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## 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).<sup>1</sup> 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.<sup>2</sup>

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.<sup>3</sup> More recently, similar clusterings received renewed attention, and several terms such as syndrome X,<sup>4</sup> the deadly quartet,<sup>5</sup> insulin resistance syndrome,<sup>6</sup> and MetS<sup>7</sup> 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.<sup>8–10</sup> 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])<sup>9</sup> and those from the World Health Organization<sup>10</sup> are most commonly used in adults. Two of the 3 common definitions<sup>8,10</sup> include measures of insulin resistance, which reflects the proposed causal or mediating role insulin action plays in the development of MetS.<sup>11,12</sup> 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.<sup>13</sup>

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.<sup>14–17</sup> 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  $\geq 90$ 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  $\geq 90$ th percentile), followed by the adult criteria for triglycerides, high-density lipoprotein cholesterol (HDL-C), blood pressure, and glucose. For youth  $\geq 16$  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.<sup>18</sup> 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%.<sup>19</sup> 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,<sup>20</sup> whereas a study of 965 Mexican children and adolescents found a 6.5% and 4.5% prevalence, respectively.<sup>16</sup> The prevalence of MetS among 2244 Canadian children and adolescents was slightly higher at 11.5%.<sup>14</sup> 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%).<sup>21</sup>

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/m<sup>2</sup>) and 49.7% of severely obese (mean BMI 40.6 kg/m<sup>2</sup>) children and adolescents.<sup>15</sup> Despite the difficulty inherent in defining the key elements of a condition modulated by so many genetic and environmental factors,<sup>22</sup> strong evidence supports obesity as the predominant correlate of cardiometabolic risk,<sup>23</sup> 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.<sup>24</sup> The magnitude of cardiometabolic risk also varies markedly in obese adults as a function of differences in degree of insulin sensitivity.<sup>25</sup> 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.<sup>26</sup> Most investigators would therefore expect that individuals with the MetS also are insulin resistant, but this relation has not been firmly established.<sup>27</sup> Nevertheless, it is accepted that the MetS and insulin resistance are “closely related”<sup>28</sup> and that insulin resistance may be a necessary but not sufficient variable for expression of the MetS.<sup>8</sup>

Although itself rare in childhood, the precursors of ASCVD are present in the young. Autopsy studies<sup>29–31</sup> 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.<sup>32,33</sup> 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 resistance<sup>34</sup>; however, because not all patients with insulin resistance develop the MetS,<sup>35</sup> 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 <sup>19</sup> and Duncan et al, <sup>226</sup> 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, <sup>271</sup> 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, <sup>272</sup> 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, <sup>20</sup> 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, <sup>14</sup> 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, <sup>15</sup> 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, <sup>273</sup> 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, <sup>164</sup> 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, <sup>20</sup> NHANES	IR or DM, plus 2 additional risk factors	≥102 cm WC (male) or ≥88 cm (female); or ≥95% BMI (CDC) <sup>14</sup>	≥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) <sup>272</sup>	>75% insulin (cohort percentile)
Katzmarzyk et al, <sup>274</sup> 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, <sup>14</sup> 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, <sup>275</sup> NHLBI Growth and Health Study	≥3/5		>90% SBP (NHBPEP) <sup>226</sup> >90% DBP (NHBPEP)	<40 mg/dL HDL >126 mg/dL LDL >104 mg/dL TG		
Raitakari et al, <sup>26</sup> 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, <sup>83</sup> 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 <sup>276</sup>		≥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.<sup>277</sup>

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

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

§American Diabetes Association guideline for defining glucose intolerance and diabetes.<sup>192</sup>

||ATP III guideline for defining MetS.<sup>280</sup>

¶Centers for Disease Control and Prevention growth chart used to define BMI.<sup>281</sup>

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

\*\*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.<sup>36,37</sup> 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 cells<sup>38</sup>; (2) insulin stimulates endothelin-1 production, with subsequent vascular smooth

muscle growth<sup>39</sup>; (3) insulin stimulates *ras*-p21 in vascular smooth muscle, which promotes increased effects of other growth factors, such as platelet-derived growth factor<sup>40</sup>; and (4) the vascular endothelial cell insulin receptor knockout mouse has lower blood pressure and endothelin-1 levels than its wild-type counterpart.<sup>41</sup> Conversely, other lines of evidence suggest that insulin may be antiatherogenic: (1) Insulin inhibits the inflammatory transcription factor nuclear factor- $\kappa$ B<sup>42</sup>; (2) insulin decreases levels of early growth response gene-1 and tissue factor<sup>43</sup>; (3) insulin decreases tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )<sup>44</sup>; and (4) insulin stimulates nitric oxide to lower blood pressure.<sup>45</sup> 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.<sup>46</sup> 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

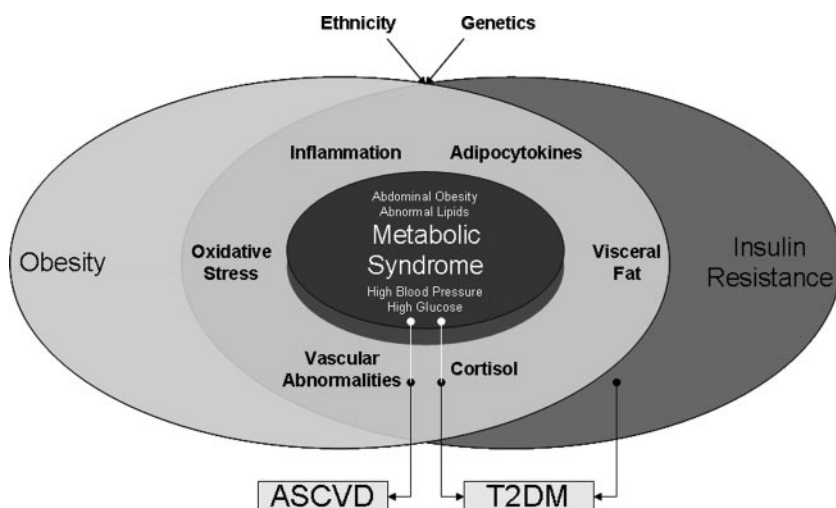


Figure. Schematic of components of the MetS.

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.<sup>47</sup> The primary role of hepatic insulin resistance in MetS is recapitulated in several animal models.<sup>48–50</sup> Either impaired hepatic or adipose responses to insulin, or both, can lead to the buildup of circulating free fatty acids,<sup>51</sup> which can lead to a compensatory increase in the secretion of insulin from pancreatic  $\beta$ -cells.<sup>46,52</sup>

Over time, individuals with insulin resistance become hyperinsulinemic. This can take the form of insulin hypersecretion or reduced insulin clearance.<sup>53</sup> As long as the pancreas can adequately compensate for insulin resistance, blood glucose concentrations remain normal; however, in some patients, the capacity of the  $\beta$ -cell erodes over time,<sup>54</sup> which leads to  $\beta$ -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,<sup>55</sup> 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.<sup>56</sup> 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.<sup>57</sup> 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.<sup>21</sup>

A transient insulin-resistant state occurs in children during normal pubertal development.<sup>58–61</sup> 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.<sup>61</sup> 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.<sup>62</sup>

## Obesity

Obesity has been strongly associated with insulin resistance,<sup>63</sup> T2DM,<sup>64</sup> and ASCVD.<sup>65</sup> Data from the Framingham Study have established an increased incidence of cardiovascular events in both men and women with increasing weight<sup>66</sup>; body weight and mortality were directly related in the Harvard Alumni Health Study,<sup>67</sup> and weight loss was associated with a decrease in inflammatory cytokines<sup>68</sup> and insulin concentration and an increase in insulin sensitivity in adults<sup>69</sup> and adolescents.<sup>70</sup> Currently, more than 20% of all children and adolescents in the United States are overweight.<sup>71</sup> Childhood obesity has been associated with ele-

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

However, BMI only accounts for 60% of the variance of insulin resistance in adults,<sup>85</sup> which suggests that other factors are important. Indeed, in a Spanish population, children with premature adrenarche and insulin resistance were thin.<sup>86</sup> Recent evidence in children shows that waist circumference is more associated with visceral fat, whereas BMI is more associated with subcutaneous fat.<sup>87</sup> 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.<sup>88</sup> 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.<sup>21</sup> In adults, it is well established that visceral fat is related to increased cardiovascular risk independent of total body fat.<sup>89,90</sup> Waist-to-hip ratio and waist circumference are often used as markers of visceral fat.<sup>91</sup> Recently, waist circumference in children was found to be an independent predictor of insulin resistance.<sup>92</sup> The relationship between waist circumference–measured abdominal obesity and health outcomes appears to be explained by its strong association with visceral adipose tissue,<sup>92</sup> an independent predictor of metabolic and cardiovascular disease.<sup>93</sup> Visceral fat measured in a small sample of adolescent girls<sup>94</sup> was associated with dyslipidemia and glucose intolerance, especially in the obese. Waist circumference has also been associated with inflammatory biomarkers such as CRP<sup>95</sup> and adiponectin<sup>96,97</sup> in youth. Given the significant increase in waist circumference among US children and adolescents over the past 2 decades,<sup>98</sup> 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.”<sup>99</sup>

## Adipocytokines

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

adipose tissue<sup>103</sup> overproduce IL-6. Expression of TNF- $\alpha$  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.<sup>104</sup> IL-6 and TNF- $\alpha$  mediate lipolysis indirectly and augment hepatic synthesis of fatty acids, thereby increasing serum levels of fatty acids and triglycerides.<sup>105</sup> The inflammatory cascade triggered by these cytokines is in turn further enhanced by hyperinsulinemia.<sup>106</sup> IL-6 and TNF- $\alpha$  also act directly at the insulin receptor to decrease receptor signaling and increase insulin resistance.<sup>107</sup>

### 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.<sup>108</sup> CRP is produced in the liver and regulated by inflammatory cytokines, principally IL-6 and TNF- $\alpha$ .<sup>109,110</sup> CRP has been localized to atherosclerotic plaques and infarcted myocardium, where it promotes activation of complement.<sup>111,112</sup> Obesity in adults is strongly associated with CRP, which suggests that it may represent a chronic state of low-grade inflammation.<sup>113–115</sup> An association of CRP with adiposity, fasting insulin, dyslipidemia, and blood pressure has been shown in a cohort of healthy prepubertal children.<sup>77</sup> 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.<sup>116</sup> Conversely, a longitudinal adult study documented change in inflammatory biomarkers that preceded accelerated weight gain and, by inference, obesity and insulin resistance.<sup>117</sup> 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.<sup>118</sup> 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.<sup>119</sup> Free fatty acids may stimulate, either independently or in concert with hyperglycemia, the production of reactive oxygen species (oxidative stress).<sup>120</sup> 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 transport<sup>121</sup> and target-organ damage such as that related to T2DM and ASCVD.<sup>122</sup> A significant association has been documented in adolescents between hypertension and oxidative

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

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.<sup>124</sup> 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.<sup>125–128</sup> Psychosocial stresses correlate with risk of myocardial infarction in adults.<sup>129</sup> 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.<sup>130</sup>

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.<sup>131</sup> 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.<sup>132,133</sup> 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.<sup>134</sup> It is generally agreed that endothelial dysfunction occurs early in the pathogenesis of atherosclerosis.<sup>135</sup> 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,<sup>136</sup> platelet aggregation,<sup>137</sup> and vascular smooth muscle proliferation,<sup>138</sup> thereby conferring a protective effect on the vasculature. Insulin resistance is associated with endothelial dysfunction and impaired insulin-mediated nitric oxide-dependent vasodilation.<sup>139</sup> 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.<sup>81</sup> 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.<sup>140</sup>

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.<sup>32</sup> 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.<sup>33</sup> 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.<sup>141</sup>

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 disease<sup>142</sup> and predicts the likelihood of cardiovascular events<sup>143–145</sup> in adults. C-IMT in children was increased with type 1 diabetes mellitus<sup>146,147</sup> and hypertension.<sup>148</sup> 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.<sup>149</sup> Others have shown that adolescent offspring of adults with premature ASCVD had increased C-IMT and abnormal flow-mediated vasodilation compared with control subjects.<sup>150</sup>

### Hypertension

The relation between hypertension and insulin resistance is confounded by the significant independent relation between hypertension and obesity.<sup>151</sup> Hypertension is an integral component of the MetS.<sup>2</sup> Increased sympathetic tone has been associated with obesity in adolescents, and both insulin and leptin<sup>152</sup> appear to have a direct effect on sympathetic nervous system activity.<sup>153</sup> Insulin infusions stimulate sodium retention by the kidney,<sup>154</sup> and insulin stimulates vascular smooth muscle growth.<sup>155</sup> Fasting insulin, used as an estimate of insulin resistance, has been significantly correlated with blood pressure in children and adolescents.<sup>156</sup> 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.<sup>55</sup> 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.<sup>157</sup> Studies in 11- to 15-year-olds<sup>158</sup> 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.<sup>159</sup>

### Lipid Abnormalities

Lipid abnormalities, particularly high triglycerides and low HDL-C, are strongly associated with insulin resistance<sup>160</sup> 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.<sup>161</sup> 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.<sup>162,163</sup> 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.<sup>164</sup> The hypertriglyceridemic waist phenotype has been proposed in adults as a predictor of the MetS.<sup>165</sup> A recent study in more than 3000 adolescents that used the modified ATP III cut points for serum triglycerides ( $\geq 110$  mg/dL) and waist circumference ( $\geq 90$ 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.<sup>166</sup>

Apolipoprotein CIII, a marker of the triglyceride-rich lipoproteins increased in MetS, retards triglyceride clearance.<sup>167</sup> 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.<sup>168–170</sup> In adults<sup>171</sup> and more recently in children,<sup>172,173</sup> 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.<sup>174,175</sup> Independent of weight and insulin status, blacks have lower apolipoprotein CIII levels than other racial subgroups.<sup>176</sup> 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.<sup>177</sup> 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 T2DM<sup>178</sup> or cardiovascular morbidity.<sup>179</sup>

### 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<sup>180,181</sup> and children.<sup>182,183</sup> In adults, weight loss has been shown to reverse this progression, with frank diabetes regressing to insulin resistance.<sup>184</sup> 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.<sup>185</sup> 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.<sup>186</sup> 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.<sup>187</sup>

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.<sup>188,189</sup> This trend parallels the increase in childhood obesity. In series of children with T2DM, the mean BMI ranged from 26 to 38 kg/m<sup>2</sup>.<sup>187</sup> 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).<sup>190,191</sup> 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.<sup>192</sup> Current American Diabetes Association guidelines recommend routine glucose testing in obese children >10 years of age with 2 additional risk factors for T2DM.<sup>192</sup> 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.<sup>193</sup>

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.<sup>188</sup> Essential hypertension is known to be associated with diabetes in adults,<sup>194</sup> 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.<sup>195</sup> 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.<sup>196</sup> 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.<sup>197</sup> 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,<sup>198</sup> is difficult to estimate in children, because the diagnosis is confirmed only by liver biopsy.<sup>199</sup> A recent study of autopsy specimens suggests a prevalence in 13% of children and 38% of obese children.<sup>200</sup> Alanine transaminase elevations, along with abdominal ultrasound, may be useful in the diagnosis<sup>201</sup>; 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.<sup>202</sup>

**Table 2. Treatment Recommendations**

General Comments	Step 1	Step 2
<b>Lifestyle</b>		
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 <sup>2</sup> , 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
<b>Blood pressure</b>		
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
<b>Lipids: TG</b>		
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	
<b>Glucose</b>		
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 <sub>1c</sub> <7%		

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; F/U, follow-up; TG, triglycerides; FG, fasting glucose; and HbA<sub>1c</sub>, 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.<sup>260,284–297</sup>

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.<sup>203–205</sup> Familial influences on development of cardiovascular risk are

well known. Because ASCVD aggregates in families,<sup>206–208</sup> parental history of ASCVD is accepted as a measure of the offspring's cardiovascular risk and has been used in prevention and intervention algorithms.<sup>209,210</sup> 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).<sup>211</sup> 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.<sup>211–214</sup> Twin and family studies have found substantial familial aggregation for the MetS risk factors.<sup>203–205</sup> 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.<sup>154</sup> Conversely, most obese children have at least 1 parent who is obese,<sup>215</sup> and the risk of adult obesity among children <10 years old is more than doubled if a parent is obese.<sup>216</sup> The familial nature of insulin action in Pima Indians has been known for many years.<sup>217</sup> Relatives of diabetic patients tend to have higher insulin levels than relatives of nondiabetic individuals.<sup>218–220</sup> A positive family history of T2DM was associated with higher levels of insulin resistance (insulin clamp studies) in 10-year-old black children.<sup>221</sup> 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.<sup>222</sup>

### **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.<sup>223,224</sup> 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.<sup>225</sup>

Similar to adults, black youth have lower total cholesterol and triglycerides and higher HDL-C levels than white children,<sup>11</sup> and Hispanic adults and children have an increased prevalence of high triglycerides.<sup>226</sup> Although Weiss et al<sup>15</sup> 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.<sup>227</sup> 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.<sup>228</sup>

A number of studies have shown that black and Hispanic children are more insulin resistant than white children.<sup>229–232</sup> Yet, the rates of the MetS in black youth are lower when the same ATP III criteria are used.<sup>11,19,233</sup> 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.<sup>231</sup> Other studies found that black adolescents have higher first- and second-phase

insulin concentrations than white subjects when evaluated by the hyperglycemic clamp.<sup>232</sup> 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.<sup>229</sup> 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,<sup>234–236</sup> 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.<sup>237</sup> 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.<sup>238</sup> There is evidence for an association between physical activity and lower levels of inflammatory cytokines and markers of oxidative stress.<sup>239,240</sup> Higher levels of physical activity are also positively correlated with insulin sensitivity in adolescents<sup>241</sup> and with improved endothelial function and HDL-C, even in the absence of weight loss.<sup>154</sup> 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<sup>242,243</sup> 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.<sup>244–247</sup> 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.<sup>244</sup> The same relation was noted among the overweight and obese adolescents,<sup>244</sup> as well



as in adults.<sup>245</sup> A significant inverse association between fiber intake and the MetS has been described in adults<sup>248</sup> and in the Framingham Offspring Study.<sup>249</sup> Conversely, the prevalence of the MetS is significantly higher among individuals in the highest relative to the lowest quintile category of glycemic index.<sup>250</sup> 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.<sup>251</sup> 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.<sup>245,252</sup> Studies in adults have shown inverse relations of inflammatory factors with vitamin C, carotene, magnesium, and long-chain fatty acids.<sup>246,253,254</sup> 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,<sup>255</sup> higher BMI,<sup>256,257</sup> and higher all-cause, ASCVD, and cancer mortality.<sup>258</sup> 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.<sup>259</sup> 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.<sup>260</sup>

### 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.<sup>261</sup> Similar effects have been observed for endothelial dysfunction, with the greatest improvements occurring when combined dietary and exercise interventions are used in overweight children.<sup>262</sup>

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.<sup>263,264</sup> In small studies, metformin has been used effectively in adolescents with T2DM to decrease BMI and improve glucose tolerance.<sup>265,266</sup>

### 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.<sup>267</sup> 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.<sup>268</sup> 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.<sup>29</sup> 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.<sup>269</sup> However, marked instability has been shown in the categorical diagnosis of MetS in adolescence.<sup>270</sup> 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.<sup>271–297</sup>

## Disclosures

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\*Modest.

†Significant.

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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

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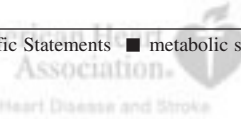


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