300 mg/d; control subjects received usual care. At baseline, cholesterol intake averaged 156 mg/d in the PCAT tutorial group, 163 mg/d in the dietary counseling group, and 176 mg/d in the control group. After 3 months, those in the PCAT and the dietary counseling groups, compared with those in the high cholesterol control group, had significantly lower intakes of total fat as percentage of calories (-1.5 percent in PCAT; -1.6 percent in diet counseling; +0.2 percent in high cholesterol controls) and saturated fat (-0.8 percent in PCAT; -1.0 percent in dietary counseling; no change in high-cholesterol control group). Cholesterol intake averaged 133 mg/d in the intervention group and138 mg/d in the dietary counseling group and was essentially unchanged at 183 mg/d in the usual care control group. Mean LDL–C levels decreased significantly more in the PCAT intervention group by 10 mg/dL, compared with 4.1 mg/dL in the dietary counseling group and 3.4 mg/dL in the control group. These results were maintained at 1-year followup.[97] Another pediatric office-based nutritional education program also effectively decreased total fat, saturated fat, and cholesterol intakes, with significant decreases in TC and LDL–C levels after 16 weeks.[98]

In prepubertal children with FH, a restricted diet with 23 percent ± 5 percent of energy from total fat, 8 percent ± 2 percent from saturated fat, 5 percent ± 1 percent from polyunsaturated fat, 8 percent ± 2 percent from monounsaturated fat, 15 percent ± 2 percent from protein, 62 percent ± 5 percent from carbohydrate, and cholesterol 67 ± 28 mg/1,000 kcal for 1 year lowered TC and LDL–C levels by 4 percent and 5.5 percent, respectively. HDL–C, TG, apoB, ferritin, weight for height, and height velocity were unchanged.[99]

The Child and Adolescent Trial for Cardiovascular Health was a group randomized school trial designed to examine the outcomes of multilevel and multicomponent health behavior intervention in 56 intervention and 40 control public schools in California, Louisiana, Minnesota, and Texas. The trial followed 5,106 initially third-grade students from ethnically diverse backgrounds.[100] In half of the intervention schools, there were school food service modifications to lower fat and sodium contents plus enhanced physical education and classroom health curricula; the other half received the same intervention plus family education. Compared with control schools, intervention schools had a significant decrease in total fat, from 38.9 percent to 31.9 percent of energy in cafeteria lunches, and an increase in the amount of vigorous physical activity. However, after this 2.5 year intervention, there was no difference between the intervention and control groups in TC levels, the primary outcome. There was no evidence of any deleterious effect on growth or development.

Adolescents

The STRIP trial has results to age 14 years, at which time intervention group children still consumed less total and saturated fats and more carbohydrates and polyunsaturated fat and had lower TC and LDL–C levels than children in the control group; the difference between groups was only significant in males. These results were present at the first evaluation at age 13 months and sustained throughout the study period.[101] There were no harmful effects identified on growth, micronutrient intake, development, or neurologic function.[93,94,101,102]

The Dietary Intervention Study in Children[103] assessed the efficacy and safety of an intervention to lower dietary intakes of total fat, saturated fat, and cholesterol in order to lower elevated LDL–C levels (between the 80th and 98th percentiles), starting in prepubertal boys (N = 362) and girls (N = 301) ages 8–10 years and continuing for 3 years. The children were randomized to an

intervention group or a usual care control group in a six-center clinical trial. A behavioral-based, nutritionist-tailored intervention was used to promote a diet similar to the NCEP Step II diet—with 28 percent of calories from fat, less than 8 percent from saturated fat, less than 9 percent from polyunsaturated fat, and cholesterol less than 75 mg/1,000 kcal/d, not to exceed 150 mg/d; the control group received dietary literature. At 3-year followup, dietary total fat, saturated fat, and cholesterol were decreased significantly in the intervention group compared with the usual care control group; this was accompanied by small but significant differences in LDL–C levels (reduction of 15.4 mg/dL in the intervention group versus reduction of 11.9 mg/dL in the control group). Greater sexual maturation and BMI were found to increase the normal decrease in LDL–C level during adolescence.[104] There were no differences between the two groups for multiple safety measures. After 3 years, the intervention was modified to include a more appropriate approach for adolescents; the significant differences between the two groups in total fat, saturated fat, and cholesterol intakes were maintained, with no differences in any of the safety measures, but LDL–C levels did not differ between the intervention and control groups at 7-year followup.[104,105,106]

Young Adulthood, Ages 18–21 Years

Little information is available for this age group. A small study in university students with moderate LDL–C elevations showed that a multisession educational intervention significantly improved knowledge and attitudes about dietary changes compared with controls, but this was not associated with any significant decreases in TC and LDL–C levels.[107]

OVERVIEW OF THE EVIDENCE FOR LOWERING TC AND LDL–C LEVELS WITH DIETARY SUPPLEMENTS

Plant Stanol Esters and Plant Sterol Esters

Background

Under normal conditions, few if any plant stanol esters and only very small amounts of plant sterol esters are absorbed by the human intestine. Both of these compounds inhibit the absorption of cholesterol, either by displacing cholesterol from its mixed micelle or by competing with cholesterol for high-affinity binding sites on the surfaces of intestinal cells, leading to decreased cholesterol in chylomicrons and less cholesterol delivered to the liver, a decrease in the hepatic pool of cholesterol, an induction of LDL–C receptors, and an ultimate decrease of the LDL–C level.[16] This is associated with increased biosynthesis of hepatic cholesterol, which limits the efficacy of these compounds.

Use of Plant Stanols in the General Population

The effect of replacing dietary fat with plant stanol ester was investigated in a subset of 81, 6-year-old children from the STRIP trial. TC and LDL–C levels decreased by 5.4 percent and 7.5 percent, respectively, in those who consumed a plant stanol-enriched margarine as replacement for 20 grams per day (g/d) of dietary fat intake compared with control margarine. There was no effect on HDL–C or TG levels. These changes were accompanied by decreased cholesterol absorption. Safety was judged to be excellent.[108] Increasing dietary plant sterols did not alter cholesterol precursor sterol concentrations in these children.[109] Presence of the apoE–4 variant did not affect the response to plant stanols in the same group of 6-year-olds.[37] There was no significant difference in decreased cholesterol absorption between boys (36.3 percent) and girls

(42.0 percent), but the compensatory increase in hepatic cholesterol synthesis was significantly higher in girls (19.5 percent) than in boys (7.6 percent). This might explain the greater decrease in LDL–C levels in boys (-9.1 percent) than in girls (-5.8 percent). These plant stanol results were confirmed in a small group of healthy 2- to 5-year-old U.S. preschool children.[110]

Plant Sterol Esters and Plant Stanol Esters in Children With Familial Hypercholesterolemia

Five RCTs of plant sterols and plant stanols have been performed, primarily in FH prepubertal children ages 2–12 years. In each of these studies, both stanol and sterol esters lowered TC and LDL–C levels significantly, with decreased absorption of cholesterol accompanied by increased cholesterol biosynthesis.[111,112,113,114]

Two separate studies in children with FH assessed the effect of plant sterols on endothelial function and found that despite significant decreases in TC and LDL–C levels, there was no improvement in endothelial function, as judged by FMD.[113,115] This negative result was ascribed to a relatively small decrease in LDL–C levels compared with that achieved with statins, which have been shown to improve FMD in FH children.

Other Dietary Supplements

Dietary supplementation with garlic,[116] soy protein,[117] and DHA[118] did not lower LDL–C levels in hypercholesterolemic children. However, DHA supplementation restored impaired FMD. In some but not all studies, psyllium significantly lowered LDL–C levels from 5 to 10 percent, but there was no identification of dietary sources of fiber, so results are difficult to interpret.[119,120,121] In a single study, adding vitamins C and E to the low-fat diets of FH or FCHL children was associated with an improvement in FMD, independent of changes in blood lipid and lipoprotein levels.[122]

OVERVIEW OF THE EVIDENCE FOR DIETARY MANAGEMENT OF HYPERTRIGLYCERIDEMIA

Elevated TG levels are very responsive to weight loss, diet composition, and exercise. Most importantly, in overweight and obese children and adolescents with elevated TG levels, even small amounts of weight loss are associated with significant decreases in TG levels and increases in HDL–C levels.[123,124,125,126] Exercise training alone, when associated with a decrease in body fat, has also been shown to be associated with a significant decrease in TG levels, with reversion to baseline when children became less active.[127]

Regarding dietary composition, substitution of soy milk for low-fat cow's milk induced significant reductions in TG and VLDL–C levels and increased HDL–C levels in a small series of children.[128] In adults with hypertriglyceridemia, a low-carbohydrate, high-fat diet (40 percent carbohydrate, 39 percent total fat, 8 percent saturated fat, 15 percent monounsaturated fat) significantly decreased TG by a mean of 63 percent, with associated mean increases in LDL–C of 22 percent and HDL–C of 8 percent. A subsequent high-carbohydrate, low-fat diet (54 percent carbohydrate, 28 percent total fat, 7 percent saturated fat, 10 percent monounsaturated fat) significantly increased TG back to baseline levels.[129] In children, a 12-month followup study of 21-month-old children with elevated TG levels treated with a carbohydrate-restricted diet showed a decrease in sugar and carbohydrate intakes associated with a decrease in TG from a mean of 274.1 +/- 13.1 mg/dL before treatment to 88.8 +/- 13.3 mg/dL after 12 months.[130] In an analysis of adolescents from NHANES, the U.S. Department of Agriculture's Center for Nutrition Policy and Promotion's Healthy Eating Index (HEI) was used to provide an overall picture of dietary quality relative to the metabolic syndrome constellation of central obesity, elevated TG, elevated BP, reduced HDL–C level, and impaired fasting glucose level.[131] There was a significant inverse association between the overall HEI score plus the fruit intake score and the

prevalence of the metabolic syndrome components. There was also a trend toward lower prevalence of the metabolic syndrome components, including elevated TG in adolescents with high activity levels, although this was not significant. The concept of glycemic load has also been evaluated in the setting of obesity and dyslipidemia in adolescents and adults. The glycemic index is a measure of the blood glucose response to a 50 g portion of a selected carbohydrate; the glycemic load is the mathematic product of the glycemic index and the carbohydrate amount.[132] In adolescents and young adults, there is evidence that low glycemic-load diets are at least as effective as low-fat diets in achieving weight loss, with decreased TG and increased HDL in subjects on the low glycemic-load diet.[133,134,135] In adolescents, a low-carbohydrate diet associated with weight loss has been shown to significantly reduce TG levels.[136]

CONCLUSIONS AND GRADING OF THE EVIDENCE REVIEW FOR DIETARY MANAGEMENT OF DYSLIPIDEMIA

- A diet with total fat at 25–30 percent of calories, saturated fat less than 10 percent of calories, and cholesterol intake less than 300 mg/d, as recommended by the original NCEP Pediatric Panel, has been shown to safely and effectively reduce the levels of TC and LDL–C in healthy children. (Grade A). There is some evidence this is also the case when the diet begins in infancy and is sustained throughout childhood into adolescence (Grade B). The Cardiovascular Health Integrated Lifestyle Diet (CHILD 1), described in Section V. Nutrition and Diet of these Guidelines, has this composition.
- In children with identified hypercholesterolemia and elevated LDL–C levels, a more stringent diet, with saturated fat <7 percent of calories and dietary cholesterol limited to 200 mg/d, has been shown to be safe and modestly effective in lowering LDL–C levels (CHILD 2-LDL, Table 9-8) (Grade A).

- Use of dietary adjuncts, such as plant sterol or stanol esters, up to 2 g/d can safely enhance the LDL–C-lowering effects short term in children with FH (Grade A). However, long-term studies on the safety and effectiveness of plant sterol and stanol esters have not been completed. Their clinical use is therefore usually reserved for children with primary elevations of LDL–C who do not achieve LDL–C goals with dietary treatment alone. Such an approach may lower LDL–C sufficiently to avoid the necessity of drug treatment. Food products containing plant stanol esters, such as some margarines, are marketed directly to the general public. In two short-term trials, they have been shown to be safe with minimal LDL-lowering effects in healthy children (Grade B).
- Evidence for use of other dietary supplements is insufficient for any recommendation (no grade).
- In children with elevated TG, weight loss and reduction of simple carbohydrate intake are associated with decreased TG levels. (CHILD 2-TG, Table 9-8) (Grade B). When elevated TG are associated with obesity, decreased calorie intake and increased activity levels are of paramount importance.
- A behavioral approach that engages the child and family delivered by a registered dietitian has been shown to be the most consistently effective approach for achieving dietary change (Grade B).

The approach to management of dyslipidemias is staged, as in the original NCEP Pediatric Panel recommendations. For all children with identified dyslipidemia in whom the response to a low-fat/low saturated fat/low cholesterol diet has not been evaluated, the CHILD 1 diet described in Section V. Nutrition and Diet is recommended as the first step, with implementation guided by a registered dietitian. For obese children with identified dyslipidemia, age- and BMI-specific additional recommendations addressing calorie restriction and increased activity appear in Section X. Overweight and Obesity. If, after a 3-month trial of CHILD 1/lifestyle management, fasting lipid profile findings exceed the therapeutic goals in Tables 9–1 and 9–2, lipid parameter-specific diet changes outlined in Table 9–8 are recommended. Dyslipidemia management is also outlined in the algorithms in Figures 9–1 and 9–2.

Table 9–8. Evidence-Based Recommendations for Dietary Management of Elevated LDL–C, Non-HDL–C, and TG

Grades reflect the findings of the evidence review. **Recommendation levels** reflect the consensus opinion of the Expert Panel. **Supportive actions** represent expert consensus suggestions from the Expert Panel provided to support implementation of the recommendations; they are not graded.		
NOTE: Values given are in mg/dL. To convert to SI units, divide the results for total cholesterol (TC), low-density lipoprotein cholesterol (LDL–C), high-density lipoprotein cholesterol (HDL–C), and non-HDL–C by 38.6; for triglycerides (TG), divide by 88.6.		
ELEVATED LDL–C: CHILD 2 – LDL		
2–21 years	Refer to a registered dietitian for family medical nutrition therapy:	Grade B Strongly recommend
	• 25–30% of calories from fat, ≤7% from saturated fat, ~10% from monounsaturated fat; <200 mg/d of cholesterol; avoid trans fats as much as possible	Grade A Recommend
	Supportive actions:	
	• Plant sterol esters and/or plant stanol esters* up to 2 g/d as replacement for usual fat sources can be used after age 2 years in children with familial hypercholesterolemia. • Plant stanol esters as part of a regular diet are marketed directly to the public. Short-term studies show no harmful effects in healthy children. • The water-soluble fiber psyllium can be added to a low-fat, low saturated fat diet as cereal enriched with psyllium at a dose of 6 g/d for children 2–12 years, and 12 g/d for those ≥12 years. • As in all children, 1 hour/day (h/d) of moderate to vigorous physical activity and <2 h/d of sedentary screen time are recommended.	
	* Can be found added to some foods, such as some Margarines	

ELEVATED TG OR NON-HDL–C: CHILD 2 – TG

2–21 years	Refer to a registered dietitian for family medical nutrition therapy:*	Grade B Recommend
	• 25–30% of calories from fat , ≤7% from saturated fat, ~10% from monounsaturated fat; <200 mg/d of cholesterol; avoid trans fats as much as possible	Grade A Recommend
	• Decrease sugar intake: ○ Replace simple with complex carbohydrates ○ No sugar sweetened beverages	Grade B Recommend
	• Increase dietary fish to increase omega-3 fatty acids**	Grade D Recommend

***** If child is obese, nutrition therapy should include calorie restriction, and increased activity (beyond that recommended for all children) should be prescribed. See Section X. Overweight and Obesity for additional age-specific recommendations.

** The Food and Drug Administration (FDA) and the Environmental Protection Agency are advising women of childbearing age who may become pregnant, pregnant women, nursing mothers, and young children to avoid some types of fish and shellfish and eat fish and shellfish that are low in mercury. For more information, call the FDA's food information line toll free at 1–888–SAFEFOOD or visit http://www.cfsan.fda.gov/~dms/admehg3.html.

MEDICATION THERAPY FOR HYPERLIPIDEMIAS

Background

1992 NCEP Recommendations/American Heart Association Scientific Statement/ American Academy of Pediatrics' Committee on Nutrition Recommendations

In addition to making recommendations for screening and lifestyle management of LDL abnormalities, the 1992 NCEP Pediatric Panel report made recommendations regarding medication therapy.[1] It was recommended that treatment with medications be considered only in children ages 10 years and older after an adequate 6- to 12-month trial of lifestyle/dietary modification. The criteria for initiation included LDL–C levels ≥190 mg/dL or LDL ≥160 mg/dL, together with either a positive family history of premature CVD or the presence of two or more

other CVD risk factors. The only medication recommended was a bile acid sequestrant. At that time, no data were available regarding the safety and efficacy of statin use in children.

Since the NCEP Pediatric Panel guidelines were published in 1992, new evidence, as described in the opening section, provides the impetus for their reevaluation and modification. In 2007, the American Heart Association (AHA) published a scientific statement with updated treatment recommendations for children and adolescents.[137] The AHA guidelines recommended that the presence of overweight and obesity was an additional indication for screening with a fasting lipid profile (FLP) and that the presence of overweight and lipid abnormalities indicated screening for other abnormalities associated with insulin resistance/metabolic syndrome. For patients meeting the criteria for pharmacologic therapy, the AHA recommended a statin as a first-line agent. The presence of other risk factors and high-risk conditions should be considered in making decisions regarding medication therapy, including LDL–C levels and age for beginning treatment and target LDL–C levels to be achieved. However, the AHA made no specific recommendation about how these other risk factors and conditions were to be considered; this was left to the discretion of the treating health care provider.

More recently, the American Academy of Pediatrics' Committee on Nutrition published guidelines for the screening and management of lipid abnormalities in children.[138] In these recommendations, pharmacologic therapy is primarily considered at or after age 10 years. Rarely, initiation of treatment with medications could be considered in FH patients ages 8 years and older. Children younger than age 8 years with extreme elevation of LDL–C levels, above 500 mg/dL (as with hoFH), also might be considered for pharmacologic therapy. The Committee also recommended that children with diabetes mellitus and LDL–C ≥130 mg/dL be considered for drug therapy.

Consideration of Associated Risk Factors/High-Risk Conditions

Both pathology studies and studies using noninvasive assessment of vascular markers have shown an exponential increase in arterial abnormalities with increasing numbers of risk factors. For such patients, intensification of therapy and revised thresholds for initiation and treatment targets should be considered, particularly if those other risk factors are present at a higher magnitude or there is a higher level of individual risk. In addition, some patients may have high-risk conditions that are associated with established premature CVD or that serve as additional accelerators to the atherosclerotic process. These high-risk conditions have been highlighted and their management discussed in an AHA scientific statement on CV risk reduction in high-risk pediatric patients.[86] A high-risk condition was defined as one associated with manifest CAD at younger than age 30 years; high-risk conditions included hoFH, T1DM, chronic or end-stage renal disease or postrenal transplant, Kawasaki disease complicated by persistent coronary artery aneurysms/stenoses/occlusions, and patients with orthotopic heart transplantation. It was recommended that patients with these conditions be routinely screened for CV risk factors and that those identified be aggressively managed. Moderate-risk conditions were defined as those associated with pathophysiologic evidence that the atherosclerotic process was accelerated and included FH, Kawasaki disease with regressed coronary artery aneurysms, T2DM, and chronic inflammatory disease (juvenile onset rheumatoid arthritis and systemic lupus erythematosus). It was recommended that these patients also be routinely screened for CV risk factors, although levels for initiation of intervention and therapeutic targets were less aggressive. For these Guidelines, either T1DM or T2DM is considered a high-risk condition, and HIV and nephrotic syndrome are added as moderate-risk conditions (Table 9–7). Specific management of these high-risk conditions is outlined in Section XI. Diabetes Mellitus and Other Conditions Predisposing to the Development of Accelerated Atherosclerosis.

OVERVIEW OF THE EVIDENCE FOR SAFETY AND EFFICACY OF MEDICATION THERAPY

Since the 1992 NCEP Pediatric Panel guidelines, a series of RCTs of medications to treat lipid abnormalities in children and adolescents have been completed; all of these are outlined in Table 9–10 and included in the evidence tables that will be available at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. Several clinical trials of statins[21,22,23,139,140,141, 142,143,144,145] (Add ref # 146 here; references must be renumbered from this point forward.) and bile acid sequestrants[99,146,147,148] (Add reference #149 here) for the treatment of severe elevations of LDL–C in children with FH have been completed and are shown in Table 9–11. These studies have been conducted in children and adolescents with severe dyslipidemia or FH who met the recommendations of the 1992 NCEP guidelines for initiation of medication therapy.[1] FH in children was defined as having a family history of elevated LDL–C, atherosclerosis, or CAD in conjunction with having elevated LDL–C. The LDL levels for trial eligibility ranged from a lower limit of 154–189 mg/dL or 95th percentile for age and gender. Per the 1992 NCEP recommendations, almost all the studies tested drug therapy after a trial of diet. The studies have been of relatively short duration, ranging from 6 weeks to 2 years, with several longer than 4 months; one trial was extended as an open-label study to 7.4 years, with both randomized groups receiving drug therapy. Patients in early puberty have been included. Trial subjects were monitored carefully throughout the treatment period. No impact on growth, development, or sexual maturation has been identified; adverse event profiles and efficacy were similar to those noted in studies of adults. Because of problems with palatability, compliance with the bile acid sequestrants has been generally problematic. The details of the safety and efficacy of the statin medications in children are described below with the management of FH. The specific LDL–C-lowering effects of each medication are shown in Table 9–10.

There is limited published experience in children with use of niacin and fibrates, which may be useful in treating patients with combined dyslipidemias.[149,150] Efficacy and safety data are limited, and no data are available regarding newer formulations. In adults, cholesterol absorption inhibitors have been advocated as an adjunct to statin therapy for patients who do not reach LDL–C therapeutic targets. Since their action is independent of and complementary to that of statins, the LDL–C-lowering effect is additive. No pediatric studies of monotherapy with cholesterol absorption inhibitors had been published during the time period for this evidence review. Use of niacin, fibrates, and cholesterol-absorption inhibitors should be instituted only in consultation with a lipid specialist.

OVERVIEW OF THE EVIDENCE OF THE IMPACT OF MEDICATION THERAPY ON VASCULAR MARKERS

Although it is unlikely that studies will ever document that treatment of lipid abnormalities in youths will reduce manifest atherosclerotic disease and CV events when they become adults, there is emerging evidence using noninvasive vascular markers that lipid-lowering therapy improves arterial function and structure. From this evidence review, brachial artery reactivity by ultrasound FMD has been assessed as a measure of endothelial function in a clinical trial of simvastatin for children and adolescents with FH.[23] At baseline, both placebo and statin intervention FH groups had impaired FMD in response to reactive hyperemia, but this improved significantly in the group treated with simvastatin for 28 weeks. Carotid intima-media thickness by ultrasound has been evaluated as a marker of early atherosclerosis in a clinical trial of pravastatin for children and adolescents with FH.[21] After 2 years, cIMT had increased in the placebo group, but there was significant regression in the group treated with pravastatin. An open-label followup study of these patients for an average of 4.5 years reported that earlier initiation of statin therapy was associated with smaller cIMT at followup, after adjusting for baseline cIMT, gender, and duration of treatment.[22] This study included patients who had started treatment at age 8 years. These findings contrast with a nonplacebo-controlled, single-arm study with fluvastatin for 2 years, in which no significant changes in cIMT or wall stiffness were noted in response to LDL–C reduction.[140] It is important to note that the changes observed in these studies occurred despite the fact that patients did not necessarily achieve recommended LDL–C target cut points and had important residual elevations in LDL–C. These findings represent early evidence that therapy with statins in youth may have a significant positive impact on the atherosclerotic process. These results and findings of better endothelial function assessed by FMD in adolescent boys with lower LDL from infancy[20] suggest the potential benefit of initiation of LDL-lowering treatment in childhood. The atherosclerotic

process is not uniform over a lifetime, and it is probable that early lesions are more effectively treated and reversed than more advanced lesions; this provides some additional potential rationale for initiating drug therapy in youth with severely elevated LDL–C levels.

OVERVIEW OF THE EVIDENCE FOR MANAGEMENT OF SPECIFIC LIPID ABNORMALITIES

Heterozygous Familial Hypercholesterolemia

Heterozygous FH is associated with markedly elevated LDL–C levels and with normal or low HDL–C and usually but not always normal TG levels. FH is inherited as an autosomal dominant trait, with prevalence in the general population of 1:500 but higher in certain ethnic groups (e.g., French Canadians, South Africans, Lebanese). More than 500 mutations resulting in abnormalities of the LDL–C receptor have been identified, ranging from null alleles blocking LDL–C receptor formation and processing to defects resulting in defective receptors with diminished functionality. Alternatively, a similar phenotype is noted for patients with defects of the LDL–C receptor ligand apoB. All these abnormalities result in impaired LDL–C clearance. FH is associated with acceleration of atherosclerosis and premature CVD or events, beginning at ages thirties to forties in men and forties to fifties in women. The risk for clinical events is influenced by the presence of other risk factors or conditions. It is unclear whether FH confers an increased risk beyond that associated with the attendant lipid abnormalities; the fact that the lipid abnormalities are unrelenting from birth may impart an increased cumulative risk beyond that of other conditions and acquired abnormalities. In children with FH, LDL–C elevations are such that the vast majority will meet the criteria for treatment with medication with statins as the mainstay, as reviewed below and in Table 9–11.[21,22,23,139,140,141,142,143,144,145,151]

A recent systematic review and meta-analysis of statin therapy in children with FH analyzed studies that included almost 800 children.[152] No statistically significant differences were found between statin-treated and placebo-treated children for the occurrence of adverse events, sexual development, muscle toxicity, or liver toxicity; there was a minimal difference in growth in favor of the statin group. The LDL–C level and the timing for introduction of medication therapy are outlined in the algorithm (see Figure 9–1), and recommended medications appear in Tables 9–10 and 9–11. Response to the statins can be variable and may relate to the underlying specific genetic abnormality; some patients may require additional therapy, such as bile acid sequestrants, to achieve target LDL–C levels.[99,146,147,148,153] Cholesterol absorption inhibitors have also been recommended in this situation. A recent RCT of pediatric patients ages 10–17 years with FH demonstrated that coadministration of the cholesterol absorption inhibitor ezetimibe with simvastatin resulted in significantly greater reductions in LDL–C than did simvastatin alone; the combination was safe and well-tolerated up to 53 weeks.[154] For those with associated HDL–C and TG abnormalities, intensification of statin therapy or additional therapy with fibrates or niacin would be recommended. Any combination therapy should be undertaken in consultation with a lipid specialist. At this time, the need for therapy and monitoring is lifelong.

Homozygous Familial Hypercholesterolemia

Homozygous FH results in extreme elevations of LDL–C levels (often 5–10 times the upper limit of normal) and decreased HDL–C levels. The magnitude of LDL–C abnormalities may be influenced by which of the two mutations is inherited; these are often not concordant. CVD is usually manifest by the second decade, consisting primarily of coronary ostial stenoses and occlusions, aortic valve thickening with stenosis and/or regurgitation, and extensive

atherosclerosis of the aortic root. The most common mode of presentation of hoFH is physical manifestations in infancy and early childhood, consisting of primarily fleshy cutaneous xanthomata between the fingers and toes and over the buttocks, elbows, and knees and tendonous xanthomata, most marked in the Achilles tendon, with nodularity and thickening. Because of the cutaneous manifestations, the diagnosis is often made by dermatologists; additional investigation and management should be made by a lipid specialist. A complete cardiologic investigation is indicated at the time of presentation, since important CVD already may be present, and ongoing careful monitoring is important. There are no RCTs of treatment for hoFH. Despite severely reduced LDL–C receptor capacity, patients may respond somewhat to high doses of statins and to cholesterol absorption inhibitors.[16,155] However, the majority of patients will require artificial clearance of circulating LDL. LDL apheresis specifically removes LDL and is preferred to plasmapheresis, which depletes HDL as well as LDL. LDL apheresis usually is performed biweekly in medical centers with this expertise. At this time, the need for therapy and monitoring is lifelong. Liver transplantation is no longer recommended for children with hoFH because of the marked side effect profile of the procedure. The current goal of therapy is palliation of the disease until a time when effective and safe gene therapy becomes available.

Severe Primary Hypertriglyceridemias

In children with severe hypertriglyceridemia for whom diet and exercise interventions are insufficient, there are nutriceutical and medication options that can be considered. The TG level and the timing for introduction of more advanced therapy are outlined in the algorithm (see Figure 9–2), and recommended medications are shown in Tables 9–10 and 9–11. A recent systematic review demonstrated that omega-3 fish oil capsules are both safe and effective in

adults, reducing TG by 30–45 percent, with significant associated increases in HDL–C.[156] For children, the safety of omega-3 fish oil was observed in their use in children with immunoglobulin A nephropathy and in a small series of children with dyslipidemia.[157] Because fish oil preparations are marketed directly to the public, pediatric care providers can expect to encounter children who are taking these supplements. Information about how to evaluate the various preparations available is provided at the bottom of Table 9–11. In adults, fibrates have been used to lower TG levels, and a small series in children demonstrated effective reductions in TG levels and an associated increase in HDL–C levels.[150] Finally, niacin has been used extensively in adults, but there is limited experience in children, with a single series demonstrating a high rate of side effects.[149] The use of either fibrates or niacin in youths should be undertaken only with the assistance of a lipid specialist.

Children with sustained TG levels ≥500 mg/dL present a rare and serious clinical problem that is usually associated with an underlying genetic defect (LPL deficiency, HL deficiency, or apoC–II deficiency). They are at high risk for pancreatitis beginning in infancy. Management of these patients should always be in consultation with a lipid specialist. These children require a very low-fat diet (<10 percent fat) undertaken with a nutritionist to ensure adequate calories and intake of essential fatty acids. Medium-chain TG, which are absorbed directly into the portal system and do not require chylomicrons for transport to the liver, can have a significant lowering effect on TG levels, especially in those with defective or deficient LPL. Patients with either LPL or apoC–II deficiency do not respond to lipid-altering medications, but patients with HL deficiency will respond to fibrates, niacin, or statins. As indicated in the algorithm, management of these patients should always be in consultation with a lipid specialist.

Isolated Low HDL–C Levels

Isolated low HDL–C levels can occur as a primary abnormality in HDL–C metabolism; this is associated with an increased risk of premature CVD in affected family members. Currently, it is unclear whether this condition contributes to accelerated atherosclerosis in youth, there is no evidence concerning management of this condition in youth, and there is no evidence that treatments aimed at increasing HDL–C levels are effective and safe. There has been some beneficial effect on HDL–C levels associated with niacin therapy.[16,149] There are no RCTs of medication therapy for isolated low HDL–C levels in childhood. Current recommendations for management of this abnormality include attention to lifestyle modification and to abnormalities in TG, LDL–C, and non-HDL–C levels, including lower levels at which to initiate therapy and lower therapeutic target levels. For example, some patients who present with isolated HDL–C levels can have an elevation in the number of small, dense LDL particles that can be detected by determining the apoB level under the direction of a lipid specialist. More aggressive management of other risk factors/conditions is also indicated in the presence of isolated low HDL–C levels.

Elevated Lipoprotein(a)

There is currently no medication therapy specific for elevated Lp(a), and similar to isolated low HDL–C levels, management may focus on addressing other risk factors and on more aggressively managing concomitant elevations of LDL–C, TG, and non-HDL–C.
In adults, niacin will lower Lp(a) approximately 15 percent, but this has not been studied in children.

Combined Lipid Abnormalities

The most common combination of lipid abnormalities is that associated with obesity, the triad of low HDL–C, high TG, and a mild increase in LDL–C levels, with a qualitative change in LDL molecules such that the particle is smaller and denser and particle numbers are higher, contributing to a more atherogenic milieu. In general, these patients do not meet the criteria for pharmacologic therapy, and management focuses on reducing adiposity and changing diet composition as described in the previous lipid subsection on the dyslipidemias. Diet and lifestyle management for elevated TG levels are outlined in the subsection on the dietary treatment of the dyslipidemias, the CHILD 2-TG diet (Table 9–8). However, given that some patients will have clustering of risk factors, there may be a selective role for pharmacologic therapy, most commonly directed at elevations in non-HDL–C levels. Treatment with statins, omega-3 fish oil, or fibrates might be considered, but evidence for this in children is very limited, and there have been no RCTs.

Several primary dyslipidemias are associated with elevations in VLDL–C level, which is often manifest as an elevated LDL–C level together with a high TG level. Specific therapies are not available, and pharmacologic therapy is usually guided by non-HDL–C levels. Statins, omega-3 fish oil, or fibrates should be considered as first-line agents for patients who meet the criteria for medication therapy, under the direction of a lipid specialist.

Guidelines for Initiating and Monitoring Medication Therapy

Statins (Hydroxymethylglutaryl Coenzyme A Reductase Inhibitors)

Given the widespread experience with statins in adult patients, their greater efficacy and tolerance, and the presence of a number of well-designed (albeit relatively short-term) studies in children and adolescents (see Table 9–11),[21,22,23,140,141,142,143,144,145, 151] statin therapy is recommended as the initial medication of choice for treating patients with sufficiently elevated LDL–C or non-HDL–C levels (see algorithm in Figure 9–1). The statins inhibit hydroxymethylglutaryl coenzyme A reductase, which is a rate-limiting enzyme in the endogenous cholesterol synthesis pathway. This results in a decrease in the intracellular pool of cholesterol, which signals upregulation of LDL–C receptors and increased clearance of circulating LDL–C.

The starting dose used for each of the statin medications in the RCTs is shown in Table 9–11. These are preparation specific. Use of these medications requires that practitioners become familiar with the dose recommendations for one of the statins. Statin use should begin with the lowest available dose given once daily. If LDL–C target levels are not achieved with at least 3 months of compliant use, then the dose may be increased by one increment. The risk and effectiveness of dose escalation have been explored in several of the statin clinical trials in children, with no additional safety issues identified.

Adverse effects from statins are rare at standard doses but include myopathy and hepatic enzyme elevation. Asymptomatic hepatic enzyme elevation is fairly common in adults on statin therapy but is reversible with medication change and is not clearly associated with increased

risk of liver disease. In the meta-analysis of statin use in children, evidence of hepatic enzyme elevation did not differ between the statin and placebo groups.[152] Myopathy—muscle pain and weakness with creatine kinase elevations more than 10 times the upper limits of normal range—typically occurs in fewer than 1 in 10,000 adult patients. Evidence of muscle toxicity did not differ between the statin and placebo groups in the meta-analysis of statin use in children.[152] Rhabdomyolisis, a very rare occurrence in adults on statin therapy reported at 3 per 100,000 person-years, did not occur in any of the pediatric trials but the total number of subjects is too small to evaluate that risk. The risk of rhabdomyolysis increases with use of higher doses and interacting drugs. Drug interactions with statins occur primarily with drugs that are metabolized by the cytochrome P–450 system, the primary mode of metabolism for the majority of statins. Drugs that potentially interact with statins include fibrates, azol antifungals, macrolide antibiotics, antiarrhthymics, and protease inhibitors. When statin use is initiated, prescribing information must be routinely consulted for potential drug interactions. Patients need to be cautioned about potential future medication interactions, and pediatric care providers need to assess this whenever any new medication is introduced.

In addition to significantly lowering LDL–C levels, statins may increase HDL–C levels modestly and lower TG modestly—effects that are considered beneficial. In adults, treatment with statins also decreases inflammation as judged by the lowering of high-sensitivity C-reactive protein, considered to be a pleiotropic effect of statins. This test is not established for use in the management of lipid disorders in children and adolescents. The statins do not influence levels of the essential fatty acids necessary for early central nervous system maturation and have not been shown to affect neurodevelopment, although studies in infants and very young children have not yet been conducted. Clinical trials have included both male and female children studied over the time of puberty and have shown no impact on sexual maturation or height velocity. Specific guidelines for the use of statins are given in Table 9–12.

Bile Acid Sequestrants

Bile acid sequestrants were the initial medication of choice recommended in the original *NCEP Pediatric Guidelines*. The rationale was that these agents were not systemically absorbed and thus were believed to be safer for children and adolescents. The sequestrants bind bile salts within the intestinal lumen and prevent their enterohepatic reuptake in the terminal ileum, resulting in a depletion of bile salts in the liver and a signal for increased production. Since bile salts are synthesized from intracellular cholesterol in the liver, the intracellular pool of cholesterol becomes depleted, signaling increased production of LDL–C receptors and increased clearance of circulating LDL–C to replenish the intracellular cholesterol pool for increased production of bile salts. The sequestrants are available in tablet and powder formulations (to be swallowed with or mixed with a liquid of preference). Studies of bile acid sequestrants (cholestyramine, colestipol, colesevelam) in children and adolescents with FH and hence more extreme elevations of LDL–C levels, show reductions of LDL–C levels of 10–20 percent and sometimes a modest elevation in TG levels (see Table 9–11).[99,147,148,153] The primary adverse effects of the bile acid sequestrants tend to be gastrointestinal in nature, including bloating, nausea, diarrhea, and constipation; these significantly affect compliance. Since the bile acid sequestrants reduce bile salts, which are important for intestinal lipid absorption, there has been some concern regarding malabsorption of fat-soluble vitamins (A, D, E),[99,158] and routine supplementation with a daily multivitamin and folate may be indicated. Also, bile acid sequestrants may interfere with the absorption of some medications; this potential interaction should be specifically evaluated whenever any additional medication is needed.

The efficacy and adverse effects of bile acid sequestrants are somewhat dose dependent. The degree of LDL–C reduction is often insufficient to achieve LDL–C target levels for the majority of those patients who meet the criteria for pharmacologic therapy, and tolerance and compliance have been reported to be variable in children and may be influenced by the formulation used.[99, 147,148] (Add ref # 149 here) The initial tablet dose (colestipol) is five tablets (5 g)/d and for the powder (cholestyramine) one packet (4 g)/d. The dose can be titrated upward according to tolerance to a maximum of 20 g/d. The dosage can be divided throughout the day according to the patient's preferences and can be taken with meals. Tablets should not be chewed or divided. Colesevelam is in tablet form with starting dose of 1.875 g/day; dose can be up-titrated to 3.75 g/day; in the clinical trial, compliance with colesevelam was satisfactory. Since the formulation can be a matter of personal preference, patients intolerant or noncompliant with one formulation may do better with the other. Fasting lipid profiles and growth and maturation should be monitored every 6–12 months. No other laboratory testing for safety is required.

The bile acid-binding sequestrants may be used in combination with a statin for patients who fail to meet LDL–C target levels with either medication alone. One pediatric study assessed this combination and showed no increase in adverse effects.[148] As expected, the efficacy of the two agents together appears to be additive. Compliance should be closely monitored, since noncompliance with bile acid sequestrants may cause some patients to become noncompliant with the more effective statin as well.

Cholesterol Absorption Inhibitors

Ezetimibe, a cholesterol absorption inhibitor, lowers LDL–C levels by upregulating LDL–C receptors in a manner similar to the bile acid sequestrants, although the mechanism of action differs. Intestinal cholesterol absorption is inhibited at the level of the intestinal villus, resulting in inhibition of absorption of dietary cholesterol. Absorption of bile salts occurs in the ileum by a different mechanism and is not affected by the use of cholesterol absorption inhibitors. Studies in adults have shown that the effect is additive when used with statins, giving an additional 20 percent lowering of LDL–C levels. Adverse effects are minimal, and a dose of 10 mg/d is recommended. At present, there is no evidence that the addition of ezetimibe to a statin provides benefit in the prevention of atherosclerosis or events, and there are no published studies of its use as monotherapy in children. A study of ezetimibe for patients with hoFH, including some children, showed good efficacy and safety regarding lipid lowering.[155] A recent RCT of pediatric subjects ages 10–17 years with FH demonstrated that coadministered ezetimibe and simvastatin resulted in significantly greater reductions in LDL–C levels than did simvastatin alone; the combination was safe and well-tolerated for up to 53 weeks.[154] Currently, ezetimibe might be considered for children and adolescents who, under the care of a lipid specialist, do not meet LDL–C therapeutic targets on a statin alone or as potential monotherapy for patients with lower LDL–C levels who meet the criteria for pharmacologic therapy. In 2009, the U.S. Food and Drug Administration released a safety alert about potential adverse effects of ezetimibe in combination with statins in adults. Until more data are available on its safety, ezetimibe should be used only in consultation with a lipid specialist. Results of future trials should clarify safety issues surrounding use of ezetimibe in children.

CONCLUSIONS AND GRADING OF THE EVIDENCE REVIEW FOR USE OF MEDICATION TO TREAT DYSLIPIDEMIA

When medication is recommended, this should always be in the context of the complete CV risk profile of the patient and in consultation with the patient and the family.

NOTE: Values given are in mg/dL. To convert to SI units, divide the results for total cholesterol (TC), low-density lipoprotein cholesterol (LDL–C), high-density lipoprotein cholesterol (HDL–C), and non-HDL–C by 38.6; for triglycerides (TG), divide by 88.6.

- Decisions regarding the need for medication therapy should be based on the average of results from at least two fasting lipid profiles obtained at least 2 weeks but no more than 3 months apart (Grade C) (Figure 9–1).
- The cut points used to define the level at which drug therapy should be considered from the 1992 *NCEP Pediatric Guidelines* have been used as the basis for multiple drug safety and efficacy trials in dyslipidemic children (Grade B):
    - LDL–C $\geq$ 190 mg/dL after a 6-month trial of lifestyle management (CHILD 1 → CHILD 2-LDL) for children ages $\geq$ 10 years.
    - LDL–C 160–189 mg/dL after a 6-month trial of lifestyle/diet management (CHILD 1 → CHILD 2-LDL) in a child $\geq$ age 10 years with a positive family history of premature CVD/events in first-degree relatives (Table 9–6) or at least one high-level risk factor or risk condition or at least 2 moderate-level risk factors or risk conditions (Tables 9–6, 9–7, and 9–12) (Figure 9–1).
    - LDL–C 130–190 mg/dL in a child $\geq$ age 10 years with a negative family history of premature CVD in first-degree relatives and no high-level or moderate-level risk factor or risk condition, management should continue to focus on lifestyle changes (CHILD 1→ CHILD 2-LDL) based on lipid profile findings (Figure 9–1) plus weight management if BMI is at least the 85th percentile.
    - The goal of LDL-lowering therapy in childhood and adolescence is LDL–C below the 95th percentile (≤130 mg/dL).

- Children with homozygous FH and extremely elevated LDL–C levels (>500 mg/dL) have undergone effective LDL-lowering therapy with biweekly LDL apheresis under the care of lipid specialists in academic medical centers (Grade C).
- Multiple cohort studies have shown benefits of LDL-lowering therapy in children at high risk for accelerated atherosclerosis (Table 9-7). Children and adolescents with chronic kidney disease, T1DM or T2DM, Kawasaki disease with coronary aneurysms, or postcardiac transplantation) should be considered for initiation of medication therapy. (Grade C) (see Section XI. Diabetes Mellitus and Other Conditions Predisposing to the Development of Accelerated Atherosclerosis).
- The bile acid sequestrants are medications that bind bile salts within the intestinal lumen and prevent their enterohepatic reuptake in the terminal ileum, resulting in a depletion of bile salts in the liver and a signal for increased production. Since bile salts are synthesized from intracellular cholesterol in the liver, the intracellular pool of cholesterol becomes depleted, signaling increased production of LDL receptors and increased clearance of circulating LDL–C to replenish the intracellular cholesterol pool for increased production of bile salts. Studies of bile acid sequestrants in children and adolescents ages 6–18 years with LDL–C levels from 131 to 190 mg/dL show TC reduction of 7-17 percent and reduction of LDL–C of 10–20 percent, sometimes with a modest elevation in TG levels. The bile acid sequestrants commonly have gastrointestinal side effects, and these significantly affect compliance. However, they are safe and moderately effective (Grade A).
- Statin medications inhibit hydroxymethylglutaryl coenzyme A reductase, which is a rate-limiting enzyme in the endogenous cholesterol synthesis pathway. This results in a decrease in the intracellular pool of cholesterol, which signals upregulation of LDL receptors and increased clearance of circulating LDL–C. As a group, statins have been

shown to reduce LDL–C in children and adolescents with marked LDL–C elevation or FH (defined as elevated LDL–C in the child in conjunction with a family history of elevated LDL–C and/or atherosclerosis or CAD) when used from 8 weeks to 2 years for children ages 8–18 years. The lower LDL–C level for eligibility into the statin trials was ≥190 mg/dl or ≥ 160 mg/dl with 2 or more additional risk factors, after a trial period on diet. Trial subjects were monitored carefully throughout treatment; adverse impacts on growth, development, or sexual maturation were not seen, and adverse event profiles and efficacy were similar to those in studies of adults (Grade A).

- Adverse effects from statins are rare at standard doses but include myopathy and hepatic enzyme elevation. In the meta-analysis of statin use in children, evidence of hepatic enzyme elevation and muscle toxicity did not differ between the statin and placebo groups. Routine monitoring of hepatic enzymes and clinical assessment for muscle toxicity are strongly recommended for children and adolescents on statin therapy (Table 9–12). The risk of adverse events increases with use of higher doses and interacting drugs, the latter occurring primarily with drugs that are metabolized by the cytochrome P–450 system, which is the primary mode of metabolism for the majority of statins. Drugs that potentially interact with statins include fibrates, azol antifungals, macrolide antibiotics, antiarrhthymics, and protease inhibitors (Grade A).
- Bile acid-binding sequestrants may be used in combination with a statin for patients who fail to meet LDL–C target levels with either medication alone. One pediatric study assessed this combination and showed no increase in adverse effects. The efficacy of the two agents together appears to be additive (Grade B).
- There is limited published experience in children with use of niacin and fibrates, which have been useful in treating adult patients with combined dyslipidemias. Efficacy and safety data are limited, and no data are available regarding newer formulations. In adults, cholesterol absorption inhibitors have been advocated as an adjunct to statin

therapy for patients who do not reach LDL–C therapeutic targets. Since their action is independent of and complementary to that of statins, the LDL–C-lowering effect is additive. No pediatric studies of monotherapy with cholesterol absorption inhibitors had been published during the time period for this evidence review. Use of niacin, fibrates, and cholesterol absorption inhibitors should be instituted only in consultation with a lipid specialist (Grade C).

- Medication therapy is rarely needed for children with elevated TG who respond well to weight loss and lifestyle changes (Grade B). When TG levels exceed 500 mg/dL, patients are at risk for pancreatitis and require care in consultation with a lipid specialist (Grade B). In adults, use of omega-3 fish oil has been shown to lower TG by 30–40 percent and to raise HDL by 6–17 percent. Experience with fish oil in children is limited to small case series with no safety concerns identified; there have been no RCTs of fish oil in children (Grade D).

AGE-BASED RECOMMENDATIONS FOR MEDICATION THERAPY OF CHILDREN WITH DYSLIPIDEMIA

Children Younger Than Age 10 Years

- Children younger than age 10 years should not be treated with a medication unless they have a severe primary hyperlipidemia or a high-risk condition that is associated with serious medical morbidity (homozygous hypercholesterolemia/ LDL–C ≥400 mg/dL; primary hypertriglyceridemia with TG ≥500 mg/dL; evident CVD in the first two decades of life; post cardiac transplantation) (Grade C).

Children Ages 10–21 Years (see algorithms, Figures 9–1 and 9–2)

- Decisions regarding the need for medication therapy should be based on the average of results from ≥ two FLPs obtained at least 2 weeks but no more than 3 months apart. (Grade C) (Figure 9–1)
- Children with average LDL–C ≥ 250 mg/dL or average TG ≥ 500 mg/dL should be referred directly to a lipid specialist (Grade B).
- Children with lipid abnormalities should have a detailed family history taken and be assessed for causes of hyperlipidemia, additional risk factors, and risk conditions (Grade C) (Tables 9–3, 9–6, and 9–7).
- Children with lipid abnormalities (other than LDL–C ≥250 mg/dL or TG ≥500 mg/dL) should be initially managed for 3–6 months with diet changes (CHILD 1→CHILD 2-LDL or CHILD 2-TG, Table 9–8) based on specific lipid profile findings (Figures 9–1 and 9–2); if BMI is ≥ 85th percentile, add increased physical activity, reduce screen time, and restrict calories. Assessment for associated secondary causes (Table 9–3), additional risk factors, or high-risk conditions (Tables 9–6 and 9–7) is recommended. Children at high risk who are unlikely to achieve lipid targets with this strategy alone (severe primary

dyslipidemia, cardiac transplantation) should concomitantly be considered for initiation of medication therapy (Grade C) (Section XI. Diabetes Mellitus and Other Conditions Predisposing to the Development of Accelerated Atherosclerosis).

LDL–C: Treatment for children with severe elevation of LDL–C is based on assessment of lipid levels and associated risk factors or risk conditions (Tables 9–6 and 9–7; Figures 9–1 and 9–2):

- Children with average LDL–C $\geq$ 250 mg/dL should be referred directly to a lipid specialist (Grade B).
- If LDL–C remains $\geq$ 190 mg/dL after a 6-month trial of lifestyle/diet management (CHILD 1→CHILD 2-LDL) for children ages 10 years and older, statin therapy should be considered (Grade A) (Figure 9–1) (Table 9–12).
- If LDL–C remains 130–190 mg/dL in a child age 10 years or older with a negative family history of premature CVD in first-degree relatives and no high-level or moderate-level risk factor or risk condition (Tables 9–6 and 9–7), management should continue to focus on diet changes (CHILD 2-LDL) based on lipid profile findings (Figure 9–1) plus weight management if BMI is $\geq$ 85th percentile. Pharmacologic therapy is not generally indicated, but treatment with bile acid sequestrants might be considered, the latter in consultation with a lipid specialist (Grade B).
- If LDL–C remains 160–189 mg/dL after a trial of lifestyle/diet management (CHILD 1→CHILD 2-LDL) in a child age 10 years or older with a positive family history of premature CVD/events in first-degree relatives (Table 9–6) or at least one high-level risk factor or risk condition or at least two moderate-level risk factors or risk conditions (Tables 9–6 and 9–7), then statin therapy should be considered (Grade B) (Figure 9–1) (Table 9–12).

- If LDL–C remains ≥ 130 to 159 mg/dL after a trial of lifestyle/diet management (CHILD 1→CHILD 2-LDL) in a child age 10 years or older with at least two high-level risk factors or risk conditions or at least one high-level risk factor or risk condition together with at least two moderate-level risk factors or risk conditions (Tables 9–6 and 9–7), then statin therapy should be considered (Grade C) (Figure 9–1) (Table 9–12).
- For children ages 8 and 9 years with LDL–C persistently ≥ 190 mg/dL after a trial of lifestyle/diet management (CHILD 1→CHILD 2-LDL), together with multiple first-degree family members with premature CVD/events, or the presence of at least one high-level risk factor or risk condition or the presence of at least two moderate-level risk factors or risk conditions (Figure 9–1) (Tables 9–6 and 9–7), statin therapy might be considered (Grade B) (Table 9–12).
- Statin use should begin with the lowest available dose given once daily. If LDL–C target levels are not achieved with at least 3 months of compliant use, then the dose may be increased by one increment (usually 10 mg). If LDL–C target levels are still not achieved with at least 3 months of compliant use, then the dose may be further increased by one increment. The risk and effectiveness of dose escalation has been explored in several of the statin clinical trials in children with no additional safety issues identified (Grade B). Alternatively, a second agent such as a bile acid sequestrant or cholesterol absorption inhibitor may be added under the direction of a lipid specialist (Grade B) (Table 9–12).
- Children taking a statin should have routine clinical monitoring for symptoms of muscle toxicity and assessment of hepatic transaminases and creatine kinase (Grade A) (Table 9–12).
- Pediatric care providers should be on the alert for, and children and their families should be counseled about, potential medication interactions (Grade D) (Table 9–12).

- Females taking a statin should be counseled about risks associated with pregnancy and appropriate contraception strategies if indicated. Use of oral contraceptives in combination with statins is not contraindicated (Grade D) (Table 9–12).

TG, non-HDL–C: Children with elevated TG or elevated non-HDL–C after control of LDL–C are managed based on lipid levels (Figure 9–2):

- Children with average fasting levels of TG $\geq$ 500 mg/dL or any single measurement $\geq$ 1,000 mg/dL related to a primary hypertriglyceridemia should be treated in conjunction with a lipid specialist; the CHILD 2-TG diet (Table 9–8) should be started and use of fish oil, fibrate, or niacin to prevent pancreatitis should be considered (Grade D) (Figure 9–2) (Tables 9–10 and 9–11).
- Children with fasting levels of TG 200–499 mg/dL after a trial of lifestyle/diet management with CHILD 1→CHILD 2-TG (Table 9–8) should have non-HDL recalculated and be managed to a goal of less than 145 mg/dL (Grade D).
- Children with fasting levels of TG 200–499 mg/dL, non-HDL $\geq$ 145 mg/dL, after a trial of lifestyle/diet management with CHILD 1→CHILD 2-TG (Table 9–8), including increased fish intake, may be considered for fish oil supplementation (Grade D) (Table 9–10).
- Children ages 10 years or older with non-HDL–C levels $\geq$145 mg/dL after the LDL–C goal is achieved may be considered for further intensification of statin therapy or additional therapy with a fibrate or niacin, in conjunction with referral to a lipid specialist (Grade D) (Figure 9–1) (Tables 9–10 and 9–11).
- Children with severe or complex mixed dyslipidemias, particularly where multiple medications are being considered, should be referred for consultation with a lipid specialist (Grade D) (Figures 9–1 and 9–2).

The age-specific recommendations for pharmacologic management of dyslipidemia are summarized in Table 9–9.

Table 9–9. Evidence-Based Recommendations for Pharmacologic Treatment of Dyslipidemia

Grades reflect the findings of the evidence review. **Recommendation levels** reflect the consensus opinion of the Expert Panel.		
When medication is recommended, this should always be in the context of the complete cardiovascular risk profile of the patient and in consultation with the patient and the family.		
NOTE: Values given are in mg/dL. To convert to SI units, divide the results for total cholesterol (TC), low-density lipoprotein cholesterol (LDL–C), high-density lipoprotein cholesterol (HDL–C), and non-HDL–C by 38.6; for triglycerides (TG), divide by 88.6.		
Birth–10 years	Pharmacologic treatment is limited to children with severe primary hyperlipidemia (homozygous familial hypercholesterolemia, primary hypertriglyceridemia with TG ≥500 mg/dL) or a high-risk condition (Tables 9–6 and 9–7) or evident cardiovascular disease; all under the care of a lipid specialist.	Grade C Recommend
≥10–21 years	Detailed family history (FHx) and risk factor (RF) assessment required before initiation of drug therapy.* High- to moderate-level RFs and risk conditions (RCs) in Tables 9–6 and 9–7.	Grade C Strongly recommend
	LDL–C:	
	If average LDL–C ≥250 mg/dL*, consult lipid specialist.	Grade B Strongly recommend
	If average LDL–C ≥130–250 mg/dL, or non-HDL ≥145 mg/dL: • Refer to dietitian for medical nutrition therapy with Cardiovascular Health Integrated Lifestyle Diet (CHILD 1) → CHILD 2-LDL (Table 9–8) × 6 months --> repeat fasting lipid panel (FLP)	Grade A Strongly recommend
	Repeat FLP:	
	• → LDL–C <130 mg/dL, continue CHILD 2-LDL, reevaluate in 12 months	Grade A Strongly recommend
	• → LDL–C ≥190** mg/dL, consider initiation of statin therapy per Tables 9–11 and 9–12	Grade A Strongly recommend
	• → LDL–C ≥130–189 mg/dL, FHx (-), no other RF or RC, continue CHILD 2-LDL, reevaluate q. 6 months	Grade B Recommend
	• → LDL–C = 160–189 mg/dL + FHx positive OR ≥1 high-level RF/RC OR ≥2 moderate-level RFs/RCs, consider statin therapy per Tables 9–11 and 9–12	Grade B Recommend
	• → LDL–C ≥130–159 mg/dL + ≥2 high-level RFs/RCs OR 1 high-level + 2 moderate-level RFs/RCs, consider statin therapy per Tables 9–11 and 9–12	Grade B Recommend

	Children on statin therapy should be counseled and carefully monitored per Table 9–12. ***** Consideration of drug therapy based on the average of ≥2 FLPs, obtained at least 2 weeks but no more than 3 months apart. ****** If average LDL–C ≥190 mg/dL after CHILD 2-LDL and child is age 8–9 years with + FHx OR ≥1 high-level RF/RC OR ≥ 2 moderate-level RFs/RCs, statin therapy may be considered.	Grade A Strongly recommend
≥10–21 years	Detailed FHx and RF/RC assessment required before initiation of drug therapy.* High- and moderate-level RFs/RCs in Tables 9–6 and 9–7**	Grade C Strongly recommend
	TG:	
	If average TG ≥500 mg/dL, consult lipid specialist	Grade B Recommend
	If average TG ≥100 mg/dL in a child <10 years, ≥130 mg/dL in a child age 10–19 years, <500 mg/dL:	
	• Refer to dietitian for medical nutrition therapy with CHILD 1 → CHILD 2-TG (Table 9–8) × 6 months	Grade B Strongly recommend
	Repeat fasting lipid profile:	
	• → TG <100 (130) mg/dL, continue CHILD 2-TG, monitor q. 6–12 months	Grade B Strongly recommend
	• → TG >100 (130) mg/dL, reconsult dietitian for intensified CHILD 2 TG diet counseling	Grade C Recommend
	• → TG ≥200–499 mg/dL, non-HDL ≥145 mg/dL, consider fish oil +/- consult lipid specialist	Grade D Recommend
	Non-HDL:	
	Children ≥10 years with non-HDL–C ≥145 mg/dL after LDL–C goal achieved may be considered for additional treatment with statins, fibrates, or niacin in conjunction with a lipid specialist.	Grade D Optional
	* Consideration of drug therapy based on the average of ≥2 fasting lipid profiles obtained at least 2 weeks but no more than 3 months apart. ** If child is obese, nutrition therapy should include calorie restriction and increased activity beyond that recommended for all children. See Section X. Overweight and Obesity for additional age-specific recommendations.	

Table 9–10. Medications for Managing Hyperlipidemia

Type of Medication	Mechanism of Action	Major Effects	Examples	Adverse Reactions	FDA Approval in Youths as of This Writing
HMG CoA (3-Hydroxy-3-Methyl-Glutaryl Coenzyme A reductase inhibitors) (statins)	Inhibits cholesterol synthesis in hepatic cells, decreases cholesterol pool, resulting in upregulation of LDL receptors	Mainly lowers LDL–C; some decrease in TG and modest increase in HDL–C	Atorvastatin Fluvastatin Lovastatin Pravastatin Rosuvastatin Simvastatin	Raised hepatic enzymes, raised creatine kinase, myopathy possibly progressing to rhabdomyolysis	All statins listed approved as an adjunct to diet to lower LDL–C in adolescent boys and postmenarchal girls ages 10–18 years (8+ years for pravastatin) with heFH and LDL–C ≥190 mg/dL, or ≥160 mg/dL with FHx of premature CVD and 2+ CVD risk factors in the pediatric patient
Bile acid sequestrants	Binds intestinal bile acids, interrupting enterohepatic recirculation, more cholesterol converted into bile acids, decreases hepatic cholesterol pool, upregulates LDL receptors	Lowers LDL–C; small increase in HDL; raises TG	Cholestyramine Colestipol Colesevelam	Limited to gastrointestinal tract: gas, bloating, constipation, cramps	No pediatric indication listed for cholestyramine or colestipol; colesevelam indicated as monotherapy or with statin for LDL–C reduction in boys and postmenarchal girls ages 10–17 years with FH after diet trial if LDL–C ≧190 mg/dL or if LDL–C ≧160 mg/dL with FHx premature CVD or 2+ more CVD risk factors in the pediatric patient
Cholesterol absorption inhibitors	Inhibits intestinal absorption of cholesterol and plant sterols, decreases hepatic cholesterol pool, upregulates LDL receptors	Mainly lowers LDL–C; some decrease in TG and small increase in HDL–C	Ezetimibe	Myopathy, gastrointestinal upset, headache	No
Fibric acid derivatives	Agonist for peroxisome proliferator-activated alpha nuclear receptors that upregulate LPL and downregulate apoC–III, both increasing degradation of VLDL–C and TG. Hepatic synthesis of VLDL–C may also be decreased.	Mainly lowers TG and raises HDL–C, with little effect on LDL–C	Fenofibrate Gemfibrozil	Dyspepsia, constipation, myositis, anemia	No
Nicotinic acid (extended release)	Inhibits release of FFA from adipose tissue; decreases VLDL–C and LDL–C production and HDL–C degradation	Lowers TG and LDL–C and raises HDL–C; can decrease Lp(a)	Niacin, extended release	Flushing, hepatic toxicity, can increase fasting blood glucose, uric acid; hyperacidity	Use not recommended in children <2 years of age

Omega-3 fish oil	Decreases hepatic FA and TG synthesis while enhancing FA degradation/ oxidation, with subsequent reduced VLDL–C release	Lowers TG, raises HDL–C, increases LDL–C and LDL–C particle size	Omega-3 acid ethyl esters	Occasional gastrointestinal side effects but no adverse effect on glucose levels or muscle or liver enzymes or bleeding	Only one FDA-approved fish oil preparation for adults, but many generic fish oil capsules commercially available

Table 9–11. Clinical Trials of Lipid-Lowering Medication Therapy in Children and Adolescents

BILE ACID BINDING RESINS

Study	Medication	Subjects/Gender/ Condition	Daily Dose	Effect on Lipid Profile			
				TC	LDL–C	HDL–C	TG
Tonstad et al.[99] RCT 1 year	Cholestyramine	72/both/FH (LDL ≥190 mg/dL without FHx premature CVD or LDL ≥160 with FHx after 1-year diet; ages 6–11 years)	8 g	-12%	-17%	+8%	NA
McCrindle et al.[146] RCT crossover 2 × 8 weeks	Cholestyramine	40/both/FH (1 parent with FH; LDL–C ≥131 mg/dL; on diet; ages 10–18 years)	8 g	-7 to -11%	-10 to -15%	+2 to +4%	+6 to +9%
Tonstad et al.[147] RCT 8 weeks; open-label 44–52 weeks	Colestipol	66/both/FH (TC ≥239 mg/dL and TG ≤115 mg/dL; ages 10–16 years)	2–12 g	-17%	-20%	-7%	-13%
McCrindle et al.[148] RCT crossover 2 × 18 weeks	Colestipol	36/both/FH/FCHL (LDL ≥160 mg/dL after 6 months diet counseling; ages 8–18 years)	10 g	-7%	-10%	+2%	+12%
Stein et al[149]	Colesevelam	191/both/ FH (LDL≥190mg/dL or LDL≥ plus 2 additional RFs after 6 months diet counseling; ages 10-17 years.	1.875 g 3.75 g	-3% -7%	-6% -13%	+5% +8%	+6% +5%

HMG COA REDUCTASE INHIBITORS (STATINS)

Study	Medication	Subjects/Gender/ Condition	Daily Dose	Effect on Lipid Profile TC	LDL–C	HDL–C	TG
McCrindle et al.[139] RCT; open-label 26 weeks	Atorvastatin	187/both/FH/ Severe hyperlipidemia (LDL–C ≥190 mg/dL or ≥160 mg/dL with FHx; and TG <400 mg/dL; ages 10–17 years)	10–20 mg	-30%	-40%	+6%	-13%
Van der Graaf et al.[140] Open-label 2 years	Fluvastatin	85/both/FH (LDL–C ≥190 mg/dL or LDL–C ≥160 mg/dL and 1+ risk factor or LDL receptor mutation; ages 10–16 years)	80 mg	-27%	-34%	+5%	-5%
Lambert et al.[141] RCT 8 weeks	Lovastatin	69/males/FH (LDL–C >95th percentile, FHx atherosclerosis and hyperlipidemia; on diet; mean age 13 years)	10 mg 20 mg 30 mg 40 mg	-17% -19% -21% -29%	-21% -24% -27% -36%	+9% +2% +11% +3%	-18% +9% +3% -9%
Stein et al.[142] RCT 48 weeks	Lovastatin	132/males/FH (LDL 189–503 mg/dL + FHx of high LDL; or 220–503 mg/dL + FHx CAD death; AHA diet 4+ months; ages 10–17 years)	10 mg 20 mg 40 mg	-13% -19% -21%	-17% -24% -27%	+4% +4% +5%	+4% +8% +6%
Clauss et al.[143] RCT 24 weeks	Lovastatin	54/females/FH (FHx FH; LDL 160–400 mg/dL and TG <350 mg/dL; 4-week diet placebo run-in and 20-week tx; ages 10–17 years, postmenarchal)	40 mg	-22%	-27%	+3%	-23%

Knipscheer et al.[144] RCT 12 weeks	Pravastatin	72/ both/FH (FHx hypercholesterol or premature atherosclerosis; LDL >95th percentile; diet × 8 weeks; ages 8–16 years)	5 mg 10 mg 20 mg	-18% -17% -25%	-23% -24% -33%	+4% +6% +11%	+2% +7% +3%
Wiegman et al.[21] RCT 2 years	Pravastatin	214/both/FH (LDL–C ≥155 mg/dL and TG ≤350 mg/dL; diet × 3 months; ages 8–18 years)	20–40 mg	-19%	-24%	+6%	-17%
Rodenburg et al.[22] Open-label 2-year RCT; 4.5 year open-label followup	Pravastatin	186/both/FH (LDL–C ≥154 mg/dL and TG <154 mg/dL; 3 months on diet; ages 8–18 years)	20 mg (ages <14 years) or 40 mg (ages >14 years)	-23%	-29%	+3%	-2%
de Jongh et al.[145] RCT 48 weeks	Simvastatin	173/both/FH (LDL–C: 158–397 mg/dL; ages 10–17 years)	10–40 mg	-31%	-41%	+3%	-9%
de Jongh et al.[23] RCT 28 weeks	Simvastatin	50/both/FH (LDL–C above 95th percentile, FHx hyperlipidemia, or LDL receptor mutation; ages 9–18 years)	40 mg	-30%	-40%	+5%	-17%
Avis et al[146] RCT 12 weeks; then, 40 week open label followup	Rosuvastatin	177/both/FH (LDL-C≥190 mg/dL or LDL-C>160 mg/dL plus (+)FHx of early CVD or ≥ 2 other RFs for CVD	5 mg 10 mg 20 mg	-30% -34% -39%	-38% -45% -50%	+4% +10% +9%	-13% -15% -16%

OTHER AGENTS

Study	Medication	Subjects/Gender Condition	Daily Dose	Effect on Lipid Profile			
				TC	LDL–C	HDL–C	TG
Wheeler et al.[150] RCT 26 weeks	Bezafibrate	14/both/FH (TC >269 mg/dL, nl TG + FHx of FH or premature CAD; ages 4–15 years)	10–20 mg	-22%	NC	+15%	-23%
Colletti et al.[149] Open-label 1–19 months	Niacin	21/both/FH (mean LDL = 243 ± 45 mg/dL on low-fat diet; mean TG = 87 ± 39 mg/dL; ages 4–14 years)	500–2,200 mg	-13%	-17%	+4%	+13%
McCrindle et al.[148] RCT crossover 2 × 18 weeks	Pravastatin and Colestipol	36/both/FH/FCHL (LDL >160 mg/dL + FHx of FH or premature CAD; TG >177 mg/dL in 10/36; ages 10–18 years)	Pravastatin, 10 mg (with Colestipol, 5g)	-13%	-17%	+4%	+8%
van der Graaf et al.[154] RCT 6 and 27 weeks; open-label to 53 weeks	Simvastatin and Ezetimibe	248/both/FH (LDL >159 mg/dL + genotype-confirmed FH or + parental genotype-confirmed FH or + parental LDL >210 mg/dL or + tendinous xanthomas or LDL >189 mg/dL + FHx of hypercholesterolemia; ages 10–17 years)	Simvastatin 10–40 mg with Ezetimibe 10 mg	- 38%	- 49%	+7%	-17%
Addendum: *Goldberg et al.*[157] Omega-3 fatty acid review in adults; *no RCTs in children*	*Omega-3 fish oils** (1 gram/capsule)*	-	*1–4 g/d*	*NC*	*+17–31%*	*+6–17%*	*-30–40%*

ABBREVIATIONS: AHA = American Heart Association; CAD = coronary artery disease; d = day; FHx = family history; g = grams; mg = milligrams; NA = not available; NC = not calculated; TC = total cholesterol; FH = heterozygous familial hypercholesterolemia; FCHL = familial combined hyperlipidemia; RCT = randomized controlled trial. tx = treatment

** There is only one FDA-approved fish oil preparation, but there are many generic forms of fish oil capsules that are commercially available. The University of Wisconsin maintains a preventive cardiology patient education Web site. The "fish oil" section includes information about the content of various preparations. The Web site is updated every 6 months (https://www.heartdecision.org/chdrisk/v_hd/patient_edu_docs/Fish_Oil_11-2007.pdf).

Table 9–12. Recommendations for Use of HMG CoA Reductase Inhibitors (Statins) in Children and Adolescents

Patient Selection

1. Use algorithm (Figure 9–1) and risk factor categories (Tables 9–6 and 9–7) to select statin therapy for patients.

2. Include preferences of patient and family in decision making.

3. In general, do not start treatment with statins before age 10 years (patients with high-risk family history, high-risk conditions, or multiple risk factors (Tables 9–6 and 9–7) might be considered for medication initiation at age 10 years or younger).

4. Precaution/contraindication with potentially interactive medications (cyclosporine, niacin, fibric acid derivatives, erythromycin, azole antifungals, nefazodone, and many HIV protease inhibitors).

Check for potential interaction with all current medications at baseline.

5. Conduct baseline hepatic panel and creatine kinase (CK) before initiating treatment.

Initiation and Titration

1. Choice of particular statin is a matter of preference. Clinicians are encouraged to develop familiarity and experience with one of the statins, including dosage regimen and potential drug–drug interactions.

2. Start with the lowest dose once daily, usually at bedtime. Atorvastatin and rosuvastatin can be taken in the morning or evening because of their long half-lives.

3. Measure baseline CK, alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

4. Instruct the patient to report all potential adverse effects, especially muscle cramps, weakness, asthenia, and more diffuse symptoms suggestive of myopathy.

5. Advise female patients about concerns with pregnancy and the need for appropriate contraception.

6. Advise about potential future medication interactions, especially cyclosporine, niacin, fibric acid derivatives, erythromycin, azole antifungals, nefazodone, and HIV protease inhibitors.

Check for potential interaction whenever any new medication is initiated.

7. Whenever potential myopathy symptoms present, stop medication and assess CK; determine relation to recent physical activity. The threshold for worrisome level of CK is 10 times above the upper limit of reported normal, considering the impact of physical activity. Monitor the patient for resolution of myopathy symptoms and any associated increase in CK. Consideration can be given to restarting the medication once symptoms and laboratory abnormalities have resolved.

8. After 4 weeks, measure fasting lipid profile (FLP), ALT, and AST and compare with laboratory-specific reported normal values.

- The threshold for worrisome levels of ALT or AST is ≥3 times the upper limit of reported normal.
- Target levels for low-density lipoprotein cholesterol (LDL–C): minimal <130 mg/dL; ideal <110 mg/dL.

9. If target LDL–C levels are achieved and there are no potential myopathy symptoms or laboratory abnormalities, continue therapy and recheck FLP, ALT, and AST in 8 weeks and then 3 months.

10. If laboratory abnormalities are noted or symptoms are reported, temporarily withhold the medication and repeat the blood work in 2 weeks. When abnormalities resolve, the medication may be restarted with close monitoring.

11. If target LDL–C levels are not achieved, increase the dose by one increment (usually 10 mg) and repeat the blood work in 4 weeks. If target LDL–C levels are still not achieved, dose may be further increased by one increment or another agent (bile acid sequestrant or cholesterol

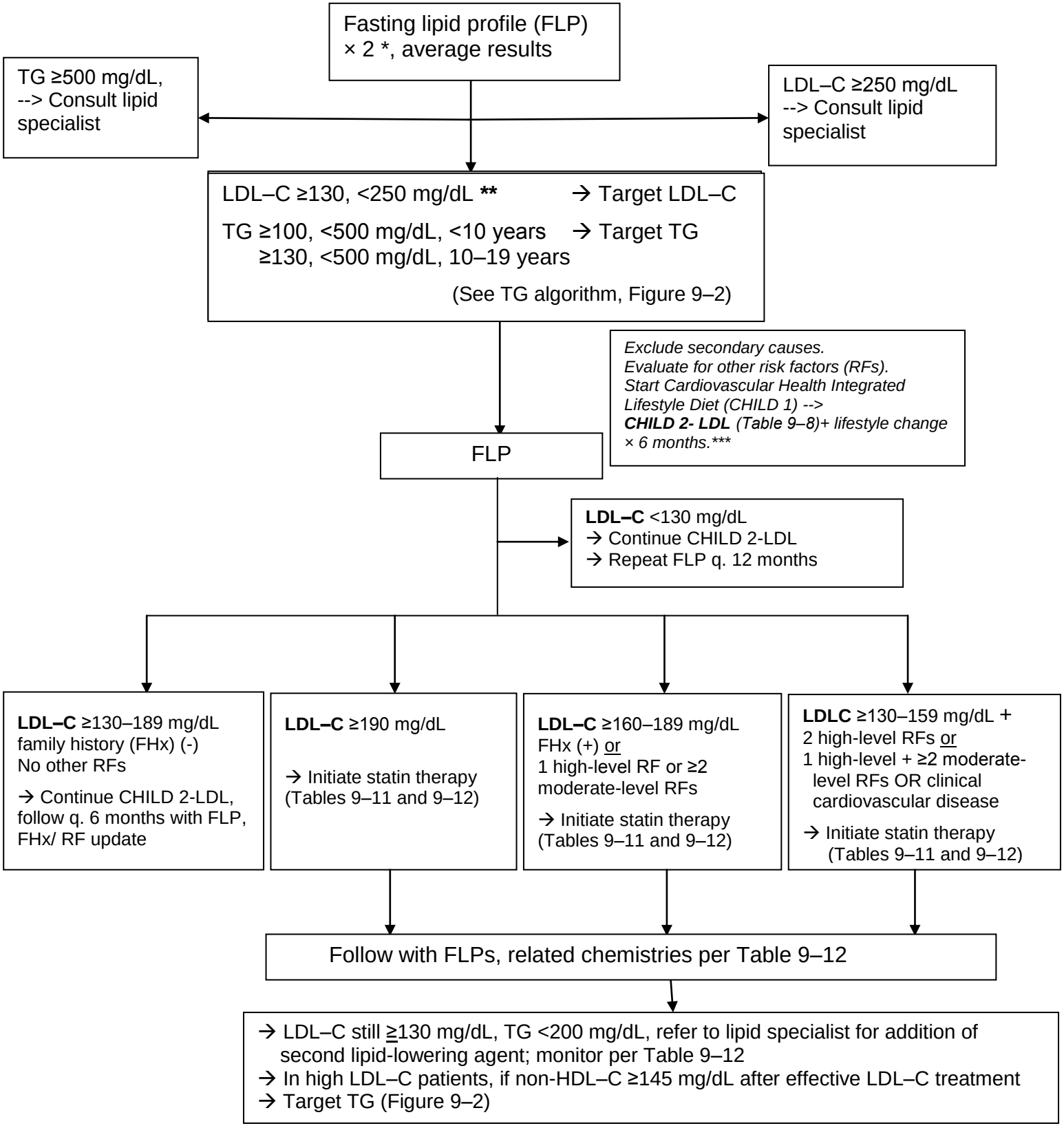
absorption inhibitor) may be added under the direction of a lipid specialist.

Maintenance Monitoring

1. Monitor growth (height, weight, and body mass index relative to normal growth charts), sexual maturation, and development.
2. Whenever potential myopathy symptoms present, stop medication and assess CK.
3. Monitor FLP, ALT, and AST every 3–4 months during the first year, every 6 months during the second year and beyond, and whenever clinically indicated.
4. Monitor and encourage compliance with lipid-lowering dietary and medication therapy. Serially assess and counsel for other risk factors, such as weight gain, smoking, and inactivity.
5. Counsel adolescent females about statin contraindications in pregnancy and the need for abstinence or use of appropriate contraceptive measures. Use of oral contraceptives is not contraindicated if medically appropriate. Seek referral to an adolescent medicine or gynecologic specialist as appropriate.

Figure 9–1. Dyslipidemia Algorithm: TARGET Low-Density Lipoprotein Cholesterol

NOTE: Values given are in mg/dL. To convert to SI units, divide results for total cholesterol (TC), low-density lipoprotein cholesterol (LDL–C), high-density lipoprotein cholesterol (HDL–C), and non-HDL–C by 38.6; for triglycerides (TG), divide by 88.6.



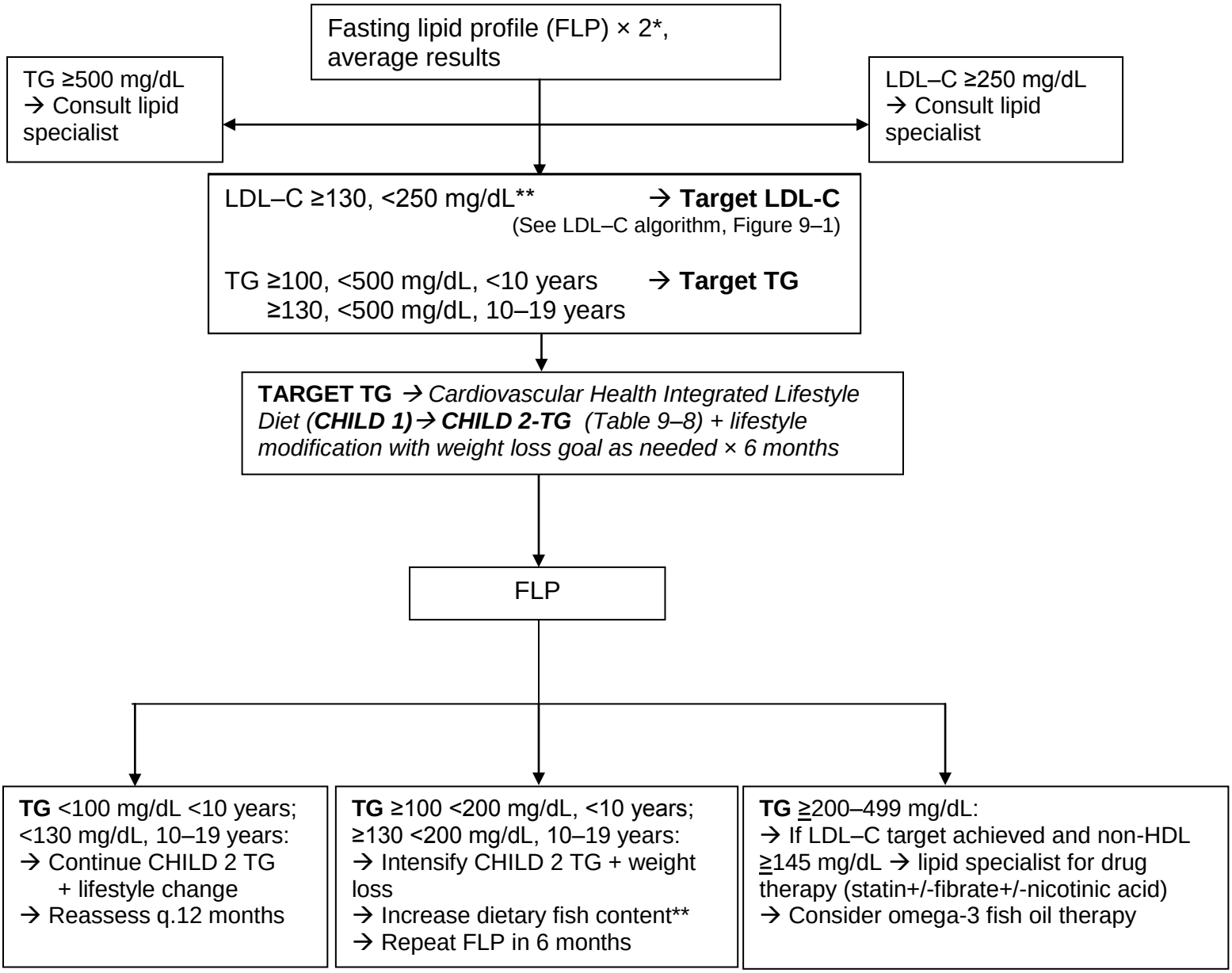
*** Obtain FLPs at least 2 weeks but no more than 3 months apart**

**** Per Table 9–5, use of drug therapy is limited to children ages ≥10 years with defined risk profiles.**

***** In a child with LDL–C >190 mg/dL and other RFs, trial of CHILD 2 LDL–C may be abbreviated.**

Figure 9–2. Dyslipidemia Algorithm: TARGET Triglycerides

NOTE: Values given are in mg/dL. To convert to SI units, divide the results for total cholesterol (TC), low-density lipoprotein cholesterol (LDL–C), high-density lipoprotein cholesterol (HDL–C), and non-HDL–C by 38.6; for triglycerides (TG), divide by 88.6.



*Obtain FLPs at least 2 weeks but no more than 3 months apart.
** The Food and Drug Administration (FDA) and the Environmental Protection Agency are advising women of childbearing age who may become pregnant, pregnant women, nursing mothers, and young children to avoid some types of fish and shellfish and eat fish and shellfish that are lower in mercury. For more information, call the FDA's food information line toll free at 1–888–SAFEFOOD or visit http://www.cfsan.fda.gov/~dms/admehg3.html.

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10. OVERWEIGHT AND OBESITY

INTRODUCTION

This section of the Guidelines provides recommendations to pediatric care providers on management of overweight and obesity in their patients. The section begins with background information on the current prevalence of overweight and obesity in childhood and the association between childhood overweight and obesity and cardiovascular (CV) risk factors. This is followed by a subsection addressing the identification of overweight and obesity and then individual subsections on the prevention and treatment of overweight and obesity in childhood, with the Expert Panel's summaries of the evidence reviews in each of these areas. The evidence review and the development process for the Guidelines are outlined in Section I. Introduction and are described in detail in the Appendix: Methodology. This evidence review combines a systematic review with an Expert Panel consensus process that incorporates and grades the quality of all relevant data based on preidentified criteria. Because of the large volume of included studies and the diverse nature of the evidence, the Expert Panel also provides a critical overview of the studies reviewed for each risk factor, highlighting those that in its judgment provide the most important information. Detailed information from each study has been extracted into the evidence tables, which will be available at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. Each subsection ends with the conclusions of the review, grading of the evidence, and age-specific recommendations for the evaluation, prevention, and treatment of overweight and obesity in pediatric practice. Where evidence is inadequate, recommendations are a consensus of the Expert Panel. References are listed sequentially at the end of the section, with references from the evidence review identified by unique PubMed identifiers (PMID) in bold text. Additional references do not include the PMID number.

BACKGROUND

Dramatic increases in childhood overweight and obesity in the United States since 1980 are an important public health focus. Despite efforts over the past decade to prevent and control overweight and obesity, recent reports from the National Health and Nutrition Examination Survey (NHANES) show sustained high prevalence, with 17 percent of children and adolescents with a body mass index (BMI) above the 95th percentile for age and gender.[1] Section 2. State of the Science: Cardiovascular Risk Factors and the Development of Atherosclerosis in Childhood reviews in detail the evidence that atherosclerosis in childhood and adolescence is associated with the presence and extent of individual risk factors, including obesity. To summarize, two major post mortem studies have demonstrated that the presence of obesity in childhood and adolescence is associated with increased evidence of atherosclerosis at autopsy, especially in males.[2,3,4,5] Because of the strong association with elevated blood pressure, dyslipidemia, and insulin resistance (IR), obesity is even more powerfully correlated with atherosclerosis; this association has been shown for each of these risk factors in all of the major pediatric epidemiologic studies.[6,7,8,9,10,11,12] Longitudinal studies have demonstrated tracking of elevated BMI and increased adiposity in childhood to the presence of obesity in adulthood.[13,14,15,16] Improvement in weight status and decrease in body fatness have been shown to be associated with decreases in systolic and diastolic blood pressures (BPs),[17,18,19,20] total cholesterol (TC), low-density lipoprotein cholesterol (LDL–C) and/or triglycerides (TG),[18,20,21,22,23,24] IR,[17,20,22,24] and inflammatory markers.[20,25] Subclinical vascular changes indicative of atherosclerosis have been demonstrated in overweight and obese children;[20,26,27,28] exercise and weight loss have been shown to result in significant improvement in these measures.[20,28] Finally, epidemiologic studies

have demonstrated that measures of obesity in childhood (greater skinfold thickness, higher BMI percentile) correlated significantly with greater evidence of arterial vascular abnormalities in adulthood, even after adjustment for adult contemporaneous risk factor status.[29,30,31,32,33] Using childhood BMI z-scores and national death registry data, an epidemiologic study of 10,235 men and 4,318 women enrolled between 1930 and 1976 and followed up after age 25 years demonstrated that for each one unit increase in BMI z-score from ages 7–13 years in males and ages 10–13 years in girls, there was a significant increase in risk for a coronary heart disease event.[34] Using an established computer-simulation, state-transition model of coronary heart disease (CHD in U.S. citizens older than age 35 years) and NHANES data for adolescents above the 95th percentile for weight in 2000, an analysis estimated that adolescent obesity will likely increase adult CHD by 5–16 percent over the next 25 years, with more than 100,000 excess cases of CHD attributable to obesity in childhood.[35]

IDENTIFICATION OF OVERWEIGHT AND OBESITY IN CHILDREN AND ADOLESCENTS

To identify overweight and obesity in children living in the United States, BMI percentile distributions relative to gender and age on the Centers for Disease Control and Prevention (CDC) 2000 growth charts are now the preferred reference.[36] The CDC growth charts were not developed as a health-related standard. Instead, the growth charts present percentiles of the BMI distribution derived from measurements taken during several NHANES surveys as points of reference. Although the charts were published in 2000, they include selected data from the 1963 to 1980 surveys and thus are not representative of the U.S. population in 2000. These BMI percentile growth charts provide the best reference data available for describing normal growth in U.S.

children. They are, however, a screening tool and not an instrument for the diagnosis of overweight and obesity.

An expert committee jointly convened by the American Medical Association (AMA), the CDC, and the Maternal and Child Health Bureau (MCHB) of the Health Resources and Services Administration, U.S. Department of Health and Human Services (HHS), recently recommended that BMI be used to assess weight-for-height relationships in children.[37] This conclusion was reached because BMI can be easily calculated from height and weight, correlates strongly with direct measures of body fat (especially at higher BMI values), associates only weakly with height, and identifies individuals with the highest body fat correctly with acceptable accuracy, particularly above the 85th BMI percentile.[38] Pediatric care providers need a feasible standard for identifying overweight and obesity in their patients, since parents recognize a child's overweight status in less than half of cases.[39] The AMA/CDC/MCHB Expert Committee defined a BMI at or greater than the 95th percentile as obese and a BMI between the 85th and 94th percentiles as overweight; children in the latter BMI category have a great deal of variation with respect to prediction of future risk. The Expert Panel for these Guidelines concluded that BMI is a sufficient measure for screening children and adolescents to identify those who need evaluation for CV risk factors associated with body adiposity and that the scientific evidence linking elevated BMI to CV risk factors and morbidity is strong and well-supported.

The Expert Panel recommends that children and adolescents ages 2–18 years with a BMI at or greater than the 95th percentile be described as "obese" and identified as needing assessment for CV risk factors. For children with a BMI that falls between the 85th and 95th percentiles, the term "overweight" should be used, and the position of the

child's BMI on the growth chart should be used to express concern regarding weight-for-height disproportion. It is very important to follow the pattern of growth over time, using these cut points to identify children who require more frequent followup and further assessment rather than to assign a diagnosis. Some may feel that "obese" is an unacceptable term for children and parents, so as with all health conditions, the practitioner is encouraged to use descriptive terminology that is appropriate for each child and family, with a thorough explanation and discussion. Each patient and family should be considered on an individual basis in deciding how best to convey the seriousness of this issue and to develop management plans.

OVERVIEW OF THE EVIDENCE ON PREVENTION OF OVERWEIGHT AND OBESITY: ROLE OF DIET OR COMBINED DIET AND PHYSICAL ACTIVITY INTERVENTIONS

Dietary recommendations for children and adolescents focus on promoting optimal health by including all foods and beverages necessary to provide required macronutrients and micronutrients and calories, consistent with HHS and U.S. Department of Agriculture *2010 Dietary Guidelines for Americans* (2010 *DGA*).[40] Prevention of overweight and obesity throughout childhood is a primary goal for the recommendations of these Guidelines and represents an important health objective for all children. The evidence review and the recommendations for nutrition and diet in all children are presented in Section 5. Nutrition and Diet. In this section, the focus of the evidence review is on studies that specifically addressed prevention of overweight and obesity in children and adolescents using primarily lifestyle interventions. Given the major overlap between the two dietary goals for children—promotion of CV health and prevention of obesity—the majority of the obesity prevention recommendations are the same as those developed for the promotion of CV health in all children.

The Expert Panel's evidence review for overweight and obesity included a large number of studies: 30 systematic reviews, 12 meta-analyses, 121 randomized controlled trials (RCTs), and 47 observational studies. There were five systematic reviews of intervention studies to prevent obesity, four of which were published between 2004 and 2006. The most recent was a rigorous review that selected only RCTs that included a control group and that directly addressed prevention of overweight and obesity in a normal population, with followup of at least 12 months and with obesity-specific outcome measures.[41] The review included a total of 24 studies, and of these, all but 2 were school-based. The intervention was described for the 10 most recent studies and involved a combined dietary and physical activity intervention in 8 and a pure dietary intervention in 2; each of these is described below. The evidence review concluded that overall, the interventions described significantly reduced obesity measures, with 41 percent of studies reporting positive results.

The RCTs in the Expert Panel's evidence review for overweight and obesity were reviewed to identify a total of 17 studies that specifically addressed dietary intake in normal children within the context of overweight and obesity prevention. Many of these studies evaluated dietary interventions designed to address the prevention of overweight and obesity by lowering fat intake and increasing fruit and vegetable intake to meet the published nutritional goal of five servings per day of fruits and vegetables. Most were school-based and often were part of multicomponent programs designed to simultaneously change dietary intake and increase physical activity levels.[42,43,44,45,46,47,48,49,50,51,52] The age groups addressed ranged from preschoolers to teenagers, and the study sizes from 213 to over 5,000 subjects. Measures of overweight and obesity varied and included weight, BMI, BMI percentile, and BMI z-

score. Dietary intake was assessed by a variety of methods, including parental report, self-report, diet records, and direct observation of meals. Most studies were minimally successful in improving dietary quality, with small decreases in fat intake, small increases in fruit and vegetable intake, and small increases in physical activity; however, measures of obesity were rarely changed. As an example of this kind of study, a 2-year school-based health behavior intervention in children in grades 6–8 used sessions taught by classroom teachers focused on decreasing the consumption of high-fat foods, increasing fruit and vegetable intake, decreasing TV viewing, and increasing moderate and vigorous physical activity.[46] There was no attempt to change caloric intake. Obesity was defined as a composite indicator based on BMI and triceps skinfold thickness greater than or equal to age- and gender-specific 85th percentiles. After 2 years, fruit and vegetable consumption increased, and TV viewing time decreased in boys and girls. There was no change in time spent in moderate and vigorous physical activity, the primary outcome of the trial. Prevalence of obesity decreased among girls but not boys.

Another example is the Child and Adolescent Trial for Cardiovascular Health (CATCH), the largest school-based study ever funded in the United States, taking place in 96 schools.[51] This multicomponent school CV health promotion intervention for middle-school children resulted in improvement in children's diets, with significantly lower saturated fat intakes and significantly more vigorous physical activity by children in the intervention schools, findings that were sustained for 3 years after the end of the trial.[52] CATCH intervention goals were not focused on obesity, and there were no differences in BMI during the original study or at late followup. The Pathways school RCT in American Indian schoolchildren used similar approaches to CATCH in changing the school diet and physical activity environments, in addition to teaching lifestyle approaches through curricula. The Pathways trial focused on obesity prevention; however, there were no

significant differences in obesity measures between the randomized groups, although measures of diet and physical activity did improve.[53]

An example of a primary dietary intervention study is the Special Turku Coronary Risk Factor Intervention Project (STRIP), which randomized 1,062 Finnish infants to a conventional diet or a low-saturated fat diet at age 7 months.[54] The intervention families received individualized counseling biannually by a dietitian who focused on lowering saturated fat in the diet and a physician who consistently recommended increased physical activity with no specific activity intervention. Since the study began in 1990, the children have been evaluated at least annually. Review of growth data indicates that there have been consistently fewer overweight girls in the intervention group beginning at age 2 years. At age 10 years, 10.2 percent of girls in the intervention group were overweight (defined as 20 percent above weight for height of average Finnish children) compared with 18.8 percent of controls (P = 0.04); there was no difference in overweight prevalence between groups among boys. There was no significant difference between intervention and control groups in weight for height or obesity (40 percent above average weight for height) at any single age. At 9-year followup, both male and female children in the intervention group reported consuming less total fat and saturated fat and had higher insulin sensitivity than did controls.[55,56] A detailed evaluation of macronutrient and micronutrient intakes, linear growth, and neurologic status has identified no adverse effects from the intervention.

To evaluate the relationship between calcium intake and body fat in the prevention of obesity, an RCT of calcium supplementation and physical activity was conducted in preschool children. Analysis of body composition and calcium intake showed no association for the entire group. Among children in the lowest tertile of calcium intake,

fat mass gain was lower in the calcium group, but this was not correlated with total calcium intake.[57]

Observational studies described in detail in Section 5. Nutrition and Diet have linked increased consumption of sugar-sweetened beverages with the development of overweight and obesity. One RCT assigned adolescents with a BMI above the 25th percentile for age and gender who regularly consumed at least one sugar-sweetened beverage/day to an intervention in which noncaloric beverages were delivered to the home free of charge for 25 weeks.[58] Consumption of sugar-sweetened beverages was reduced dramatically, by 82 percent in the intervention group, with no change in controls. BMI increased in both groups; although the increase was less in the intervention group than in the control group, the difference between groups was not significant. However, among subjects in the highest tertile for BMI at baseline (above the 75th percentile), reduction of sugar-sweetened beverages was accompanied by a significant decrease in BMI compared with an increase in BMI in controls. This pilot study suggests that reducing sugar-sweetened beverage intake may have a beneficial effect on body weight in overweight and obese adolescents. Another study was a cluster RCT testing the reduced intake of carbonated drinks on obesity in six primary schools in England; carbonated drinks were reduced by a 0.7 net servings/day along with a modest decrease in overweight/obese children.[59]

Innovative methods for teaching nutrition and changing diet to prevent overweight and obesity have been explored. A computer game-based intervention with overweight and obesity as a secondary outcome was associated with improved nutritional knowledge and better food choices than a conventional curriculum among students in the last three grades of primary school.[43] A 10-session multimedia game designed to increase

preference for fruits and vegetables was successful among fourth-grade students in increasing their fruit and vegetable consumption over a 5-week intervention.[60]

CONCLUSIONS OF THE EVIDENCE REVIEW ON PREVENTION OF OVERWEIGHT AND OBESITY WITH DIET OR COMBINED DIET AND PHYSICAL ACTIVITY INTERVENTIONS

The Expert Panel concluded that there is good evidence that the dietary behavior of children can be safely improved with interventions that result in lower saturated fat intake, reduced intake of sugar-sweetened beverages, and increased consumption of fruits and vegetables. None of these studies included any intervention to change calorie intake. In a small number of studies, the changes described are associated with significantly lower BMI or BMI percentile on followup. Most studies also had specific interventions aimed at changing physical activity behaviors, so it is difficult to separate benefits related to diet change alone. Although calorie balance is generally seen as a key issue for weight control, intervention studies addressing both diet and physical activity had mixed results, perhaps because most offered relatively weak interventions at the community level rather than targeting individual, at-risk youths. No evidence was identified that diets that address lowering saturated fat intake, reducing intake of sugar-sweetened beverages, and increasing consumption of fruits and vegetables are harmful.

For pediatric patients with a BMI below the 85th percentile for age and gender, the recommendations in these Guidelines for nutrition and diet for reducing CV risk for all children, which build on the 2010 *DGA* for the general public (CHILD 1, Section V. Nutrition and Diet), specifically address optimizing the diet in each of these areas, as well as increasing intake of whole grains and matching energy intake to growth and

energy expenditure with monitoring of BMI and dietary intake over time.[40] No additional dietary recommendations to prevent obesity are indicated based on this evidence review. As described above, it is very important to follow the pattern of growth over time to identify children who require more frequent followup, further assessment, and intervention.

OVERVIEW OF THE EVIDENCE ON PREVENTION OF OVERWEIGHT AND OBESITY: ROLE OF PHYSICAL ACTIVITY

There is strong evidence for the beneficial effects of physical activity and limiting sedentary time on the overall health of children and adolescents.[61,62] Section 6. Physical Activity reviewed the evidence on the benefits of physical activity and limited sedentary time on overall CV health, including a decrease in BMI, especially if subjects are overweight or obese. The recommendations for activity for all children in these Guidelines address both the limitation of sedentary activity and the prescription of daily physical activity. A recent evidence-based review of physical activity included 850 studies in children and recommended at least 60 minutes of moderate to vigorous physical activity daily to achieve beneficial effects on health.[61] The authors concluded that such a program would have little influence on BMI in normal-weight children.

From the evidence review for these Guidelines, studies were identified that addressed obesity prevention through a pure physical activity intervention to increase physical activity and/or decrease sedentary time. These are not common, with one systematic review and eight RCTs identified in which a physical activity intervention was tested to prevent obesity. A systematic review by The Cochrane Collaboration addressed prevention of overweight and obesity and selected 22 studies published between 1990

and 2005 for inclusion.[63] Two of 10 long-term studies lasting at least 12 months and 4 of 12 short-term studies focused on physical activity alone, and each is included in the RCT review below. Overall, the Cochrane reviewers concluded that physical activity "interventions employed to date have, largely, not impacted weight status of children to any degree." The Cochrane reviewers noted that, as a group, the studies have been underpowered and/or poorly designed, with interventions often set for short-term impact.

From the RCTs in the evidence review for these Guidelines, a 6-month, classroom-based trial in third- and fourth-grade students was effective in decreasing sedentary activity (TV and video use), with associated significant relative decreases in BMI, triceps skin folds, waist circumference, and waist-to-hip ratio in the intervention group compared with the control group.[64] A school-based trial in fourth-grade students compared three groups: three 30-minute physical activity classes/week taught by an exercise specialist, three classes taught by a teacher, and no activity classes.[65] After 3 school years, there was no significant improvement in BMI or body fat measures, but interpretation of results was complicated by differences between the groups at baseline. In a small group of nonobese sedentary adolescent males, a 5-week prospective trial of endurance training was associated with decreased thigh fat but no change in BMI or intra-abdominal fat.[66] In nonobese African American girls, a 12-week pilot intervention with an afterschool dance class and education to reduce sedentary activity at home was associated with a significant decrease in home TV use and fewer meals in front of the TV, increased physical activity, decreased BMI, and decreased waist circumference; the latter results were not significant, but the study was not powered for these outcomes.[67] A year-long enhanced physical activity program in nursery schools in Scotland had no effect on BMI or measures of physical activity and sedentary behavior at 6 and 12 months.[68]

Gender differences in response to interventions were reported in two school-based trials. After an intervention that combined education and activity for inner-city high school students, health knowledge was improved in males and females, but eating habits and fitness and cholesterol levels were significantly improved only in females, with no change in males; neither males nor females had any change in BMI.[69] Among second-grade American Indian children enrolled in a physical activity intervention, boys were seen to be more active at baseline and followup.[70] Activity levels were increased among children in the intervention schools compared with controls, but there was no difference in BMI or percentage of body fat.

CONCLUSIONS OF THE EVIDENCE REVIEW ON PREVENTION OF OVERWEIGHT AND OBESITY WITH PHYSICAL ACTIVITY

The RCTs described above have evaluated the effect of interventions that addressed only physical activity and/or sedentary behavior on prevention of overweight and obesity. In a small number of these, the intervention was effective. Notably, these successful interventions often addressed reduction in sedentary behavior rather than attempts to increase physical activity. In the majority of studies, there was no significant difference in any measure of body size, including BMI, BMI percentile, or percentage of body fat. Sample sizes were often small, and followup was often short, frequently less than 6 months. The results of one study suggested that gender-specific programs may be more successful in changing physical activity behavior. Overall, the Expert Panel concluded that, based on the evidence review, increasing physical activity in isolation is of little benefit in preventing obesity. By contrast, the review suggests that reducing sedentary behavior may be beneficial in preventing the development of obesity. The physical activity recommendations in these Guidelines specifically address the CV health benefits of limiting sedentary behavior and increasing physical activity in all children

(Section VI. Physical Activity). No additional specific recommendations addressing activity in preventing obesity beyond those developed for all children are indicated based on this evidence review.

OVERVIEW OF THE EVIDENCE ON CHILDREN AT INCREASED RISK FOR OVERWEIGHT AND OBESITY

Certain populations of children who are of normal weight are at risk for developing overweight and obesity as they grow older. Observational studies have identified risk factors that put these children at greater risk; however, research is lacking regarding an appropriate intervention. Despite that fact, epidemiologic associations suggest that primary care providers should be alert to increasing BMI trends and excessive weight gain beyond what is anticipated for height increase or pubertal change when dealing with these children and should consider intervention before the child becomes overweight.

From the evidence review for these Guidelines, observational studies have identified sample populations that are at special risk for obesity as follows:

1. Children with BMI between the 85th and 95th percentiles.[14,15,16,71,72]
2. Children in whom there is a positive family history of obesity in one or both parents.[13,14,15,16,73,74,75]
3. Early onset of increasing weight beyond that appropriate for increase in height. This can be identified early, beginning in the first year of life.[72,74]
4. Excessive increase in weight during adolescence, particularly in Black girls.[71,72]
5. Children who previously had been very active and become inactive or adolescents who are inactive in general (e.g., a child who has previously participated in organized sports and has stopped, particularly in adolescence).[76]

No RCTs that specifically address these populations were identified. Despite this absence of RCT evidence, the Expert Panel believes that lifestyle recommendations addressing energy balance—diet and physical activity—with a goal of prevention of excess weight gain are needed for normal-weight children with characteristics consistent with these special risks for the development of overweight and obesity. The diet and activity recommendations proposed for all children in these Guidelines should be vigorously reinforced in these children. In any child, the development of a BMI between the 85th and 95th percentiles should be taken as a sign that increased attention to diet and activity, as well as BMI-specific followup, is indicated.

OVERVIEW OF THE EVIDENCE ON TREATMENT OF OBESITY

In children who are already obese, the primary goal of obesity treatment is to improve weight-for-height disproportion through weight loss in older children or through weight maintenance during linear growth through adoption of a healthier lifestyle in younger children. From this evidence review, many studies measuring intermediate variables have shown a significant decrease in CV risk factors with an improvement in weight and/or decrease in body fatness: decreases in systolic and diastolic BPs;[17,18,19,20,77,78] decreases in TC, LDL–C, and/or TG[18,19,20,21,22] decrease in IR;[17,19,20,22,23,24] decrease in inflammatory markers;[25] and improvement in subclinical measures of atherosclerosis.[20,28,79] If weight improvements are sustained, these studies suggest that the improved weight profile should be associated with improved overall health and CV risk, reduced incidence of type 2 diabetes mellitus (T2DM), and other problems known to be associated with obesity in childhood.

The evidence review for overweight and obesity for these Guidelines identified 5 systematic reviews, 2 meta-analyses, and 69 RCTs addressing the treatment of obesity.

Of these, a major systematic review from the U.S. Preventive Services Task Force (USPSTF) in 2005 considered all treatment intervention trials applicable to primary care settings published since 1985 in Western industrialized nations.[80] Of 23 identified studies, the majority involved short-term, behavioral counseling interventions in small numbers of primarily White school-aged children. At followup, mean BMI percentiles decreased from above the 95th percentile at baseline to between the 90th and 95th percentiles at 1-year followup; no long-term followup results were available. Six studies in the USPSTF review involved adolescents, as did an additional review of 17 studies confined to adolescents.[81] Only half of the interventions were associated with any mean change in BMI at short-term followup. No long-term followup results were available. In all adolescent studies, high dropout rates, as high as 45 percent, complicate the interpretation of results. No adverse effects on eating behaviors, eating disorder symptoms, or weight dissatisfaction were reported, but these results often were not specifically provided. Both published reviews concluded that the evidence that behavioral counseling interventions are effective treatment for obese children and adolescents is fair to poor because of small, short-term studies with limited generalizability.

By contrast, a 2008 systematic review from the Agency for Healthcare Research and Quality evaluated RCTs of weight interventions in obese and overweight children and adolescents released between 2005 and 2007; the review concluded that medium- to high-intensity (defined as meeting for at least 25 hours over 6 months) behavioral management programs were effective in achieving small to moderate weight loss that was sustained for up to 12 months after the end of treatment.[82] The majority of studies took place in specialized centers for obesity research, with only rare studies in clinical practice settings.

A 2007 meta-analysis quantitatively evaluated the efficacy of RCTs that used lifestyle interventions—defined as any combination of diet, physical activity, and/or behavioral treatment—published before August 2005. Lifestyle interventions were compared with no-treatment control groups or information/education-only controls. Effect sizes were calculated from the means and standard deviations of the change scores of the weight loss measure (percentage overweight, BMI z-score, BMI, or weight) from the beginning of treatment to the end of treatment and/or followup; only one weight measure was included for each study. Compared with both kinds of controls, there was a significant effect size at the end of treatment and at followup.[83]

A majority of RCTs in the evidence review for these Guidelines tested a hypocaloric diet and an increase in physical activity with behavior change counseling to support these changes. Twenty-one RCTs described this type of combined intervention, and obesity measures included percentage overweight, weight, relative weight, BMI percentile, BMI z-score, body fat percentile, and/or waist circumference. Thirteen of 21 trials reported a significant decrease in at least one of these measures on short-term followup, when intervention and control groups were compared.[84,85,86,87,88,89,90,91,92,93,94,95,96] Two of these studies were initiated in primary care settings, and the remainder occurred in research clinics. Of note, in obese adolescents, inclusion of peers in a cognitive-behavioral diet and activity intervention was successful in achieving significant weight loss sustained at 10-month followup.[93] Ten-year followup of obese children (ages 6–12 years at enrollment) documented sustained improvement in weight-for-height measures of family-based interventions based on training children and parents in optimal food choices in a research setting.[88,94] This is the first evidence that weight regulation in children can be achieved and maintained over extended periods from childhood through adolescence.

Change in physical activity in addition to dietary change was significantly associated with reduced obesity in this report. Another significant variable from this study that has been replicated by others was the importance of a treatment focus on parents in children this age.[92,94,95,96] Another RCT tested an intervention designed for weight maintenance after an active weight loss treatment program in 204 healthy children ages 7–12 years with elevated BMI; the trial found that maintenance-targeted treatment improved weight loss short term compared with no maintenance treatment, but effects were not significant at 2 years.[97]

There were 21 studies in this evidence review that specifically evaluated an exercise intervention alone or in combination with dietary change, either an increase in physical activity, a decrease in sedentary activity, or a combination. Of these, nine involved a pure physical activity intervention with no recommended diet change versus no intervention.[79,98,99,100,101,102,103,104,105,106,107] Most showed a decrease in body fat and/or an increase in fat-free mass in the exercise group, but only one showed a decrease in weight and BMI.[104] In this study, points scored with activity allowed children to earn TV time, and weight changes were accompanied by a significant increase in moderate to vigorous activity and a decrease in sedentary activity. Exercise alone was shown to decrease IR[102,105] and improve subclinical measures of atherosclerosis even without weight change.[79,98,100] In the remainder of these studies, an activity intervention and diet change were compared with diet alone.[17,18,20,23,108,109,110,111,112,113,114] The combination of dietary change and a specific exercise intervention was universally more effective at achieving decreases in weight and BMI, as well as decreases in body fat when compared with an isolated dietary intervention.

Seven studies that met the criteria for inclusion in the Expert Panel evidence review evaluated specific dietary interventions. Three studies compared a low glycemic-load diet to a low-fat diet; two of these were in young adults (ages 18–40 years), and one was in adolescents.[78,115,116] In all three trials, both diet groups lost weight, but loss was greater in the low-glycemic index group. One study compared a low-carbohydrate diet to a low-fat diet over 12 weeks in 39 adolescents, with greater BMI decrease in the low-carbohydrate group.[19] In two studies, a fiber supplement was added to a hypocaloric diet with no difference in outcomes when compared with diet alone.[117,118] Finally, a short-term, protein-sparing modified fast was compared with a hypocaloric balanced diet in a very small group of children ages 7–15 years, with marked decrease in weight and BMI at 10-week followup for the protein-sparing, modified-fast diet group.[119] Results were sustained at 4.5-months followup but not at 10.5 months when loss to followup was significant. In addition, in this study, the two groups were not comparable at baseline.

Addition of medication to behavioral lifestyle counseling for diet and exercise was investigated in a series of RCTs in pediatric populations, which are detailed below. Three small metformin trials (N = 24–29) enrolled male and female adolescents with severe elevation of BMI (mean greater than 35 kg/m^2) and hyperinsulinism without diabetes or with impaired glucose tolerance. Each study used a different metformin dose (500 mg–1 g bid). Treatment duration was 6 months in two studies and 8 weeks in the third. All three reported statistically significant decreases in weight and/or BMI and fasting insulin with metformin compared to placebo. In the two studies that included lipids as a secondary outcome, the effect was improvement in one and no effect in the other.[24,120,121]

For adolescents older than age 12 years, adding orlistat, which causes fat malabsorption through inhibition of enteric lipase, to a comprehensive lifestyle weight loss program was investigated in four trials. A large multicenter RCT enrolled 539 obese 12- to 16-year-olds, excluding those with BMI 44 kg/m^2 or higher, diabetes requiring medication, and other medical and psychiatric conditions. After 52 weeks, 65 percent of participants were retained; there was significantly greater lowering of all obesity measures in the orlistat group compared with controls.[122] In a smaller trial, use of orlistat was associated with a significantly greater decrease in BMI and body weight from baseline after 1 year of treatment; absolute BMI was also lower in the orlistat treatment group, but this difference was not significant.[123] In a small 6-month trial, orlistat was not associated with a significant difference in any obesity measure.[124] In a small study designed to investigate mineral balance in adolescent obese volunteers, there was no difference in any of 6 selected microminerals or macrominerals after 21 days of orlistat treatment.[125] In all of these studies, there was a high reported rate of gastrointestinal symptoms with orlistat involving up to 32 percent of subjects.

In adolescents (ages 12–16 years) with severe elevation of BMI (32–44 kg/m^2), the addition of sibutramine, a serotonin reuptake inhibitor, to a comprehensive lifestyle weight loss program significantly improved weight loss, BMI, and measures of metabolic risk at 6- to 12-month followup in three RCTs.[22,126,127,128] The trials excluded subjects with comorbidities, such as elevated BP, diabetes mellitus, CV disease, and/or elevated heart rate. A large RCT involved 498 participants, ages 12–16 years. After 1 year, 76 percent of sibutramine subjects and 62 percent of placebo subjects completed the study. The sibutramine group had significantly greater decreases in BMI and body weight.[22] Potential CV side effects were investigated in a separate analysis of this trial.[126] Tachycardia was significantly more common in the sibutramine group but did not lead to

increased drug withdrawal. Medication was stopped for BP in 1 percent of subjects in the sibutramine group versus none in the placebo group. After 1 year, systolic and diastolic BPs and heart rates were decreased from baseline in both intervention and control subjects, with no significant difference between groups.[22,126] In one small trial, 9 of 43 subjects on sibutramine had medication decreased or stopped for an increase in BP, heart rate, or both, above a prespecified threshold.[127] A third small trial (N = 46) did not report stopping sibutramine for BP or heart rate in any subject.[128] Sibutramine was withdrawn from the U.S. market on October 8, 2010. This withdrawal was due to a 16-percent increase in risk of major CV adverse events demonstrated in the Sibutramine Cardiovascular Outcomes trial in adults: a composite of nonfatal myocardial infarction, nonfatal stroke, resuscitation after cardiac arrest and CV death.[129]

A single study of hospitalized adolescents with severe elevation of BMI (all greater than 35 kg/m^2) treated with fenfluramine showed no advantage over diet alone.[130]

Recent studies have examined adolescents receiving bariatric surgery.[131,132] One examined nationwide use of bariatric surgery in adults and adolescents, concluding that bariatric surgery in adolescents is uncommon compared with use in adults. There were 771 bariatric procedures performed in the United States in 2003, triple the number performed in 2000; 12 percent of adolescents receiving the surgery had comorbid conditions.[131] The other study was a case series (N = 38) examining outcomes from bariatric surgery in adolescents; mean preoperative BMI was 60 +/- 8 kg/m^2 compared with 40 +/- 8 kg/m^2 at a mean followup of 10 months. The study found significant improvements in CV measures on postoperative followup.[132] Generally, bariatric procedures have been performed in academic centers as part of research protocols. There are no long-term data on followup after bariatric surgery in adolescents.

CONCLUSIONS AND GRADING OF THE EVIDENCE REVIEW ON TREATMENT OF OBESITY

- There is good evidence for the effectiveness of combined weight loss programs that included behavior change counseling, negative energy balance through diet, and increased physical activity in addressing obesity in children older than age 6 years with a BMI at or greater than 95th percentile and no comorbidities (Grade A). However, such programs have primarily been shown to be effective in a comprehensive weight loss program or research settings, with only a small number shown to be effective in primary care settings.

- No data were identified on weight loss programs for children younger than age 6 years.

- No single negative energy diet plan was identified from the evidence review. Dietary plans should be determined for each child, based on baseline body size, energy requirements for growth, and physical activity level (Grade D).

- Increasing dietary fiber from corn bran, wheat flour, wheat bran, oat flakes, corn germ meal, or glucomannan does not significantly improve weight loss (Grade A).

- Various diets have been inadequately studied as to their effects on obesity in children and adolescents, including low glycemic-load diets, low-carbohydrate diets, fiber supplements, and protein-sparing modified fasts.

- For children ages 6–12 years:

- Family-based programs in research settings have been shown to be effective at initiating and sustaining weight loss over a followup of 10 years (Grade A).
- The greatest weight loss is achieved when parents are the focus of the intervention (Grade A).

- For adolescents:
  - Comprehensive programs in research settings were effective at achieving weight loss in the short term (Grade A).
  - The greatest weight change was achieved when the adolescent was the primary focus of the intervention (Grade B).
  - Behavior change programs that involved peers achieved more sustained weight loss (Grade B).

- In overweight and obese youth, the combination of diet and a specific physical activity intervention that reduced sedentary activity and/or increased physical activity was universally more effective at achieving decreases in weight and BMI, as well as decreases in body fat compared with an isolated diet intervention:
  - In both children and adolescents, exercise training improved weight loss and body composition (decreasing fat mass and reducing visceral fat), decreased IR, reduced BP, normalized dyslipidemia, and normalized subclinical measures of atherosclerosis (Grade A).
  - In children ages 7–12 years, reduction in sedentary activity, independent of increasing physical activity, produced weight loss (Grade B). In this age group, reductions in sedentary activity were effectively accomplished by rewarding children for time spent being physically active with TV viewing time (Grade B).

- Girls did not respond as well as boys to combined treatments that both reduced sedentary behaviors and increased physical activity (Grade B).

- For adolescents with or without significant comorbidities, with a BMI greater than or equal to the 95th percentile and for adolescents with a BMI greater than 35 kg/m^2 who have failed a comprehensive lifestyle weight loss program, addition of medication under the care of a physician experienced in managing weight loss with medication can be safe and effective in achieving weight loss with followup of 4–12 months. However, long-term safety and efficacy data are not available:
  - In adolescents with severe obesity and IR, the addition of metformin to a comprehensive lifestyle weight loss program improved fasting insulin and significantly reduced weight and BMI (Grade B). (metformin is currently approved by the U.S. Food and Drug Administration (FDA) for pediatric patients ages 10 years and older with T2DM but is not approved for weight loss for either children or adults.)
  - For obese adolescents older than age 12 years, the addition of orlistat to a comprehensive lifestyle weight loss program improved weight loss and BMI (Grade A); however, use of this medication had a high rate of gastrointestinal side effects. Orlistat (under the trade name xenical) is approved by the FDA for weight loss in pediatric patients ages 12 years and older in conjunction with a reduced calorie diet. In August 2009, the FDA released an early communication about an ongoing safety review regarding reports of liver-related adverse events in some patients taking orlistat. In May 2010, the orlistat labeling was updated to incorporate safety information pertaining to the occurrence of rare postmarketing

cases of severe liver injury, including hepatic failure resulting in liver transplant or death.

- Dropout rates are substantial for all weight treatment programs.

- No studies defining an appropriate rate for weight loss in any age group were identified by the Guidelines evidence review. The 2010 *DGA* recommends slowing weight gain while allowing normal growth and development. For those with BMI greater than or equal to the 95th percentile without comorbidities, both the AMA/CDC/MCHB Expert Committee and the American Academy of Pediatrics (AAP) recommend weight maintenance resulting in decreasing BMI as age increases. With BMI greater than or equal to the 95th percentile with comorbidities, the AMA/CDC/MCHB Expert Committee and the AAP recommend gradual weight loss not exceeding 1 pound per month in children ages 2–11 years or 2 pounds per week in adolescents (no grade).

- For adolescents with BMI far above 35 kg/m^2 and associated comorbidities, bariatric surgery on a research protocol, in conjunction with a comprehensive lifestyle weight loss program, improved weight loss, BMI, and other outcomes—such as IR, glucose tolerance, and CV measures—in a small case series (Grade D).

Table 10–1. Evidence-Based Recommendations for Management of Child and Adolescent Patients With Overweight and Obesity

Grades reflect the findings of the evidence review.
Recommendation levels reflect the consensus opinion of the Expert Panel.

Birth–24 months	No weight-for-height specific recommendations CHILD 1 diet (Section V. Nutrition and Diet) is recommended for pediatric care providers to use with their child and adolescent patients to reduce cardiovascular risk	
2–5 years	Identify children at high risk for obesity because of parental obesity and excessive BMI increase→ Focused CHILD 1 diet and physical activity education BMI percentile stable→ Reinforce current program, followup in 6 months Increasing BMI percentile→ Registered dietitian (RD) counseling for energy balanced diet, intensify physical activity change; 6-month followup	Grade B *Recommend*
	BMI 85th to <95th percentile: Excess weight gain prevention with parents as focus for energy-balanced diet; reinforce physical activity recommendations x 6 months • Improvement in BMI percentile→ Continue current program • Increasing BMI percentile→ RD counseling for energy-balanced diet; intensify physical activity recommendations; 6-month followup	Grade D *Recommend*
	BMI ≥95th percentile: Specific assessment for comorbidities* Family-based weight gain prevention with parents as focus; RD counseling and followup for energy-balanced diet; moderate-to-vigorous physical activity (MVPA) prescription; limit sedentary screen time; 3-month followup	Grade B *Strongly recommend* Grade B *Recommend*

6–11 years	Identify children at increased risk for obesity because of parental obesity, change in physical activity +/- excessive gain in BMI for focused CHILD 1 diet/physical activity education • BMI percentile stable→ Reinforce current program, 6-month followup • Increasing BMI percentile→ RD counseling for energy-balanced CHILD 1 diet, intensified physical activity, 3-month followup	Grade B *Recommend*
	BMI 85th - <95th percentile: Excessive weight gain prevention with parents as focus for energy-balanced diet; reinforce physical activity recommendations; 6-month followup • Stable/improving BMI percentile→ Reinforce current program, 6-month followup • Increasing BMI percentile→ RD counseling for energy-balanced CHILD 1 diet, intensified physical activity recommendations, 3-month followup	Grade D *Recommend*
	BMI ≥95th percentile: Specific assessment for comorbidities*	Grade B *Strongly recommend*
	BMI ≥95th percentile with no comorbidities: Office-based weight loss plan: Family-centered program with parents as focus for behavior modification, (-) energy balance diet counseling by RD, prescription for increased MVPA, decreased sedentary time x 6 months • Improvement in BMI percentile, comorbidities→ Continue current plan • No improvement in BMI percentile→ Referral to comprehensive multidisciplinary lifestyle weight loss program	Grade A *Strongly recommend*
	BMI ≥95th percentile with comorbidities, BMI ≥ 97th percentile, or progressive rise in BMI despite therapy: Refer to comprehensive multidisciplinary weight loss program for intensive management x 6 months • Improvement in BMI percentile→ Continue present program • No improvement in BMI percentile→ Consider referral to another comprehensive multidisciplinary weight loss program	Grade A *Strongly recommend*

12–21 years	Identify adolescents at increased risk for obesity because of parental obesity, change in physical activity +/- excess gain in BMI for focused diet/physical activity education x 6 months • BMI/BMI percentile stable→ Reinforce current program, 6-month followup • Increasing BMI/BMI percentile→ RD counseling for energy-balanced CHILD 1 diet, intensified physical activity x 3 months	Grade B *Recommend*
	BMI 85th - <95th percentile: Excess weight gain prevention with adolescent as change agent for energy-balanced, CHILD 1 diet, reinforced physical activity recommendations x 6 months • Improvement in BMI percentile→ Continue current program • Increasing BMI percentile→ RD counseling for energy-balanced weight control diet, intensified physical activity, 3-month followup	Grade B *Recommend*
	BMI ≥95th percentile: Specific assessment for comorbidities*	Grade B *Strongly recommend*
	BMI ≥95th percentile with no comorbidities: Office-based weight loss plan: Family-centered with adolescent as change agent for behavior modification counseling, RD counseling for (-) energy-balanced diet, prescription for increased MVPA, decreased sedentary time x 6 months • Improvement in BMI/BMI percentile→ Continue current program • No improvement in BMI/BMI percentile→ Referral to comprehensive multidisciplinary weight loss program with peers • No improvement in BMI/BMI percentile→ Consider initiation of medication (orlistat) under care of experienced M.D. x 6–12 months	Grade B *Strongly recommend*

	BMI ≥95th percentile with comorbidities or BMI >35 kg/m^2: Refer to comprehensive lifestyle weight loss program for intensive management x 6–12 months • Improvement in BMI/BMI percentile→ Continue present program • No improvement in BMI/BMI percentile→ Consider initiation of orlistat under care of experienced clinician x 6–12 months • BMI far above 35 kg/m^2 and comorbidities unresponsive to lifestyle therapy for >1 year→ Consider bariatric surgery/referral to center with experience/expertise in procedures	Grade A *Strongly recommend*
* Comorbidities: Hypertension, dyslipidemia, type 2 diabetes mellitus (T2DM)		

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11. DIABETES MELLITUS AND OTHER CONDITIONS PREDISPOSING TO THE DEVELOPMENT OF ACCELERATED ATHEROSCLEROSIS

INTRODUCTION

This section of the Guidelines provides recommendations for pediatric care providers on managing cardiovascular (CV) risk factors in children and adolescents with diabetes mellitus and other conditions that predispose them to accelerated atherosclerosis. The evidence review did not address management of hyperglycemia, and this is not addressed in the recommendations. The section begins with background information on the importance of diabetes as a risk factor for CV disease (CVD). This is followed by the Expert Panel's summary of the evidence review relative to diabetes, separated for type 1 and type 2 diabetes mellitus, and then by a subsection on other predisposing conditions. The evidence review and the development process for the Guidelines are outlined in the Section I. Introduction and are described in detail in Appendix A. Methodology. As described, the evidence review augments a standard systematic review, where the findings from the studies reviewed constitute the only basis for recommendations, with each study described in detail. This evidence review combines a systematic review with an Expert Panel consensus process that incorporates and grades the quality of all relevant evidence based on preidentified criteria. Because of the diverse nature of the evidence, the Expert Panel provides a critical overview of the studies reviewed for each risk factor. Detailed information from each study has been extracted into the evidence tables, which will be available at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. Following its review of the limited available evidence for this subject, the Expert Panel elected to employ expert opinion by expanding on the recommendations of the 2006 guidelines from the American Heart

Association (AHA),[1] which addressed CV risk management in high-risk pediatric patients, including those with diabetes. This approach is described in detail in this section, relative to the management of other conditions predisposing to the development of accelerated atherosclerosis. References are listed sequentially at the end of the section, with references from the evidence review identified by unique PubMed identifier (PMID) number in bold text. Additional references do not include the PMID number.

BACKGROUND

Diabetes mellitus is an established risk factor for early CVD. Metabolically, diabetes is characterized by hyperglycemia due to defects in insulin secretion (type 1 diabetes mellitus (T1DM)) and insulin function and/or secretion (type 2 diabetes mellitus (T2DM)). Both T1DM and T2DM are associated with vascular disease.[2,3,4] Autopsy and noninvasive imaging studies suggest that the extent of vascular involvement may reflect the duration of the disease and the severity of the chronic metabolic derangement.[5,6,7,8,9,10] The epidemiologies of the two types differ significantly. T1DM presents at a younger age, with 25 percent of patients diagnosed between ages 5 and 10 years and another 40 percent between ages 10 and 15 years. If not treated adequately, the degree of hyperglycemia is severe, and patients are highly symptomatic. By contrast, in T2DM, the majority of patients present in adult life, but a small and growing number present in adolescence, and most are relatively asymptomatic, with only mild to moderate hyperglycemia in combination with obesity.[11,12]

OVERVIEW OF THE EVIDENCE FOR TYPE 1 DIABETES MELLITUS

In adults with T1DM, clinical heart disease, cerebrovascular disease, and peripheral vascular disease represent the most common causes of morbidity and mortality.[13] Children with T1DM

have been shown to have pathologic vascular changes in the form of microangiopathy in the eye and the kidney and subclinical evidence of atherosclerosis, with increased carotid intima-media thickness, reduced endothelium-dependent arterial flow-mediated dilation (FMD), and increased arterial stiffness.[10,14,15,16,17,18] Recent studies of youth with T1DM demonstrate that between one-fourth and three-fourths of subjects have at least one CV risk factor.[19,20] Unfortunately, few are prescribed treatment directed at these abnormalities.[21] Although obesity appears to be related to CV risk in T1DM patients, hyperglycemia drives the production of advanced glycolation end products, which are the primary mediators of the vascular process.[22,23] The Diabetes Control and Complications Trial in T1DM patients aged 13–39 years found that intensive glycemia control reduced microvascular outcomes and, in an observational followup period, found lower rates of CVD events in those previously treated intensively for glycemia.[24,25] Therefore, glucose management should be intensive in T1DM, under the care of an endocrine specialist. In evaluating the risk for CVD in adults, the presence of diabetes is considered to be the equivalent of a history of coronary disease.[26] Management of other risk factors related to T1DM should be aggressive, with the cut points marking effective therapy mandating intensive risk reduction.[27]

The evidence review for these Guidelines was designed to identify systematic reviews, meta-analyses, randomized controlled trials (RCTs), and observational studies from selected large longitudinal cohorts. The evidence review identified only two RCTs relevant to T1DM that met the inclusion criterion of having CV outcomes. A randomized crossover trial in a small number of children with T1DM showed a decline in diastolic blood pressure during sleep with melatonin therapy.[28] The authors propose that melatonin be considered in trials to prevent the development of hypertension in individuals with T1DM. In children with T1DM, administration of folate and vitamin B6 each led to immediate normalization of FMD, which

was sustained at 8-week followup.[29] Findings suggest that, in the setting of T1DM with a high risk for vascular disease, folate and B6 therapy could be beneficial, but the findings in these two trials have not been duplicated.

OVERVIEW OF THE EVIDENCE FOR TYPE 2 DIABETES MELLITUS

The incidence of T2DM has increased in parallel with the increased incidence of obesity.[11,12] The highest prevalence of T2DM is seen in certain racial/ethnic groups, specifically Native Americans, Hispanics, African Americans, Asians, and Pacific Islanders. The hallmark of T2DM is insulin resistance, which is strongly associated with obesity.[30] Among obese adolescents, insulin resistance has been reported in 16 percent of Caucasians, 27 percent of African Americans, and 26 percent of Hispanics. Although type 2 diabetes is widely diagnosed in adults, its frequency has markedly increased in the pediatric age group over the past two decades. Depending on the population studied, type 2 diabetes now represents 8–45 percent of all new cases of diabetes reported among children and adolescents.[31] Typically, children with T2DM are overweight or obese, are members of a high-risk racial/ethnic group, and have a positive family history of T2DM. Current guidelines from the American Diabetes Association (ADA) recommend routine testing for T2DM in high-risk children starting at age 10 years, as shown in Table 11–1.[32]

Table 11–1. ADA Screening Recommendations for Type 2 Diabetes Mellitus (T2DM) in Childhood

Criteria:
• Overweight, defined by:
– BMI ≥85th percentile for age and gender, OR
– Weight for height ≥85th percentile, OR
– Weight >120 percent of ideal for height
Plus any two of the following risk factors:

• Family history of T2DM in first- or second-degree relative
• Race/ethnicity (Native American, African American, Latino, Asian, Pacific Islander)
• Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome)

Screening procedure:

Age of initiation:

≥10 years, or at onset of puberty, if puberty occurs at a younger age

Frequency:

Every 2 years

Test:

Fasting plasma glucose

Patients with T2DM are at risk for accelerated atherosclerosis because of hyperinsulinemia and hyperglycemia and because of the strong association between T2DM and other major risk factors for CVD, including obesity, hypertension, and dyslipidemia.[31,33,34,35,36] As with T1DM, control of hyperglycemia in T2DM is mandatory and should be in a setting where consultation with an endocrine specialist is possible if needed. No recommendations for managing hyperglycemia are provided here. Aggressive management of associated CV risk factors has been shown to improve vascular outcomes.[37,38,39] On the other hand, aggressive control of glycemia in T2DM has not been shown to reduce CVD events in adults with well-established and long-duration disease.[40,41,42,43] In evaluating the risk for CVD in adults, the presence of diabetes is considered to be the equivalent of a history of coronary disease.[26]

The evidence review for these Guidelines identified only two studies relevant to CV risk reduction in children or adolescents with T2DM . A single systematic review addressing community-based lifestyle interventions to prevent T2DM in children included eight studies published between 1990 and 2001.[44] The interventions were all set in high-risk populations,

and design problems included the absence of comparison groups and brief intervention periods. On short-term followup, results indicated improvements only in knowledge and preventive behaviors. An RCT of metformin in children with T2DM showed significant improvements in glycemic control with medication at up to 16-week followup.[45]

OVERVIEW OF THE EVIDENCE REVIEW FOR OTHER PREDISPOSING CONDITIONS

In certain pediatric disease states, the process of atherosclerosis is dramatically accelerated, with clinical coronary events occurring in childhood and in early adulthood. Probably the best example of this is homozygous familial hypercholesterolemia, an extremely rare condition in which low-density lipoprotein cholesterol (LDL–C) levels are markedly elevated from birth due to the absence or near absence of functional hepatic LDL receptors. In this diagnosis, clinical coronary events begin in the first decade of life, and aggressive lipid management is needed. For these Guidelines, management of hypercholesterolemia is described in Section IX. Lipids and Lipoproteins. Diabetes, another high-risk diagnosis, is addressed above, but there are other conditions in which the risk of accelerated atherosclerosis is known to be high, that are not necessarily identified in a risk factor-based evidence review such as the one preformed for these Guidelines.

The Expert Panel recognized the importance of reviewing the evidence for these conditions so that appropriate recommendations could be made to guide pediatric practice. A separate category was created as part of the evidence review that identified potential relevant diagnoses and included Kawasaki disease, postorthotopic heart transplant, chronic kidney disease, nephrotic syndrome, human immunodeficiency virus (HIV) infection, and chronic

inflammatory disease—all of which may increase the risk for early atherosclerosis and may require more aggressive control of CV risk factors. Although data exist demonstrating a higher prevalence of early CVD and CV risk factors in conditions such as these, the evidence review for these Guidelines was designed to identify high-level studies, including systematic reviews, meta-analyses, RCTs, and observational studies from selected large longitudinal cohorts.[46,47] Given the relatively small number of children with these diagnoses and the early stage of knowledge in this area, it is not surprising that the evidence review identified only three relevant RCTs, all in patients with chronic kidney disease.

In the first of these, a small number of children with advanced chronic kidney disease were treated with folic acid and placebo, and red cell folate levels, homocysteine levels, and FMD were compared.[48] On folic acid treatment, red cell folate levels increased, homocysteine levels decreased, and FMD improved significantly. A second similar trial of oral L-arginine from the same investigators showed no improvement in FMD.[49] Finally, a protein restriction trial was shown to result in higher polyunsaturated/saturated fat ratios in the diets of children with chronic kidney disease, with an associated decrease in total and LDL–C compared with a control group on a normal diet.[50] These studies support the concept that risk factors can be changed and that arterial function can be improved in patients with chronic kidney disease.

CONCLUSIONS OF THE EVIDENCE REVIEW FOR DIABETES AND OTHER PREDISPOSING CONDITIONS

Children with T1DM or T2DM represent the prototype of the child at special risk for accelerated atherosclerosis and early clinical CVD. To maximize identification of T2DM in childhood and adolescence, the ADA screening algorithm is recommended for screening in all children (see Table 11–1).

A very limited number of high-quality studies were found addressing CV risk reduction in children with conditions predisposing them to accelerated atherosclerosis, including diabetes mellitus, which is insufficient for development of evidence-based recommendations. The Expert Panel therefore elected to modify the recommendations of an expert pediatric panel convened by the AHA that published its recommendations for risk factor management in children with these conditions in 2006, after an extensive conventional literature search; these recommendations are endorsed by the American Academy of Pediatrics and are included in the database for these Guidelines.[1] These recommendations therefore represent the expert consensus of the Panel (Grade D).

The AHA statement recommends specific risk identification and management stratified by risk based on defined conditions that parallel the recommendations for adults with diabetes or other CVD equivalents (see Table 11–2). For the high-risk category, the disease process has been associated with clinical coronary disease before age 30 years. For the moderate-risk category, the disease process has been shown to be associated with pathologic, physiologic, or subclinical evidence of accelerated atherosclerosis.

The Expert Panel believes that these recommendations should be used for the management of children and adolescents with diabetes and other conditions predisposing to the development of accelerated atherosclerosis, as outlined in the algorithm in Figure 11–1 and in Tables 11–2 and 11–3. With the growing evidence of CVD in children with T2DM, the Expert Panel believes it is prudent to include both T1DM and T2DM in the high-risk category.[51,52] With the increasing evidence of vascular dysfunction in children with HIV[53,54] and treatment-resistant nephrotic syndrome,[55] these two conditions are included in the selected disease settings in the moderate-risk category. Patients in the high-risk category require intensive

management, with more aggressive goals for therapy than those in the moderate-risk category as outlined in the algorithm in Figure 11–1.

Table 11–2. Special Risk Pediatric Conditions: Stratification by Risk Category

High Risk:

Manifest coronary artery disease, ages 30 years and older: Clinical evidence

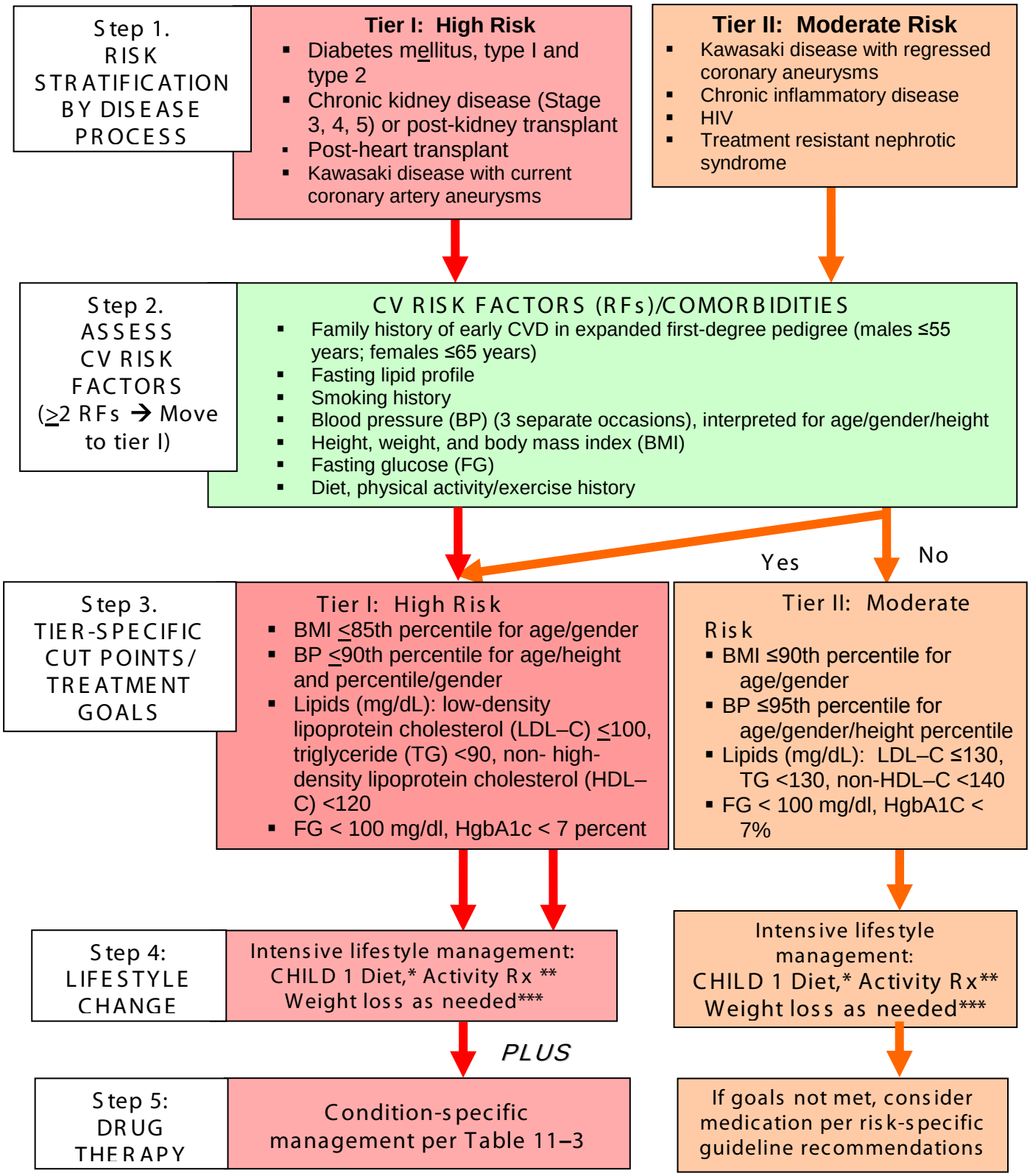
- T1DM or T2DM
- Stage 3, 4, or 5 chronic kidney disease or post renal transplant
- Postorthotopic heart transplantation
- Kawasaki disease with current coronary aneurysms

Moderate Risk:

Accelerated atherosclerosis: Pathophysiologic evidence

- Kawasaki disease with regressed coronary aneurysms
- Chronic inflammatory disease (systemic lupus erythematosus, juvenile rheumatoid arthritis)
- Human immunodeficiency virus infection
- Treatment-resistant nephrotic syndrome

Figure 11–1. Risk-Stratification and Treatment Algorithm for High-Risk Pediatric Conditions



Directions: *Step 1:* Risk stratification by disease process (Table 11–2). *Step 2:* Assess all cardiovascular risk factors. If there are at least comorbidities, move tier II patient to tier I for subsequent management. *Step 3:* Tier-specific treatment goals/cut points defined. *Step 4:* Initial therapy: For tier I, initial management is therapeutic lifestyle change **PLUS** disease-specific management (Table 11–3). For tier II, initial management is therapeutic lifestyle change. *Step 5:* For tier II, if goals are not met, consider medication per risk factor specific recommendations in these Guidelines.

* CHILD 1 (Cardiovascular Health Integrated Lifestyle Diet) per Section 5. Diet and Nutrition. ** Activity Rx–Activity Recommendations per Section 6. Physical Activity. *** Weight loss recommendations per Section 10. Overweight and Obesity.

Table 11–3. Condition-Specific Treatment Recommendations

- Rigorous age-appropriate education in diet, activity, and smoking cessation for all
- Specific therapy as needed to achieve blood pressure (BP), low-density lipoprotein cholesterol (LDL–C), glucose, and HbA1C goals indicated for each tier, as outlined in algorithm; timing individualized for each patient and diagnosis

Diabetes mellitus regardless of type:

- For T1DM, intensive glucose management per endocrinologist with frequent glucose monitoring/insulin titration to maintain optimal plasma glucose and HbA1c for age.
- For T2DM, intensive weight management and glucose control, in consultation with an endocrinologist as needed to maintain optimal plasma glucose and HbA1c for age.
- Assess body mass index (BMI), fasting lipids: Step 4 lifestyle management of weight, lipids for 6 months.
- If LDL goals not achieved, proceed to Step 5; consider statin therapy if age ≥10 years to achieve tier I treatment goals for LDL–C.
- Initial BP ≥90th percentile: Step 4 lifestyle management plus no added salt, increased activity for 6 months.
- BP consistently ≥95th percentile for age/sex/height: Initiate angiotensin-converting enzyme inhibitor therapy with BP goal <90th percentile for sex/height or <120/80, whichever is lower.

Chronic kidney disease (stage 3,4,5) /post renal transplant:

- Optimization of renal failure management with dialysis/transplantation per nephrology.
- Assess BMI, BP, lipids, fasting glucose (FG): Step 4 lifestyle management for 6 months.
- If LDL goals not achieved, proceed to Step 5; consider statin therapy if age ≥10 years to achieve tier I treatment goals for LDL–C.
- BP consistently ≥95th percentile for age/gender/height: Initiate angiotensin-converting enzyme inhibitor therapy with BP goal <90th percentile for gender/height or <120/80, whichever is lower.

After heart transplantation:

- Optimization of antirejection therapy, treatment for cytomegalovirus infection, and routine evaluation by angiography/perfusion imaging per transplant physician.
- Assess BMI, BP, lipids, FG: Initiate Step 5 therapy, including statins, immediately in all patients age ≥1 year to achieve tier I treatment goals.

Kawasaki disease with current coronary aneurysms:

- Antithrombotic therapy, activity restriction, and ongoing myocardial perfusion evaluation per cardiologist.
- Assess BMI, BP, lipids, FG: Step 4 lifestyle management for 6 months.
- If goals not achieved, proceed to Step 5; consider pharmacologic therapy for LDL–C and BP if age ≥10 years to achieve tier I treatment goals.

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12. RISK FACTOR CLUSTERING AND THE METABOLIC SYNDROME

INTRODUCTION

This section of the Guidelines provides recommendations to pediatric care providers on an approach to the metabolic syndrome in children and adolescents. The evidence review and the development process for the Guidelines are outlined in Section I. Introduction and are described in detail in Appendix A. Methodology. This section begins with background information on the prevalence of the risk factor cluster known as the metabolic syndrome. This is followed by the Expert Panel's summary of the evidence review on the metabolic syndrome cluster and its recommendations for management in pediatric practice. The complete evidence tables will be available at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. Because of the paucity of the evidence, recommendations are a consensus of the Expert Panel. References are listed sequentially at the end of the section, with references from the evidence review identified by unique PubMed identifier (PMID) number in bold text. Additional references do not include the PMID number.

BACKGROUND

As in adults, traditional cardiovascular (CV) risk factors—such as obesity, hypertension, and dyslipidemia—demonstrate clustering in youth.[1] Behavioral risk factors—such as smoking, inadequate diet, and sedentary behavior—also demonstrate clustering, as do an advantageous diet and optimal exercise habits.[2,3,4,5,6] Becoming obese increases the prevalence of the risk factor cluster called the metabolic syndrome in adults.[7,8] In the United States, metabolic syndrome is said to affect 34–39 percent of adults,[9] including 7 percent of men and 6 percent of women in the 20- to 30-year-old age group.[10] There are varying definitions of the metabolic syndrome, and the prevalence changes depending on the specific definition used.[11] The National Heart, Lung,

and Blood Institute and the American Heart Association recently examined the various approaches and published a recommended definition of metabolic syndrome in adults, which includes elevated waist circumference, triglyceride (TG), blood pressure (BP), fasting glucose, and reduced high-density lipoprotein cholesterol (HDL–C).[12]

OVERVIEW OF THE EVIDENCE FOR RISK FACTOR CLUSTERING AND THE METABOLIC SYNDROME

There is a lack of consensus on how to define metabolic syndrome in youth, which has led to widely varying estimates of its frequency.[13,14,15,16] A recent analysis of National Health and Nutrition Examination Survey data from 1999 to 2002 yielded prevalence estimates of 2.0–9.4 percent for all teens and 12.4–44.2 percent for obese teens.[17] Regardless of the definition used, the prevalence of the metabolic syndrome risk factor cluster is higher in older children (12 to 14 years old) compared with younger children (8 to 11 years old). A recent consensus statement suggests limiting the definition to youth older than age 10 years.[18] Age-related changes in body size, lipid levels, and BP make it difficult to set rigid pediatric cut points to define metabolic syndrome.[19] Complicating matters further are the observed racial and gender differences in postpubertal lipid and insulin levels, laboratory variation in fasting insulin levels, and the biologic variability in TG levels and BP.[20,21] These factors at least partially explain why one longitudinal school-based study found that nearly half of adolescents designated as having metabolic syndrome failed to retain the diagnosis at 3-year followup, regardless of the definition used.[22]

The specific etiology for metabolic syndrome is unknown; however, it is most likely caused by the expression of various genotypes modified by environmental interactions and mediated through abdominal obesity and insulin resistance.[23] Data pointing to genetic influences include the observation that the metabolic syndrome cluster of risk factors is more common in children with a parental history of type 2 diabetes mellitus (T2DM)[24] or metabolic syndrome[25] and that African

Americans have a significantly higher prevalence of the metabolic syndrome components, beginning at puberty.[26,27] The importance of lifestyle is demonstrated in a recent study showing a significant dose-response relationship between sedentary behavior, measured in hours of screen time per day, and increased odds for the presence of the metabolic syndrome risk factor cluster.[28]

The pathophysiology by which genetic and environmental influences result in the metabolic syndrome is poorly understood. The association of elevated BP with metabolic syndrome may be mediated by a different route than that for dyslipidemia.[29,30] Factor analyses suggest that a metabolic entity (dyslipidemia, obesity) and a hemodynamic factor (elevated BP) may contribute separately to characterization of a given individual as having the full metabolic syndrome phenotype through a shared correlation with hyperinsulinemia/insulin resistance.[31,32] Despite disagreement on a definition, there is evidence that the high population prevalence of obesity in children and adolescents has led to an increased prevalence of clustering of metabolic syndrome risk factors over the past decade.[33] More research is needed in understanding the biologic processes that result in the cluster of risk factors identified as metabolic syndrome in adults.

Data are emerging on the utility of diagnosing the metabolic syndrome in youth as a predictor of future CV disease (CVD). Longitudinal studies of cohorts in which the metabolic syndrome cluster was present in childhood identify an increased incidence of both T2DM and clinical CV events over a followup of 25 years.[34] Many observational studies have focused on the metabolic syndrome and have demonstrated a strong association between obesity in early childhood and subsequent development of the metabolic syndrome constellation in adulthood. Obesity associated with elevated insulin levels from early childhood and the combination of obesity and elevated insulin strongly predicted future metabolic syndrome.[35] When obesity is associated with hypertension in childhood, the risk of future metabolic syndrome is also significantly increased.[36] Waist circumference as a measure of abdominal obesity and BMI in children and adolescents both

predict future development of the metabolic syndrome.[37] Emerging data suggest that use of the metabolic syndrome as a diagnosis in children and adolescents may increase the ability to predict subclinical target organ damage in adulthood.[38,39] Cross-sectional studies of the relationship between metabolic syndrome risk factors and vascular dysfunction in youth are less clear.[40,41,42] Additional longitudinal studies are needed to determine whether metabolic syndrome in childhood predicts CV outcomes beyond that associated with individual risk components.

Treatment of CV risk factor clustering in youth has not been thoroughly evaluated. Maintenance of low levels of CV risk factors starting in childhood is associated with a lower prevalence of end organ damage as assessed by carotid intima-media thickness in adults.[43] Several nonrandomized, single-arm diet and exercise intervention trials show improvement in metabolic syndrome-associated CV risk factors, although all involve small numbers of subjects and limited followup.[44,45,46] A small number of randomized controlled trials (RCTs) address treatment of the metabolic syndrome cluster with medication in obese adolescents with insulin resistance.[47,48,49] All of these RCTs used metformin as an insulin-sensitizing agent, and in each, metformin was associated with greater weight loss, an improvement in endocrine-metabolic measures and some decrease in abdominal fat mass compared with the control group. An additional study was conducted in an entirely Asian population, which limited generalizability, and another was a retrospective chart review. Additional large RCTs with long-term followup in children are needed before insulin-sensitizing agents can be routinely recommended for either treatment of obesity or prevention of diabetes in youth with metabolic syndrome.

RECOMMENDATIONS FOR MANAGEMENT OF RISK FACTOR CLUSTERING AND THE METABOLIC SYNDROME

The metabolic syndrome concept is important because it identifies a common multiple CV risk phenotype in pediatrics. However, the absence of a defined etiology, lack of consensus on definition, and paucity of high-level evidence addressing management in childhood led the Expert Panel to conclude that the metabolic syndrome should not be considered as a separate risk factor in childhood and adolescence. Prevention of the development of obesity is the most important strategy to lower the prevalence of metabolic syndrome in adults, and this appears strongly applicable in childhood. Given the strong relationship of obesity and physical inactivity to the metabolic syndrome and insulin resistance, the Expert Panel makes the following recommendations. Due to the paucity of evidence available, the recommendations are a consensus of the Expert Panel (Grade D).

- Presence of any combination of multiple risk factors should prompt intensification of therapy, with an emphasis on lifestyle modification, which may improve individual metabolic syndrome risk factor levels.
- Presence of obesity should prompt specific evaluation of all other CV risk factors, including family history of premature CVD (Section IV), high BP (Section VIII), dyslipidemia (Section IX), diabetes (Section XI), and tobacco exposure (Section VII).
- Coexistence of obesity with any other major CV risk factor should be recognized by clinicians as a setting in which:
    - ✓ Intensive weight reduction should be initiated per the recommendations in Section X. Overweight and Obesity, along with specific risk factor management, including pharmacologic therapy, as needed, per the risk factor-specific sections in these Guidelines (Section VIII. High Blood Pressure; Section IX. Lipids and Lipoproteins;

Section XI. Diabetes Mellitus and Other Conditions Predisposing to the Development of Accelerated Atherosclerosis; Section VII. Tobacco Exposure).

- ✓ Prompt evaluation for diabetes mellitus, liver function abnormalities, left ventricular hypertrophy, and sleep apnea should be undertaken.

These recommendations are supported by knowledge that CV morbidity has a continuous relationship across the risk distribution spectrum and that youths with multiple borderline risk factors may, in fact, have risk equivalent to an individual with extreme abnormality of a single major risk factor. A patient's presentation like this should lead to intense nutrition and exercise management with close followup, and if lifestyle intervention is unsuccessful, consideration should be given to referral to an endocrine specialist. Table 12–1 provides definitions for levels of metabolic syndrome-associated variables which, when combined, represent significantly increased CV risk.

Table 12–1. Metabolic Syndrome Component Levels for Evaluation of Children with Multiple Risk Factors

Risk Factor			Cut Point	Reference
Obesity	Body mass index		≥85th to <95th percentiles	Centers for Disease Control and Prevention growth charts[50]
	Waist circumference		≥90th to <95th percentiles	National Health and Nutrition Examination Survey[51]
Blood pressure			≥90th to <95th percentiles	*The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents*[52]
Dyslipidemia	High-density lipoprotein cholesterol (HDL–C)		≥40 to ≤45 mg/dL	See Section IX. Lipids and Lipoproteins in these Guidelines for normative values
	Triglycerides	Age 0–9 years	≥75 to <100 mg/dL	
		Age ≥10 years	≥90 to <130 mg/dL	
	Non-HDL–C		≥120 to <140 mg/dL	
Glycemia	Fasting glucose		≥100 to <126 mg/dL	American Diabetes Association screening recommendations[53]
	Fasting insulin (FI)		Elevated FI level—above normal for gender, race, and pubertal status—is considered evidence of insulin resistance.	

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13. PERINATAL FACTORS

INTRODUCTION

This section of the Guidelines provides recommendations to pediatric care providers on management of perinatal factors that predispose children to accelerated atherosclerosis. The section begins with background information on the role of pediatric care providers in perinatal risk exposure and the decision to focus on maternal smoking cessation. This is followed by the Expert Panel's summary of the evidence review. The evidence review and the development process for the Guidelines are outlined in Section I. Introduction and are described in detail in Appendix A. Methodology. As described, the evidence review augments a standard systematic review, whereby the findings from the studies reviewed constitute the only basis for recommendations, with each study described in detail. This evidence review combines a systematic review with an Expert Panel consensus process that incorporates and grades the quality of all relevant data based on preidentified criteria. Because of the large volume of the included studies and the diverse nature of the evidence, the Expert Panel also provides a critical overview of the studies for each risk factor, highlighting those that, in its view, provide the most important information. Detailed information from each study has been extracted into the evidence tables, which will be available at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm. This section ends with the conclusions of the review, grading of the evidence, and the recommendations. Where evidence is inadequate, the recommendations are the consensus opinion of the Expert Panel. References are listed sequentially at the end of the section, with references from the evidence review identified by unique PubMed identifier (PMID) number in bold text. Additional references do not include the PMID number.

BACKGROUND

Increasing evidence links prenatal exposures to adverse health outcomes.[1] Perinatal cardiovascular (CV) risk reduction is an area in which pediatric care providers can be effective since they are often the only physicians that a mother sees between pregnancies. The Expert Panel identified three potential areas for consideration: maternal obesity, choice of neonatal feeding method, and maternal smoking cessation. Maternal obesity is associated with gestational diabetes, higher birth weight, childhood obesity as measured by increased body mass index (BMI), and increased risk of the metabolic syndrome and type 2 diabetes mellitus (T2DM) in offspring.[2,3] However, the Expert Panel could not identify any prepregnancy or postpartum studies addressing maternal obesity in a pediatric health care setting, and more general approaches to preventing or treating obesity in women of reproductive age are beyond the scope of these Guidelines, which are for pediatric care providers. A detailed discussion of childhood obesity is the subject of Section X. Overweight and Obesity. With regard to choice of neonatal feeding method, the CV advantages of breastfeeding as the primary source of nutrition for infants are reviewed in detail in Section V. Nutrition and Diet. The evidence review for this section therefore focuses on maternal smoking cessation.

OVERVIEW OF THE EVIDENCE ON MATERNAL SMOKING CESSATION

Smoking during pregnancy is strongly associated with fetal growth retardation. Epidemiologic studies show that lower birth weight is associated with central adiposity, insulin resistance, hypertension, T2DM, and increased risk of coronary heart disease decades later.[4,5] In most of these studies, lower birth weight probably represents reduced fetal growth rather than shorter gestational duration, although some recent studies suggest that preterm birth also is associated

with these adverse outcomes. Among pregnant women who smoke, the rate of low birth weight increases directly as the number of cigarettes/day increases. Despite decades of knowledge of its adverse health effects, cigarette smoking remains common among women of childbearing age, reported at 22–23 percent in 2000, although rates are lower during pregnancy in the United States and other developed countries. Perhaps paradoxically, maternal smoking during pregnancy is associated with increased rates of subsequent obesity in offspring and, in some studies, elevated blood pressure (BP). A recent meta-analysis of observational studies estimated a pooled odds ratio (OR) of 1.50 (95 percent confidence interval (CI) = 1.36–1.65) of obesity among offspring of mothers who smoked during pregnancy compared with those who did not.[6]

Because pediatric care providers are often the only physicians that a mother sees between pregnancies, these health care professionals have the potential to initiate and support maternal smoking cessation. If successful, such interventions have the potential to reduce not only the harms associated with fetal growth restriction but also the risk of obesity in the next generation. In the evidence review for these Guidelines, there were 2 randomized controlled trials (RCTs) of smoking cessation restricted to the postpartum period, and smoking cessation studies during pregnancy included 3 relevant systematic reviews, 2 meta-analyses, and 11 RCTs. A 2004 comprehensive review by The Cochrane Collaboration included all identifiable smoking cessation trials during pregnancy dating back to 1976. Pooled across 48 trials and including 6 of the 11 RCTs identified by this review, the authors reported that the included interventions resulted in a relative reduction of 6 percent (RR = 0.94, 95 percent CI = 0.93–0.95) in maternal smoking between the intervention and control groups. The subset of 16 trials that provided information on perinatal outcomes showed a mean increase in birth weight of 33 g (95 percent = 11–55 g), along with a reduction in both low-birth-weight babies (pooled relative risk (RR) = 0.81, 95 percent CI = 0.70–0.94) and preterm births (pooled RR = 0.84, 95 percent CI = 0.72–

0.98).[7] Most trials combined pregnancy-specific education, advice, and reinforcement. The authors of the review noted that an intervention that combined rewards with social support used in two trials led to greater smoking reduction than other strategies. In the five trials that included smoking relapse prevention, the authors did not find that interventions prevented women from resuming smoking in late pregnancy (pooled RR = 0.81; 95 percent CI = 0.63–1.04).

Among the five RCTs published after the most recent systematic review, a majority took place in public clinic settings, with one trial extending the intervention to include the pediatric clinic.[8,9,10,11] Results were similar to those in the systematic review, with three of four interventions resulting in a decrease in maternal smoking during pregnancy. No study was associated with sustained cessation in the postpartum period, which also was consistent with the systematic review. One trial set in prenatal clinics addressed smoking cessation in pregnant adolescents using an intervention based on cognitive behavior theory.[12] Subjects were randomized to usual care, the "Fresh Start" or "Fresh Start Plus" intervention programs, with a female friend. Smoking status was assessed by self-report and cotinine levels. At 8 weeks postrandomization, those in the Fresh Start Plus group were significantly more likely to be abstinent than those in the usual care group (OR = 2.106 (0.542, 8.190)); there was no difference between the program alone and either comparison group. However, at 1-year postrandomization, there was no difference in abstinence rates between any of the groups.

Two studies addressed smoking cessation in the postnatal period, with subjects identified via the newborn nursery. The first study in breastfeeding mothers addressed reducing the infant's exposure to passive smoke. Intervention subjects received specific guidance about limiting the infant's exposure to cigarette smoke and a room air cleaner to be placed in the infant's bedroom.[13] Tobacco exposure was assessed by nicotine and cotinine levels in breast milk and in infant urine samples. In both the intervention and usual care groups, women smoked twice

as much at 2 and 5 weeks postdelivery as they did during pregnancy. Infant urinary nicotine and cotinine levels increased over time in both groups, with no significant difference between the groups at 2, 3, or 5 weeks. A much larger study enrolled 2,901 mothers at the first infant postnatal visit to the pediatric clinic.[14] Half of the mothers received the usual advice about limiting smoke exposure at that visit. The other half received specific antismoking guidance at each nonurgent visit in the first 6 months of life, an average of 4 exposures. When babies were age 6 months, there were significantly fewer smokers in the intervention group among both those who had stopped smoking for the pregnancy and those who had continued to smoke. However, this difference was not sustained at 1-year followup.[15]

CONCLUSIONS AND GRADING OF THE EVIDENCE REVIEW ON MATERNAL SMOKING CESSATION

- The Expert Panel finds that strong evidence supports a benefit for interventions directed at maternal smoking cessation during pregnancy (Grade A). Weaker evidence suggests that these interventions do not prevent relapse postpartum. Trials of cessation in the postpartum period, which would be the most applicable to pediatric providers, are limited in number and suggest that for maternal smoking cessation to be sustained, specific continued support in the pediatric care setting is required.

- No smoking cessation interventions reported any adverse effects related to the interventions (no grade).

- The Expert Panel believes that pediatric care providers can play a role in helping mothers remain smoke free or quit smoking in the interpregnancy interval. For most women, this interval extended to the early first trimester of any subsequent pregnancy. The pediatric well-child schedule calls for about 10 visits in the first 2 years of life; since mothers attend most

visits, the pediatric care provider usually sees women in this period more than any other health care professional. Pediatric care providers often have a sustained relationship with mother and baby, and many already advocate for parental smoking cessation in their efforts to promote a smoke-free environment for children. Pediatric providers and/or their staffs need to be trained to either deliver or refer to a long-term maternal smoking cessation program (no grade).

Table 13–1. Evidence-Based Recommendations for Maternal Smoking Cessation

Grades reflect the findings of the evidence review.
Recommendation levels reflect the consensus opinion of the Expert Panel.
Supportive actions represent expert consensus suggestions from the Expert Panel provided to support implementation of the recommendations.

Smoking cessation guidance during pregnancy is strongly advised. Grade A
Strongly recommend

Supportive actions:

Pediatric care providers should be provided with appropriate training and materials to deliver, or refer to, a smoking cessation program in the postpartum period for all smoking women of childbearing age.

This intervention should be linked to ongoing smoke-free home recommendations directed at all young mothers and fathers, as described in Section VII. Tobacco Exposure.

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14. INFLAMMATORY MARKERS

Because inflammation is an important part of the atherosclerotic process in adults, it was included as an independent risk factor for the evidence review, with specific inflammatory markers identified as outcome measures, as outlined in Appendix A. Methodology. No systematic reviews, meta-analyses, or randomized controlled trials (RCTs) that addressed inflammation in children or adolescents were identified. A small number of RCTs and observational studies included measurement of selected inflammatory markers, and these were reviewed. The Expert Panel concluded that the available evidence was not sufficient either to make any statement regarding the role of inflammation in atherosclerosis, as assessed by measurement of inflammatory markers in childhood, or to include any recommendation regarding measurement of inflammatory markers in the pediatric age group.

15. INTEGRATED CARDIOVASCULAR HEALTH SCHEDULE*

Risk factor	Age					
	Birth–12 m	**1–4 y**	**5–9 y**	**9–11 y**	**12–17 y**	**18–21 y**
Family history (FHx) of early CVD		At age 3 y, evaluate FHx for early CVD: parents, grandparents, aunts/uncles, M ≤ 55 y, F ≤ 65 y. Review with parents, refer prn. (+) FHx identifies children for intensive CV RF attention.	Update at each nonurgent health encounter.	Reevaluate FHx for early CVD in parents, grandparents, aunts/uncles, M ≤ 55 y, and F ≤ 65 y.	Update at each nonurgent health encounter.	Repeat FHx evaluation with patient.
Tobacco exposure	Advise smoke-free home; offer smoking cessation assistance or referral to parents.	Continue active antismoking advice with parents. Offer smoking cessation assistance and referral as needed.	Begin active antismoking advice with child.	Assess smoking status of child. Active antismoking counseling or referral as needed.	Continue active antismoking counseling with patient. Offer smoking cessation assistance or referral as needed.	Reinforce strong antismoking message. Offer smoking cessation assistance or referral as needed.
Nutrition/diet	Support breastfeeding as optimal to age 12 m if possible. Add formula if breastfeeding decreases or stops before age 12 m.	Age 12–24 m, may change to cow's milk with **%** fat per family and pediatric care provider. After age 2 y, fat-free milk for all; juice ≤4 oz/d; transition to CHILD 1* Diet by age 2 y.	Reinforce CHILD 1* diet messages.	Reinforce CHILD 1* diet messages as needed.	Obtain diet information from child and use to reinforce healthy diet and limitations and provide counseling as needed.	Review healthy diet with patient.
Growth, overweight/ obesity	Review FHx for obesity → Discuss wt for ht tracking, growth chart, healthy diet.	Chart ht/wt/BMI → classify wt by BMI from age 2 y; review with parent.	Chart ht/wt/BMI and review with parent. BMI ≥ 85th %ile, crossing %iles, intensify diet/activity focus x 6 m. If no change → RD referral, manage per obesity algorithms. BMI ≥ 95th %ile, manage per obesity algorithms.	Chart ht/wt/BMI and review with parent and child. BMI ≥ 85th %ile, crossing %iles, intensify diet/activity focus x 6 m. If no change → RD referral, manage per obesity algorithms. BMI ≥ 95th %ile, manage per obesity algorithms.	Chart ht/wt/BMI and review with child and parent. BMI ≥ 85th %ile, crossing %iles, intensify diet/activity focus x 6 m. If no change → RD referral, manage per obesity algorithms. BMI ≥ 95th %ile, manage per obesity algorithms.	Review ht/wt/BMI and norms for health with patient. BMI ≥ 85th %ile, crossing %iles, intensify diet/activity focus x 6 m. If no change → RD referral, manage per obesity algorithms. BMI ≥ 95th %ile, manage per obesity algorithms.
Lipids	No routine lipid screening.	Obtain fasting lipid profile only if FHx (+), parent with dyslipidemia, any other RFs (+), or high-risk condition.	Obtain fasting lipid profile only if FHx (+), parent with dyslipidemia, any other RFs (+), or high-risk condition.	Obtain universal lipid screen with nonfasting non-HDL = TC – HDL, or fasting lipid profile → Manage per lipid algorithms as needed.	Obtain fasting lipid profile if FHx (+), parent with dyslipidemia, any other RFs (+), or high-risk condition; manage per lipid algorithms as needed.	Measure nonfasting non-HDL-C or fasting lipid profile in all x 1 → Review with patient; manage with lipid algorithms/ATP as needed.

Risk factor	Age					
	Birth–12 m	**1–4 y**	**5–9 y**	**9–11 y**	**12–17 y**	**18–21 y**
Blood pressure	Measure BP in infants with renal/urologic/ cardiac diagnosis or Hx of neonatal ICU.	Measure annual BP in all from age 3 y; chart for age/gender/ht %ile and review with parent.	Check BP annually and chart for age/gender/ht → Review with parent; work up and/or manage per BP algorithm as needed.	Check BP annually and chart for age/gender/ht → Review with parent, work up and/or manage per BP algorithm as needed.	Check BP annually and chart for age/gender/ht → Review with adolescent and parent, work up and/or manage per BP algorithm as needed.	Measure BP → Review with patient. Evaluate and treat as per *JNC 7 guidelines.*
Physical activity	Encourage parents to model routine activity. No screen time before age 2 y.	Encourage active play; limit sedentary/ screen time to ≤ 2 h/d. No TV in bedroom.	Recommend MVPA ≥ 1h/d; limit screen/sedentary time to ≤ 2 h/d.	Obtain activity Hx from child → recommend MVPA ≥ 1 h/y; screen/ sedentary time ≤ 2 h/d.	Use activity Hx with adolescent to reinforce MVPA ≥ 1 h/d, leisure screen time ≤ 2 h/d.	Discuss lifelong activity, sedentary time limits with patient.
Diabetes				Measure fasting glucose per ADA guidelines, refer to endocrinologist as needed.	Measure fasting glucose per ADA guidelines, refer to endocrinologist as needed.	Obtain fasting glucose if indicated, refer to endocrinologist as needed.

* *The Full and Summary Report of the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents* also may be found on the NHLBI Web site: http://www.nhlbi.nih.gov/

16. IMPLICATIONS OF THE GUIDELINES FOR PUBLIC POLICY, REIMBURSEMENT, MEDICAL EDUCATION, AND RESEARCH

These Guidelines for the reduction of risk of cardiovascular (CV) disease (CVD) in children and adolescents provide an important, up-to-date, evidence-based framework for implementation in primary care offices and in specialty referral programs for higher risk patients. We anticipate that clinical implementation will result in the improvement of CV health in children and adolescents, but the Expert Panel recognizes that releasing clinical guidelines will not be sufficient to optimize CV health in children. From the standpoint of population health, most CV events occur in individuals with moderate risk rather than in those with extreme risk; therefore, physician-based, high-risk targeted approaches will not be sufficient to control the CVD epidemic. Environmental factors strongly influence risk. The home environment, built environment, food industry, media, advertising, tax structure, schools, and cultural differences all influence the adoption and maintenance of behaviors related to CV health. Insufficient numbers of registered dietitians and other health care providers, such as physician assistants and nurses with training in pediatrics, inadequate resources for the comprehensive management of obesity, and inadequate reimbursement for preventive services will all hamper efforts by health care providers to implement guidelines in the clinical setting.

A public policy agenda is needed to support these clinical care recommendations. Cardiovascular health promotion and low risk of CVD should be normative in society. Public health policies should include (1) support for improved availability and affordability of fruits and vegetables, whole-grain foods, and low-fat dairy products; (2) restriction of food advertisements of unhealthy foods aimed at children; (3) support of a healthier built environment, including aspects that promote family activity and diminish sedentary time;

(4) increased taxes on and increased cost of tobacco products; and (5) support of clean indoor air legislation. In schools, health behaviors should be taught routinely, and the food and physical activity environments should be consistent with recommended health behaviors. Examples include routine availability of high-quality fruits and vegetables, restricted availability of competitive energy-dense and high-salt foods, inclusion of 60 minutes of moderate-to-vigorous physical activity in every school day, and inclusion of education in the fundamentals of nutrition and food preparation in high school curricula.

Marked ethnic and socioeconomic disparities in the risk of CVD begin in childhood and progress through adolescence into adulthood. This fact places a priority on the prevention of these disparities early in life. Public policymakers should better understand and address these ethnic and socioeconomic disparities. Cultural diversity must be better understood as it relates to both CV health and risk. Culturally competent approaches that incorporate healthy behaviors from low-risk populations and limit adverse behaviors from high-risk populations must be developed and implemented. Of particular importance is improvement in educational opportunities for disadvantaged youths, since better education is strongly associated with better health behaviors. Simply translating the messages contained in these Guidelines into various languages will not be sufficient to accomplish this important task.

These Guidelines also have implications for education in medical schools, nursing schools, training programs for registered dietitians, and other relevant health education programs. To achieve a high level of adoption and adherence by families to dietary and physical activity recommendations, a higher skill level in behavioral management and access to skilled dietary counseling will be needed by providers. Without improved medical education concerning effective interventions, successful implementation of

these evidence-based Guidelines is likely to be limited. Given the strong evidence that dietary change has been most effectively accomplished with counseling by registered dietitians, efforts are needed to increase the supply of these skilled professionals.

There are many areas in these Guidelines where more and different types of evidence than currently exist would help in the development of future guidelines. Evidence gaps identified in these Guidelines must be addressed, which will require support from Government funding agencies, industry, and other research support agencies. True promotion of CV health from childhood into adulthood will require the cooperation of all those involved in public policy development, public education, and the training of health care providers. Additional information on evidence-based public health approaches can be found in *The Guide to Community Preventive Services,* which is coordinated by the Centers for Disease Control and Prevention (http://www.thecommunityguide.org/index.html).

APPENDIX A. METHODOLOGY

I. Background

For more than 35 years, the National Heart, Lung, and Blood Institute (NHLBI) has supported the development of clinical guidelines related to reducing cardiovascular (CV) risk. In October 2006, NHLBI Director Elizabeth Nabel, M.D., appointed an Expert Panel to develop an integrated clinical guideline addressing the known pediatric risk factors for the development of atherosclerosis to be used by pediatric care providers in caring for their patients. The goal of the guideline was to make it possible for the known CV risk factors to be identified and managed as part of routine pediatric care. The Expert Panel was chaired by Stephen R. Daniels, M.D., Ph.D., and included representatives from the medical specialties of pediatrics, family medicine, internal medicine, nutrition, epidemiology, and nursing—from both academic medicine and private practice. Previous NHLBI-supported CV risk-reduction guidelines for hypertension and cholesterol in children and adolescents were developed by expert panel consensus based on a traditional literature review and dealt with a single clinical topic. These guidelines differed in that a formal systematic review (SR) of the evidence initiated the process of recommendation development.

The goal of this panel was defined as development of a comprehensive evidence-based guideline addressing all of the major risk factors to assist pediatric care providers in both the promotion of CV health and the identification and management of specific risk factors from infancy into young adult life. From the outset, the panel realized that an innovative approach to the evidence review and to the guideline development process would be

needed to develop the required comprehensive integrated product for the following reasons:

- A focus on CV risk reduction in children and adolescents addresses a disease process—atherosclerosis—in which the clinical end point of manifest cardiovascular disease (CVD) is remote. The recommendations would therefore need to address two different goals: the prevention of risk factor development (i.e., primordial prevention) and the prevention of future CVD by effective management of identified risk factors (i.e., primary prevention).

- A traditional systematic evidence-based-medicine review deals with a single, finite question; the rigorous review process usually results in only a handful of articles for inclusion; only randomized controlled trials (RCTs), SRs, and meta-analyses (MAs) of RCTs published over a defined time period are usually included, and there is a defined format for abstraction of studies, grading of the evidence, and presentation of results. By contrast, this evidence review needed to deal with many questions, each addressing multiple risk factors over a time span extending from birth to age 21 years during which enormous physiologic changes occur; studies with followup into adult life would need to be included. Thus, the evidence review would be extensive, and the review process complex.

- Because of known gaps in the evidence base relating risk factors and risk reduction in childhood to clinical events in adult life, the review must include evidence informing the evaluation and treatment of risk factors in childhood, and there must be explicit Expert Panel involvement in the evidence review process.

The panel defined 14 critical questions for the search and the risk factors to be addressed, as detailed below. Questions 1–9 address the development of atherosclerosis relative to the presence and intensity of the risk factors in childhood and adolescence; the first phase of the evidence review was based on these. Questions 10–14 assess the evidence for the safety and efficacy of reduction of each risk factor and the impact of risk factor change on the atherosclerotic process; the second phase of the review was based on these.

Two additional types of studies were considered in addition to the classic schema of RCTs, SRs, and MAs to provide evidence related to the development of atherosclerosis. Longitudinal observational studies were included to examine the tracking of risk factors from youth into adulthood and the relationship of risk factors in youth to the development of atherosclerosis. The Expert Panel selected 12 major epidemiologic studies for this part of the review, which are detailed below. Natural history studies of genetic disorders known to alter CV risk status were included to provide models of the consequences of prolonged risk exposure or risk protection.

After the establishment of the Expert Panel, seven subcommittees were formed to focus on particular aspects of the Guidelines, with several Expert Panel members participating on more than one subcommittee. In addition, two oversight committees were formed: a Science Team to ensure the scientific quality of the process and a Clinical Team to maintain the relevance of the recommendations to clinical practice throughout the Guidelines development process. The primary work occurred at the subcommittee level, with oversight by the full Expert Panel and coordination by NHLBI staff. The Expert Panel developed these Guidelines and report in the following steps:

- Framing the scope of and conducting the systematic literature review.
- Reviewing abstracts and full text of retrieved studies to identify relevant studies for inclusion.
- Selecting outcome variables to be recorded and compiling the data from included studies into evidence tables.
- Evaluating the quality of individual studies and assigning grades to each study; the process for this is described below.
- Critically reviewing and summarizing the content of the evidence tables.
- Identifying pertinent findings from the evidence review.
- Formulating draft recommendations for potential use in routine pediatric practice.
- Reaching consensus within the Expert Panel subcommittees and the full Expert Panel regarding final recommendations; the consensus process is described below.
- Developing grades for each recommendation based on the body of evidence reviewed.
- Developing supporting report text and graphics.
- Circulating a draft of the Guidelines and report for multiple levels of external review, including a public comment period.
- Preparing the final Guidelines and report for dissemination.

As can be easily appreciated, this is a modified evidence review process that combines the methodology of a traditional review with the explicit involvement of an Expert Panel. The following sections provide more detail regarding each of these steps, including the methodology used to conduct the systematic literature review and the process employed to translate the findings of this review into the Guidelines' recommendations.

II. Systematic Evidence Review

A. Scope of Review

The foundation of the systematic evidence review performed in support of the guideline development process was a series of critical questions related to CVD risk and prevention in youth. The questions encompassed defined risk factors, predefined outcome measures for each risk factor, and, most importantly, measures of CVD and target organ damage (TOD). Each of these elements was developed and refined through a review of the existing evidence by the Expert Panel.

- ***Critical questions.*** The critical questions (Table A–1) framed the search strategy for evidence to support the Expert Panel deliberations during the Guidelines development process. These questions pertained to the etiology and progression of the atherosclerotic process—spanning the prenatal period into young adult life—and the identification, treatment, and prevention of risk factors for CVD over that same time period. Within these areas, the critical questions considered multiple risk factors, the relationship of risk factors to measures of atherosclerosis, TOD and CVD, and risk factor reduction to delay the progression of atherosclerosis and the risk of future clinical CVD.

Table A–1. Critical Questions

	Critical questions
Q1	What is the evidence that atherosclerosis and/or atherosclerosis-related target organ damage begins in childhood?
Q2	What is the evidence that the presence of risk factor(s) in childhood affects the development and/or progression (i.e., initiation and/or acceleration) of atherosclerosis and atherosclerosis-related target organ damage during childhood?
Q3	What is the evidence that the presence of risk factor(s) in childhood affects the progression of atherosclerosis and atherosclerosis-related target organ damage in adult life?
Q4	What is the evidence that indicates the relative importance of each risk factor in the development and/or progression (i.e., initiation and/or acceleration) of atherosclerosis and atherosclerosis-related target organ damage in childhood?
Q5	What is the evidence that racial or ethnic background, geographic region, or socioeconomic status affect cardiovascular risk factor status in childhood/adolescence?
Q6	What is the evidence that risk factors cluster in childhood?
Q7	What is the evidence that risk factor clustering is consistent in childhood?
Q8	What is the evidence that risk factors present in childhood persist (i.e., track) into adult life?
Q9	What is the evidence that an increase in the number and/or intensity of risk factors in childhood alters the development and/or progression (i.e., initiation and/or acceleration) of atherosclerosis and atherosclerosis-related target organ damage in childhood?
Q10	What is the evidence that risk factor(s) in children can be decreased?
Q11	What is the evidence that a decrease in risk factor(s) in childhood can be sustained?
Q12	What is the evidence that a decrease in risk factor(s) in childhood alters: a) the development and progression of atherosclerosis and atherosclerosis-related target organ damage in childhood? b) the development and progression of atherosclerosis and atherosclerosis-related target organ damage in adult life? c) the development of clinical cardiovascular disease in adult life?
Q13	What is the evidence that acquisition of risk factors or risk behaviors can be prevented in children and adolescents?
Q14	What is the evidence that preservation of a low-risk state from childhood, adolescence, or young adult life into later adult life is associated with: a) decreased development/progression of atherosclerosis and atherosclerosis-related target organ damage? b) decreased incidence of clinical cardiovascular disease?

- ***Risk factors*.** A set of 14 risk factors (Table A–2) for CVD further defined the search for and organization of the relevant body of evidence.

Table A–2. Risk Factors for Cardiovascular Disease

	Risk factor category
RF1	Family history of cardiovascular disease
RF2	Sex/gender
RF3	Age/duration of risk exposure
RF4	Blood pressure
RF5	Blood lipids
RF6	Diabetes mellitus
RF7	Inflammation/inflammatory markers
RF8	Obesity
RF9	Diet/nutrition
RF10	Tobacco exposure
RF11	Physical activity/sedentary behavior
RF12	Other predisposing conditions
RF13	Prenatal/maternal risk factors
RF14	Metabolic syndrome/insulin resistance

- ***In-scope outcome measures for each risk factor*.** A list of relevant end points or outcome measures was developed for each risk factor. The number of outcome measures varied according to risk factor and ranged from as few as 2 (for blood pressure (BP)) to as many as 17 (for diet/nutrition). Table A–8—shown in the Methodology: Additional Tables subsection—provides a complete list of in-scope outcome measures by risk factor. Risk factor studies that did not report assessing at least one of these outcomes and/or did not meet other inclusion criteria as specified in Table A–8 were excluded from further analysis.

- ***Cardiovascular disease or target organ damage*.** In addition to these risk factors, outcomes related to CVD and measures of TOD were considered to be in scope.

To facilitate review, each study was categorized according to whether it addressed atherosclerosis or clinical CVD. Those that addressed atherosclerosis were further categorized according to whether they assessed measures of TOD, including left ventricular mass or subclinical measures of atherosclerosis—including coronary calcium/calcification, carotid intima-media thickness, flow-mediated endothelium-dependent arterial dilation, or arterial distensibility.

To inform the identification of studies related to the critical questions, the Expert Panel held an inservice training with the contractor staff members who would be involved in overseeing the literature review to initiate the evidence review process. In addition, a series of group training sessions was held with the contractor staff at appropriate points throughout the process to clarify the scope of the review and expectations for supporting the production of high-quality, evidence-based guidelines.

B. Search Parameters

Based on the critical questions, risk factors, and types of CVD TOD of interest, search parameters were developed to identify published studies relevant to pediatric CV risk reduction. This process involved determining appropriate databases, dates, terms, and limits for the search, as described below.

1. *Databases*

Searches were performed in the following databases:

- **PubMed/MEDLINE.** Administered by the National Library of Medicine, National Institutes of Health (NIH), PubMed is an online interface that allows users to access

more than 17 million citations from MEDLINE and other life science journals published since the 1950s.[1]

- **Cochrane Database of Systematic Reviews.** Part of the Cochrane Library, the Cochrane Database of Systematic Reviews includes more than 3,000 high-quality, independent SRs on a range of clinical topics.[2]
- **National Guideline Clearinghouse (NGC).** An initiative of the U.S. Department of Health and Human Services' (HHS') Agency for Healthcare Research and Quality, the NGC is a comprehensive repository of evidence-based clinical practice guidelines and related documents.[3]

Searches were first conducted in PubMed/MEDLINE. Only unique studies from subsequent searches in the Cochrane database and the NGC were retained for consideration (i.e., those studies that were not already captured in the initial PubMed/MEDLINE search).

In addition to these databases, a preliminary search of EMBASE was conducted. The great majority of studies identified in this preliminary search were also found in the other databases; therefore, it was determined that proceeding with a complete EMBASE search would not contribute significant additional information to the review.

The literature search allowed for further input by the Expert Panel to ensure that in-scope studies were not overlooked. Members of the Expert Panel contributed additional relevant studies based on their routine scanning of the literature. A supplementary literature search was also conducted to identify potentially relevant studies authored by members of the Expert Panel. Additional studies identified by these supplementary methods were included only if they met the same criteria for inclusion established for the primary evidence review.

2. *Search Dates*

Original searches in PubMed/MEDLINE, Cochrane, and the NGC captured studies published between January 1, 1985, and December 31, 2006. Recognizing the timelag inherent in screening a large body of literature and developing evidence tables, the Expert Panel then called for an update of these searches to be conducted for the period between January 1, 2007, and June 30, 2007.

The Expert Panel established June 30, 2007, as the closing publication date for literature to be entered into the evidence review for these Guidelines. The Expert Panel recognized that, given the scope of these Guidelines and the nature of ongoing research in relevant areas, research findings might appear thereafter with the potential to have a material impact on one or more recommendations in the Guidelines. Therefore, to optimize the currency of the Guidelines, the Expert Panel sought, prospectively, to enable consideration of directly relevant, significant peer-reviewed evidence that might appear after the closing date. During a conference call convened on January 21, 2008, the Expert Panel Science Team established the following criteria to guide the full Expert Panel's consideration of studies published after the closing date:

- Any peer-reviewed published study identified by a member of the Expert Panel, as part of his or her routine surveillance of the literature, that is directly relevant to the recommendations of the Expert Panel will be considered for inclusion.
- To be included by the Expert Panel as evidence, the corresponding Risk Factor Team, or the full Expert Panel if applicable at a broader level, must judge that the findings of such recently published studies have the potential for a material impact on the content or strength of the recommendations of the Expert Panel.

- Such studies must meet the same basic criteria for inclusion established for the primary evidence review.
- If there is a difference of opinion about inclusion of a study, a final decision will be made by the Expert Panel Chair.
- Studies that are selected for inclusion will undergo abstraction and full text review by the process established for the primary evidence review. To distinguish it from the body of evidence assembled via the systematic literature search conducted through the closing date of June 30, 2007, the body of evidence from any such more recent studies will be documented separately from the evidence tables comprising data from the original search.

3. *Search Terms*

To explore the most appropriate search strategy and examine the sensitivity and specificity of particular search terms, an initial search was done in PubMed/MEDLINE. This search used broad medical subject heading (MeSH) terms and text words for the concepts of pediatric/young adult populations, CVD/TOD, and the risk factors. Terms were combined using the Boolean operators "AND," "OR," and "NOT," which are described briefly in Table A–3.

Table A–3. Boolean Operators Used To Combine Search Terms[4]

Boolean operator	Function
AND	Retrieves results that include all the search terms
OR	Retrieves results that include at least one of the search terms
NOT	Excludes the retrieval of terms from the search

The preliminary, broad search of PubMed/MEDLINE identified in excess of 1 million citations, signaling the need to refine the search terms to identify the most relevant ones.

In consultation with the Expert Panel, key refinements in the search strategy were made, including (1) the use of major MeSH terms rather than MeSH terms, where appropriate; (2) the use of title and abstract terms rather than text words; (3) a reduction of the number of terms for each concept, leaving only the most central and essential terms; and (4) the application of excluded concepts to the search (in the form of "NOT" terms).

In the final search strategy, a combination of MeSH terms, major MeSH terms, and title and abstract terms was employed to identify the full range of relevant literature. Search terms were identified to capture studies in the pediatric and young adult target populations (ages 0–21 years) that also addressed CVD/TOD and/or at least one of the risk factors. Specific search terms are provided in Table A–9 in the Methodology: Additional Tables section.

4. *Search Limits*

A set of limits was applied to the search to help refine the results to the most useful types of studies. The first level of basic search limits included:

- *Publication date*: published between January 1, 1985, and June 30, 2007
- *Language*: English language abstract or full text
- *Publication type*: no editorials, letters, comments, case reports, or non-SRs

Search terms and field tags used to apply these limits to the search are provided in Table A–9 in the Methodology: Additional Tables section.

In addition to these basic limits, search terms were used to exclude studies examining certain out-of-scope conditions. For example, during a preliminary review of the

literature, many studies were identified that focused on various pediatric conditions such as Kawasaki disease, otitis media, or congenital heart diagnoses. Through consultation with the Expert Panel, search terms were developed for the most commonly observed out-of-scope conditions. Studies containing these terms were prospectively excluded by using the Boolean operator "NOT."

5. Search Results

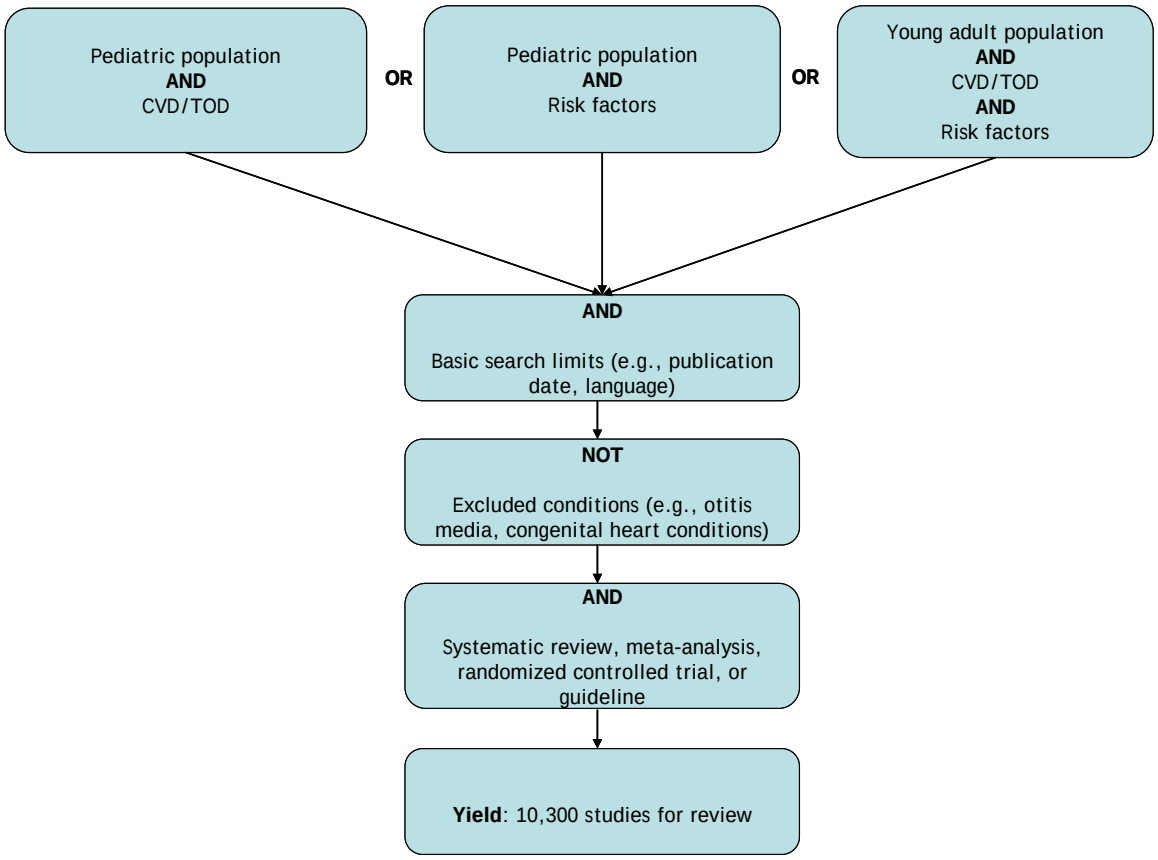
Systematic Reviews, Meta-Analyses, Randomized Controlled Trials, and the Guidelines

After applying the initial limits and using terms to eliminate out-of-scope concepts, the number of results returned from the original literature searches was still in excess of 60,000 citations. Given the size of these literature results, the Expert Panel determined that part of the review would focus on certain study types that would be most useful to the Expert Panel during Guidelines development: SRs, MAs, RCTs, and guidelines. Search terms and field tags identifying study type were used to select these studies in the PubMed/MEDLINE database.

Secondary studies, such as SRs and MAs, compile results from primary analyses and, in some cases, review of these study types may lessen the need to examine primary evidence on a topic. However, given the breadth of this evidence review, there were no instances in which an SR or MA captured the entire scope of interest of a critical question; therefore, this review depended on RCTs as an important source of primary data on relevant interventions.

The schematic in Figure A–1 presents a simplified, high-level depiction of how the key search concepts were combined to achieve the overall search strategy.

Figure A–1. Overview of General Search Strategy for Identification of Relevant Systematic Reviews, Meta-Analyses, Randomized Controlled Trials, and Guidelines



Major Observational Studies

In childhood, much of the evidence linking risk factors to atherosclerosis comes from epidemiologic studies. Therefore, in addition to including SRs, MAs, RCTs, and guidelines in the review, the Expert Panel determined that it was necessary for the evidence review to include major epidemiologic studies selected by the Expert Panel. These studies represent landmark longitudinal and natural history studies and other sentinel work that have provided important information and insight about atherosclerosis and CV risk in children. The major observational studies that were included are listed in Table A–4.

TABLE A–4. Selected Major Observational Studies

NHANES	National Health and Nutrition Examination Survey
Bogalusa	Bogalusa Heart Study
PDAY	Pathobiological Determinants of Atherosclerosis in Youth
Muscatine	Muscatine Study
Princeton	Princeton Lipid Research Clinics Follow-Up Study
Young Finns	Cardiovascular Risk in Young Finns Study
NGHS	NHLBI Growth and Health Study
STRIP	Special Turku Coronary Risk Factor Intervention Project (observational data from this RCT)
CARDIA	Coronary Artery Risk Development in Young Adults
Minnesota	Minnesota Children's Blood Pressure Study
Beaver County	Beaver County Lipid Study
Fels	Fels Longitudinal Study

A separate targeted search of PubMed/MEDLINE was conducted to identify literature relevant to these major studies related to the risk factors for the inclusive period of the evidence review from January 1, 1985, to June 30, 2007. The observational literature was also updated by the Expert Panel using the same criteria developed for the classic evidence review. Terms used to conduct this search are provided in Table A–10 in the Methodology: Additional Tables section. NHLBI staff reviewed the titles and then the abstracts for studies to be included based on the 14 risk factors under review. When a

longitudinal study reported results of the same variables at increasing intervals from the beginning of the observational period, the most recent report detailing the longest period of observation was selected for inclusion. Duplicate reports of the same results were excluded. The observational studies to be included in the evidence review were selected by the Expert Panel Risk Factor Teams.

Additional References

In an evidence-based review, studies included are generally limited to RCTs, SRs, and MAs. In addition to the epidemiologic studies described above, Expert Panel members also included studies that provided important information for each risk factor, defining the context in which the Guidelines' recommendations were developed. These references are not part of the evidence tables but are identified sequentially throughout the text and will be listed in Appendix B by section in numeric order, as identified in the text. Of particular importance were studies of genetic conditions impacting CV risk status and natural history studies of specific diseases known to be associated with accelerated atherogenesis.

Inclusion and Exclusion Criteria

In preparation for review of the literature, inclusion and exclusion criteria were developed by the the Expert Panel. These criteria outlined additional boundaries for the review. Certain criteria were applied only by the Expert Panel, given that judgments regarding the application of these criteria required relevant clinical expertise; these criteria are marked with an asterisk below.

Inclusion criteria:

- Pertained to at least one of the specified risk factors and measured at least one of the predetermined outcomes
- Related to at least one of the critical questions
- Focused on the target population (ages 0–21 years)
    - For longitudinal studies and other studies with extended followup periods, the population was required to be in this age range at initiation, and this subcohort could be identified in subsequent analyses.
    - For the Guidelines, the target population was required to include at least part of this age range.
- Conducted in Europe, North America, Australia, New Zealand, Japan, or Israel
- In 2004, an NHLBI Task Force published *The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents*. This report included a complete review of the current evidence on this subject and detailed recommendations for managing BP throughout childhood.[5] These recommendations were used as the basic recommendations for BP management for these Guidelines and are considered complete until 2003 when the review for the report ended. The literature review for BP, therefore, was limited to January 1, 2003, through June 30, 2007; selected studies from 2008 identified by the Expert Panel that met all the criteria for inclusion in the evidence review were also included.

Exclusion criteria:

- Any study not meeting the above requirements was excluded from the review.
- Studies that otherwise met inclusion criteria but that were found, upon examination, to have measured risk factors in only an incidental way or as part of assessing the safety of an intervention were excluded. For example, a study

of an asthma medication might measure BP to ensure that there were no adverse effects of the medication. Such studies that measured in-scope outcomes that were not linked to a risk factor condition were excluded from the review.

- Duplicate reports of findings based on the same original studies were generally excluded. For instances in which a series of studies (typically longitudinal studies or large RCTs) reported results for the same outcome measures over a period of time, the most recent studies and main results of trials were typically retained and older studies were excluded. These determinations were made individually during the review of each study.
- Studies that did not meet basic internal/external validity standards (e.g., as a result of narrowly defined patient population) were excluded.
- Studies that addressed the target population, often as part of a broader age range, but did not provide findings specific to patients in the target age range were excluded.
- Studies were excluded that on closer inspection were found not to be SRs, MAs, RCTs, guidelines, or reports from the selected epidemiologic studies.
- Studies were excluded that had an insufficient number of patients at followup to draw meaningful conclusions.
- Studies conducted in patients with diabetes focused on interventions that were related exclusively to glycemic control were excluded.
- For studies that focused on smoking as a risk factor, those that reported on interventions related to policymaking or merchant behavior were excluded.

During the review process, inclusion and exclusion criteria were modified to account for topics identified as irrelevant and certain included topics were clarified. Throughout this

process, abstractorsand the Expert Panel were in close contact to resolve questions regarding the application of inclusion/exclusion criteria to individual studies.

C. Literature Review Process

After completing electronic searches in each database, a total of 11,231 SRs, MAs, RCTs, guidelines, and major observational studies were identified for review. The distribution of search results by database and study type is presented in Table A–5. Abstracts and citations for these studies were compiled and organized using Reference Manager.

Table A–5. Distribution of Search Results by Database and Study Type for Studies Published Between January 1, 1985, and June 30, 2007

	Study type					
Database	SR	MA	RCT	Guideline	Major observational study	Total
PubMed/MEDLINE	3,100	221	3,982	1,202	931	9,436
Cochrane Database of Systematic Reviews*	414	0	0	0	0	414
National Guideline Clearinghouse (NGC)*	0	0	0	1,381	0	1,381
Total	3,514	221	3,982	2,583	931	11,231

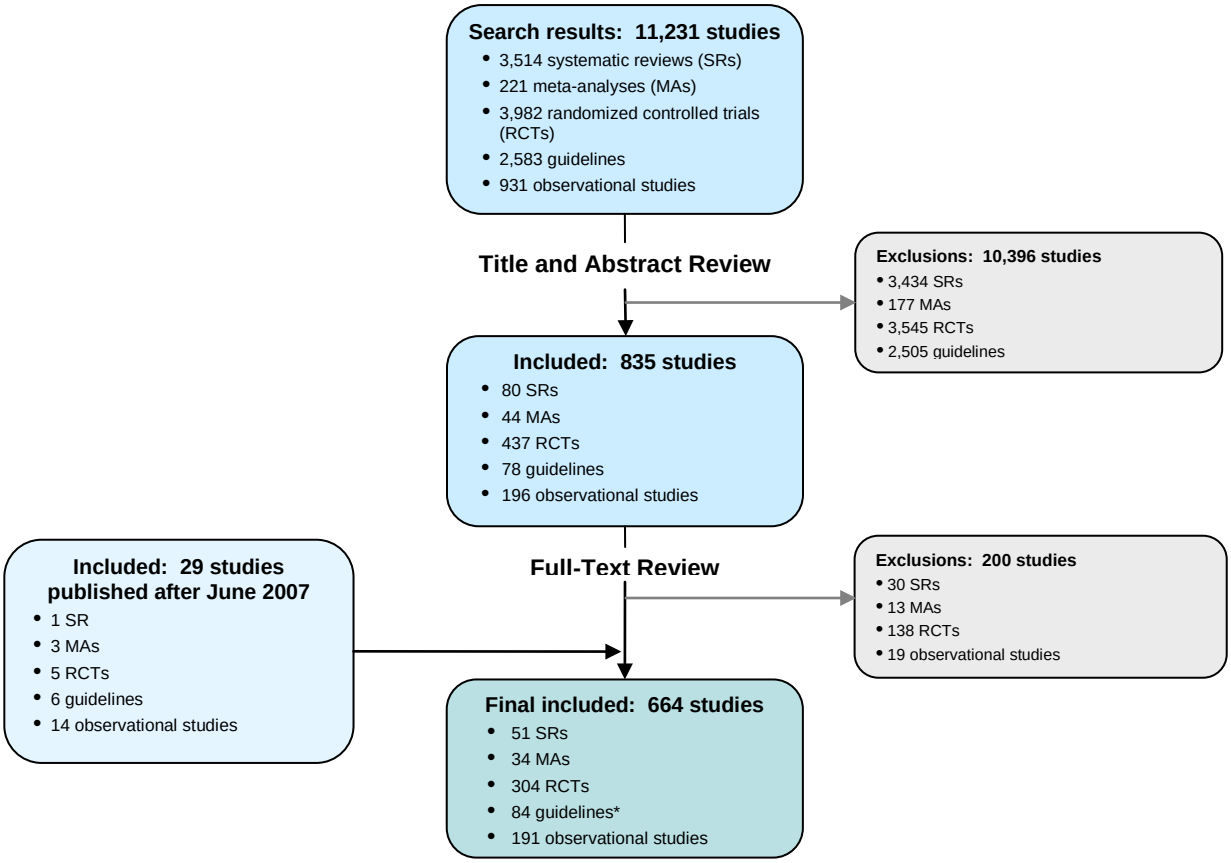
** Only unique results from Cochrane and NGC are displayed (i.e., duplicates of PubMed/MEDLINE results were excluded).*

Figure A–2 outlines the phases of the literature review process and the number of studies excluded at each stage. Throughout each review phase the Expert Panel provided guidance regarding the appropriate application of inclusion and exclusion criteria.

Abstracts and citations for these studies were compiled and organized using Reference Manager software. A review of titles and abstracts was first conducted for SRs, MAs, RCTs, and guidelines by trained abstractors. For the observational studies, titles and abstracts were reviewed by NHLBI staff. This phase of the review process resulted in a total of 561 SRs, MAs, and RCTs, as well as 78 guidelines and 196 observational studies, which were found to be potentially relevant, as indicated in Figure A–2.

Following the review of titles and abstracts, trained abstractors conducted a full-text review of the studies and excluded additional studies. NHLBI staff also reviewed the full text of these studies and identified additional studies to exclude. Following the full-text review phase, an additional 200 studies were excluded. Citations for studies excluded at the full-text level are provided online, along with the complete evidence tables.

Figure A–2. Overview of Review Phases and Excluded Studies at Each Phase



* Guidelines were reviewed only at the title and abstract/summary levels.

In addition to a review of the studies captured through the literature search process (i.e., studies published between January 1, 1985, and June 30, 2007), the NHLBI and the Expert Panel identified an additional 29 relevant studies that were published after June 30, 2007, for inclusion in the review.

At the end of the review process, a total of 664 studies were included for review—including 51 SRs, 34 MAs, 304 RCTs, 84 guidelines, and 191 observational studies.

The distribution of the 664 studies included SRs, MAs, RCTs, major observational studies, and guidelines by risk factor is provided through the NHLBI Web site.

D. Data Collection and Quality Control

Systematic Reviews, Meta-Analyses, Randomized Controlled Trials, and Guidelines

To capture information from in-scope studies, Excel tables were developed and used for data abstraction of each study type (i.e., SR, MA, RCT). Through discussion the Expert Panel, the types of information collected and the format of the tables were refined. Data collected in the abstraction tables included basic information about the study (e.g., year of publication), objective, patient population, intervention and comparator/control (if applicable), outcomes measured, and results. Data abstracted varied by study type. A complete list of data fields and definitions for these fields is provided through the NHLBI Web site.

To complete the data abstraction tables, trained abstractors reviewed full-text versions of each in-scope study. Two reviewers examined each full-text study; the first reviewer abstracted the appropriate data from each study, while the second reviewer concentrated on ensuring the accuracy and quality of data entered by the first reviewer as part of a thorough quality control process. For RCTs, contractor staff abstracted information for specific columns, including basic information about the study, objective, patient population, intervention and comparator/control (if applicable), and outcomes measured. For SRs and MAs, the contractor staff abstracted information for all columns. For observational studies, contractor staff abstracted the basic informational data, but full-text review and data entry were performed by NHLBI staff.

After data abstraction by the contractor, the data abstraction tables were submitted to the NHLBI and the Expert Panel for review and/or completion of abstraction. For all study types, Expert Panel members were responsible for verifying data entered by the contractor. For RCTs, Expert Panel members and NHLBI staff selected the outcome variables to be abstracted and entered the results in the evidence tables, as well as recorded study results and conclusions. To facilitate this process, studies were forwarded to the relevant subcommittee within the Expert Panel, according to the primary risk factor of focus. For example, a study that examined the use of an intervention to improve cholesterol levels would have been forwarded to the subcommittee on lipids. Study reviews were rotated to ensure that each was reviewed by two subcommittee members. Subcommittee members completed abstraction of established columns and, in several cases, requested the addition of extra columns in the evidence tables to capture more specific information pertaining to the risk factor of interest. When Expert Panel members were not in agreement regarding such matters as study relevance or abstraction of specific data, these matters were brought to the Expert Panel Chair for resolution.

In addition to basic information about study design and results, aspects of study quality were considered by the Expert Panel during data abstraction. A customized quality grading system was developed to support the Expert Panel's interpretation of individual studies, particularly with regard to methodology and study design considerations. This novel grading system, the development of which drew largely from several existing grading schemes, was incorporated into the electronic data abstraction tables. The system used an algorithm that generated a quality grade for individual RCTs, according

to the criteria outlined in Tables 11 and 12. SRs, MAs, and observational studies did not receive an individual quality grade.

After completion of data abstraction, evidence tables displaying key study information were developed from the data abstraction tables using Excel for use by the Expert Panel. These standard evidence tables were then sorted in a customized way for each subcommittee, so as to best support the Guidelines development process. Final evidence tables for all included SRs, MAs, RCTs, and observational studies will be provided online at http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm.

Although reports of guidelines were captured as part of the literature search, they were not incorporated into evidence tables. Instead, the guidelines were reviewed for relevance, and those that were in scope were categorized according to the risk factor(s) addressed. A list of the in-scope guidelines was made available to Expert Panel members for their reference; full-text versions were made available as needed. Citations for in-scope guidelines, by risk factor, are also provided online.

Major Observational Studies

Excel tables were also developed for the epidemiologic observational studies, with basic information about each study entered into tables by skilled abstractors from contractor staff. Full-text review and abstraction of each study were performed by NHLBI staff, including identification of outcome variables and review of results and conclusions. These tables were then reviewed by Expert Panel members, who selected 191 studies as relevant to the evidence review. The tables were primarily categorized by risk factor and then sorted using the terms developed by the relevant Risk Factor Teams for inclusion in the review. Expert Panel members added additional relevant reports from

any of these observational studies that appeared after conclusion of the formal review. The evidence tables for the observational studies also will be included on the NHLBI Web site.

III. Guidelines Development Process

A. Expert Panel and Subcommittee Discussion

Following establishment of the Expert Panel, in-person meetings were held in October 2006, February 2007, June 2008, and October 2008. These meetings enabled Expert Panel members to discuss key elements of the systematic evidence review, consider the approach and scope of the Guidelines, and review and refine the Guidelines' recommendations.

To facilitate discussion of the evidence related to particular risk factors, multiple subcommittee conference calls were held from February to December 2008, along with a continuous electronic correspondence. Across the seven subcommittees, more than 500 conference calls were completed. During these calls, subcommittee members established processes for developing and finalizing the Guidelines' recommendations for each risk factor and progressively shaped the final recommendations in the Guidelines. A SharePoint Web site was created to enable subcommittee members to share draft recommendations.

B. Established Parameters for Guidelines Recommendation Development

The Expert Panel adopted an evidence grading system from the American Academy of Pediatrics (AAP) to assess the quality of the body of evidence as a whole and the evidence in support of particular statements.[6] The grading system is shown in Table A–

6; it was modified by the addition of genetic natural history studies to the grade B evidence category; an example of a genetic natural history study is the development of atherosclerosis in a child with homozygous familial hypercholesterolemia who has severely elevated cholesterol levels from birth. Studies of such genetic conditions are believed to represent a natural intervention and to function as surrogates for a specific lifelong risk exposure. Genetic variation shares features with random assignment in clinical trials in that the variation occurs by chance within a society and the presence of the genetic variation does not alter exposure to environmental or other factors.[7] Table A–6 shows the modified system used to assess the quality of the body of evidence.

Table A–6. Evidence Quality for Grades of Evidence

Grade	Evidence
A	Well-designed randomized controlled trials or diagnostic studies performed on a population similar to the Guidelines' target population
B	Randomized controlled trials or diagnostic studies with minor limitations; genetic natural history studies; overwhelmingly consistent evidence from observational studies
C	Observational studies (case-control and cohort design)
D	Expert opinion, case reports, or reasoning from first principles (bench research or animal studies)

Drawing from the same AAP system, Table A–7 depicts the Guidelines' definitions for evidence-based statements.

Table A–7. Guidelines' Definitions for Evidence-Based Statements

Statement type	Definition	Implication
Strong recommendation	The benefits of the recommended approach clearly exceed the harm, and the quality of the supporting evidence is excellent (Grade A or B). In some clearly defined circumstances, strong recommendations may be made on the basis of lesser evidence (e.g., Grade C or D) when high-quality evidence is impossible to obtain and the anticipated benefits clearly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	The benefits exceed the harms but the quality of the evidence is not as strong (Grade B or C). In some clearly defined circumstances, strong recommendations may be made on the basis of lesser evidence (e.g., Grade D) when high-quality evidence is impossible to obtain and the anticipated benefits clearly outweigh the harms.	Clinicians should generally follow a recommendation but remain alert to new information and sensitive to patient preferences.
Option	Either the quality of the evidence that exists is suspect (Grade D) or well-performed studies (Grade A, B, or C) show little clear advantage to one approach versus another.	Clinicians should be flexible in their decisionmaking regarding appropriate practice, although they may set boundaries on alternatives; patient preference should have a substantial influencing role.
No recommendation	There is both a lack of pertinent evidence (Grade D) and an unclear balance between benefits and harms.	Clinicians should be minimally constrained in their decisionmaking and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

The Expert Panel also developed a definition of consensus to guide decisionmaking regarding Guidelines recommendations within the subcommittees and among the full Expert Panel. The final definition included the following elements:

- Committee deliberations regarding a given recommendation generally reflected deference to the expert risk factor subcommittee that was originally charged with critically appraising the evidence and drafting the recommendation.
- Voting was "in support of" or "opposed to" a recommendation.
- Agreement by at least 80 percent (or 11 of 14 members) of the Expert Panel constituted a strong consensus. A recommendation with this level of agreement is presented in the Guidelines as a consensus of the Expert Panel. However, discussion of the issues in the Guidelines document may address areas of difference.
- A proposed recommendation that was supported by less than 60 percent (or less than 8 of 14 members) of the Expert Panel was not included in the Guidelines. However, review of the subject could be included in the discussion for that risk factor area.
- Agreement by 60–80 percent (9 or 10 of 14 members) of the Expert Panel constituted a moderate consensus in support of the recommendation. A recommendation with this level of agreement was presented with that language in the Guidelines and accompanied by discussion of the conflicting issues. In developing the discussion in support of a recommendation, the actual vote of the Expert Panel was considered.

In considering the various pediatric age groups covered by the Guidelines' recommendations, the Expert Panel agreed to formulate the Guidelines' recommendations according to the chronological timetable used by the AAP *Bright Futures* program:[8]

- Preconception/prenatal

- 0–12 months
- 1–4 years
- 5–10 years
- 11–17 years
- 18–21 years

Studies were not always specific to an age group, and the Expert Panel used judgment in determining how those studies informed age-specific recommendations.

C. Completion of the Guidelines

At the final full Expert Panel meeting in October 2008, the Expert Panel reviewed each recommendation proposed by each subcommittee in detail. According to the established definition of consensus, the Expert Panel agreed on a complete set of recommendations and supporting text in the draft Guidelines report.

In April 2009, a draft version of the Guidelines was circulated to other NIH Agencies and multiple professional organizations for review and comment. The draft version was also posted on the NHLBI Web site for public comment for a 30-day period from June 19 to July 20, 2009. In total, the Expert Panel considered more than 1,000 comments from more than 50 reviewers, and individual responses were developed for more than 1,000 comments. The draft version of the Guidelines also underwent a separate review by the NHLBI and HHS. After considering all comments, consistent with applicable Federal requirements, the Expert Panel made appropriate revisions to the draft report, which was published in final form in November 11, 2011.

Methodology: Additional Tables

Table A–8. Outcome Measures

Risk factor	Outcome measures/specific inclusion criteria
RF1	Included studies that related family history of cardiovascular disease (CVD) to CVD/target organ damage (TOD) or risk factors for CVD in pediatric/young adult patients
RF2	Included studies that related sex/gender to measures of CVD/TOD or risk factors (e.g., via subgroup analysis reporting outcomes according to sex/gender)
RF3	Included studies that related age/duration of risk exposure to measures of CVD/TOD or risk factors (e.g., via subgroup analysis reporting outcomes according by age or age group)
RF4	▪ Systolic blood pressure ▪ Diastolic blood pressure
RF5	▪ Total cholesterol ▪ Triglycerides ▪ High-density lipoprotein cholesterol (HDL–C) ▪ Low-density lipoprotein cholesterol (LDL–C) ▪ Very low-density lipoprotein cholesterol (VLDL–C) ▪ Non-high-density lipoprotein cholesterol (non-HDL–C) ▪ Apolipoprotein A–1 (Apo A–1) ▪ Apolipoprotein B (Apo B) ▪ Apolipoprotein B/Apolipoprotein A–1 (Apo B/Apo A–1)
RF6	▪ Fasting glucose ▪ Fasting insulin ▪ Fasting glucose to insulin ratio ▪ Fasting plasma glucose level/blood glucose level ▪ Oral glucose tolerance test: 2-hour glucose, 2-hour insulin, or areas under the curve ▪ Homeostatic model assessment (HOMA), including HOMA1–IR, HOMA2–IR, HOMA2–%S, and HOMA2–%B ▪ Quantitative insulin sensitivity check index ▪ Hemoglobin A1c level

Risk factor	Outcome measures/specific inclusion criteria
RF7	Included studies in patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) and studies that designated patients as at risk for T2DM; these studies were required to address at least one of the other risk factors Excluded studies focused exclusively on pharmacologic treatments (e.g., insulin therapy) for T1DM Included studies that linked inflammation with CVD/TOD or at least one of the risk factors
RF8	Included studies that linked inflammation with CVD/TOD or at least one of the risk factors
RF9	▪ Energy intake ▪ Carbohydrate intake ▪ Fiber intake ▪ Fruit and vegetable consumption ▪ Protein intake ▪ Total fat intake ▪ Saturated fat or saturated fatty acid intake ▪ Monounsaturated fat or monounsaturated fatty acid intake ▪ Polyunsaturated fat or polyunsaturated fatty acid intake ▪ *Trans* fat intake ▪ n-3 fatty acid/omega-3 fatty acid intake, including: - α-Linolenic acid or 18:3 - Stearidonic acid or 18:4 - Eicosatetraenoic acid or 20:4 - Eicosapentaenoic acid or 20:5 - Docosapentaenoic acid or 22:5 - Docosahexaenoic acid or 22:6 ▪ Calcium intake ▪ Iron intake ▪ Zinc intake ▪ Vitamin D intake ▪ Potassium intake ▪ Sodium intake

Risk factor	Outcome measures/specific inclusion criteria
RF10	▪ Knowledge of health risks of smoking ▪ Readiness to change scale ▪ Measures of smoking (e.g., cigarettes smoked per day, nicotine levels) ▪ Smoking status Selected RF10 for individuals ages 0–21 years who smoke (or who are receiving intervention to prevent smoking) or who are exposed to environmental tobacco smoke outside the home
RF11	▪ Self-reported physical activity ▪ Preferences for physical activity and sedentary behaviors ▪ Electronic or mechanical monitoring of physical activity (e.g., via accelerometer, pedometer) ▪ Minutes or percentage of time at different intensity levels of physical activity (e.g., vigorous, moderate, light, sedentary) ▪ Direct observation and rating of physical activity (through in-person observation or recorded video) ▪ Energy expenditure (e.g., via indirect calorimetry) ▪ Cardiorespiratory fitness testing, including but not limited to: ° Treadmill exercise ° Endurance time ° Bicycle exercise ergometry ° Metabolic equivalents ° Distance runs, timed runs ° 20-meter shuttle test/Pacer ° Step-tests ° Resting heart rate ▪ Sedentary time (e.g., screen time, TV time, computer time, video/DVD/movie time, video game time, phone time) Included studies measuring these and other indicators of physical activity; did not limit to these outcomes because physical activity is measured in so many different ways across studies
RF12	Included studies in patients with these conditions that addressed at least one of the other risk factors or measures of CVD/TOD

Risk factor	Outcome measures/specific inclusion criteria
RF13	Includes terms for: 1. Maternal smoking when tied to babies that have low birth weight 2. Maternal or parental smoking cessation outcomes 3. Maternal weight gain/prepregnancy and between pregnancy body mass index (BMI) 4. Maternal or parental obesity (BMI) when tied to pediatric obesity (BMI) (cite RF8 and RF13) Note: Smoking by the child and exposure to environmental smoke (i.e., passive smoking outside the home) are listed as RF10. Select RF13 for pediatric individuals who are exposed to risk factors in utero
RF14	▪ Fasting glucose ▪ Fasting insulin and other insulin/insulin resistance measurements ▪ Oral glucose tolerance test: 2-hour glucose, 2-hour insulin, or areas under the curve ▪ HOMA, including HOMA1–IR, HOMA2–IR, HOMA2–%S, and HOMA2–%B ▪ Quantitative insulin sensitivity check index ▪ Hemoglobin A1c level

Table A–9. Search Terms and Limits

Search concept	Search terms
Population	
Pediatric population (0–18 years)	infant [majr] OR child [majr] OR adolescent [majr] OR pediatrics [majr] OR infant* [tiab] OR child* [tiab] OR adolescen* [tiab] OR youth* [tiab] OR pediatric* [tiab]
Young adult population (18–21 years)	adult [majr] OR young adult* [tiab]
Cardiovascular disease/target organ damage	
Cardiovascular disease/target organ damage (CVD/TOD)	heart diseases [majr] OR vascular diseases [majr] OR arteriosclerosis [majr] OR atherosclerosis [mesh] OR atherosclerosis [tiab] OR cardiovascular* [tiab] OR coronary* [tiab] OR arteriosclerosis* [tiab]) OR ((heart diseases [majr] OR vascular diseases [majr] OR arteriosclerosis [majr] OR atherosclerosis [mesh] OR atherosclerosis [tiab] OR cardiovascular* [tiab] OR coronary* [tiab] OR arteriosclerosis* [tiab]) AND (target organ damage [tiab] OR TOD [tiab] OR target organ [tiab] OR organ damage [tiab])
Risk factors	
RF1: Family history	No specific search terms—RF1 was only considered relevant if linked to CVD/TOD or one of the other risk factors
RF2: Sex/gender	No specific search terms—RF2 was only considered relevant if linked to CVD/TOD or one of the other risk factors
RF3: Age/duration of risk exposure	No specific search terms—RF3 was only considered relevant if linked to CVD/TOD or one of the other risk factors
RF4: Blood pressure	blood pressure [majr] OR hypertension [majr] OR hypertrophy, left ventricular [majr] OR blood pressure [tiab] OR hypertens* [tiab] OR left ventricular hypertrophy [tiab] OR ventricular mass [tiab]
RF5: Lipids	apolipoproteins [majr] OR dyslipidemias [majr] OR lipids [majr] OR receptors, LDL [majr] OR xanthomatosis [majr] OR triglycer* [tiab] OR hypertriglycer* [tiab] OR apolipoprotein* [tiab] OR lipoprotein* [tiab] OR dyslipidemi* [tiab] OR lipid* [tiab] OR hyperlip* [tiab] OR cholester* [tiab] OR hypercholester* [tiab] OR LDL* [tiab] OR HDL* [tiab] OR xanthoma* [tiab]
RF6: Diabetes mellitus	glucose metabolism disorders [majr] OR insulin [majr] OR diabet* [tiab] OR hypoglycemi* [tiab] OR insulin* [tiab] OR hyperinsulin* [tiab]
RF7: Inflammation	No specific search terms—RF7 was only considered relevant if linked to CVD/TOD or one of the other risk factors
RF8: Body weight	overweight [majr] OR anti-obesity agents [majr] OR body weight [majr] OR abdominal fat [majr] OR skinfold thickness [majr] OR body fat distribution [majr] OR waist-hip ratio [majr] OR body mass index [majr] OR body fat [tiab] OR abdominal fat [tiab] OR weight reduction [tiab] OR weight control [tiab] OR obes* [tiab] OR body mass index [tiab] OR overweight [tiab] OR adiposity [tiab] OR body weight [tiab] OR BMI [tiab] OR adiposity rebound [tiab] OR post-natal weight gain [tiab] OR postnatal weight gain [tiab] OR excessive weight gain [tiab]
RF9: Diet	diet [majr] OR feeding behavior [majr] OR drinking behavior [majr] OR overnutrition [majr] OR nutrition therapy [majr] OR fats [majr] OR diet [tiab] OR dietary [tiab] OR diets [tiab] OR dieting [tiab] OR eating habits [tiab] OR energy balance [tiab] OR energy imbalance [tiab] OR fat intake [tiab] OR trans fat* [tiab] OR nutrition* [tiab] OR calori* [tiab]
RF10: Tobacco smoking	smoking [majr] OR tobacco use cessation [majr] OR tobacco [majr] OR tobacco use disorder [majr] OR tobacco smoke pollution [majr] OR tobacco* [tiab] OR smok* [tiab]

RF11: Physical activity	physical fitness [majr] OR exercise [majr] OR sports [majr] OR television [majr] OR video games [majr] OR physical activit* [tiab] OR physical fitness [tiab] OR physical education [tiab] OR energy expenditure* [tiab] OR sedentary* [tiab] OR exercis* [tiab] OR television* [tiab] OR TV [tiab] OR video game* [tiab] OR "screen time" [tiab]
RF12: Other predisposing conditions/factors	No specific search terms—RF12 conditions (e.g., polycystic ovary syndrome) were only considered relevant if noted in studies addressing CVD/TOD or one of the other risk factors
RF13: Maternal/parental	pre-pregnancy body mass index [tiab] OR pre-pregnancy BMI [tiab] OR maternal weight gain [tiab] OR maternal smoking [tiab] OR parental smoking [tiab] OR (parents [mesh] AND smoking [majr]) OR (weight gain [majr] AND parents [mesh]) OR ((maternal [tiab] OR paternal [tiab] OR parental [tiab]) AND obesity [tiab])
RF14: Metabolic syndrome	metabolic syndrome X [majr] OR "metabolic syndrome" [tiab]
Search limits	
Basic limits	(("1985/01/01 01.00" : "2007/06/30 23.59" [PDAT]) AND humans [mesh] NOT (editorial [pt] OR letter [pt] OR comment [pt] OR case reports [pt] OR (review [pt] NOT (system* [tw] OR comprehensive [tw] OR method* [tw]))) AND (English[lang] OR hasabstract))

Table A–10. Search Terms for Major Longitudinal and Other Sentinel Studies

Search Concept	Search String
Major longitudinal and other sentinel studies (identified by the NHLBI and the Expert Panel)	Bogalusa OR Pathobiological Determinants of Atherosclerosis in Youth OR PDAY OR Cardiovascular Risk in Young Finns OR Special Turku Coronary Risk Factor Intervention Project for Children OR (STRIP [ti] AND study [ti]) OR Muscatine OR Coronary Artery Risk Development in Young Adults OR CARDIA [ti] OR Minnesota Children Blood Pressure OR Princeton School District Study OR Beaver County Lipid
Search limits	(("1985/01/01 01.00" : "2007/06/30 23.59" [PDAT]) AND humans [mesh] NOT (editorial [pt] OR letter [pt] OR comment [pt] OR case reports [pt] OR (review [pt] NOT (system* [tw] OR comprehensive [tw] OR method* [tw]))) AND (English[lang] OR hasabstract))

Table A–11. Quality Criteria for Assessment of Individual Randomized Controlled Trials

	Study characteristics	Criteria needed for "Y" selection	Data values
Inclusion/ exclusion	Inclusion/exclusion criteria specified	• Inclusion/exclusion criteria specified (e.g., risk status, diagnostic or prognosis criteria) with sufficient detail	• Y • N
	Criteria applied equally to study arms	• Same inclusion/exclusion criteria applied to each study arm	• Y • N
	Comparable patient characteristics	• Health, demographics, and other characteristics of subjects/patients described • Distribution of health, demographics, and other characteristics similar across study arms at baseline	• Y • N
Bias	Appropriate randomization	• Method of randomizing subjects to arms described • Method of randomizing subjects to arms free from bias (e.g., random number generator)	• Y • N
	Allocation concealment	• Prevention of foreknowledge of treatment assignment through adequate concealment schemes (e.g., central randomization)	• Y • N • NR
	Blinding: Patients	• Patients or subjects blinded to treatment as appropriate	• Y • N
	Blinding: Assessors	• Provider or other treatment administrator blinded to treatment as appropriate • Data collectors/analysts or others with ability to affect results blinded as appropriate	• Y • N • NR
	Low attrition rates	• Low rate of attrition for each arm • Withdrawals and reasons for withdrawal similar across arms	• Y • N
	Conflicts of interest	• Sources of funding and investigators' affiliations described ** Selection does not affect quality grade.*	• Y • N • NR/unknown
	Industry sponsorship	Industry sponsorship beyond provision of drug or placebo (If a listed author is from industry, then select "Y." If industry only supplies free drug and placebo, then there is no industry sponsorship.) ** Selection does not affect quality grade; an asterisk will appear by quality grade if selection is "Y."*	• Y • N • NR
Data collection and analysis— Appropriate and adequate description of:	Study protocol	• Protocol described for all intervention components/regimens studied • Description of extra or unplanned treatments	• Y • N
	Outcome(s) measured	• Primary and secondary outcome(s)/end point(s) described • Primary and secondary outcomes(s)/end point(s) relevant to the objective	• Y • N
	Duration/followup	• Duration of intervention sufficient to detect meaningful effect on primary and secondary outcomes • Period of followup long enough for important outcome(s) to occur	• Y • N

	Study characteristics	Criteria needed for "Y" selection	Data values
	Statistical analysis	• Statistical analyses described • Appropriate statistical test used and assumptions of test not violated • Statistics reported with levels of significance and/or confidence intervals • Intent-to-treat analysis of outcomes • Adequate adjustment for effects of confounding factors that might have affected the outcomes • Results/findings address statistical significance • Confidence interval or power calculations reported for null findings ** Consider all criteria listed; however, not all criteria must be met for a "Y."*	• Y • N
	Clinical significance	• Results/findings address clinical significance	• Y • N
	Discussion of findings	• Findings and implications discussed • Biases and study limitations identified, including assessment of how well an intervention was delivered	• Y • N
	Adverse events	• Safety outcomes/adverse events specifically reported • Appropriate sample size and duration to detect safety outcome(s)	• Y • N • N/A
Generalizability— Clearly defined and applicable:	Study population	• Study population is appropriate to answer research question	• Y • N
	Intervention	• Intervention can be feasibly conducted in a general practice/routine/community setting	• Y • N
	Outcome(s)	• Outcome(s)/end point(s) are associated with an increase or decrease in cardiovascular disease risk factor(s) or cardiovascular disease risk during childhood or adulthood • Outcome(s)/end point(s) can be feasibly measured in a general practice/routine/community setting	• Y • N

Table A–12. Randomized Controlled Trial Grading Scheme

Grade	Inclusion/Exclusion (3 fields total)	Bias (7 fields total)	Data Collection and Analysis (6 fields total)	Generalizability (3 fields total)
A	"Y" selected for: • All Inclusion/Exclusion fields	If intervention is pharmacologic, then "Y" selected for: • Appropriate randomization • Blinding: Patients • Blinding: Assessors • Low attrition rates If other type of intervention, then "Y" selected for: • Appropriate randomization • Blinding: Assessors • Low attrition rates	"Y" selected for: • All Data Collection and Analysis fields	"Y" selected for: • All Generalizability fields
B	"Y" selected for: • Inclusion/exclusion criteria specified • ≥1 other Inclusion/Exclusion field	If intervention is pharmacologic, then "Y" selected for: • Appropriate randomization • Blinding: Patients • Blinding: Assessors • Low attrition rates If other type of intervention, then "Y" selected for: • Appropriate randomization • Low attrition rates	"Y" selected for: • Study protocol • Outcome(s) measured • Statistical analysis	"Y" selected for: • All Generalizability fields
C	"Y" selected for: • Inclusion/exclusion criteria specified	"Y" selected for: • Appropriate randomization	"Y" selected for: • Study protocol • Outcome(s) measured	"Y" selected for: • Study population
D	Does not meet criteria for higher grades			

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