# The Metabolic Syndrome in Children and Adolescents

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The metabolic syndrome was recently defined by the Adult Treatment Panel III. Despite a lack of uniform definition of the syndrome in pediatrics, recent studies have shown that the syndrome develops during childhood and is highly prevalent among overweight children and adolescents. The hypothesized central role of insulin resistance and obesity as a common underlying feature of the metabolic syndrome also appears to be already manifested in childhood. In view of the current obesity epidemic in children and adolescents, there is a vital need to provide adequate guidelines for the definition of the metabolic syndrome in pediatrics and for the development of screening and treatment strategies. This article focuses on the above issues, as well as on the impact of the syndrome on two major disease outcomes, type 2 diabetes and cardiovascular disease.

## Introduction

Although the components of the metabolic syndrome were first described over 40 years ago, it was only recently that both the World Health Organization (WHO) and the United States (US) National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III provided a clinical definition of the syndrome. These criteria, although similar in that they focus on obesity, dyslipidemia, hyperglycemia, and hypertension, differ in the individual constituents and threshold levels. The uniform case definition of the syndrome has promoted epidemiologic investigations to establish the prevalence and characteristics of the syndrome across different adult populations [1–7]. Most importantly, these studies have provided new evidence to support the role of the syndrome as an entity that places individuals at risk for type 2 diabetes [6,7] and cardiovascular disease [4,5] that is associated with increased cardiovascular disease mortality [4,5]. The findings from studies in adults, coupled with the obesity epidemic in childhood, have resulted in a renewed interest in the study of the metabolic syndrome in youth and on its potential impact on the health and well-being of children and adolescents.

This article presents the following information: 1) Provides evidence to show that the metabolic syndrome develops during childhood, has a higher prevalence in overweight children, and is more pronounced in certain ethnic minorities. 2) Examines the underlying pathophysiology of the syndrome during childhood and argues that the underlying defect suggested in adults (obesity coupled with insulin resistance) is evident early in life. 3) Looks at available evidence linking the metabolic syndrome (and its individual components) with disease outcomes during childhood, namely type 2 diabetes and cardiovascular disease. 4) Proposes the creation of a working definition of the metabolic syndrome in children. 5) Suggests strategies for screening and treatment of the syndrome in youth.

## Prevalence of the Metabolic Syndrome in Children and Adolescents

Several large population studies have established the prevalence of the metabolic syndrome during childhood [8••,9–11]. Although direct comparison across studies is hampered due to differences in the definition of the syndrome, the overall prevalence in children and adolescents is relatively low (3% to 4%) when compared to the adult population. For instance, the age-adjusted prevalence of the metabolic syndrome based on the ATP III definition in US adults was 23.7%, whereas in adults aged 20 to 29 years it was 6.7% [2].

In the Bogalusa Heart study (a population-based longitudinal study of cardiovascular disease risk factors in black and white children), the metabolic syndrome was defined as having four components ≥ 75th percentile for age and gender derived from their own population data (Table 1) [10]. Based on this definition, the prevalence of the metabolic syndrome was 4% and 3% in white and black children, respectively [10]. Similarly, in the Cardiovascular Risk in Young Finns Study (a large multicenter study of risk factors for heart disease in children and young adults), the prevalence of the metabolic syndrome was 4% (Table 1). More recently, the prevalence of the metabolic syndrome was established in US adolescents ($n$ = 2400) aged 12 to 19 years who participated in NHANES III (third National Health and Nutrition Examination Survey) [8••]. In this study the authors chose to use a definition similar to that proposed in ATP III (Table 1) with threshold values based on pediatric

**Table 1. Summary of the prevalence of the MS in children and adolescents**

| Characteristics | Chen *et al.* [9] | Raitakari *et al.* [11] | Cruz *et al.* [12•] | Cook *et al.* [8••] | |
|---|---|---|---|---|---|
| Population | White (*n* = 3631) and black children (*n* = 2127) | Finnish children (*n* = 1865) | Overweight Hispanic children (mean BMI 97th percentile; *n* = 126) | White (*n* = 646), black (*n*= 824), Mexican-American (*n* = 846) children | |
| Age, *y* | 5–17 | 6–18 | 8–13 | 12–19 | |
| Definition of MS | 4 components ≥ 75th percentile for age and gender | 3 components ≥ 75th percentile for age and gender | ≥ 3 components | ≥ 3 components | |
| Components of the MS | | | | | |
| Obesity | BMI | NA | Waist circumference ≥ 90th percentile for age/gender/ethnicity (NHANES III) | Waist circumference ≥ 90th percentile for age/gender | |
| Hyperglycemia | NA | NA | Impaired glucose tolerance (2-hour glucose ≥ 140 mg/dL) | Impaired fasting glucose (glucose ≥ 110 mg/dL) | |
| Hypertension | Mean arterial pressure | Blood pressure | High blood pressure (≥ 90th percentile for height, age, and gender) | High blood pressure (≥ 90th percentile for height, age, and gender) | |
| Dyslipidemia | TG/HDL ratio | TGs ≥ 75th percentile; HDL cholesterol (≤ 25th percentile) | TGs ≥ 90th percentile for age/gender; HDL ≤10th percentile for age and gender (NHANES III) | TGs > 110 mg/dL; HDL < 40 mg/dL | |
| Insulin resistance | Fasting insulin | NA | NA | NA | |
| | | | | Overall | Overweight |
| Prevalence of MS | 4% in white and 3% in black children | 4% | 30% | 4.2% | 28.7% |
| Prevalence of components, % | | | | Overall | Overweight |
| High waist circumference | | | 62 | 9.8 | 74.5 |
| Hyperglycemia | | | 27 | 1.5 | 2.6 |
| Low HDL cholesterol | | | 67 | 23.3 | 50 |
| High triglycerides | | | 26 | 23.4 | 51.8 |
| High blood pressure | | | 22 | 4.9 | 11.2 |

BMI—body mass index; HDL—high-density lipoprotein; MS—metabolic syndrome; NA—not available; NHANES—third National Health and Nutrition Examination Survey; TGs—triglycerides.

guidelines. The overall prevalence of the metabolic syndrome in US adolescents was 4.2%. Prevalence rates were higher in men (6.1%) than in women (2.1%). The prevalence of one and two components of the metabolic syndrome was 41% and 14.2%, respectively. The most commonly found abnormality was high triglycerides and low high-density lipoprotein (HDL) cholesterol. In contrast, the prevalence rates of high fasting glucose were very low (1.5%).

### Impact of obesity on the metabolic syndrome

Although the previous studies suggest that overall the prevalence rates of the metabolic syndrome in childhood are low, the perspective is very different in overweight adolescents [8••,12•]. In NHANES III, the prevalence of the metabolic syndrome was 28.7% in overweight adolescents (body mass index [BMI] ≥ 95th percentile), compared to 6.1% in adolescents at risk for overweight (BMI ≥ 85th but lower than the 95th percentile) and 0.1% in those with a BMI below the 85th percentile [8••]. Eighty-nine percent of overweight adolescents had at least one abnormality of the metabolic syndrome and more than half (56%) had two abnormalities. In this NHANES III adolescent population, the vast majority (80%) of youth who were classified as having the metabolic syndrome were also classified as being overweight based on a BMI greater than the 95th percentile.

In view of the increasing rise in childhood overweight, the overall prevalence of the metabolic syndrome in US adolescents is likely to be higher than that estimated from NHANES III data. Results from the 1999 to 2000 NHANES indicate that an estimated 15% of children and adolescents ages 6 to 19 years are overweight (BMI > 95th percentile), a value 4% higher than that reported in NHANES III (1988 to 1994) [13].

### Impact of ethnicity on the metabolic syndrome

In US adults, the prevalence of the metabolic syndrome has been shown to be higher among Hispanic (31.9%) and

lower among black (21.6%) compared to white adults (23.8%) [2]. Likewise, the prevalence of the metabolic syndrome in US adolescents was highest among Hispanics (5.6%) and lowest among black (2.0%) compared to white adolescents (4.8%). The higher prevalence of the metabolic syndrome among Hispanic adolescents is likely to be associated with the high prevalence of overweight in this ethnic group. The prevalence of overweight in Hispanic youth has approximately doubled in the past 10 years, such that 23.4% of Hispanic adolescents are now overweight compared to 12.7% of white adolescents [14].

We recently explored the prevalence of the metabolic syndrome among a group of overweight Hispanic children (aged 8 to 13 years) with a family history for type 2 diabetes [12•], who are part of an ongoing longitudinal study on the natural history of type 2 diabetes in childhood known as the Solar Diabetes Project. We developed a pediatric definition of the metabolic syndrome based on the ATP III guidelines as a model. Our cut points were based on a combination of clinical [12•] and pediatric guidelines [15], as well as on child and adolescent NHANES III data [16] as outlined in Table 1. Using this definition, we found that 30% of overweight Hispanic children with a family history for type 2 diabetes have the metabolic syndrome [12•]. Furthermore, nine out of 10 Hispanic overweight children with a family history for type 2 diabetes have at least one feature of the metabolic syndrome (Table 1) [12•], which is similar to that reported in overweight US adolescents [8••].

Although the prevalence of obesity among African-American adolescents in the United States is also high (23.6%), paradoxically African-American children and adolescents have a lower prevalence of the metabolic syndrome [8••,9,10], at least when a similar definition of ATP III is used. This is not entirely surprising because African-American youth (like adults) have lower triglycerides and higher HDL cholesterol levels compared to their white counterparts, although blacks have higher blood pressure [9]. These findings suggest that the impact of obesity on the components of the metabolic syndrome may vary by ethnic group, as has been shown to be the case in South Asians, in whom the prevalence of the syndrome is higher than in white persons [17].

## Pathophysiology of the Metabolic Syndrome in Childhood

Although a consensus was reached in terms of defining the metabolic syndrome in adults [5,18], controversy regarding the underlying etiologic factor(s) still remains. Nevertheless, the most accepted hypothesis, and one that is supported by prospective studies, is that obesity and insulin resistance [19–22] may be the key underlying abnormalities of the metabolic syndrome. The role of obesity and insulin resistance in the etiology of the metabolic syndrome has recently been explored in children through cross-sectional and prospective studies [12•,23].

The Cardiovascular Risk in Young Finns Study was one of the first groups to explore the childhood predictors of the metabolic syndrome [11]. In this study, fasting insulin at baseline was related to the development of the metabolic syndrome (defined as having the three following factors: high triglyceride and high blood pressure [> 75th percentile] and low HDL cholesterol [< 25th percentile]) after 6 years of follow-up in 1865 children and adolescents (6 to 18 years). The results from this study showed that baseline insulin concentration was higher in children who subsequently developed the metabolic syndrome, lending support to the view that insulin resistance precedes the development of the metabolic syndrome in childhood. Because obesity in childhood is closely associated with insulin resistance, it would have been important to establish if children and adolescents who developed the metabolic syndrome after a 6-year follow-up period were also more overweight.

More recently, researchers from the Bogalusa Heart Study (a bi-racial longitudinal cohort) attempted to disentangle the relative contribution of childhood obesity (measured via BMI) versus insulin resistance (measured via fasting insulin) to the adulthood risk of developing the metabolic syndrome [24]. A total of 718 children, aged 8 to 17 years at baseline, were followed for an average of 11.6 years. The metabolic syndrome was defined as having the following four factors: BMI, fasting insulin, systolic (or mean arterial blood pressure), and triglyceride/HDL ratio in the highest quartile for age, gender, ethnicity, and study year. Significant positive trends were seen between childhood BMI as well as insulin quartiles and the incidence of clustering in adulthood. Children in the top quartile of BMI and insulin versus those in the bottom quartile were 11.7 and 3.6 times more likely to develop clustering, respectively, as adults. A high childhood BMI was significantly associated with the incidence of clustering in adulthood, even after adjustment for childhood insulin levels. However, in this study, adjustment for childhood BMI eliminated the influence of insulin on the incidence of clustering in adulthood. Thus, in this bi-ethnic, community-based study, childhood obesity (measured via BMI) was more closely associated with the presence of the metabolic syndrome in adulthood than was fasting insulin. These findings suggest that obesity in childhood precedes the development of the metabolic syndrome in adulthood.

Although obesity in childhood may be more closely associated with the development of the metabolic syndrome than insulin resistance, the question remains as to why some obese children develop the metabolic syndrome and others do not. The recent NHANES III data on the prevalence of the metabolic syndrome among US adolescents found that approximately 30% of overweight children (BMI > 95th percentile) had the metabolic syndrome whereas the remaining 70% did not. We recently addressed this issue in a cohort ($n$ = 126) of overweight Hispanic adolescents (mean BMI percentile 97 ± 2.9; age 8 to 13 years) with a family history for type 2 diabetes [12•]. We hypothesized that in overweight

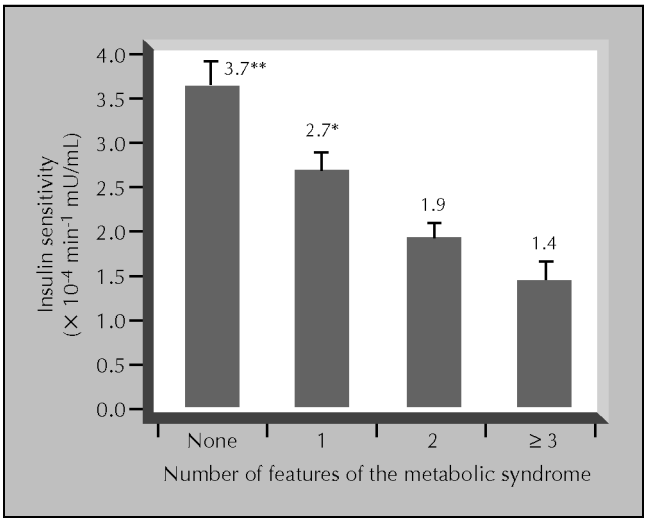


**Figure 1.** Estimated marginal means for insulin sensitivity in overweight Hispanic youth according to a number of features of the metabolic syndrome. For clarity of interpretation, data are presented using the non-log transformed insulin sensitivity. However, statistical analysis was performed on log-transformed insulin sensitivity. Data were adjusted for gender, age, Tanner stage, total body fat, and total lean mass. *One asterisk* (*) indicates log-insulin sensitivity was different between subjects with zero features of the metabolic syndrome versus those with two or ≥ three features ($P < 0.001$). *Two asterisks* (**) indicate log-insulin sensitivity was different between subjects with one feature of the metabolic syndrome versus those with two or ≥ three features ($P < 0.01$). Log-insulin sensitivity was not different between children with one versus two features or between those with two versus three features. (*From* Cruz *et al.* [12•].)

Hispanic children, insulin resistance would be more closely associated with the metabolic syndrome than overall adiposity. In this study, insulin sensitivity was measured via the frequently sampled intravenous glucose tolerance test and minimal modeling, and overall adiposity was measured via dual-energy x-ray absorptiometry. We found that insulin sensitivity (after adjustment for differences in adiposity) was 62% lower in overweight youth with the metabolic syndrome (defined as having ≥ three of the following: hypertriglyceridemia, low HDL cholesterol, high blood pressure, high waist circumference, or impaired glucose tolerance) compared to overweight youth without the metabolic syndrome (Fig. 1). Furthermore, in multivariate regression analysis, insulin sensitivity, but not fat mass, was independently and negatively related to triglycerides and blood pressure and positively related to HDL cholesterol. These results suggest that the effect of adiposity on lipids and blood pressure control is mediated via insulin resistance.

Our findings in overweight Hispanic youth are in agreement with previous results in children, in which directly measured insulin sensitivity has been shown to be independently associated with the separate components of the metabolic syndrome [23,25]. For instance, we previously reported that after adjustment for differences in body composition (fat and lean tissue mass), insulin sensitivity (measured via the frequently sampled intravenous tolerance test) was negatively associated with systolic blood pressure in a mixed cohort of African-American and white pre-pubertal children with wide varying degrees of adiposity [25]. Insulin sensitivity measured via the euglycemic insulin clamp has also been shown to be correlated with fasting triglycerides and HDL cholesterol in white children and adolescents ($n = 357$, mean age ~ 13 years), and this relationship remained after adjustment for BMI [23].

Despite significant differences in the definition of the metabolic syndrome and in the pediatric populations studied, collectively, the above findings suggest that both obesity and insulin resistance contribute to the development of the metabolic syndrome during childhood. It is likely that among overweight children, insulin resistance may be more important than overall adiposity in the development of the metabolic syndrome. In this respect, the preferential accumulation of visceral fat, as opposed to subcutaneous abdominal fat, or alternatively increased ectopic fat storage, may play a significant role in the pathophysiology of the metabolic syndrome in childhood. We have recently shown that visceral fat in addition to total fat are important contributors to differences in insulin sensitivity among overweight Hispanic youth with a family history for type 2 diabetes [26]. Similarly, a recent study showed that both visceral fat (measured via magnetic resonance imaging) and intramyocellular lipid accumulation (measured via nuclear magnetic resonance spectroscopy) were inversely related to the glucose disposal and nonoxidative glucose metabolism in overweight children and adolescents [27].

In summary, results in children and adolescents suggest that obesity and perhaps more importantly, central obesity, or ectopic fat storage, coupled with increased susceptibility to insulin resistance, may contribute to the development of the metabolic syndrome in childhood.

## Impact of the Metabolic Syndrome on Premature Cardiovascular Disease and Type 2 Diabetes

In adults, the metabolic syndrome is a risk factor for type 2 diabetes and cardiovascular disease [18] that is associated with increased cardiovascular disease mortality [4]. Although no studies to date have directly explored the impact of the metabolic syndrome on disease outcomes in childhood, autopsy studies in youth have shown that cardiovascular risk factors (including obesity, high blood pressure, high triglycerides, and low HDL cholesterol) are related to the early stages of coronary atherosclerosis [28,29]. Furthermore, the extent of lesions increases markedly with the presence of multiple risk factors [28]. Therefore, the high prevalence of the metabolic syndrome among overweight youth coupled with the epidemic increase in childhood obesity could lead to a disproportionate increase in cardiovascular disease in adulthood.

Type 2 diabetes and impaired glucose tolerance have recently emerged as a critical health problem in overweight adolescents [30,31,32•]. Although little is known regarding

the pathophysiology of type 2 diabetes in childhood, the disease process is likely to be similar to that of adults. In this respect, a state of impaired fasting glucose or impaired glucose tolerance in adults is considered an intermediate stage in the natural history of type 2 diabetes and predicts the risk of development of diabetes [33–35]. Furthermore, insulin resistance and insulin secretory dysfunction, commonly found in subjects with impaired glucose homeostasis, predict the development of type 2 diabetes [36–38].

The prevalence of impaired fasting glucose in childhood is relatively low (1.8%), even among overweight children (2.5%) [8••,39]. In contrast, the prevalence of impaired glucose tolerance after a glucose challenge is strikingly high among overweight children and adolescents [30,32•]. Several reports have found that the prevalence of impaired glucose tolerance in overweight children and adolescents ranged from 21% to 28% [30,32•]. A state of impaired glucose tolerance in overweight children and adolescents was associated with decreased insulin sensitivity [27], in some but not all studies [32•], and a deterioration in β-cell function [27,32•] and may, as in adults, signal the premature development of disease.

In summary, overweight in children and adolescents may serve to accelerate the onset of type 2 diabetes in childhood, through early and chronic exposure of the β cell to chronic insulin resistance, which may in turn result in insulin secretory dysfunction.

## Definition of the Metabolic Syndrome in Children and Adolescents

In considering a definition of the metabolic syndrome in children at least three major issues need to be confronted: 1) Should a definition be created at all? 2) What components should define the syndrome? 3) What thresholds should be used? As one can imagine, these three issues alone could generate considerable debate.

### Should the metabolic syndrome be defined in children and adolescents?

To address this initial question, it may be important to first consider findings in adults. In recent years, both the US NCEP ATP III and the WHO provided a clinical definition of the metabolic syndrome in adults. In general, the ATP III definition is more of a risk factor–based definition (Table 1), whereas the WHO definition is a disease-based definition in which impaired glucose tolerance, diabetes, and insulin resistance are thought to be central components. Regardless of the differences in the individual features and threshold values applied, surprisingly, the prevalence of the metabolic syndrome has been shown to be consistent and very common in adult populations [1–5]. Those with the syndrome are more insulin resistant [3] and are at greater predicted risk for coronary heart disease [3–5] and diabetes [6,7]. Furthermore, the presence of the metabolic syndrome doubles the risk for coronary heart disease events and dramatically increases the risk for type 2 diabetes. More importantly, these studies have shown that specific clustering of traits better predicts the risk burden of coronary heart disease or type 2 diabetes in diverse populations. Because several of these traits, particularly lipid risk factors and blood pressure [40], not to mention obesity [41], tend to track into adulthood, early identification of the clustering of risk factors in childhood should prove very valuable in targeting efforts for chronic disease prevention. In summary, evidence from both adult and pediatric studies supports the need to create a definition of the metabolic syndrome in childhood.

### What components should be included in a definition of the metabolic syndrome in children and adolescents?

Based on evidence that several traits of the metabolic syndrome track into adulthood, it seems appropriate for the most part to include the same set of risk factors that in adults have the most predictive power on disease outcomes. Perhaps with this in mind it may be appropriate to develop a definition in childhood that is comparable to that of adults, as has been implemented in two recent studies [8••,12•]. Two specific components need further evaluation in pediatrics. For instance, we and others have shown that the prevalence of impaired fasting glucose in childhood is very low, even among children at high risk for type 2 diabetes [8••,12•, 30,32•]. In contrast, impaired glucose tolerance (defined as 2-hour glucose ≥ 140 mg/dL) is fairly common, at least in overweight children [30,32•]. This raises the issue of whether impaired glucose tolerance as opposed to fasting glucose should be one of the components of the syndrome. Alternatively, perhaps the fasting glucose threshold should be lowered as was suggested recently by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus in their follow-up report on the diagnosis of diabetes [42]. In this report, the committee decided to lower the threshold for the diagnosis of impaired fasting glucose from 110 to 100 mg/dL [42], a value that is somewhat arbitrary. Ideally, the threshold value of fasting plasma blood glucose should be one at which the risk of a clinical or metabolic outcome rises sharply; however, this remains to be established.

Finally, the question remains as to whether BMI percentile or waist circumference should be included as a component of the syndrome; we favor the latter but recommend only screening overweight children (BMI ≥ 95th percentile), as outlined in Table 2.

### What threshold values should be used?

Earlier studies in childhood focused on the clustering of risk factors for cardiovascular disease [9,11], used their own study cut-off values, and were less concerned with the risk for type 2 diabetes or the presence of hyperglycemia. In contrast, and probably in response to the need to be able to compare prevalence rates in childhood to those of adults, recent studies in children adopted a definition based on ATP III (Table 1) [8••,12•]; however, there were significant differences in the

**Table 2. Summary of pediatric guidelines for the prevention and treatment of disease states associated with the MS**

| Guidelines | Obesity [44] | Type 2 diabetes [31] | Hypertension [15] | CVD health [43,45,46] | Proposed guidelines for MS |
|---|---|---|---|---|---|
| Screening | Obesity | Type 2 diabetes | Hypertension/high BP | CVD risk factors | MS |
| Type of screening | Calculation of BMI percentile | Fasting glucose or oral glucose tolerance test | BP measurement | Family Hx, BMI, BP, diet and physical activity, smoking, fasting lipids | BMI, oral glucose tolerance test, waist circumference, fasting lipids, BP |
| Who should be screened | All children | Children ≥ 10 y of age (or at onset of puberty) with a BMI percentile ≥ 85th + 2 more risk factors (+ family Hx for T2D, ethnic minority, signs of insulin resistance) | All children ≥ 3 y of age | All children ≥ 2 y of age; lipids: only in those with positive premature family Hx of CVD or when other risk factors are present (*eg*, BMI > 95th percentile, diabetes, smoking, hypertension) | All children with BMI ≥ 95th percentile |
| Who should be treated | Children with BMI > 85th percentile with complications and children with BMI > 95th percentile with or without complications | Children with T2D | Children with BP > 95th percentile for height/age/gender | LDLC > 160 mg/dL; TGs ≥ 150 mg/dL; HDLC ≥ 35 mg/dL; BP ≥ 95th percentile; BMI ≥ 95th percentile; smokers; people with T2D | Children with ≥ 3 features of the syndrome |
| Aim of therapy | Weight loss or weight maintenance | Normalization of glucose and hemoglobin $A_{1c}$; weight loss | Lower BP to value < 95th percentile; weight loss | Improve lipids and BP; weight loss; management of T2D; cessation of smoking | Improve insulin resistance |
| Type of therapy | Lifestyle modification (dietary and physical activity based) | Lifestyle modification (dietary and physical activity based) and pharmacologic | Lifestyle modification (dietary and physical activity based) and pharmacologic | Lifestyle modification (dietary and physical activity based); pharmacologic when LDLC > 190 mg/dL or TGs > 400 mg/dL | Lifestyle modification (dietary and physical activity based); need research on pharmacologic approaches |

BMI—body mass index; BP—blood pressure; CVD—cardiovascular disease; HDLC—high-density lipoprotein cholesterol; Hx—history; MS—metabolic syndrome; LDLC—low-density lipoprotein cholesterol; T2D—type 2 diabetes; TGs—triglycerides.

**Table 3. Proposed cut-off values for the various features of the MS in children and adults**

| Features of MS | Age, y | Males | Females |
|---|---|---|---|
| High glucose* | | | |
| Fasting | — | ≥ 100 mg/dL | ≥ 100 mg/dL |
| 2-hour after a standard oral glucose tolerance test | — | ≥ 140 mg/dL | ≥ 140 mg/dL |
| Systolic blood pressure, *mm Hg*† | 8 | 112 | 111 |
| | 12 | 119 | 119 |
| | 15 | 125 | 124 |
| | 17 | 133 | 125 |
| | Adult** | ≥ 130 | ≥ 130 |
| Diastolic blood pressure, *mm Hg*† | 8 | 73 | 71 |
| | 12 | 77 | 76 |
| | 15 | 79 | 80 |
| | 17 | 83 | 81 |
| | Adult | ≥ 85 | ≥ 85 |
| Triglycerides, *mg/dL*‡ | 12–19 | 135 | 170 |
| | 16–19 | 165 | 168 |
| | NCEP†† | ≥ 150 | ≥ 150 |
| | Adult | ≥ 150 | ≥150 |
| HDL cholesterol, *mg/dL*§ | 6–8 | 37 | 37 |
| | 9–11 | 39 | 38 |
| | 12–15 | 35 | 36 |
| | 16–19 | 33 | 37 |
| | NCEP | ≤35 | ≤35 |
| | Adult | ≤40 | ≤50 |
| Waist circumference, *cm*¶ | 8 | 70.9 | 70.4 |
| | 12 | 84.5 | 81.9 |
| | 15 | 94.4 | 89.8 |
| | 17 | 101 | 97 |
| | Adult | ≥ 102 | ≥ 88 |

*Data are based on the American Diabetes Association recommendations and are the same for children and adults [26,31,47].
†Data are from the Update on the Task Force for High Blood Pressure in Children and Adolescents [15]. Data are values for the 90th percentile assuming a height percentile of 50. Data are available for ages 1 to 17 years.
‡Data are from the NHANES III [16]. Values are 90th percentile for age and gender. Values for children from 8 to 11 years are not published.
§Data are from NHANES III [16]. Values are 10th percentile for age and gender.
¶Data are from NHANES III (Unpublished data). Values are 90th percentile for age, gender, and white or African-American ethnicity. The 90th percentile for Hispanics is slightly higher.
**Adult Treatment Panel definition of the MS in adults [18].
††National Cholesterol Education Program (NCEP) [47].
HDL—high-density lipoprotein; MS—metabolic syndrome; NHANES III—third National Health and Nutrition Examination Survey.

threshold values applied (Table 3). This is particularly true for lipid risk factors and waist circumference because pediatric recommendations either may require revision, as in the case of lipids (current guidelines are based on NCEP recommendations set over a decade ago [43]), or may not exist as in the case of waist circumference.

As discussed earlier, another issue that needs to be addressed is whether impaired fasting glucose (recently defined as fasting glucose ≥ 100 mg/dL) as opposed to impaired glucose tolerance should be used as the threshold for hyperglycemia in childhood. Also, the question of whether cut-off values should be ethnic and gender specific needs to be addressed. We would like to propose that in developing a pediatric definition of the metabolic syndrome three issues be considered: 1) Individual components should be similar to those of adults for the sake of comparison and to evaluate tracking. 2) Current recommendations and cut-off values need to be developed or re-evaluated, particularly for waist circumference, dyslipidemia, and perhaps hyperglycemia. 3) The use of single cut-off values (as opposed to multiple cut-off values depending on gender, age, and ethnicity) may be easier to apply but less sensitive in identifying children at risk. A working definition of the metabolic syndrome in childhood should certainly be put forth, but will require consensus among both clinicians and scientists and hopefully will be developed in the near future.

## Strategies for Screening and Treatment of the Metabolic Syndrome in Children and Adolescents

### Who should be screened?

Despite the lack of a uniform definition of the metabolic syndrome in childhood, and the use of different cut-off values, the data summarized in Table 1 demonstrate that the prevalence of the metabolic syndrome in childhood and

adolescence is relatively low, irrespective of the definition used. The exception is overweight youth. Two recent studies have shown that the metabolic syndrome is strikingly high among overweight children and adolescents [8••,12•], and suggest that Hispanic youth (predominantly of Mexican-American ancestry ) may be at increased risk compared to white youths [8••]. These findings suggest that although screening for the metabolic syndrome is probably not warranted in the pediatric population as a whole, screening of overweight children and adolescents, and particularly those belonging to specific minority groups, may be necessary.

Although current pediatric guidelines recommend screening for obesity [44], type 2 diabetes [31], hypertension [15], and dyslipidemias [43,45,46,48] in at-risk children and adolescents, they do so under the domain of individual pediatric specialties (Table 2). Therefore, screening for the metabolic syndrome in overweight children and adolescents (as opposed to screening for individual disease outcomes related to the syndrome) may help simplify screening strategies and raise awareness, both at the physician level and in the individual member or family level of the combined risk for both type 2 diabetes and cardiovascular disease among overweight youth. In addition, it may simplify the need for multiple recommendations and guidelines for the identification and treatment of overweight youth for separate diseases processes (*eg,* obesity, hypertension, type 2 diabetes), which in reality overlap due to a shared pathophysiology (Table 2). Although this may be viewed by some as cumbersome and difficult to implement, the fact is that the current recommendations for screening put forth by the different established guidelines already include screening for several features of the syndrome and all agree that overweight youth are at particular risk. The exception is waist circumference (for which there are no recommendations), and to a certain extent fasting lipids. Based on our current understanding of obesity, insulin resistance, and the metabolic syndrome, screening for adverse lipids should be instituted in all overweight children and adolescents. Support for this view is provided by the finding that adverse lipids (*eg,* high triglycerides and low HDL cholesterol) are by far the most common risk factor associated with the metabolic syndrome in childhood [8••,12•] and appear to be due to underlying insulin resistance [12•].

In summary, pediatric recommendations may need to be updated so that the multiple guidelines that exist are more consistent and address the purpose of screening, identifying, and treating children at risk. The development of comprehensive guidelines to screen and identify children with the metabolic syndrome may prove more useful in the prevention of the major disease outcomes related to the metabolic syndrome, type 2 diabetes, and cardiovascular disease in childhood.

### Strategies for treatment of the metabolic syndrome

The identification of children with the metabolic syndrome may help to direct treatment strategies by focusing on the underlying pathophysiology (*eg,* insulin resistance) rather than on individual risk factors. We propose that targeting insulin resistance (as opposed to weight loss) may be more effective in preventing or delaying the onset of cardiovascular disease and type 2 diabetes in high-risk youth, because strategies aimed at reducing body weight have been, for the most part, unsuccessful. For instance, insulin resistance and its associated risk factors may be improved directly or indirectly through specific exercise modalities, dietary interventions, or through pharmacologic agents without the need to make large changes in body fatness. For example, a recent study showed that high-intensity physical training for 8 months in overweight adolescents resulted in improvements in fasting plasma triglycerides, low-density lipoprotein particle size, and diastolic blood pressure despite little changes in body fatness [49]. Alternatively, non–weight-bearing activities such as strength training may be more acceptable in overweight children and may serve to enhance long-term health [50]. Specific nutrients such as dietary fiber, for example, may improve insulin sensitivity and glucose homeostasis through various mechanisms related to decreased gastric emptying, increased fat oxidation, decreased hepatic output of glucose, and stimulation of glucagon-like peptide-1 secretion [51]. Support for this view comes from a recent report in which whole grain consumption was found to be associated with greater insulin sensitivity and lower BMI in adolescents and that this association was stronger among the heaviest adolescents [23].

Other nutrients that may have beneficial effects on insulin sensitivity are the phytoestrogens. Nutritional intervention studies performed in animals and humans suggest that the ingestion of soy protein associated with isoflavones and flaxseed rich in lignans improves glucose control and insulin resistance [52]. Also, in very high-risk insulin-resistant children, pharmacotherapy may be indicated. A recent double-blind randomized trial in obese, insulin-resistant youth aged 12 to 19 years treated with metformin for 6 months resulted in significant improvements in glucose tolerance and fasting insulin [53]. Other agents that may prove beneficial in the treatment of insulin resistance in high-risk youth are the thiazolidinediones, which are much more potent insulin sensitizers than metformin. Thiazolidinediones have been shown to improve insulin sensitivity, glucose tolerance, and cardiovascular risk factors in type 2 diabetes, impaired glucose tolerance, and in nondiabetic insulin-resistant obese subjects [54–57].

In summary, more research needs to be conducted to establish the effectiveness of different types of interventions on insulin sensitivity in children. It is likely that beneficial and long-lasting health effects will only be achieved through the combined approaches that are gender, age, and culture sensitive.

## Conclusions

The prevalence of the metabolic syndrome, although very low in normal weight children (BMI < 85th percentile), is

high in those who are overweight (BMI > 95th percentile). Approximately 30% of overweight children have the metabolic syndrome and nine out of 10 have at least one feature of the syndrome. The underlying insulin resistance of obesity seems to be an important pathophysiologic event contributing to the syndrome, and this is already evident in childhood. Because the number of overweight children is increasing, and because it is evident that the pathology begins early in life, we advocate the creation of a definition of the metabolic syndrome in childhood with comprehensive screening of overweight children based partly on current pediatric guidelines. Future research is needed to investigate the effects of lifestyle and pharmacologic interventions aimed at improving insulin resistance in overweight children.

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