

Progress and Challenges in Metabolic Syndrome in Children and Adolescents

A Scientific Statement From the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism

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The present document is an update of the 2003 American Heart Association Scientific Statement on Obesity, Insulin Resistance, Diabetes, and Cardiovascular Risk in Children from the Atherosclerosis, Hypertension, and Obesity in the Young Committee (Council on Cardiovascular Disease in the Young) and the Diabetes Committee (Council on Nutrition, Physical Activity, and Metabolism).¹ Since the writing of the above document, substantial new information has emerged in children on the clustering of obesity, insulin resistance, inflammation, and other risk factors and their collective role in conveying heightened risk for atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes mellitus (T2DM). A constellation of these interrelated cardiovascular risk factors in adults has come to be known as the metabolic syndrome (MetS), a construct useful both in clinical and research areas. Most recently, the American Heart Association and the National Heart, Lung, and Blood Institute produced a consensus statement intended to provide up-to-date guidance on the diagnosis and management of the MetS in adults.²

The aim of this statement is to provide not a definition of the MetS but a set of fundamental questions about what the MetS means in a clinical or research setting. It calls attention to the fact that the stability of the MetS, especially for adolescents, is low, which raises questions about the utility of the MetS in a clinical context. For these reasons, we have focused on cardiometabolic risk factors and have called for the types of research that would hopefully provide much

needed answers in this area. This statement aims to represent a balanced and critical appraisal of the strengths and weaknesses of the MetS concept in pediatric patients. It focuses on the pediatric issues related to cardiometabolic risk factors, primarily on the progress that has been made in recognizing the components of the MetS in children, their interrelations, and their importance as predictors of longitudinal risk for ASCVD and T2DM, based on evidence accumulated over recent years and on the consensus of experts in the field. It also addresses the need for early detection and preventive measures regarding cardiometabolic risk factors in children and adolescents, with a strong focus on obesity, inflammation, insulin resistance, dyslipidemia, and hypertension, which emerge as core elements of morbidity. Because of the limited data that track individuals from childhood to adulthood, little is known about how well pediatric MetS predicts adult disease. This statement also defines the limits of our current knowledge and provides suggestions for needed future research. To provide more insightful and concrete recommendations for clinicians and families as we face the increasing burden of childhood obesity, lipid abnormalities, diabetes mellitus, high blood pressure, and other associated morbidities, the urgent need for vigorous research at the national and international level is obvious, so that lifestyle modification and at times medication may be used to reduce ASCVD risk to follow.

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In adults, the aggregation of multiple cardiovascular risk factors was observed in the early part of the 20th century.³ More recently, similar clusterings received renewed attention, and several terms such as syndrome X,⁴ the deadly quartet,⁵ insulin resistance syndrome,⁶ and MetS⁷ have been proposed to describe the connection between obesity, insulin resistance, hypertension, dyslipidemia, T2DM, and ASCVD. In adults, the definition of MetS varies in terms of the indicators featured and the cut points used.^{8–10} The criteria proposed by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III])⁹ and those from the World Health Organization¹⁰ are most commonly used in adults. Two of the 3 common definitions^{8,10} include measures of insulin resistance, which reflects the proposed causal or mediating role insulin action plays in the development of MetS.^{11,12} Inclusion of high-sensitivity C-reactive protein (CRP) among the diagnostic criteria for MetS has also been proposed to capture emerging evidence that suggests that inflammation and insulin resistance may both be required for full manifestation of this condition.¹³

In the pediatric literature, a number of attempts have been made to characterize the MetS or a related construct with a meaning similar to the adult MetS.^{14–17} Barriers to a consistent, accepted definition for children and adolescents include the use of adult cut points or a single set of cut points for all ages throughout childhood, the fact that disturbances seen in the metabolic indicators in most children are quantitatively moderate, the lack of a normal range for insulin concentration across childhood, the physiological insulin resistance of puberty, the lack of central obesity (waist) cut points linked to obesity morbidity or MetS for children, and differences in baseline lipid levels among various races. Because there is still no universally accepted definition of the MetS in children and adolescents, the criteria used in pediatric studies have been variably adapted from adult standards with the use of gender- and age-dependent normal values.

Recently, the International Diabetes Federation published its definition of the MetS in children and adolescents. This panel recommends the following criteria: (1) for children 6 years to <10 years old, obesity (defined as ≥ 90 th percentile of waist circumference), followed by further measurements as indicated by family history; (2) for age 10 to <16 years, obesity (defined as waist circumference ≥ 90 th percentile), followed by the adult criteria for triglycerides, high-density lipoprotein cholesterol (HDL-C), blood pressure, and glucose. For youth ≥ 16 years of age, the panel recommends using the existing International Diabetes Federation criteria for adults. This definition is based on percentile definitions and is standard across the age range. As with others, this definition will have to be evaluated scientifically (Table 1). According to these criteria, the prevalence of MetS in children varies widely. For example, using 2 different cutoff criteria in a single data set, a recent report determined prevalence rates of 15.3% versus 23.0% in girls.¹⁸ An assessment of the MetS in 2430 children from the Third National Health and Nutrition Examination Survey (1988–1994) reported a prevalence of 4%, but the prevalence in

overweight children was 30%.¹⁹ Using ATP III and World Health Organization criteria, a school-based study of 1513 North American adolescents found a 4.2% and 8.4% prevalence of MetS, respectively,²⁰ whereas a study of 965 Mexican children and adolescents found a 6.5% and 4.5% prevalence, respectively.¹⁶ The prevalence of MetS among 2244 Canadian children and adolescents was slightly higher at 11.5%.¹⁴ In a population of 357 healthy subjects enrolled during childhood in a longitudinal study of the influence of insulin resistance and obesity on development of cardiovascular risk, a steady increase was observed in the prevalence of the MetS, according to the adult ATP III definition, from mean age 13 years (3%) to age 19 years (9%).²¹

As the degree of obesity increases, the prevalence of MetS increases, with obesity occurring in 38.7% of moderately obese (mean body mass index [BMI] 33.4 kg/m²) and 49.7% of severely obese (mean BMI 40.6 kg/m²) children and adolescents.¹⁵ Despite the difficulty inherent in defining the key elements of a condition modulated by so many genetic and environmental factors,²² strong evidence supports obesity as the predominant correlate of cardiometabolic risk,²³ especially when the adiposity is centrally distributed. In the Framingham Heart Study, among overweight and obese individuals, the prevalence of hypertension, impaired fasting glucose, and dyslipidemia increased linearly and significantly across increasing visceral adipose quartiles, assessed by multidetector computed tomography.²⁴ The magnitude of cardiometabolic risk also varies markedly in obese adults as a function of differences in degree of insulin sensitivity.²⁵ Furthermore, baseline insulin concentration was higher in children who subsequently showed clustering of high triglycerides, low HDL-C, and high systolic blood pressure levels at follow-up in the longitudinal Cardiovascular Risk in Young Finns Study.²⁶ Most investigators would therefore expect that individuals with the MetS also are insulin resistant, but this relation has not been firmly established.²⁷ Nevertheless, it is accepted that the MetS and insulin resistance are “closely related”²⁸ and that insulin resistance may be a necessary but not sufficient variable for expression of the MetS.⁸

Although itself rare in childhood, the precursors of ASCVD are present in the young. Autopsy studies^{29–31} have shown that the extent of early atherosclerosis of the aorta and coronary arteries is directly associated with levels of lipids, blood pressure, and obesity in childhood and adolescence. Moreover, a growing body of research in noninvasive measures of peripheral vascular morphology and function, a surrogate for coronary artery health, shows associations between subclinical atherosclerosis and cardiometabolic risk factors as early as childhood.^{32,33} Obesity, especially abdominal obesity, and insulin resistance are directly related both clinically and epidemiologically to the development of the MetS and cardiovascular risk. The relations between insulin resistance and the components of the MetS are complex. Confirmatory factor analysis of adult data suggests one pathophysiological mechanism underlying the MetS is insulin resistance³⁴; however, because not all patients with insulin resistance develop the MetS,³⁵ there are likely other factors involved. In addition to obesity, other metabolic and pathological factors (inflammatory factors, adipocytokines, corti-

Table 1. Pediatric Studies for MetS Using Modified ATP III, WHO, and EGIR Criteria

Study	No. of Risk Factors	Obesity	High Blood Pressure	Dyslipidemia	Glucose Intolerance	Insulin Resistance
Cook et al ¹⁹ and Duncan et al, ²²⁶ NHANES	≥3	≥90% WC (NHANES III)*	≥90% for age, sex, and height (3rd report NHBPEP)†	≥110 mg/dL TG (Lipid Research Clinics)‡ ≤40 mg/dL HDL (Lipid Research Clinics)	≥110 mg/dL fasting glucose (ADA)§	
Cruz and Goran, ²⁷¹ SOLAR Diabetes Project	≥3	≥90% WC (NHANES III)	≥90% for age, sex, and height (3rd report NHBPEP)	≥90% TG for age and sex (NHANES III) ≤10% HDL for age and sex (NHANES III)	≥110 mg/dL fasting glucose (ADA)	
de Ferranti et al, ²⁷² NHANES	≥3	>75% WC (NHANES III)	>90% for age, sex, and height (3rd report NHBPEP)	≥97 mg/dL TG (Lipid Research Clinics, ≥80%) <50 mg/dL HDL (Lipid Research Clinics, <40%)	≥110 mg/dL fasting glucose (ADA)	
Goodman et al, ²⁰ Cincinnati	≥3	≥102 cm WC, male; ≥88 cm WC female (ATP III)	≥130/85 mm Hg BP (ATP III)	≥150 mg/dL TG (ATP III) ≤40 mg/dL HDL male, ≤50 mg/dL female (ATP III)	≥110 mg/dL fasting glucose (ADA)	
Lambert et al, ¹⁴ Quebec Study	≥3	≥85% BMI for age and sex (cohort percentile)	≥75% SBP for age and sex (cohort percentile)	≥75% TG for age and sex (cohort percentile) ≤25% HDL for age and sex (cohort percentile)	≥110 mg/dL fasting glucose (ADA) ≥75% insulin for age and sex (cohort percentile)	
Weiss et al, ¹⁵ Yale and Cincinnati	≥3	>97% BMI (CDC growth chart)¶ or z score >2 for study cohort	>95% for age, sex, and height (3rd report NHBPEP)	>95% TG for age, sex, and race (NHLBI Growth and Health Study)# <5% HDL for age, sex, and race (NHLBI Growth and Health Study)	≥140 mg/dL, <200 mg/dL 2-h glucose, OGTT (ADA)	
Chu et al, ²⁷³ Taipei Children's Heart Study	3/3		≥90% for age and sex (cohort percentile)	≥90% TG or TC for age and sex (cohort percentile)	≥90% fasting glucose for age and sex (cohort percentile)	
Freedman et al, ¹⁶⁴ Bogalusa	≥3/5		≥95% for age, height, sex, and race (cohort percentile)	<35 mg/dL HDL ≥130 mg/dL TG ≥130 mg/dL LDL		≥95% fasting insulin for age and sex (cohort percentile)
Goodman et al, ²⁰ NHANES	IR or DM, plus 2 additional risk factors	≥102 cm WC (male) or ≥88 cm (female); or ≥95% BMI (CDC) ¹⁴	≥130/85 mm Hg BP	≤35 mg/dL HDL (male) or ≤39 mg/dL (female), or ≥150 mg/dL TG	≥110 mg/dL or known diabetes (ADA) ²⁷²	>75% insulin (cohort percentile)
Katzmarzyk et al, ²⁷⁴ Bogalusa	≥3/6		>80% BP for age (cohort percentile)	<20% HDL for age (cohort percentile) >80% LDL for age (cohort percentile) >80% TG for age (cohort percentile)	>80% glucose for age (cohort percentile)	>80% insulin for age (cohort percentile)
Lambert et al, ¹⁴ Quebec Study	IR plus 2 additional risk factors	≥85% BMI for age and sex (cohort percentile)	≥75% SBP for age and sex (cohort percentile)	≤25% HDL for age and sex (cohort percentile) ≥75% TG for age and sex (cohort percentile)	≥110 mg/dL (ADA)	≥75% insulin for age and sex (cohort percentile)
Morrison et al, ²⁷⁵ NHLBI Growth and Health Study	≥3/5		>90% SBP (NHBPEP) ²²⁶ >90% DBP (NHBPEP)	<40 mg/dL HDL >126 mg/dL LDL >104 mg/dL TG		
Raitakari et al, ²⁶ Young Finns Study	3/3	≥75% skinfold** for age and sex (cohort percentile)	≥75% SBP for age and sex (cohort percentile)	≥75% LDL for age and sex (cohort percentile)		
Srinivasan et al, ⁸³ Bogalusa	4/4	>75% BMI for age, sex, race, and study year (cohort percentile)	>75% SBP or MAP for age, sex, race, and study year (cohort percentile)	>75% TC/HDL or TG/HDL for age, sex, race, and study year (cohort percentile)		>75% fasting insulin for age, sex, race, and study year (cohort percentile)

(Continued)

Table 1. Continued

Study	No. of Risk Factors	Obesity	High Blood Pressure	Dyslipidemia	Glucose Intolerance	Insulin Resistance
Adult EGIR modified ²⁷⁶		≥91%	≥95% height	≥160 mg/dL TG ≤31 mg/dL HDL-C	110–142 mg/dL	Male: ≥35 pmol/L; female: ≥40 pmol/L

WHO indicates World Health Organization; EGIR, European Group for the Study of Insulin Resistance; NHANES, National Health and Nutrition Examination Survey; WC, waist circumference; NHBPEP, National High Blood Pressure Education Program; TG, triglycerides; HDL, high-density lipoprotein; ADA, American Diabetes Association; SOLAR, Study of Latinos at Risk; BP, blood pressure; SBP, systolic blood pressure; CDC, Centers for Disease Control and Prevention; NHLBI, National Heart, Lung, and Blood Institute; OGTT, oral glucose tolerance test; LDL, low-density lipoprotein; IR, insulin resistance; DM, diabetes mellitus; MAP, mean arterial pressure; and TC, total cholesterol.

*National Health and Nutrition Examination Survey III data used to define waist circumference, triglyceride, and HDL-C percentiles.²⁷⁷

†Third National High Blood Pressure Education Program guideline for defining high blood pressure.²⁷⁸

‡Lipid research clinics data used to define triglyceride and HDL-C percentiles.²⁷⁹

§American Diabetes Association guideline for defining glucose intolerance and diabetes.¹⁹²

||ATP III guideline for defining MetS.²⁸⁰

¶Centers for Disease Control and Prevention growth chart used to define BMI.²⁸¹

#National Heart, Lung, and Blood Institute Growth and Health Study data used to define triglyceride and HDL-C percentiles.²⁸²

**Skinfold was the sum of biceps, triceps, and subscapular skinfolds.

sol, oxidative stress, vascular factors, heredity, and lifestyle factors) are operative in this process. The Figure presents our concept of the components of MetS as they emerge from interactions between vascular abnormalities, oxidative stress, visceral fat, inflammation, adipocytokines, and cortisol, as part of the larger environment of obesity and insulin resistance, and under the influence of genetic and ethnic predispositions that ultimately result in disease. The truest picture of cardiometabolic risk due to obesity not only requires attention to the traditional markers of the MetS but also requires a full metabolic panel, family history, and review of lifestyle behaviors.

Insulin Resistance

The role of insulin in the development of cardiovascular morbidity remains controversial. Fasting hyperinsulinemia, a marker of insulin resistance, is associated with atherosclerosis and cardiovascular morbidity.^{36,37} Several lines of evidence suggest insulin may directly promote cardiovascular pathology: (1) Insulin stimulates mitogen-activated protein kinase, mitogenesis, and plasminogen activator inhibitor-1 within vascular smooth muscle cells³⁸; (2) insulin stimulates endothelin-1 production, with subsequent vascular smooth

muscle growth³⁹; (3) insulin stimulates *ras*-p21 in vascular smooth muscle, which promotes increased effects of other growth factors, such as platelet-derived growth factor⁴⁰; and (4) the vascular endothelial cell insulin receptor knockout mouse has lower blood pressure and endothelin-1 levels than its wild-type counterpart.⁴¹ Conversely, other lines of evidence suggest that insulin may be antiatherogenic: (1) Insulin inhibits the inflammatory transcription factor nuclear factor- κ B⁴²; (2) insulin decreases levels of early growth response gene-1 and tissue factor⁴³; (3) insulin decreases tumor necrosis factor- α (TNF- α)⁴⁴; and (4) insulin stimulates nitric oxide to lower blood pressure.⁴⁵ As with other hormone-receptor interactions, the duration and amplitude of insulin effects may play a role, because chronic hyperstimulation by excessive ligand may lead to alternative cellular responses (eg, cortisol) or tachyphylaxis (eg, opioids), which would alter hormone action.

In healthy individuals, insulin suppresses hepatic glucose production and promotes the uptake, utilization, and storage of glucose by the liver and peripheral tissues.⁴⁶ The majority of peripheral glucose metabolism takes place in muscle (\approx 80%). Insulin resistance is believed by many to play a central role in the pathogenesis of the MetS, as exemplified

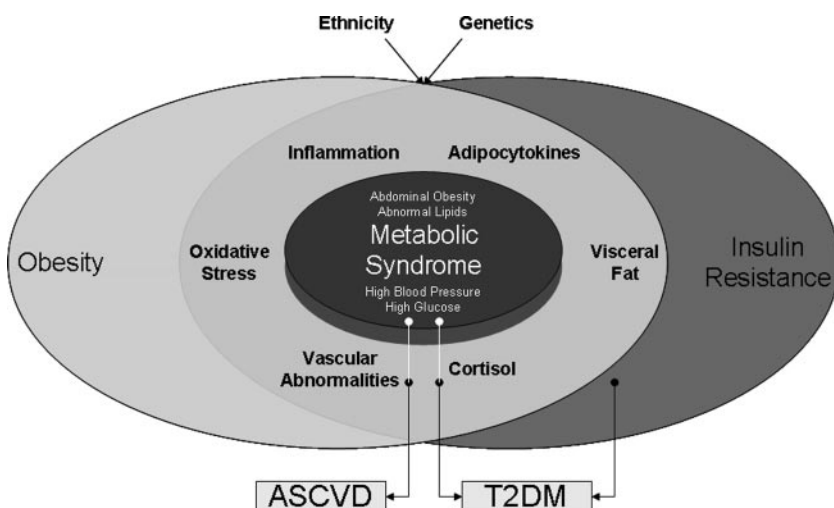


Figure. Schematic of components of the MetS.

by the World Health Organization's criteria in adults. Differential sensitivity of various tissues to insulin likely plays a role in the variability of expression of the MetS. Frequently, the liver manifests insulin resistance relative to the periphery; this leads to de novo lipogenesis and dyslipidemia. Hepatic insulin resistance leads to free fatty acid exportation to the muscles to promote muscle insulin resistance.⁴⁷ The primary role of hepatic insulin resistance in MetS is recapitulated in several animal models.^{48–50} Either impaired hepatic or adipose responses to insulin, or both, can lead to the buildup of circulating free fatty acids,⁵¹ which can lead to a compensatory increase in the secretion of insulin from pancreatic β -cells.^{46,52}

Over time, individuals with insulin resistance become hyperinsulinemic. This can take the form of insulin hypersecretion or reduced insulin clearance.⁵³ As long as the pancreas can adequately compensate for insulin resistance, blood glucose concentrations remain normal; however, in some patients, the capacity of the β -cell erodes over time,⁵⁴ which leads to β -cell failure and subsequent T2DM.

An independent effect of insulin resistance on cardiovascular risk in children has also been suggested. Fasting insulin levels in 6- to 9-year-old children predicted the children's level of blood pressure at age 9 to 15 years,⁵⁵ and in 5- to 9-year-old Pima Indian children, fasting insulin was associated with the level of weight gain during the subsequent 9 years of childhood.⁵⁶ The Bogalusa Heart Study has shown a strong relation over an 8-year period of observation between persistently high fasting insulin levels and the development of cardiovascular risk factors in children and young adults.⁵⁷ In studies of insulin resistance in childhood that used the euglycemic insulin clamp, an important independent association of both body fatness and insulin resistance with increased cardiovascular risk factors was shown, as well as an interaction between body fatness and insulin resistance, so that the presence of both was associated with a level of cardiovascular risk greater than that expected with either fatness or insulin resistance alone.²¹

A transient insulin-resistant state occurs in children during normal pubertal development.^{58–61} Studies with euglycemic insulin clamps have shown that insulin resistance increases at the beginning of puberty, peaks at mid puberty, and returns to near-pubertal levels by the end of puberty.⁶¹ The increase in growth hormone, sex hormone, and insulin-like growth factor-1 levels that occurs during puberty is thought to be the cause of this form of insulin resistance.⁶²

Obesity

Obesity has been strongly associated with insulin resistance,⁶³ T2DM,⁶⁴ and ASCVD.⁶⁵ Data from the Framingham Study have established an increased incidence of cardiovascular events in both men and women with increasing weight⁶⁶; body weight and mortality were directly related in the Harvard Alumni Health Study,⁶⁷ and weight loss was associated with a decrease in inflammatory cytokines⁶⁸ and insulin concentration and an increase in insulin sensitivity in adults⁶⁹ and adolescents.⁷⁰ Currently, more than 20% of all children and adolescents in the United States are overweight.⁷¹ Childhood obesity has been associated with ele-

vated blood pressure,⁷² elevated triglycerides,^{73,74} low HDL-C,^{73,74} abnormal glucose metabolism,⁵⁴ insulin resistance,^{73,75,76} inflammation,^{77–80} and compromised vascular function.⁸¹ Obesity tracks from childhood to adulthood, and childhood adiposity is a strong predictor of obesity, insulin resistance,⁸² and abnormal lipids in adulthood.⁸³ Moreover, the rate of increase in adiposity during childhood was significantly related to the development of cardiovascular risk in young adults.⁸⁴

However, BMI only accounts for 60% of the variance of insulin resistance in adults,⁸⁵ which suggests that other factors are important. Indeed, in a Spanish population, children with premature adrenarche and insulin resistance were thin.⁸⁶ Recent evidence in children shows that waist circumference is more associated with visceral fat, whereas BMI is more associated with subcutaneous fat.⁸⁷ Similarly, only visceral fat (as measured by magnetic resonance imaging), not BMI or waist-hip ratio, was associated with fasting insulin and triglycerides in obese adolescent girls.⁸⁸ Lastly, there is a statistical interaction between fatness and insulin resistance in predicting cardiovascular risk factors in adolescence, with neither BMI nor insulin resistance alone fully explaining the MetS.²¹ In adults, it is well established that visceral fat is related to increased cardiovascular risk independent of total body fat.^{89,90} Waist-to-hip ratio and waist circumference are often used as markers of visceral fat.⁹¹ Recently, waist circumference in children was found to be an independent predictor of insulin resistance.⁹² The relationship between waist circumference—measured abdominal obesity and health outcomes appears to be explained by its strong association with visceral adipose tissue,⁹² an independent predictor of metabolic and cardiovascular disease.⁹³ Visceral fat measured in a small sample of adolescent girls⁹⁴ was associated with dyslipidemia and glucose intolerance, especially in the obese. Waist circumference has also been associated with inflammatory biomarkers such as CRP⁹⁵ and adiponectin^{96,97} in youth. Given the significant increase in waist circumference among US children and adolescents over the past 2 decades,⁹⁸ a marker of abdominal obesity should be considered as an important component of the pediatric MetS definition. Thus, it appears that the distribution of body fat is an important determinant in the expression of risk as early as in childhood. Despite this recognition, in a recent statement, an expert committee of the American Medical Association and the Centers for Disease Control and Prevention Task Force on Assessment, Prevention, and Treatment of Childhood Obesity was unable to recommend the use of waist circumference for routine clinical use in children at the present time because of “incomplete information and lack of specific guidance for clinical application.”⁹⁹

Adipocytokines

The secretory role of visceral fat—derived proinflammatory cytokines (eg, interleukin-6 [IL-6], TNF- α) and adipocytokines (eg, adiponectin and leptin) appears to be directly associated with obesity and insulin resistance.¹⁰⁰ TNF- α and IL-6 are positively related to adiposity, triglycerides, and total cholesterol and negatively related to HDL-C in healthy adults.¹⁰¹ Adipocytes^{101,102} and macrophages embedded in

adipose tissue¹⁰³ overproduce IL-6. Expression of TNF- α and messenger ribonucleic acid is increased in the visceral fat of obese subjects and is positively correlated with the degree of obesity and levels of plasma insulin.¹⁰⁴ IL-6 and TNF- α mediate lipolysis indirectly and augment hepatic synthesis of fatty acids, thereby increasing serum levels of fatty acids and triglycerides.¹⁰⁵ The inflammatory cascade triggered by these cytokines is in turn further enhanced by hyperinsulinemia.¹⁰⁶ IL-6 and TNF- α also act directly at the insulin receptor to decrease receptor signaling and increase insulin resistance.¹⁰⁷

Inflammatory Mediators

Elevated levels of circulating inflammatory cytokines have been shown to be associated with the atherosclerotic process, and CRP is one of the most sensitive indicators.¹⁰⁸ CRP is produced in the liver and regulated by inflammatory cytokines, principally IL-6 and TNF- α .^{109,110} CRP has been localized to atherosclerotic plaques and infarcted myocardium, where it promotes activation of complement.^{111,112} Obesity in adults is strongly associated with CRP, which suggests that it may represent a chronic state of low-grade inflammation.^{113–115} An association of CRP with adiposity, fasting insulin, dyslipidemia, and blood pressure has been shown in a cohort of healthy prepubertal children.⁷⁷ In healthy adolescents, CRP was significantly associated with insulin resistance and components of the MetS; nevertheless, this association was attenuated after adjustment for body fatness, which suggests that obesity may precede the development of CRP elevation in the evolution of cardiovascular risk.¹¹⁶ Conversely, a longitudinal adult study documented change in inflammatory biomarkers that preceded accelerated weight gain and, by inference, obesity and insulin resistance.¹¹⁷ In a study of overweight Swiss children, elevated concentrations of inflammatory markers were present as early as 6 years of age, and dietary fat and antioxidant intake rather than insulin resistance were predictors of CRP levels.¹¹⁸ The temporal and causal relationships between these cyclic metabolic derangements remain unclear.

Oxidative Stress

Experimental animal models suggest that early obesity on a high-calorie, high-fat diet is characterized by increased vascular oxidative stress and endothelial dysfunction, before the development of insulin resistance and systemic oxidative stress.¹¹⁹ Free fatty acids may stimulate, either independently or in concert with hyperglycemia, the production of reactive oxygen species (oxidative stress).¹²⁰ Reactive oxygen species and reactive nitrogen species, by inflicting macromolecular damage, may play a key direct role in the pathogenesis of diabetes. Reactive oxygen species also function as signaling molecules (analogous to second messengers) to activate several stress-sensitive pathways (indirect role). In addition, in T2DM, there is growing evidence that activation of stress-sensitive pathways by elevations in glucose and possibly free fatty acid levels leads to both insulin resistance and impaired insulin secretion. Oxidative stress in turn is associated with a reduction in insulin-stimulated glucose transport¹²¹ and target-organ damage such as that related to T2DM and ASCVD.¹²² A significant association has been documented in adolescents between hypertension and oxidative

stress, independent of BMI,¹²³ and a report in 295 adolescents has shown significant relations for oxidative stress with adiposity and insulin resistance.²¹

In a recent pediatric study, the presence of MetS components in overweight children was associated with increased levels of 8-isoprostane, a marker of systemic oxidative stress, and adipocytokines associated with endothelial dysfunction.¹²⁴ The levels of these plasma biomarkers were higher in children with components of the MetS than in normal-weight children or overweight children without components of the MetS. Despite these reports, there currently is insufficient evidence relating oxidative stress to MetS components in children, and this remains an important area for future research.

Cortisol

In humans, stress, depression, and cortisol are linked to the MetS.^{125–128} Psychosocial stresses correlate with risk of myocardial infarction in adults.¹²⁹ Hypercortisolemia leads to visceral obesity and the accelerated and severe cardiovascular mortality of Cushing's syndrome. Even exogenous glucocorticoid administration is a risk factor for cardiovascular events.¹³⁰

Evidence of associations between elevated cortisol and psychological distress with abdominal fat distribution in adults is compelling. For instance, urinary glucocorticoid excretion is linked to aspects of the MetS, including blood pressure, fasting glucose, insulin, and waist circumference.¹³¹ It has been proposed that the MetS is equivalent to "Cushing's syndrome of the abdomen." The role of cortisol in mediating visceral fat accumulation, insulin resistance, and T2DM has been elegantly demonstrated in animal models.^{132,133} The data suggest that cortisol is important both in increasing visceral adiposity and in promoting the MetS.

Vascular Structure and Function

Given that early atherosclerosis may involve the endothelium of many arteries, abnormalities of peripheral arteries may reflect changes in the coronary arteries.¹³⁴ It is generally agreed that endothelial dysfunction occurs early in the pathogenesis of atherosclerosis.¹³⁵ The endothelium plays a prominent role in the maintenance of both basal and dynamic vascular tone and function, predominantly through the release of vasoactive substances such as nitric oxide. Nitric oxide has been shown to possess antiatherogenic properties, such as inhibition of leukocyte adhesion,¹³⁶ platelet aggregation,¹³⁷ and vascular smooth muscle proliferation,¹³⁸ thereby conferring a protective effect on the vasculature. Insulin resistance is associated with endothelial dysfunction and impaired insulin-mediated nitric oxide-dependent vasodilation.¹³⁹ In a study of brachial artery endothelial function and stiffness in 48 severely obese children and 27 normal-weight control children, the obese children had lower arterial compliance, lower distensibility, increased wall stress, increased incremental elastic modulus (measure of stiffness), impaired endothelial function, and increased insulin resistance compared with the normal-weight children.⁸¹ Moreover, 8 weeks of aerobic exercise training by stationary cycling improved arterial endothelial function in overweight children and adolescents; of particular interest in this group is that body weight and body composition remained the same after exer-

cise, yet improvements in endothelial function still occurred, which suggests that exercise may have a direct beneficial role on the health of the vasculature.¹⁴⁰

Increased arterial stiffness has been associated with the MetS. Increased carotid stiffness was found in adults with increasing numbers of MetS risk factors measured in childhood.³² Few data exist in children, but 1 study did find increased carotid stiffness in children with MetS even after adjustment for age, sex, and level of inflammation.³³ Decreased resting brachial distensibility (not flow mediated) has also been associated with insulin resistance, and a graded relation has been found between a number of MetS components and worsening brachial artery function.¹⁴¹

The common carotid artery intima-media thickness (C-IMT) measured by ultrasound imaging is also a marker of preclinical atherosclerosis. C-IMT relates to the severity and extent of coronary artery disease¹⁴² and predicts the likelihood of cardiovascular events^{143–145} in adults. C-IMT in children was increased with type 1 diabetes mellitus^{146,147} and hypertension.¹⁴⁸ A recent study in 79 healthy children 10.5±1.1 years of age showed that CRP was a significant independent predictor of C-IMT and flow-mediated vasodilation.¹⁴⁹ Others have shown that adolescent offspring of adults with premature ASCVD had increased C-IMT and abnormal flow-mediated vasodilation compared with control subjects.¹⁵⁰

Hypertension

The relation between hypertension and insulin resistance is confounded by the significant independent relation between hypertension and obesity.¹⁵¹ Hypertension is an integral component of the MetS.² Increased sympathetic tone has been associated with obesity in adolescents, and both insulin and leptin¹⁵² appear to have a direct effect on sympathetic nervous system activity.¹⁵³ Insulin infusions stimulate sodium retention by the kidney,¹⁵⁴ and insulin stimulates vascular smooth muscle growth.¹⁵⁵ Fasting insulin, used as an estimate of insulin resistance, has been significantly correlated with blood pressure in children and adolescents.¹⁵⁶ The Cardiovascular Risk in Young Finns study showed a significant correlation between fasting insulin and blood pressure in children and adolescents and also showed that the level of fasting insulin predicted the level of blood pressure 6 years later.⁵⁵ Similarly, leptin has direct central effects that increase sympathetic outflow to the kidney. It has been hypothesized that selective leptin resistance maintains leptin-induced sympathetic activation in obesity, which permits leptin to play an important role in the pathogenesis of obesity-related hypertension and MetS.¹⁵⁷ Studies in 11- to 15-year-olds¹⁵⁸ showed a lack of significant correlations for blood pressure with fasting insulin (adjusted for BMI), insulin resistance (measured with the euglycemic clamp), triglycerides, HDL-C, and low-density lipoprotein (LDL) cholesterol. However, when the MetS factors (triglycerides, HDL-C, fasting insulin, and BMI) were considered together as a cluster and comparisons made between children with high and low blood pressure, the cluster score was significantly higher in the high blood pressure group. Thus, despite the lack of a significant relation between blood pressure and the individual risk factors, its relation with the cluster of risk factors is consistent with a

clinical association of blood pressure and the MetS before adulthood. Most recently, the Fels Longitudinal Study showed a strong association between childhood hypertension and adult MetS.¹⁵⁹

Lipid Abnormalities

Lipid abnormalities, particularly high triglycerides and low HDL-C, are strongly associated with insulin resistance¹⁶⁰ and are criteria for the MetS. Studies in rats have shown that hyperinsulinemia stimulates the synthesis of fatty acids by increasing the transcription of genes for lipogenic enzymes in the liver.¹⁶¹ Fatty acids in turn stimulate increased production of very-low-density lipoprotein. It is currently unknown whether insulin resistance induces dyslipidemia or whether insulin resistance and dyslipidemia are associated via an underlying cause.

Abnormal lipid profiles also are found in children with obesity and insulin resistance.^{162,163} Data from the Bogalusa Heart Study have shown that overweight children have significantly higher levels of total cholesterol, LDL cholesterol, and triglycerides and lower HDL-C levels than normal-weight children.¹⁶⁴ The hypertriglyceridemic waist phenotype has been proposed in adults as a predictor of the MetS.¹⁶⁵ A recent study in more than 3000 adolescents that used the modified ATP III cut points for serum triglycerides (≥ 110 mg/dL) and waist circumference (≥ 90 th percentile for age and sex) has shown that the concomitant presence of these criteria was significantly associated with a clustering of metabolic abnormalities, which is characteristic of the MetS.¹⁶⁶

Apolipoprotein CIII, a marker of the triglyceride-rich lipoproteins increased in MetS, retards triglyceride clearance.¹⁶⁷ This may explain why there is a preponderance of small, dense LDL particles in the setting of MetS along with hypertriglyceridemia. Small, dense LDL particles may have increased atherogenic potential, and the mechanisms proposed for this association are their low affinity to LDL receptors, propensity to undergo oxidative stress, prolonged plasma half-life, and high penetration of the intima.^{168–170} In adults¹⁷¹ and more recently in children,^{172,173} a high prevalence of small, dense LDL particles was demonstrated in association with abdominal obesity, visceral fat, and insulin resistance. Hypertriglyceridemia is less frequent in blacks, which complicates the determination of appropriate cutoffs for the diagnosis of MetS.^{174,175} Independent of weight and insulin status, blacks have lower apolipoprotein CIII levels than other racial subgroups.¹⁷⁶ Accordingly, lower apolipoprotein CIII levels in blacks correlate with less hepatic lipase degradation of triglyceride-rich precursors and less production of small, dense LDL. And yet, LDL lipoprotein sizing still correlates with triglyceride levels in blacks, just in a different range.¹⁷⁷ These findings suggest that perhaps different lipid thresholds should be used for blacks, because their lower incidence of dyslipidemia, as currently defined, does not lower their risk for T2DM¹⁷⁸ or cardiovascular morbidity.¹⁷⁹

Glucose Intolerance: T2DM

Diabetes mellitus, a metabolic disease characterized by hyperglycemia, is associated with accelerated development of vascular disease. Because insulin is the only significant

hypoglycemic hormone, hyperglycemia is the result of either impaired secretion of insulin (type 1), resistance to the effect of insulin in liver or muscle (type 2), or a combination of these pathophysiological situations.

The progression from insulin resistance and impaired carbohydrate metabolism to T2DM has been documented in adults^{180,181} and children.^{182,183} In adults, weight loss has been shown to reverse this progression, with frank diabetes regressing to insulin resistance.¹⁸⁴ Patients with impaired fasting glucose or impaired glucose tolerance are referred to as “prediabetic,” which acknowledges the relatively high risk for development of frank diabetes.¹⁸⁵ With the current obesity epidemic and its metabolic consequences, the identification of children with impaired fasting glucose, that is, fasting glucose 100 to 126 mg/dL (Table 2), is very important, because appropriate management may decrease the progression to T2DM. Nevertheless, not all children with impaired carbohydrate metabolism develop T2DM. In a study of children with impaired glucose tolerance followed up over a period of 1 year, one third became euglycemic, one third developed T2DM, and one third maintained impaired glucose tolerance.¹⁸⁶ Data from the Third National Health and Nutrition Examination Survey (NHANES III) reveal that the prevalence of type 1 diabetes mellitus in adolescents is 1.7/1000, whereas the prevalence of T2DM is 4.1/1000. This increase coincides with increasing rates of overweight and physical inactivity in children.¹⁸⁷

Considered previously to be a disease of adults, in the last decade, T2DM has become a far more common occurrence in the pediatric population. Depending on the ethnic composition of the population, between 8% and 50% of newly diagnosed adolescent diabetic patients have T2DM.^{188,189} This trend parallels the increase in childhood obesity. In series of children with T2DM, the mean BMI ranged from 26 to 38 kg/m².¹⁸⁷ Children with T2DM usually present asymptotically with mild to moderate hyperglycemia in adolescence in combination with obesity, signs of insulin resistance, and other components of the MetS. When T2DM begins in childhood, the risk for accelerated atherosclerosis is increased beyond that seen in those who develop this diagnosis as adults.

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus defines impaired fasting glucose as >100 mg/dL (5.6 mmol/L) but <126 mg/dL (7.0 mmol/L) and impaired glucose tolerance as 2-hour oral glucose tolerance test values >140 mg/dL (7.8 mmol/L).^{190,191} Specific guidelines have been defined for screening for T2DM in obese children, particularly those from high-risk racial/ethnic groups (Native American, Hispanic American, African American, Asian, and Pacific Islander), those with a positive family history of T2DM, and those with physical signs of insulin resistance.¹⁹² Current American Diabetes Association guidelines recommend routine glucose testing in obese children >10 years of age with 2 additional risk factors for T2DM.¹⁹² Because T2DM is a relatively recent problem in adolescents, there are few data on long-term follow-up. One study of Pima Indians followed up individuals for a mean of 10 years to a median age of 26 years. In that cohort, at baseline (age 5 to 19 years), 85% were obese, 14% had hypertension, 30% had total cholesterol >200 mg/dL, and

55% had triglyceride concentrations >200 mg/dL. Fifty-eight percent of the patients had microalbuminuria, and 16% had a urinary albumin/creatinine ratio >300 mg/g, which indicates that the renal effects of diabetes were already present at diagnosis. After 10 years of follow-up (to a median age of 26 years), the number of patients with increased urinary albumin excretion was increased significantly, as was the magnitude of albuminuria; however, the incidence of overt vascular disease remained relatively low.¹⁹³

Obese individuals develop different degrees of insulin resistance, but not all those with obesity develop glucose intolerance. The factors that make some individuals more likely to progress to T2DM are not well understood at the present time. A strong family predisposition is known to exist; therefore, parental history is important in risk assessment. Patients with T2DM often have other risk factors for cardiovascular disease; hypertriglyceridemia has been reported in 4% to 32% of children with T2DM.¹⁸⁸ Essential hypertension is known to be associated with diabetes in adults,¹⁹⁴ and it is estimated that cardiovascular risk doubles when hypertension and diabetes mellitus coexist; however, population-based prevalence data on hypertension in children with diabetes are not available.

Other Diseases Related to the Mets

In females, excess visceral fat is associated with hyperandrogenism.¹⁹⁵ Up to 50% of circulating testosterone may be derived from the conversion of weak adrenal and ovarian androgens to testosterone in adipose tissue. In addition, the biologically active androgen fraction tends to be higher among obese females, who have lower concentrations of sex hormone-binding globulin.¹⁹⁶ Hyperandrogenism is frequently associated with insulin resistance, although which is primary versus secondary remains controversial. One possible explanation of both phenomena is the serine phosphorylation hypothesis, which posits that defective phosphorylation of both the insulin receptor and P450c17 (the enzyme responsible for the production of androgen in the adrenal gland and ovary) leads to both increased androgen precursor synthesis and defective insulin receptor signal transduction.¹⁹⁷ These endocrine abnormalities clearly place the adolescent female with MetS at high risk for polycystic ovary syndrome as well.

The prevalence of nonalcoholic fatty liver disease, another disease associated with the MetS,¹⁹⁸ is difficult to estimate in children, because the diagnosis is confirmed only by liver biopsy.¹⁹⁹ A recent study of autopsy specimens suggests a prevalence in 13% of children and 38% of obese children.²⁰⁰ Alanine transaminase elevations, along with abdominal ultrasound, may be useful in the diagnosis²⁰¹; however, only 40% of patients will have elevated liver enzymes, and the degree of elevation does not always correlate with the degree of obesity. Insulin resistance promotes free fatty acid release from adipocytes, which are taken up the liver and which, if not processed immediately, precipitate into lipid droplets, termed “hepatic steatosis.” This condition may evolve into nonalcoholic steatohepatitis and ultimately cirrhosis.²⁰²

Table 2. Treatment Recommendations

General Comments	Step 1	Step 2
Lifestyle		
Diet evaluation, diet education for all	Adequate calories for growth. Total fat 25% to 35% of calories, saturated fat <7% of calories, trans fat <1% of calories, cholesterol <300 mg/d	
BMI 85th to 95th percentile	Maintain BMI with aging to reduce BMI to <85th percentile If BMI >25 kg/m ² , weight maintenance 2- to 4-year-olds will achieve reductions in BMI by achieving a rate of weight gain <1 kg per 2 cm of linear growth Children ≥4 years old will achieve reductions in BMI by BMI maintenance or more rapidly with weight maintenance during linear growth	
BMI >95th percentile	Younger children: weight maintenance; adolescents: gradual weight loss of 1 to 2 kg/mo to reduce BMI	Dietitian referral
BMI ≥95th percentile plus comorbidity	Gradual weight loss (1 to 2 kg/mo) to achieve healthier BMI; assess need for additional therapy of associated conditions	Dietitian referral, ± pharmacological therapy
Physical activity	Specific activity history for each child, focusing on time spent in active play and screen time (television+computer+video games). Goal is ≥1 h of active play each day; screen time limited to ≤2 h/d. Encourage activity at every encounter	Referral to exercise specialist
Blood pressure		
SBP +/- DBP=90th to 95th percentile or BP >120/80 mm Hg (3 separate occasions within 1 mo) plus excess weight	Gradual weight loss (1 to 2 kg/mo) to achieve healthier BMI by decreased calorie intake, increased physical activity	Dietitian referral
Initial SBP ± DBP >95th percentile (confirmed within 1 wk) or 6-mo F/U SBP or DBP >95th percentile		Pharmacological therapy per Fourth Task Force recommendations
Lipids: TG		
TG=150 to 400 mg/dL	Decrease simple sugars; low saturated and trans fats diet	
TG=150 to 1000 mg/dL plus excess weight	Dietitian referral for weight loss management; energy balance training plus physical activity recommendations (see above)	TG 700 to 1000 mg/dL: consider fibrate or niacin if >10 y of age
TG ≥1000 mg/dL	Consider fibrate or niacin	
Glucose		
FG=100 to 126 mg/dL plus excess weight	Gradual weight loss (1 to 2 kg/mo) to achieve healthier BMI by decreased calorie intake, increased physical activity	
Repeat FG 100 to 126 mg/dL	Endocrine referral	Insulin-sensitizing medication per endocrinologist
Casual glucose >200 mg/dL or FG >126 mg/dL	Endocrine referral; treatment for diabetes	
Maintain HbA _{1c} <7%		

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; F/U, follow-up; TG, triglycerides; FG, fasting glucose; and HbA_{1c}, hemoglobin A1c.

BMI normal values for age/gender are available at <http://www.cdc.gov/growthcharts>. Other data in the Table are from various published guidelines and recommendations.^{260,284–297}

Elevation of triglycerides to ≥1000 mg/dL is associated with significant risk for acute pancreatitis. A fasting triglyceride level of 700 mg/dL is likely to rise to >1000 mg/dL postprandially. Treatment recommendation is compatible with guidelines for management of dyslipidemia in diabetic children.

Risk Factors for the MetS

Heredity

Children of parents with MetS and increased cardiovascular risk may be at especially high risk of developing MetS and greater levels of cardiovascular risk factors themselves because of shared genetic and environmental factors.^{203–205} Familial influences on development of cardiovascular risk are

well known. Because ASCVD aggregates in families,^{206–208} parental history of ASCVD is accepted as a measure of the offspring's cardiovascular risk and has been used in prevention and intervention algorithms.^{209,210} The Bogalusa Heart Study has shown that offspring of parents with early coronary artery disease were overweight beginning in childhood and developed an adverse cardiovascular risk profile (elevated

total cholesterol, LDL cholesterol, and plasma glucose).²¹¹ In addition, children and young adults with a parental history of premature ASCVD had higher blood pressure, serum lipids, and homocysteine than those with a negative parental history.^{211–214} Twin and family studies have found substantial familial aggregation for the MetS risk factors.^{203–205} Measures of preclinical atherosclerosis such as c-IMT and functional brachial artery flow-mediated vasodilation showed evidence of early adverse changes in children of parents with premature ASCVD.¹⁵⁴ Conversely, most obese children have at least 1 parent who is obese,²¹⁵ and the risk of adult obesity among children <10 years old is more than doubled if a parent is obese.²¹⁶ The familial nature of insulin action in Pima Indians has been known for many years.²¹⁷ Relatives of diabetic patients tend to have higher insulin levels than relatives of nondiabetic individuals.^{218–220} A positive family history of T2DM was associated with higher levels of insulin resistance (insulin clamp studies) in 10-year-old black children.²²¹ In a study of 357 children and 378 parents (221 mothers and 157 fathers), children who had at least 1 parent with the MetS (defined by ATP III criteria) had significantly higher levels of obesity, particularly central obesity, and insulin resistance than children in whom neither parent had the MetS.²²²

Ethnic Differences

Significant differences in components of the MetS have been noted among ethnic groups, with most of the studies concentrated on differences among whites, blacks, and Hispanics. It is known that black children have a similarly high prevalence of obesity (23.6%) as Mexican Americans.^{223,224} Among girls 6 through 19 years of age, the prevalence of overweight among non-Hispanic white girls was significantly lower than that of non-Hispanic black and Mexican American girls. Among boys 6 through 19 years of age, Mexican American boys had a significantly higher prevalence of overweight than their non-Hispanic white and black counterparts.²²⁵

Similar to adults, black youth have lower total cholesterol and triglycerides and higher HDL-C levels than white children,¹¹ and Hispanic adults and children have an increased prevalence of high triglycerides.²²⁶ Although Weiss et al¹⁵ originally found lower prevalence rates of the MetS in black subjects, when they reanalyzed their study data using lipid threshold levels specific to blacks, the prevalence rate and the effect of obesity were similar to those of the white and Hispanic subjects in their study. Observations from the Bogalusa Heart Study found higher blood pressure levels in black children even without obesity.²²⁷ In a large study of blood pressure in youth, the overall prevalence of elevated blood pressure was 2.6% in Hispanics versus 1.6% in non-Hispanics, but this difference was accounted for by obesity.²²⁸

A number of studies have shown that black and Hispanic children are more insulin resistant than white children.^{229–232} Yet, the rates of the MetS in black youth are lower when the same ATP III criteria are used.^{11,19,233} Data from 377 children and adolescents in the Bogalusa Heart Study showed that black children, especially girls, had higher insulin responses to the oral glucose tolerance test than their white peers.²³¹ Other studies found that black adolescents have higher first- and second-phase

insulin concentrations than white subjects when evaluated by the hyperglycemic clamp.²³² Insulin resistance is similar in Hispanic and black children and greater than insulin resistance in white children, as determined by the frequently sampled intravenous glucose tolerance test.²²⁹ Thus, it may be prudent to consider the use of criteria specific for race/ethnicity in an evaluation for the MetS. The genetic and environmental factors that may contribute to ethnic differences in insulin resistance and the other components of MetS are poorly understood.

Lifestyle Behaviors

Television-Watching Habits

Epidemiological studies provide evidence that sedentary behavior, such as television watching, is positively associated with overweight among children and adults,^{234–236} although it is unknown whether watching television contributes to the development of insulin resistance and inflammation. In a recent study conducted among parents and their children enrolled in the Minnesota Heart Survey, children who watched at least 1 hour of television per day and had 1 or 2 overweight parents were at 15% or 32%, respectively, greater risk of being overweight than children with normal-weight parents.²³⁷ Furthermore, for each hour of television watched per day, the likelihood of a child being overweight increased 2%; overweight parents watched more television than normal-weight parents.

Physical Activity

Physical activity is beneficial for weight management and prevention of overweight and obesity in adults and children.²³⁸ There is evidence for an association between physical activity and lower levels of inflammatory cytokines and markers of oxidative stress.^{239,240} Higher levels of physical activity are also positively correlated with insulin sensitivity in adolescents²⁴¹ and with improved endothelial function and HDL-C, even in the absence of weight loss.¹⁵⁴ However, most of these data are cross-sectional, and few studies have directly assessed the effect of exercise training on these variables. Many of the controlled intervention studies addressing this issue have shown that exercise improves adipokine and oxidative stress levels; however, most of these trials have reported concomitant improvements in body weight or composition that occurred during the exercise training period. Because adipocytes are the main mediators of these hormones, changes in body weight/composition confound the data with regard to the direct effects of exercise on these variables. Three studies have recently challenged the notion that exercise directly stimulates improvements in adipokines and inflammatory markers in adults and children^{242,243} independent of weight loss.

Dietary Intake

Increased consumption of whole grain foods decreases the development of coronary heart disease and diabetes and improves insulin sensitivity and inflammation in adults.^{244–247} In a recent study among adolescent boys and girls, greater insulin sensitivity was observed across increasing tertiles of whole grain intake after adjustment for age, sex, race, Tanner stage, energy intake, and BMI.²⁴⁴ The same relation was noted among the overweight and obese adolescents,²⁴⁴ as well

as in adults.²⁴⁵ A significant inverse association between fiber intake and the MetS has been described in adults²⁴⁸ and in the Framingham Offspring Study.²⁴⁹ Conversely, the prevalence of the MetS is significantly higher among individuals in the highest relative to the lowest quintile category of glycemic index.²⁵⁰ In 1 study, fiber attenuated the insulin response to ingested carbohydrate, with beneficial effects on insulin sensitivity, adiposity, and pancreatic function, and it promoted satiety.²⁵¹ There is evidence that a diet rich in fruit and vegetables, and therefore, antioxidants and micronutrients in addition to fiber, reduces the risk of ASCVD.^{245,252} Studies in adults have shown inverse relations of inflammatory factors with vitamin C, carotene, magnesium, and long-chain fatty acids.^{246,253,254} Because we do not eat just 1 nutrient or 1 food, it is important to examine the role of dietary patterns and their relation with health outcomes. Previous studies in adults have shown a Western dietary pattern (a diet high in red and processed meat, fried food, high-fat dairy foods, and sugar-sweetened beverages) to be associated with adverse levels of cardiovascular risk factors,²⁵⁵ higher BMI,^{256,257} and higher all-cause, ASCVD, and cancer mortality.²⁵⁸ Conversely, a Mediterranean diet rich in fruits, vegetables, whole grains, and fish, supplemented with olive oil or nuts, has beneficial effects on cardiovascular risk factors.²⁵⁹ Despite these presumed benefits, well-controlled studies in adults and children on the effect of these nutrients on risk for ASCVD are lacking. A recent scientific statement from the American Heart Association provides nutrition recommendations for the promotion of cardiovascular health in children and adolescents and is focused on total caloric intake and eating behaviors as part of a comprehensive healthy lifestyle.²⁶⁰

Treatment

Despite a lesser amount of basic and clinical information on childhood MetS than is available from adult studies, it is clear that the adverse associations among the risk factors that compose the MetS begin in childhood. In spite of challenges posed by a lack of definitions for "abnormal" with regard to elevated risk factors and a lack of longitudinal data linking levels of the risk factors in children with adult cardiovascular morbidity and mortality, there is little doubt that in the current obesogenic environment, the components of the MetS have become increasingly prevalent in children. The combination of dietary and physical activity interventions appears to provide the most beneficial improvements in components of the MetS. Comprehensive behavioral modification in overweight children reduces body weight, improves body composition, and positively modifies many of the components of the MetS within 3 months, and these effects are maintained at 1 year.²⁶¹ Similar effects have been observed for endothelial dysfunction, with the greatest improvements occurring when combined dietary and exercise interventions are used in overweight children.²⁶²

Therefore, it is reasonable to suggest that early intervention aimed at managing obesity could reduce the risk of developing the MetS. It is conceivable that even in the absence of weight loss, overweight and obese children may improve their cardiovascular risk profile by lifestyle changes and therapies targeted toward individual components of the syndrome.

At the present time, there is no specific treatment for this clustering of risk factors in children, other than reducing obesity, increasing physical activity, and treating the various components of the MetS (eg, hypertension or hyperlipidemia; Table 2). Weight control improves glucose tolerance, with a recommended weight loss in adults of 10% to 15%. Exercise training improves insulin sensitivity and endothelial vascular function beyond the benefits of glycemic control and blood pressure reduction in adults and children.^{263,264} In small studies, metformin has been used effectively in adolescents with T2DM to decrease BMI and improve glucose tolerance.^{265,266}

Future Research

By any MetS definition, abdominal obesity, insulin resistance, and hyperinsulinemia are the common characteristics of youth with the MetS. Indeed, although the majority of children with MetS tend to be overweight or obese, not all overweight or obese children develop MetS, T2DM, or cardiovascular disease. In view of the increasing prevalence of and adverse trends in obesity and its comorbidities in children, the question is whether tools can be developed to identify children who are most at risk metabolically.

This statement recognizes that additional research is necessary to define whether or not a homogeneous entity such as MetS or a similar construct can capture the above clustering of risk factors and predict future disease. Specific directions for future research include examination of the following:

- The stability of MetS phenotypes over time in childhood and adolescence in large-scale observational/outcome studies
- The molecular basis of the syndrome
- The possibility of environmental exposures or toxins and their role in promoting the MetS
- The role of medical management of insulin resistance, prehypertension, early vascular changes, elevated triglycerides, and low HDL-C
- Studies of the pathways linking insulin resistance and obesity with other components of MetS (or cardiometabolic risk factors) beginning early in life
- Studies of leptin biology and mechanisms of weight regulation
- The role of genetic predisposition and the prenatal and neonatal milieu in promoting future insulin resistance and MetS
- Whether in diverse racial/ethnic groups, the mechanisms and pathways that link this adverse pattern of clustering vary by racial/ethnic group.

Despite the attempts of others, we have declined to include a definition of or specific criteria for MetS in children. The concept of MetS in general has recently become a subject of increasing controversy.²⁶⁷ A recent review of these attempts to provide a definition in children highlighted the limitations of deriving or adapting definitions from adults and advocated for consideration of a novel and specific approach for children.²⁶⁸ Specific concerns related to the conceptualization of the MetS include an incomplete understanding of the underlying pathophysiology and considerable variation regarding its manifestation related to age, sex, ethnicity, and maturation. Given the lack of hard clinical end points in

the pediatric setting, the relationship between the individual risk factors and their clustering on the atherosclerosis disease process is difficult to define. The dichotomous definition of the MetS is also problematic, because all of the risk factors involved span a continuum of risk, and specific inflection points are probably not present. Considerable interaction between the risk factors may also exist. There is no doubt from pathological studies in children and young adults that the atherosclerotic process is accelerated in an exponential manner with increasing numbers of cardiovascular risk factors.²⁹ The risk does not subside, as highlighted by a recent report from the Bogalusa Heart Study that showed that BMI, insulin resistance, the ratio of triglycerides to HDL-C, and mean arterial pressure were clustered both in childhood and adulthood and, importantly, longitudinally as well.²⁶⁹ However, marked instability has been shown in the categorical diagnosis of MetS in adolescence.²⁷⁰ Because specific treatment aimed at the underlying pathophysiology of the MetS does not yet exist, other than reducing adiposity and

increasing physical activity, therapy targeted at each of the risk factors present is of importance. This treatment strategy would not be improved by labeling a patient dichotomously as having the MetS. Given the possibility of interaction related to the clustering, different thresholds for increasing the aggressiveness of therapy may be needed, but insufficient evidence currently exists to guide this. What is probably needed is not a dichotomous definition but a more complex weighted scoring system that takes into account the magnitude of all of the risk factors, their interaction, and other important patient characteristics, including family history. In summary, the goals of the present scientific statement are to emphasize the importance of identifying the pediatric cardiometabolic risk factors, only some of which are associated with the current proposed definitions of MetS, and the need for studying the tracking and interactions of these risk factors in longitudinal studies from childhood to adulthood to determine the specific components that should be included in a future definition of the MetS in youth.^{271–297}

Disclosures

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*Modest.

†Significant.

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References

- Steinberger J, Daniels SR. Obesity, insulin resistance, diabetes and cardiovascular risk in children: an American Heart Association scientific statement from the Atherosclerosis, Hypertension, and Obesity in the Young Committee (Council on Cardiovascular Disease in the Young) and the Diabetes Committee (Council on Nutrition, Physical Activity, and Metabolism). *Circulation*. 2003;107:1448–1453.
- Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement [published corrections appear in *Circulation*. 2005;112:e297 and 2005;112:e298]. *Circulation*. 2005;112:2735–2752.
- Kylin E. Studien über das Hypertonie-Hyperglykämie "mie-Hyperurikämie" miesyndrom. *Zentralbl Inn Med*. 1923;44:105–127.
- Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. *Annu Rev Med*. 1993;44:121–131.
- Kaplan NM. The deadly quartet: upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med*. 1989;149:1514–1520.
- DeFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*. 1991;14:173–194.
- Björntorp P. Abdominal obesity and the metabolic syndrome. *Ann Med*. 1992;24:465–468.
- Balkau B, Charles MA. Comments on the provisional report from the WHO consultation: European Group for the Study of Insulin Resistance. *Diabet Med*. 1999;16:442–443.
- National Institutes of Health. *Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III Final Report)*. Bethesda, Md: National Institutes of Health; 2002.
- World Health Organization, Department of Noncommunicable Disease Surveillance. *Report of a WHO Consultation: Definition of Metabolic Syndrome in Definition, Diagnosis, and Classification of Diabetes Mellitus and Its Complications: Report of a WHO Consultation, Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, Switzerland: World Health Organization; 1999.
- Chen W, Srinivasan SR, Elkasabany A, Berenson GS. Cardiovascular risk factors clustering features of insulin resistance syndrome (Syndrome X) in a biracial (Black-White) population of children, adolescents, and young adults: the Bogalusa Heart Study. *Am J Epidemiol*. 1999;150:667–674.
- Raitakari OT, Porkka KV, Rönnemaa T, Knip M, Uhari M, Akerblom HK, Viikari JS. The role of insulin in clustering of serum lipids and blood pressure in children and adolescents: the Cardiovascular Risk in Young Finns Study. *Diabetologia*. 1995;38:1042–1050.
- Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation*. 2004;109:2818–2825.
- Lambert M, Paradis G, O'Loughlin J, Delvin EE, Hanley JA, Levy E. Insulin resistance syndrome in a representative sample of children and adolescents from Quebec, Canada. *Int J Obes Relat Metab Disord*. 2004;28:833–841.
- Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yockel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med*. 2004;350:2362–2374.
- Rodríguez-Morán M, Salazar-Vázquez B, Violante R, Guerrero-Romero F. Metabolic Syndrome among children and adolescents aged 10–18 years. *Diabetes Care*. 2004;27:2516–2517.
- Huang TT, Nansel TR, Belsheim AR, Morrison JA. Sensitivity, specificity, and predictive values of pediatric metabolic syndrome components in relation to adult metabolic syndrome: the Princeton LRC follow-up study. *J Pediatr*. 2008;152:185–190.
- Chi CH, Wang Y, Wilson DM, Robinson TN. Definition of metabolic syndrome in preadolescent girls. *J Pediatr*. 2006;148:788–792.
- Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988–1994. *Arch Pediatr Adolesc Med*. 2003;157:821–827.
- Goodman E, Daniels SR, Morrison JA, Huang B, Dolan LM. Contrasting prevalence of and demographic disparities in the World Health Organization and National Cholesterol Education Program Adult Treatment Panel III definitions of metabolic syndrome among adolescents. *J Pediatr*. 2004;145:445–451.
- Sinaiko A, Steinberger J, Moran A, Prineas RJ, Vessby B, Basu S, Tracy R, Jacobs DR Jr. Relation of body mass index and insulin resistance to cardiovascular risk factors, inflammatory factors, and oxidative stress during adolescence. *Circulation*. 2005;111:1985–1991.
- Jones KL. The dilemma of the metabolic syndrome in children and adolescents: disease or distraction? *Pediatr Diabetes*. 2006;7:311–321.
- Goodman E, Dolan LM, Morrison JA, Daniels SR. Factor analysis of clustered cardiovascular risks in adolescence: obesity is the predominant correlate of risk among youth. *Circulation*. 2005;111:1970–1977.
- Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, Vanarsall RS, Murabito JM, Meigs JB, Cupples LA, D'Agostino RB Sr, O'Donnell CJ. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation*. 2007;116:39–48.

25. McLaughlin T, Abbasi F, Lamendola C, Reaven G. Heterogeneity in the prevalence of risk factors for cardiovascular disease and type 2 diabetes mellitus in obese individuals: effect of differences in insulin sensitivity. *Arch Intern Med.* 2007;167:642–648.
26. Raitakari OT, Porkka KV, Viikari JS, Rönnemaa T, Akerblom HK. Clustering of risk factors for coronary heart disease in children and adolescents: the Cardiovascular Risk in Young Finns Study. *Acta Paediatr.* 1994;83:935–940.
27. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. *Endocrinol Metab Clin North Am.* 2004;33:283–303.
28. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA.* 2002;287:356–359.
29. Berenson GS, Srinivasan SR, Bao W, Newman WP III, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults: the Bogalusa Heart Study. *N Engl J Med.* 1998;338:1650–1656.
30. McGill HC Jr, McMahan CA, Herderick EE, Zieske AW, Malcom GT, Tracy RE, Strong JP; Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Obesity accelerates the progression of coronary atherosclerosis in young men. *Circulation.* 2002;105:2712–2718.
31. McGill HC Jr, McMahan CA, Zieske AW, Tracy RE, Malcom GT, Herderick EE, Strong JP. Association of coronary heart disease risk factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation.* 2000;102:374–379.
32. Juonala M, Järvisalo MJ, Mäki-Torkko N, Kähönen M, Viikari JS, Raitakari OT. Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation.* 2005;112:1486–1493.
33. Iannuzzi A, Licenziati MR, Acampora C, Renis M, Agrusta M, Romano L, Valerio G, Panico S, Trevisan M. Carotid artery stiffness in obese children with the metabolic syndrome. *Am J Cardiol.* 2006;97:528–531.
34. Pladevall M, Singal B, Williams LK, Brotons C, Guyer H, Sadurni J, Falces C, Serrano-Rios M, Gabriel R, Shaw JE, Zimmet PZ, Haffner S. A single factor underlies the metabolic syndrome: a confirmatory factor analysis. *Diabetes Care.* 2006;29:113–122.
35. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994. *Arch Intern Med.* 2003;163:427–436.
36. Ruige JB, Assendelft WJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM. Insulin and risk of cardiovascular disease: a meta-analysis. *Circulation.* 1998;97:996–1001.
37. Després JP, Lamarche B, Mauriège P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ. Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med.* 1996;334:952–957.
38. Begum N, Song Y, Rienzie J, Ragolia L. Vascular smooth muscle cell growth and insulin regulation of mitogen-activated protein kinase in hypertension. *Am J Physiol.* 1998;275(pt 1):C42–C49.
39. Nagai M, Kamide K, Rakugi H, Takiuchi S, Imai M, Kida I, Matsukawa N, Higaki J, Ogihara T. Role of endothelin-1 induced by insulin in the regulation of vascular cell growth. *Am J Hypertens.* 2003;16:223–228.
40. Goalstone ML, Natarajan R, Standley PR, Walsh MF, Leitner JW, Carel K, Scott S, Nadler J, Sowers JR, Draznin B. Insulin potentiates platelet-derived growth factor action in smooth muscle cells. *Endocrinology.* 1998;139:4067–4072.
41. Vicent D, Ilany J, Kondo T, Naruse K, Fisher SJ, Kisanuki YY, Bursell S, Yanagisawa M, King GL, Kahn CR. The role of endothelial insulin signaling in the regulation of vascular tone and insulin resistance. *J Clin Invest.* 2003;111:1373–1380.
42. Dandona P, Aljada A, Mohanty P, Ghanim H, Hamouda W, Assian E, Ahmad S. Insulin inhibits intranuclear nuclear factor kappaB and stimulates I-kappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab.* 2001;86:3257–3265.
43. Aljada A, Ghanim H, Mohanty P, Kapur N, Dandona P. Insulin inhibits the pro-inflammatory transcription factor early growth response gene-1 (Egr-1) expression in mononuclear cells (MNC) and reduces plasma tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) concentrations. *J Clin Endocrinol Metab.* 2002;87:1419–1422.
44. Fraker DL, Merino MJ, Norton JA. Reversal of the toxic effects of cachectin by concurrent insulin administration. *Am J Physiol.* 1989;256:E725–E731.
45. Miller AW, Tulbert C, Puskar M, Busija DW. Enhanced endothelin activity prevents vasodilatation to insulin in insulin resistance. *Hypertension.* 2002;40:78–82.
46. Reaven GM. Pathophysiology of insulin resistance in human disease. *Physiol Rev.* 1995;75:473–486.
47. Sinha R, Dufour S, Petersen KF, LeBon V, Enoksson S, Ma YZ, Savoye M, Rothman DL, Shulman GI, Caprio S. Assessment of skeletal muscle triglyceride content by (1)H nuclear magnetic resonance spectroscopy in lean and obese adolescents: relationships to insulin sensitivity, total body fat, and central adiposity. *Diabetes.* 2002;51:1022–1027.
48. An J, Muoio DM, Shiota M, Fujimoto Y, Cline GW, Shulman GI, Kovacs TR, Stevens R, Millington D, Newgard CB. Hepatic expression of malonyl-CoA decarboxylase reverses muscle, liver and whole-animal insulin resistance. *Nat Med.* 2004;10:268–274.
49. Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, Shoelson SE. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nat Med.* 2005;11:183–190.
50. Biddinger SB, Hernandez-Ono A, Rask-Madsen C, Haas JT, Alemán JO, Suzuki R, Scapa EF, Agarwal G, Carey MC, Stephanopoulos G, Cohen DE, King GL, Ginsberg HN, Kahn CR. Hepatic insulin resistance is sufficient to produce dyslipidemia and susceptibility to atherosclerosis. *Cell Metab.* 2008;7:125–134.
51. Kim SP, Ellmerer M, Van Citters GW, Bergman RN. Primacy of hepatic insulin resistance in the development of the metabolic syndrome induced by an isocaloric moderate-fat diet in the dog. *Diabetes.* 2003;52:2453–2460.
52. Cavaghan MK, Ehrmann DA, Polonsky KS. Interactions between insulin resistance and insulin secretion in the development of glucose intolerance. *J Clin Invest.* 2000;106:329–333.
53. Mittleman SD, Van Citters GW, Kim SP, Davis DA, Dea MK, Hamilton-Wessler M, Bergman RN. Longitudinal compensation for fat-induced insulin resistance includes reduced insulin clearance and enhanced beta-cell response. *Diabetes.* 2000;49:2116–2125.
54. Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, Savoye M, Rieger V, Taksali S, Barbetta G, Sherwin RS, Caprio S. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity [published correction appears in *N Engl J Med.* 2002;346:1756]. *N Engl J Med.* 2002;346:802–810.
55. Taittonen L, Uhari M, Nuutinen M, Turtinen J, Pokka T, Åkerblom HK. Insulin and blood pressure among healthy children: cardiovascular risk in young Finns. *Am J Hypertens.* 1996;9:194–199.
56. Odeleye OE, de Courten M, Pettitt DJ, Ravussin E. Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. *Diabetes.* 1997;46:1341–1345.
57. Bao W, Srinivasan SR, Berenson GS. Persistent elevation of plasma insulin levels is associated with increased cardiovascular risk in children and young adults: the Bogalusa Heart Study. *Circulation.* 1996;93:54–59.
58. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty: a contributing factor to poor glycemic control in adolescents with diabetes. *N Engl J Med.* 1986;315:215–219.
59. Bloch CA, Clemons P, Sperling MA. Puberty decreases insulin sensitivity. *J Pediatr.* 1987;110:481–487.
60. Caprio S, Plewe G, Diamond M, Simonson DC, Boulware SD, Sherwin RS, Tamborlane WV. Increased insulin secretion in puberty: a compensatory response to reductions in insulin sensitivity. *J Pediatr.* 1989;114:963–967.
61. Moran A, Jacobs DR Jr, Steinberger J, Hong CP, Prineas R, Luepker R, Sinaiko AR. Insulin resistance during puberty: results from clamp studies in 357 children. *Diabetes.* 1999;48:2039–2044.
62. Moran A, Jacobs DR Jr, Steinberger J, Cohen P, Hong CP, Prineas R, Sinaiko AR. Association between the insulin resistance of puberty and the insulin-like growth factor-1/growth hormone axis. *J Clin Endocrinol Metab.* 2002;87:4817–4820.
63. DeFronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM: a balanced overview. *Diabetes Care.* 1992;15:318–368.
64. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle and the risk of type 2 diabetes mellitus in women. *N Engl J Med.* 2001;345:790–797.
65. Rexrode KM, Manson JE, Hennekens CH. Obesity and cardiovascular disease. *Curr Opin Cardiol.* 1996;11:490–495.

66. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation*. 1983;67:968–977.
67. Lee IM, Manson JE, Hennekens CH, Paffenbarger RS Jr. Body weight and mortality: a 26-year follow-up of middle-aged men. *JAMA*. 1993;270:2823–2828.
68. Bastard JP, Jardel C, Bruckert E, Blondy P, Capeau J, Laville M, Vidal H, Hainque B. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. *J Clin Endocrinol Metab*. 2000;85:3338–3342.
69. Su HY, Sheu WH, Chin HM, Jeng CY, Chen YD, Reaven GM. Effect of weight loss on blood pressure and insulin resistance in normotensive and hypertensive obese individuals. *Am J Hypertens*. 1995;8:1067–1071.
70. Rocchini AP, Katch V, Schork A, Kelch RP. Insulin and blood pressure during weight loss in obese adolescents. *Hypertension*. 1987;10:267–273.
71. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA*. 2006;295:1549–1555.
72. Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. *Pediatrics*. 2004;113(pt 1):475–482.
73. Steinberger J, Moorehead C, Katch V, Rocchini AP. Relationship between insulin resistance and abnormal lipid profile in obese adolescents. *J Pediatr*. 1995;126:690–695.
74. Sinaiko AR, Jacobs DR Jr, Steinberger J, Moran A, Luepker R, Rocchini AP, Prineas RJ. Insulin resistance syndrome in childhood: associations of the euglycemic insulin clamp and fasting insulin with fitness and other risk factors. *J Pediatr*. 2001;139:700–707.
75. Arslanian S, Suprasongsin C. Insulin sensitivity, lipids, and body composition in childhood: is “syndrome X” present? *J Clin Endocrinol Metab*. 1996;81:1058–1062.
76. Caprio S, Bronson M, Sherwin RS, Rife S, Tamborlane WV. Co-existence of severe insulin resistance and hyperinsulinemia in pre-adolescent obese children. *Diabetologia*. 1996;39:1489–1497.
77. Cook DG, Mendall MA, Whincup PH, Carey IM, Ballam L, Morris JE, Miller GJ, Strachan DP. C-reactive protein concentration in children: relationship to adiposity and other cardiovascular risk factors. *Atherosclerosis*. 2000;149:139–150.
78. Ford ES, Galuska DA, Gillespie C, Will JC, Giles WH, Dietz WH. C-reactive protein and body mass index in children: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. *J Pediatr*. 2001;138:486–492.
79. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Low-grade systemic inflammation in overweight children. *Pediatrics*. 2001;107:e13.
80. Ford ES; National Health and Nutrition Examination Survey. C-reactive protein concentration and cardiovascular disease risk factors in children: findings from the National Health and Nutrition Examination Survey 1999–2000. *Circulation*. 2003;108:1053–1058.
81. Tounian P, Aggoun Y, Dubern B, Varille V, Guy-Grand B, Sidi D, Girardet JP, Bonnet D. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. *Lancet*. 2001;358:1400–1404.
82. Steinberger J, Moran A, Hong CP, Jacobs DR Jr, Sinaiko AR. Adiposity in childhood predicts obesity and insulin resistance in young adulthood. *J Pediatr*. 2001;138:469–473.
83. Srinivasan SR, Bao W, Wattigney WA, Berenson GS. Adolescents overweight is associated with adult overweight and related multiple cardiovascular risk factors: the Bogalusa Heart Study. *Metabolism*. 1996;45:235–240.
84. Sinaiko AR, Donahue RP, Jacobs DR, Prineas RJ. Relation of weight and rate of increase in weight during childhood and adolescence to body size, blood pressure, fasting insulin, and lipids in young adults: the Minneapolis Children’s Blood Pressure Study. *Circulation*. 1999;99:1471–1476.
85. Abbasi F, Brown BW Jr, Lamendola C, McLaughlin T, Reaven GM. Relationship between obesity, insulin resistance, and coronary heart disease risk. *J Am Coll Cardiol*. 2002;40:937–943.
86. Ibáñez L, Valls C, Potau N, Marcos MV, de Zegher F. Sensitization to insulin in adolescent girls to normalize hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism after precocious pubarche. *J Clin Endocrinol Metab*. 2000;85:3526–3530.
87. Brambilla P, Bedogni G, Moreno LA, Goran MI, Gutin B, Fox KR, Peters DM, Barbeau P, De Simone M, Pietrobelli A. Crossvalidation of anthropometry against magnetic resonance imaging for the assessment of visceral and subcutaneous adipose tissue in children. *Int J Obes (Lond)*. 2006;30:23–30.
88. Caprio S, Hyman LD, McCarthy S, Lange R, Bronson M, Tamborlane WV. Fat distribution and cardiovascular risk factors in obese adolescent girls: importance of the intraabdominal fat depot. *Am J Clin Nutr*. 1996;64:12–17.
89. Björntorp P. Abdominal fat distribution and disease: an overview of epidemiological data. *Ann Med*. 1992;24:15–18.
90. Björntorp P. Abdominal fat distribution and the metabolic syndrome. *J Cardiovasc Pharmacol*. 1992;20(suppl 8):S26–S28.
91. Després J-P, Prud’homme D, Poulriot MC, Tremblay A, Bouchard C. Estimation of deep abdominal adipose-tissue accumulation from simple anthropometric measurements in men. *Am J Clin Nutr*. 1991;54:471–477.
92. Lee S, Bacha F, Gungor N, Arslanian SA. Waist circumference is an independent predictor of insulin resistance in black and white youths. *J Pediatr*. 2006;148:188–194.
93. Björntorp P. “Portal” adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. *Arteriosclerosis*. 1990;10:493–496.
94. Caprio S, Hyman LD, Limb C, McCarthy S, Lange R, Sherwin RS, Shulman G, Tamborlane WV. Central adiposity and its metabolic correlates in obese adolescent girls. *Am J Physiol*. 1995;269:E118–E126.
95. Retnakaran R, Hanley AJ, Connelly PW, Harris SB, Zinman B. Elevated C-reactive protein in Native Canadian children: an ominous early complication of childhood obesity. *Diabetes Obes Metab*. 2006;8:483–491.
96. Huang KC, Lue BH, Yen RF, Shen CG, Ho SR, Tai TY, Yang WS. Plasma adiponectin levels and metabolic factors in nondiabetic adolescents. *Obes Res*. 2004;12:119–124.
97. Ogawa Y, Kikuchi T, Nagasaki K, Hiura M, Tanaka Y, Uchiyama M. Usefulness of serum adiponectin level as a diagnostic marker of metabolic syndrome in obese Japanese children. *Hypertens Res*. 2005;28:51–57.
98. Li C, Ford ES, Mokdad AH, Cook S. Recent trends in waist circumference and waist-height ratio among US children and adolescents. *Pediatrics*. 2006;118:e1390–e1398.
99. Barlow SE; Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. 2007;120(suppl 4):S164–S192.
100. Greenberg AS, McDaniel ML. Identifying the links between obesity, insulin resistance and beta-cell function: potential role of adipocyte-derived cytokines in the pathogenesis of type 2 diabetes. *Eur J Clin Invest*. 2002;32(suppl 3):24–34.
101. Mendall MA, Patel P, Asante M, Ballam L, Morris J, Strachan DP, Camm AJ, Northfield TC. Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. *Heart*. 1997;78:273–277.
102. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol*. 1999;19:972–978.
103. Fain J. Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. *Vitam Horm*. 2006;74:443–477.
104. Le Roith D, Zick Y. Recent advances in our understanding of insulin action and insulin resistance. *Diabetes Care*. 2001;24:588–597.
105. Khovidhunkit W, Memon RA, Feingold KR, Grunfeld C. Infection and inflammation-induced proatherogenic changes of lipoproteins. *J Infect Dis*. 2000;181(suppl 3):S462–S472.
106. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science*. 1993;259:87–91.
107. Marette A. Mediators of cytokine-induced insulin resistance in obesity and other inflammatory settings. *Curr Opin Clin Nutr Metab Care*. 2002;5:377–383.
108. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease

- Control and Prevention and the American Heart Association. *Circulation*. 2003;107:499–511.
109. Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. *Biochem J*. 1990;265:621–636.
 110. Castell JV, Gómez-Lechón MJ, David M, Andus T, Geiger T, Trullenque R, Fabra R, Heinrich PC. Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. *FEBS Lett*. 1989;242:237–239.
 111. Hatanaka K, Li XA, Masuda K, Yutani C, Yamamoto A. Immunohistochemical localization of C-reactive protein-binding sites in human atherosclerotic aortic lesions by a modified streptavidin-biotin-staining method. *Pathol Int*. 1995;45:635–641.
 112. Lagrand WK, Niessen HW, Wolbink GJ, Jaspars LH, Visser CA, Verheugt FW, Meijer CJ, Hack CE. C-reactive protein colocalizes with complement in human hearts during acute myocardial infarction. *Circulation*. 1997;95:97–103.
 113. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation*. 2003;107:391–397.
 114. Mendall MA, Patel P, Ballal L, Strachan D, Northfield TC. C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. *BMJ*. 1996;312:1061–1065.
 115. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA*. 1999;282:2131–2135.
 116. Moran A, Steffen LM, Jacobs DR Jr, Steinberger J, Pankow JS, Hong CP, Tracy RP, Sinaiko AR. Relation of C-reactive protein to insulin resistance and cardiovascular risk factors in youth. *Diabetes Care*. 2005;28:1763–1768.
 117. Engström G, Hedblad B, Stavenow L, Lind P, Janzon L, Lindgärde F. Inflammation-sensitive plasma proteins are associated with future weight gain. *Diabetes*. 2003;52:2097–2101.
 118. Aeberli I, Molinari L, Spinaz G, Lehmann R, L'Allemand D, Zimmermann MB. Dietary intakes of fat and antioxidant vitamins are predictors of subclinical inflammation in overweight Swiss children. *Am J Clin Nutr*. 2006;84:748–755.
 119. Galili O, Versari D, Sattler KJ, Olson ML, Mannheim D, McConnell JP, Chade AR, Lerman LO, Lerman A. Early experimental obesity is associated with coronary endothelial dysfunction and oxidative stress. *Am J Physiol Heart Circ Physiol*. 2007;292:H904–H911.
 120. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Are oxidative stress-activated signaling pathways mediators of insulin resistance and β -cell dysfunction? *Diabetes*. 2003;52:1–8.
 121. Rudich A, Tirosch A, Potashnik R, Hemi R, Kanety H, Bashan N. Prolonged oxidative stress impairs insulin-induced GLUT4 translocation in 3T3-L1 adipocytes. *Diabetes*. 1998;47:1562–1569.
 122. Nishikawa T, Edelstein D, Brownlee M. The missing link: a single unifying mechanism for diabetic complications. *Kidney Int Suppl*. 2000;77:S26–S30.
 123. Türi S, Friedman A, Bereczki C, Papp F, Kovács J, Karg E, Németh I. Oxidative stress in juvenile essential hypertension. *J Hypertens*. 2003;21:145–152.
 124. Kelly AS, Steinberger J, Kaiser DR, Olson TP, Bank AJ, Dengel DR. Oxidative stress and adverse adipokine profile characterize the metabolic syndrome in children. *J Cardiometab Syndr*. 2006;1:248–252.
 125. Vitaliano PP, Scanlan JM, Zhang J, Savage MV, Hirsch IB, Siegler IC. A path model of chronic stress, the metabolic syndrome, and coronary heart disease. *Psychosom Med*. 2002;64:418–435.
 126. Wallerius S, Rosmond R, Ljung T, Holm G, Björntorp P. Rise in morning saliva cortisol is associated with abdominal obesity in men: a preliminary report. *J Endocrinol Invest*. 2003;26:616–619.
 127. Räikkönen K, Matthews KA, Kuller LH. The relationship between psychological risk attributes and the metabolic syndrome in healthy women: antecedent or consequence? *Metabolism*. 2002;51:1573–1577.
 128. Chandola T, Brunner E, Marmot M. Chronic stress at work and the metabolic syndrome: prospective study. *BMJ*. 2006;332:521–525.
 129. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sittih-amorn C, Sato H, Yusuf S; INTERHEART Investigators. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:953–962.
 130. Souverein PC, Berard A, Van Staa TP, Cooper C, Egberts AC, Leufkens HG, Walker BR. Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. *Heart*. 2004;90:859–865.
 131. Andrew R, Gale CR, Walker BR, Seckl JR, Martyn CN. Glucocorticoid metabolism and the metabolic syndrome: associations in an elderly cohort. *Exp Clin Endocrinol Diabetes*. 2002;110:284–290.
 132. Kotelevtsev YV, Holmes MC, Burchell A, Houston PM, Schmolli D, Jamieson PM, Best R, Brown R, Edwards CR, Seckl JR, Mullins JJ. 11β -Hydroxysteroid dehydrogenase type 1 knockout mice show attenuated glucocorticoid-inducible responses and resist hyperglycemia on obesity and stress. *Proc Natl Acad Sci U S A*. 1997;94:14924–14929.
 133. Masuzaki H, Paterson J, Shinyama H, Morton NM, Mullins JJ, Seckl JR, Flier JS. A transgenic model of visceral obesity and the metabolic syndrome. *Science*. 2001;294:2166–2170.
 134. Anderson TJ, Uehata A, Gerhard MD, Meredith IT, Knab S, Delagrange D, Lieberman EH, Ganz P, Creager MA, Yeung AC. Close relation of endothelial function in the human coronary and peripheral circulations. *J Am Coll Card*. 1995;26:1235–1241.
 135. Kunsch C, Medford RM. Oxidation-sensitive transcription and gene expression in atherosclerosis. In: Keaney JF, ed. *Oxidative Stress and Vascular Disease*. Boston, Mass: Kluwer; 2000:135–154.
 136. Kubes P, Suzuki M, Granger D. Nitric oxide: an endogenous modulator of leukocyte adhesion. *Proc Natl Acad Sci U S A*. 1991;88:4651–4655.
 137. Radomski MW, Palmer RM, Moncada S. An L-arginine/nitric oxide pathway present in human platelets regulates aggregation. *Proc Natl Acad Sci U S A*. 1990;87:5193–5197.
 138. Garg UC, Hassid A. Nitric oxide-generating vasodilators and 8-bromocyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells. *J Clin Invest*. 1989;83:1774–1777.
 139. Petrie JR, Ueda S, Webb DJ, Elliott HL, Connell JM. Endothelial nitric oxide production and insulin sensitivity: a physiological link with implications for pathogenesis of cardiovascular disease. *Circulation*. 1996;93:1331–1333.
 140. Kelly AS, Wetzsteon RJ, Kaiser DR, Steinberger J, Bank AJ, Dengel DR. Inflammation, insulin, and endothelial function in overweight children and adolescents: the role of exercise. *J Pediatr*. 2004;145:731–736.
 141. Whincup PH, Gilg JA, Donald AE, Katterhorn M, Oliver C, Cook DG, Deanfield JE. Arterial distensibility in adolescents: the influence of adiposity, the metabolic syndrome, and classic risk factors. *Circulation*. 2005;112:1789–1797.
 142. Burke GL, Evans GW, Riley WA, Sharrett AR, Howard G, Barnes RW, Rosamond W, Crow RS, Rautaharju PM, Heiss G. Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 1995;26:386–391.
 143. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation*. 1997;96:1432–1437.
 144. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, Azen SP. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med*. 1998;128:262–269.
 145. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr; Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med*. 1999;340:14–22.
 146. Järvisalo MJ, Putto-Laurila A, Jartti L, Lehtimäki T, Solakivi T, Rönnemaa T, Raitakari OT. Carotid artery intima-media thickness in children with type 1 diabetes. *Diabetes*. 2002;51:493–498.
 147. Järvisalo MJ, Jartti L, Näntö-Salonen K, Irjala K, Rönnemaa T, Hartiala JJ, Celermajer DS, Raitakari OT. Increased aortic intima-media thickness: a marker of preclinical atherosclerosis in high-risk children. *Circulation*. 2001;104:2943–2947.
 148. Sorof JM, Alexandrov AV, Garami Z, Turner JL, Grafe RE, Lai D, Portman RJ. Carotid ultrasonography for detection of vascular abnormalities in hypertensive children. *Pediatr Nephrol*. 2003;18:1020–1024.
 149. Järvisalo MJ, Harmoinen A, Hakanen M, Paakkunainen U, Viikari J, Hartiala J, Lehtimäki T, Simell O, Raitakari OT. Elevated serum C-reactive protein levels and early arterial changes in healthy children. *Arterioscler Thromb Vasc Biol*. 2002;22:1323–1328.
 150. Gaeta G, De Michele M, Cuomo S, Guarini P, Foglia MC, Bond MG, Trevisan M. Arterial abnormalities in the offspring of patients with premature myocardial infarction. *N Engl J Med*. 2000;343:840–846.
 151. Sorof J, Daniels S. Obesity hypertension in children: a problem of epidemic proportions. *Hypertension*. 2002;40:441–447.

152. Haynes WG, Morgan DA, Walsh SA, Mark AL, Sivitz WI. Receptor-mediated regional sympathetic nerve activation by leptin. *J Clin Invest*. 1997;100:270–278.
153. Landsberg L. Hyperinsulinemia: possible role in obesity-induced hypertension. *Hypertension*. 1992;19(suppl):161–166.
154. DeFronzo RA, Cooke CR, Andres R, Faloona GR, Davis PJ. The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. *J Clin Invest*. 1975;55:845–855.
155. Stout RW, Bierman EL, Ross R. Effect of insulin on the proliferation of cultured primate arterial smooth muscle cells. *Circ Res*. 1975;36:319–327.
156. Sinaiko AR, Gomez-Marin O, Prineas RJ. Relation of fasting insulin to blood pressure and lipids in adolescents and parents. *Hypertension*. 1997;30:1554–1559.
157. Correia ML, Rahmouni K. Role of leptin in the cardiovascular and endocrine complications of metabolic syndrome. *Diabetes Obes Metab*. 2006;8:603–610.
158. Sinaiko AR, Steinberger J, Moran A, Prineas RJ, Jacobs DR Jr. Relation of insulin resistance to blood pressure in childhood. *J Hypertens*. 2002;20:509–517.
159. Sun SS, Grave GD, Siervogel RM, Pickoff AA, Arslanian SS, Daniels SR. Systolic blood pressure in childhood predicts hypertension and metabolic syndrome later in life. *Pediatrics*. 2007;119:237–246.
160. Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr Rev*. 2002;23:201–229.
161. Assimacopoulos-Jeannet F, Brichard S, Rencurel F, Cusin I, Jeanrenaud B. In vivo effects of hyperinsulinemia on lipogenic enzymes and glucose transporter expression in rat liver and adipose tissues. *Metabolism*. 1995;44:228–233.
162. Csábi G, Török K, Jeges S, Molnár D. Presence of metabolic cardiovascular syndrome in obese children. *Eur J Pediatr*. 2000;159:91–94.
163. Jiang X, Srinivasan SR, Webber LS, Wattigney WA, Berenson GS. Association of fasting insulin level with serum lipid and lipoprotein levels in children, adolescents, and young adults: the Bogalusa Heart Study. *Arch Intern Med*. 1995;155:190–196.
164. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. *Pediatrics*. 1999;103(pt 1):1175–1182.
165. Little P, Byrne CD. Abdominal obesity and the “hypertriglyceridaemic waist” phenotype. *BMJ*. 2001;322:687–689.
166. Esmaillzadeh A, Mirmiran P, Azizi F. Clustering of metabolic abnormalities in adolescents with the hypertriglyceridemic waist phenotype. *Am J Clin Nutr*. 2006;83:36–46.
167. Olivieri O, Bassi A, Stranieri C, Trabetti E, Martinelli N, Pizzolo F, Girelli D, Friso S, Pignatti PF, Corrocher R. Apolipoprotein C-III, metabolic syndrome, and risk of coronary artery disease. *J Lipid Res*. 2003;44:2374–2381.
168. Chait A, Brazg RL, Tribble DL, Krauss RM. Susceptibility of small, dense, low-density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B. *Am J Med*. 1993;94:350–356.
169. Chapman MJ, Guérin M, Bruckert E. Atherogenic, dense low-density lipoproteins: pathophysiology and new therapeutic approaches. *Eur Heart J*. 1998;19(suppl A):A24–A30.
170. Brewer HB Jr. Hypertriglyceridemia: changes in the plasma lipoproteins associated with an increased risk of cardiovascular disease. *Am J Cardiol*. 1999;83:3F–12F.
171. Rainwater DL, Mitchell BD, Comuzzie AG, Haffner SM. Relationship of low-density lipoprotein particle size and measures of adiposity. *Int J Obes*. 1999;23:180–189.
172. Kang HS, Gutin B, Barbeau P, Litaker MS, Allison J, Le NA. Low-density lipoprotein particle size, central obesity, cardiovascular fitness, and insulin resistance syndrome markers in obese youths. *Int J Obes*. 2002;26:1030–1035.
173. Miyashita M, Okada T, Kuromori Y, Harada K. LDL particle size, fat distribution and insulin resistance in obese children. *Eur J Clin Nutr*. 2006;60:416–420.
174. Becker DM, Yook RM, Moy TF, Blumenthal RS, Becker LC. Markedly high prevalence of coronary risk factors in apparently healthy African-American and white siblings of persons with premature coronary heart disease. *Am J Cardiol*. 1998;82:1046–1051.
175. Morrison JA, Friedman LA, Harlan WR, Harlan LC, Barton BA, Schreiber GB, Klein DJ. Development of the metabolic syndrome in black and white adolescent girls: a longitudinal assessment. *Pediatrics*. 2005;116:1178–1182.
176. Florez H, Mendez A, Casanova-Romero P, Larreal-Urdaneta C, Castillo-Florez S, Lee D, Goldberg R. Increased apolipoprotein C-III levels associated with insulin resistance contribute to dyslipidemia in normoglycemic and diabetic subjects from a triethnic population. *Atherosclerosis*. 2006;188:134–141.
177. Benton JL, Blumenthal RS, Becker DM, Yanek LR, Moy TF, Post W. Predictors of low-density lipoprotein particle size in a high-risk African-American population. *Am J Cardiol*. 2005;95:1320–1323.
178. Bacha F, Saad R, Gungor N, Janosky J, Arslanian S. Obesity, regional fat distribution, and syndrome X in obese black versus white adolescents: race differential in diabetogenic and atherogenic risk factors. *J Clin Endocrinol Metab*. 2003;88:2534–2540.
179. Clark LT. Issues in minority health: atherosclerosis and coronary heart disease in African Americans. *Med Clin North Am*. 2005;89:977–1001.
180. Lundgren H, Bengtsson C, Blohmé G, Lapidus L, Waldenström J. Fasting serum insulin concentration and early insulin response as risk determinants for developing diabetes. *Diabet Med*. 1990;7:407–413.
181. Haffner SM, Stern MP, Mitchell BD, Hazuda HP, Patterson JK. Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution. *Diabetes*. 1990;39:283–288.
182. Dolan LM, Bean J, D’Alessio D, Cohen RM, Morrison JA, Goodman E, Daniels SR. Frequency of abnormal carbohydrate metabolism in a population-based screening of adolescents. *J Pediatr*. 2005;146:751–758.
183. Weiss R, Dufour S, Taksali SE, Tamborlane WV, Petersen KF, Bonadonna RC, Boselli L, Barbetta G, Allen K, Rife F, Savoye M, Dziura J, Sherwin R, Shulman GI, Caprio S. Prediabetes in obese youth: a syndrome of impaired glucose tolerance, severe insulin resistance, and altered myocellular and abdominal fat partitioning. *Lancet*. 2003;362:951–957.
184. Wing RR, Marcus MD, Salata R, Epstein LH, Miasiewicz S, Blair EH. Effects of a very-low-calorie diet on long-term glycemic control in obese type 2 diabetic subjects. *Arch Intern Med*. 1991;151:1334–1340.
185. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2005;28(suppl 1):S37–S42.
186. Weiss R, Taksali SE, Tamborlane WV, Burgert TS, Savoye M, Caprio S. Predictors of change in glucose tolerance status in obese youth. *Diabetes Care*. 2005;28:902–909.
187. Fagot-Campagna A, Pettitt DJ, Engelau MM, Burrows NR, Geiss LS, Valdez R, Beckles GL, Saaddine J, Gregg EW, Williamson DF, Narayan KM. Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr*. 2000;136:664–672.
188. Rosenbloom AL. Increasing incidence of type 2 diabetes in children and adolescents: treatment considerations. *Paediatr Drugs*. 2002;4:209–221.
189. Pinnas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. *J Pediatr*. 1996;128:608–615.
190. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20:1183–1197.
191. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care*. 2003;26:3160–3167.
192. American Diabetes Association. Type 2 diabetes in children and adolescents. *Diabetes Care*. 2000;23:381–389.
193. Fagot-Campagna A, Knowler WC, Pettitt DJ. Type 2 diabetes in Pima Indian children: cardiovascular risk factors at diagnosis and 10 years later. *Diabetes*. 1998;47(suppl 1):A155. Abstract.
194. DeFronzo RA. Insulin resistance, hyperinsulinemia, and coronary artery disease: a complex metabolic web. *J Cardiovasc Pharmacol*. 1992;20:S1–S16.
195. Wabitsch M, Hauner H, Heinze E, Böckmann A, Benz R, Mayer H, Teller W. Body fat distribution and steroid hormone concentrations in obese adolescent girls before and after weight reduction. *J Clin Endocrinol Metab*. 1995;80:3469–3475.
196. Cousin P, Calemard-Michel L, Lejeune H, Raverot G, Yessaad N, Emptoz-Bonneton A, Morel Y, Pugeat M. Influence of SHBG gene pentanucleotide TAAAA repeat and D327N polymorphism on serum

- sex hormone-binding globulin concentration in hirsute women. *J Clin Endocrinol Metab.* 2004;89:917–924.
197. Zhang LH, Rodriguez H, Ohno S, Miller WL. Serine phosphorylation of human P450c17 increases 17,20-lyase activity: implications for adrenarche and the polycystic ovary syndrome. *Proc Natl Acad Sci U S A.* 1995;92:10619–10623.
198. Fishbein MH, Miner M, Mogren C, Chalekson J. The spectrum of fatty liver in obese children and the relationship of serum aminotransferases to severity of steatosis. *J Pediatr Gastroenterol Nutr.* 2003;36:54–61.
199. Riley MR, Bass NM, Rosenthal P, Merriman RB. Underdiagnosis of pediatric obesity and underscreening for fatty liver disease and metabolic syndrome by pediatricians and pediatric subspecialists. *J Pediatr.* 2005;147:839–842.
200. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. *Pediatrics.* 2006;118:1388–1393.
201. Alfire ME, Treem WR. Nonalcoholic fatty liver disease. *Pediatr Ann.* 2006;35:290–294, 297–299.
202. Roden M. Mechanisms of disease: hepatic steatosis in type 2 diabetes: pathogenesis and clinical relevance. *Nat Clin Pract Endocrinol Metab.* 2006;2:335–348.
203. Mitchell BD, Kammerer CM, Mahaney MC, Blangero J, Comuzzie AG, Atwood LD, Haffner SM, Stern MP, MacCluer JW. Genetic analysis of the IRS: pleiotropic effects of genes influencing insulin levels on lipoprotein and obesity measures. *Arterioscler Thromb Vasc Biol.* 1996;16:281–288.
204. Edwards KL, Newman B, Mayer E, Selby JV, Krauss RM, Austin MA. Heritability of factors of the insulin resistance syndrome in women twins. *Genet Epidemiol.* 1997;14:241–253.
205. Hong Y, Pedersen NL, Brismar K, de Faire U. Genetic and environmental architecture of the features of the insulin-resistance syndrome. *Am J Hum Genet.* 1997;60:143–152.
206. Rissanen AM, Nikkilä EA. Coronary artery disease and its risk factors in families of young men with angina pectoris and in controls. *Br Heart J.* 1977;39:875–883.
207. Khaw KT, Barrett-Connor E. Family history of heart attack: a modifiable risk factor? *Circulation.* 1986;74:239–244.
208. Shear CL, Webber LS, Freedman DS, Srinivasan SR, Berenson GS. The relationship between parental history of vascular disease and cardiovascular disease risk factors in children: the Bogalusa Heart Study. *Am J Epidemiol.* 1985;122:762–771.
209. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA.* 1993;269:3015–3023.
210. American Academy of Pediatrics. National Cholesterol Education Program: report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics.* 1992;89(pt 2):525–584.
211. Bao W, Srinivasan SR, Valdez R, Greenlund KJ, Wattigney WA, Berenson GS. Longitudinal changes in cardiovascular risk from childhood to young adulthood in offspring of parents with coronary artery disease: the Bogalusa Heart Study. *JAMA.* 1997;278:1749–1754.
212. Srinivasan SR, Dahlen GH, Jarpa RA, Webber LS, Berenson GS. Racial (black-white) differences in serum lipoprotein(a) distribution and its relation to parental myocardial infarction in children: Bogalusa Heart Study. *Circulation.* 1991;84:160–167.
213. Bao W, Srinivasan SR, Wattigney WA, Berenson GS. The relation of parental cardiovascular disease to risk factors in children and young adults: the Bogalusa Heart Study. *Circulation.* 1995;91:365–371.
214. Greenlund KJ, Srinivasan SR, Xu JH, Dalferes E Jr, Myers L, Pickoff A, Berenson GS. Plasma homocysteine distribution and its association with parental history of coronary artery disease in black and white children: the Bogalusa Heart Study. *Circulation.* 1999;99:2144–2149.
215. Schonfeld-Warden N, Warden CH. Pediatric obesity: an overview of etiology and treatment. *Pediatr Clin North Am.* 1997;44:339–361.
216. Whitaker RC, Wright JA, Pepe MS, Seidel DK, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. *N Engl J Med.* 1997;337:869–873.
217. Lillioja S, Mott DM, Zawadzki JK, Young AA, Abbott WG, Knowler WC, Bennett PH, Moll P, Bogardus C. In vivo insulin action is familial characteristic in nondiabetic Pima Indians. *Diabetes.* 1987;36:1329–1335.
218. Ho LT, Chang-ZY, Wang JT, Li SH, Liu YF, Chen YD, Reaven GM. Insulin insensitivity in offspring of parents with type 2 diabetes mellitus. *Diabet Med.* 1990;7:31–34.
219. Elbein S, Maxwell TM, Schumacher MC. Insulin and glucose levels and prevalence of glucose intolerance in pedigrees with multiple diabetic siblings. *Diabetes.* 1991;40:1024–1032.
220. Laws A, Stefanick M, Reaven G. Insulin resistance and hypertriglyceridemia in nondiabetic relatives of patients with non-insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab.* 1989;69:343–347.
221. Danadian K, Balasekaran G, Lewy V, Meza MP, Robertson R, Arslanian SA. Insulin sensitivity in African-American children with and without family history of type 2 diabetes. *Diabetes Care.* 1999;22:1325–1329.
222. Pankow JS, Jacobs DR Jr, Steinberger J, Moran A, Sinaiko AR. Insulin resistance and cardiovascular disease risk factors in children of parents with the insulin resistance (metabolic) syndrome. *Diabetes Care.* 2004;27:775–780.
223. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999–2000. *JAMA.* 2002;288:1728–1732.
224. Strauss RS, Pollack HA. Epidemic increase in childhood overweight, 1986–1998. *JAMA.* 2001;286:2845–2848.
225. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA.* 2004;291:2847–2850.
226. Duncan GE, Li SM, Zhou XH. Prevalence and trends of a metabolic syndrome phenotype among US adolescents, 1999–2000. *Diabetes Care.* 2004;27:2438–2443.
227. Berenson G, Srinivasan S, Chen W, Li S, Patel D; Bogalusa Heart Study Group. Racial (black-white) contrasts of risk for hypertensive disease in youth have implications for preventive care: the Bogalusa Heart Study. *Ethn Dis.* 2006;16(suppl 4):S4–S9.
228. Tarlton PA. Prevalence of elevated blood pressure in Hispanic versus non-Hispanic 6th graders. *J Sch Nurs.* 2007;23:47–52.
229. Batey LS, Goff DC Jr, Tortolero SR, Nichaman MZ, Chan W, Chan FA, Grunbaum J, Hanis CL, Labarthe DR. Summary measures of the insulin resistance syndrome are adverse among Mexican-American versus non-Hispanic white children: the Corpus Christi Child Heart Study. *Circulation.* 1997;96:4319–4325.
230. Arslanian S, Suprasongsin C, Janosky JE. Insulin secretion and sensitivity in black versus white prepupal healthy children. *J Clin Endocrinol Metab.* 1997;82:1923–1927.
231. Svec F, Nastasi K, Hilton C, Bao W, Srinivasan SR, Berenson GS. Black-white contrasts in insulin levels during pubertal development: the Bogalusa Heart Study. *Diabetes.* 1992;41:313–317.
232. Arslanian S, Suprasongsin C. Differences in the in vivo insulin secretion and sensitivity of healthy black versus white adolescents. *J Pediatr.* 1996;129:440–443.
233. Chen W, Bao W, Begum S, Elkasabany A, Srinivasan SR, Berenson GS. Age-related patterns of the clustering of cardiovascular risk variables of syndrome X from childhood to young adulthood in a population made up of black and white subjects: the Bogalusa Heart Study. *Diabetes.* 2000;49:1042–1048.
234. Crespo CJ, Smit E, Troiano RP, Bartlett SJ, Macera CA, Anderson RE. Television watching, energy intake, and obesity in US children: results from the third National Health and Nutrition Examination Survey, 1988–1994. *Arch Pediatr Adolesc Med.* 2001;155:360–365.
235. Robinson TN, Killen JD, Kraemer HC, Wilson DM, Matheson DM, Haskell WL, Pruitt LA, Powell TM, Owens AS, Thompson NS, Flint-Moore NM, Davis GJ, Emig KA, Brown RT, Rochon J, Green S, Varady A. Dance and reducing television viewing to prevent weight gain in African-American girls: the Stanford GEMS pilot study. *Ethn Dis.* 2003;13(suppl 1):S65–S77.
236. Ekelund U, Brage S, Froberg K, Harro M, Anderssen SA, Sardinha LB, Riddoch C, Andersen LB. TV viewing and physical activity are independently associated with metabolic risk in children: the European Youth Heart Study. *PLoS Med.* 2006;3:e488.
237. Steffen LM, Harnack LJ, Lin E, Luepker RV, Arnett DK. Parental body mass index and television watching is associated with offspring body mass index and television: the Minnesota Heart Survey. Presented at: North American Association for the Study of Obesity annual meeting; October 14, 2003; Fort Lauderdale, Fla.
238. US Department of Health and Human Services. *Physical Activity and Health: A Report of the Surgeon General.* Atlanta, Ga: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1996.

239. Roberts CK, Won D, Pruthi S, Lin SS, Barnard RJ. Effect of a diet and exercise intervention on oxidative stress, inflammation and monocyte adhesion in diabetic men. *Diabetes Res Clin Pract*. 2006;73:249–259.
240. Roberts CK, Won D, Pruthi S, Kurtovic S, Sindhu RK, Vaziri ND, Barnard RJ. Effect of a short-term diet and exercise intervention on oxidative stress, inflammation, MMP-9, and monocyte chemotactic activity in men with metabolic syndrome factors. *J Appl Physiol*. 2006;100:1657–1665.
241. Schmitz KH, Jacobs DR, Hong CP, Steinberger J, Moran A, Sinaiko AR. Association of physical activity with insulin sensitivity in children. *Int J Obes Relat Metab Disord*. 2002;26:1310–1316.
242. Marcell TJ, McAuley KA, Traustadottir T, Reaven PD. Exercise training is not associated with improved levels of C-reactive protein or adiponectin. *Metabolism*. 2005;54:533–541.
243. Nassis GP, Papantakou K, Skenderi K, Triandafilopoulou M, Kavouras SA, Yannakoulia M, Chrousos GP, Sidossis LS. Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. *Metabolism*. 2005;54:1472–1479.
244. Steffen LM, Jacobs DR Jr, Murtaugh MA, Moran A, Steinberger J, Hong CP, Sinaiko AR. Whole grain intake is associated with lower body mass and greater insulin sensitivity among adolescents. *Am J Epidemiol*. 2003;158:243–250.
245. Steffen LM, Jacobs DR, Stevens J, Shahar E, Carithers T, Folsom AR. Associations of whole grain, refined grain, and fruit and vegetable consumption with all-cause mortality and incident coronary heart disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr*. 2003;78:383–390.
246. Liu S, Stampfer MJ, Hu FB, Giovannucci E, Rimm E, Manson JE, Hennekens CH, Willett WC. Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. *Am J Clin Nutr*. 1999;70:412–419.
247. Liese AD, Schulz M, Fang F, Wolever TM, D'Agostino RB Jr, Sparks KC, Mayer-Davis EJ. Dietary glycemic index and glycemic load, carbohydrate and fiber intake, and measures of insulin sensitivity, secretion, and adiposity in the Insulin Resistance Atherosclerosis Study. *Diabetes Care*. 2005;28:2832–2838.
248. Sahyoun NR, Jacques PF, Zhang XL, Juan W, McKeown NM. Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. *Am J Clin Nutr*. 2006;83:124–131.
249. McKeown NM, Meigs JB, Liu S, Wilson PW, Jacques PF. Whole-grain intake is favorably associated with metabolic risk factors for type 2 diabetes and cardiovascular disease in the Framingham Offspring Study. *Am J Clin Nutr*. 2002;76:390–398.
250. McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW, Jacques PF. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. *Diabetes Care*. 2004;27:538–546.
251. Delzenne NM, Cani PD. A place for dietary fibre in the management of the metabolic syndrome. *Curr Opin Clin Nutr Metab Care*. 2005;8:636–640.
252. Kromhout D, Menotti A, Kesteloot H, Sans S. Prevention of coronary heart disease by diet and lifestyle: evidence from prospective cross-cultural, cohort, and intervention studies. *Circulation*. 2002;105:893–898.
253. Calder PC. Polyunsaturated fatty acids, inflammation, and immunity. *Lipids*. 2001;36:1007–1024.
254. Song Y, Ridker PM, Manson JE, Cook NR, Buring JE, Liu S. Magnesium intake, C-reactive protein, and the prevalence of metabolic syndrome in middle-aged and older US women. *Diabetes Care*. 2005;28:1438–1444.
255. Fung TT, Rimm EB, Spiegelman D, Rifai N, Tofler GH, Willett WC, Hu FB. Association between dietary patterns and plasma biomarkers of obesity and cardiovascular disease risk. *Am J Clin Nutr*. 2001;73:61–67.
256. Maskarinec G, Novotny R, Tasaki K. Dietary patterns are associated with body mass index in multiethnic women. *J Nutr*. 2000;130:3068–3072.
257. Newby PK, Muller D, Hallfrisch J, Qiao N, Andres R, Tucker KL. Dietary patterns and changes in body mass index and waist circumference in adults. *Am J Clin Nutr*. 2003;77:1417–1425.
258. Deleted in proof.
259. Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, Fiol M, Gómez-Gracia E, López-Sabater MC, Vinyoles E, Arós F, Conde M, Lahoz C, Lapetra J, Sáez G, Ros E; PREDIMED Study Investigators. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med*. 2006;145:1–11.
260. Gidding SS, Dennison BA, Birch LL, Daniels SR, Gillman MW, Lichenstein AH, Rattay KT, Steinberger J, Settler N, Van Horn L; American Heart Association; American Academy of Pediatrics. Dietary recommendations for children and adolescents: a guide for practitioners: consensus statement from the American Heart Association [published corrections appear in *Circulation*. 2005;112:2375 and 2006;113:e857]. *Circulation*. 2005;112:2061–2075.
261. Nemet D, Barkan S, Epstein Y, Friedland O, Kowen G, Eliakim A. Short- and long-term beneficial effects of a combined dietary-behavioral-physical activity intervention for the treatment of childhood obesity. *Pediatrics*. 2005;115:e443–e449.
262. Woo KS, Chook P, Yu CW, Sung RY, Qiao M, Leung SS, Lam CW, Metreweli C, Celermajer DS. Effects of diet and exercise on obesity-related vascular dysfunction in children. *Circulation*. 2004;109:1981–1986.
263. Jiang X, Srinivasan SR, Bao W, Berenson GS. Association of fasting insulin with blood pressure in young individuals: the Bogalusa Heart Study. *Arch Intern Med*. 1993;153:323–328.
264. Stewart KJ. Exercise training and the cardiovascular consequences of type 2 diabetes and hypertension: plausible mechanisms for improving cardiovascular health. *JAMA*. 2002;288:1622–1631.
265. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. *Pediatrics*. 2001;107:e55.
266. Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ. Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care*. 2002;25:89–94.
267. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature*. 2006;444:881–887.
268. Brambilla P, Lissau I, Flodmark CE, Moreno LA, Widhalm K, Wabitsch M, Pietrobelli A. Metabolic risk-factor clustering estimation in children: to draw a line across pediatric metabolic syndrome. *Int J Obes (Lond)*. 2007;31:591–600.
269. Chen W, Srinivasan SR, Li S, Xu J, Berenson GS. Clustering of long-term trends in metabolic syndrome variables from childhood to adulthood in blacks and whites: the Bogalusa Heart Study. *Am J Epidemiol*. 2007;166:527–533.
270. Goodman E, Daniels SR, Meigs JB, Dolan LM. Instability in the diagnosis of metabolic syndrome in adolescents. *Circulation*. 2007;115:2316–2322.
271. Cruz ML, Goran MI. The metabolic syndrome in children and adolescents. *Curr Diab Rep*. 2004;4:53–62.
272. de Ferranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW, Rifai N. Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. *Circulation*. 2004;110:2494–2497.
273. Chu NF, Rimm EB, Wang DJ, Liou HS, Shieh SM. Clustering of cardiovascular disease risk factors among obese schoolchildren: the Taipei Children Heart Study. *Am J Clin Nutr*. 1998;67:1141–1146.
274. Katzmarzyk PT, Srinivasan SR, Chen W, Malina RM, Bouchard C, Berenson GS. Body mass index, waist circumference, and clustering of cardiovascular disease risk factors in a biracial sample of children and adolescents. *Pediatrics*. 2004;114:e198–e205.
275. Morrison JA, Sprecher DL, Barton BA, Waclawiw MA, Daniels SR. Overweight, fat patterning, and cardiovascular disease risk factors in black and white girls: the National Heart, Lung, and Blood Institute Growth and Health Study. *J Pediatr*. 1999;135:458–464.
276. Golley RK, Magarey AM, Steinbeck KS, Baur LA, Daniels LA. Comparison of metabolic syndrome prevalence using six different definitions in overweight pre-pubertal children enrolled in a weight management study. *Int J Obes (Lond)*. 2006;30:835–860.
277. Fernández JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. *J Pediatr*. 2004;145:439–444.
278. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. *Pediatrics*. 1996;98(pt 1):649–658.
279. The Lipid Research Clinics Program Epidemiology Committee. Plasma lipid distributions in selected North American populations: the Lipid

- Research Clinics Program Prevalence Study. *Circulation*. 1979;60:427–439.
280. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
 281. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. CDC growth charts: United States. *Adv Data*. 2000;No. 314:1–27.
 282. Obesity and cardiovascular disease risk factors in black and white girls: the NHLBI Growth and Health Study. *Am J Public Health*. 1992;82:1613–1620.
 283. Kleinman RE, ed; American Academy of Pediatrics Nutrition Committee. *Pediatric Nutrition Handbook*. 5th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2004.
 284. Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Etherton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, Van Horn L, Winston M, Wylie-Rosett J. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation*. 2006;114:82–96.
 285. Daniels SR, Arnett DK, Eckel RH, Gidding SS, Hayman LL, Kumanyika S, Robinson TN, Scott BJ, St Jeor S, Williams CL. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. *Circulation*. 2005;111:1999–2012.
 286. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation*. 2006;114:2710–2738.
 287. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children. *Pediatrics*. 2004;114(suppl):555–576.
 288. Deleted in proof.
 289. American Diabetes Association. Management of dyslipidemia in children and adolescents with diabetes. *Diabetes Care*. 2003;26:2194–2197.
 290. National Kidney Foundation. K/DOQI clinical practice guidelines for managing dyslipidemias in chronic kidney disease. *Am J Kidney Dis*. 2003;41(suppl 3):S1–S92.
 291. Kasiske B, Cosio FG, Beto J, Bolton K, Chavers BM, Grimm R Jr, Levin A, Masri B, Parekh R, Wanner C, Wheeler DC, Wilson PW; National Kidney Foundation. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Working Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. *Am J Transplant*. 2004;4(suppl 7):13–53.
 292. American Diabetes Association. Standards of medical care for patients with diabetes mellitus [published correction appears in *Diabetes Care*. 2003;26:972]. *Diabetes Care*. 2003;26(suppl 1):S33–S50.
 293. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, Deeb L, Grey M, Anderson B, Holzmeister LA, Clark N; American Diabetes Association. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care*. 2005;28:186–212.
 294. American Diabetes Association. Management of dyslipidemia in children and adolescents with diabetes. *Diabetes Care*. 2003;26:2194–2197.
 295. Graham TP Jr, Driscoll DJ, Gersony WM, Newburger JW, Rocchini A, Towbin JA. Task Force 2: congenital heart disease. *J Am Coll Cardiol*. 2005;45:1326–1333.
 296. Strong WB, Malina RM, Blimkie CJ, Daniels SR, Dishman RK, Gutin B, Hergenroeder AC, Must A, Nixon PA, Pivarnik JM, Rowland T, Trost S, Trudeau F. Evidence based physical activity for school-age youth. *J Pediatr*. 2005;146:732–737.
 297. Gentile DA, Oberg C, Sherwood NE, Story M, Walsh DA, Hogan M; American Academy of Pediatrics. Well-child visits in the video age: pediatricians and the American Academy of Pediatrics' guideline for children's media use. *Pediatrics*. 2004;114:1235–1241.

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