

Is a diagnosis of metabolic syndrome applicable to children?

Rafael Nardini Queiroz Pergher,¹ Maria Edna de Melo,² Alfredo Halpern,³ Marcio Corrêa Mancini,⁴ Liga de Obesidade Infantil⁵

Abstract

Objective: To present the components of the metabolic syndrome in children and adolescents and to discuss how they are assessed in the pediatric population in addition to presenting the major metabolic syndrome classifications for the age group.

Sources: A review of literature published from 1986 to 2008 and found on MEDLINE databases.

Summary of the findings: The prevalence of childhood obesity has been increasing globally over recent decades and as a result its complications, such as diabetes mellitus, arterial hypertension and dyslipidemia, have also increased. The concept of metabolic syndrome, already common with adults, is now beginning to be applied to children through classifications using the criteria for adults modified for the younger age group. Notwithstanding, these classifications differ in terms of the cutoff points used and whether they employ body mass index or waist circumference to define obesity. The review presents these classifications, highlighting the points on which they differ and the debate about them.

Conclusions: If childhood obesity goes untreated, it will have severe consequences in the future. A number of models for classifying metabolic syndrome in children have been published, but there is considerable diversions between them. The criteria for classifying metabolic syndrome in children therefore need to be standardized in order to identify those people at greatest risk of future complications.

J Pediatr (Rio J). 2010;86(2):101-108: Childhood obesity, visceral fat, metabolic syndrome, insulin resistance.

Introduction

Over recent decades, a marked increase has been observed in the number of obese people worldwide.¹ Obesity has gradually come to be treated as a disease and characterized as a global epidemic. In line with these developments, obesity has also been increasing among children. According to epidemiological data

from the United States, the prevalence of obesity among children doubled from 1976 to 2002.² One epidemiological study conducted in the city of Pelotas, RS, Brazil found that among 960 adolescents aged 15 to 18, the prevalence of overweight and obesity were 20.9 and 5% respectively.³

1. Médico residente, Departamento de Endocrinologia e Metabologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (USP), São Paulo, SP, Brazil.
2. Médica pesquisadora, Grupo de Obesidade e Síndrome Metabólica, Liga de Obesidade Infantil, Disciplina de Endocrinologia e Metabologia, Hospital das Clínicas, Faculdade de Medicina, USP, São Paulo, SP, Brazil.
3. Chefe, Grupo de Obesidade e Síndrome Metabólica, Disciplina de Endocrinologia e Metabologia, Hospital das Clínicas, Faculdade de Medicina, USP, São Paulo, SP, Brazil.
4. Médico assistente. Doutor, Grupo de Obesidade e Síndrome Metabólica. Chefe, Liga de Obesidade Infantil, Disciplina de Endocrinologia e Metabologia, Hospital das Clínicas, Faculdade de Medicina, USP, São Paulo, SP, Brazil.
5. Grupo de Obesidade e Síndrome Metabólica, Disciplina de Endocrinologia e Metabologia, Hospital das Clínicas, Faculdade de Medicina, USP, São Paulo, SP, Brazil.

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The availability of high-calorie foods and the inactivity associated with hours spent watching television, playing video games and using computers are part of the cause of the increase in the number of obese children.⁴

As childhood obesity has increased, the complications associated with it have become more common and easier to identify. As with adults, childhood obesity leads to the emergence of diseases such as diabetes mellitus, systemic arterial hypertension and dyslipidemia, which increase the risk of cardiovascular events. For example, type 2 diabetes mellitus (DM2) has increased dramatically over the last 20 years.⁵

The association between obesity and coronary disease is already well-established in adults.⁶ This association led to the term "metabolic syndrome" being created to define the condition of those people who are at greatest risk of cardiovascular events, due to the common pathophysiologic basis shared by the syndrome's components, which in turn is possibly orchestrated by central obesity.⁷ The factors that comprise the metabolic syndrome include visceral obesity, atherogenic dyslipidemia, hypertension and insulin resistance. On the basis of these factors, criteria have been defined to identify people with metabolic syndrome so that preventative measures can be taken, thereby reducing the chances of adverse cardiovascular outcomes.

It is important to remember that there is no official definition of metabolic syndrome in children. Adaptation of the criteria used for adults is complicated because of the multiple definitions proposed by different organizations and because normal ranges for each criterion must be adjusted for each age group.

This article will present the most important classifications for metabolic syndrome in children and the way in which they were arrived at. Before this, however, the syndrome's components will be discussed, presenting their relationship with outcomes in adulthood and discussing how each is assessed in the pediatric population.

Relationships between metabolic syndrome components in children and future outcomes

The number of child obesity cases began to rise in the 1970s and continues to do so today, when a significant increase has been observed in the mean weight of children in all socioeconomic classes and ethnic and racial groups.⁸ The large numbers of obese children and adolescents being observed today are bringing the first consequences of this epidemic to medical services: increased incidence of DM2 among adolescents, hepatic steatosis, orthopedic problems, sleep apnea and others.^{9,10}

The consequences for adulthood of persistent childhood obesity will become evident in a few decades, when the chronic diseases that can lead to death from cardiovascular

complications become manifest. Some studies have already found evidence corroborating this prediction. They will be presented below.

The first question is whether children who are classified as having metabolic syndrome will continue to have the syndrome in the future? Morrison et al.¹¹ carried out a prospective assessment of 814 children and adolescents as part of a 25-30 year follow-up. Metabolic syndrome in adulthood was strongly associated with presence of metabolic syndrome and with body mass index (BMI) in childhood, with each increase in BMI percentile of the order of 10 points being linked to a 25% increase in the risk of metabolic syndrome in adulthood. Another important finding from this study was that metabolic syndrome in childhood was an independent predictor of DM2 in adulthood.

The greatest concern aroused by childhood obesity is probably cardiovascular diseases. The Bogalusa Heart Study¹² analyzed data from autopsies of people who died aged from 3 to 31 and who had previously been assessed for risk factors (lipid profile, arterial blood pressure, anthropometric data). The study results showed that the presence of fatty streaks (one of the earliest stages of atheromatous plaques) in the aorta was strongly related to total cholesterol and LDL cholesterol levels and correlated inversely with HDL cholesterol. Fibrous plaques were observed in the coronary arteries of people who had high LDL cholesterol, triglycerides and arterial blood pressure and low HDL. Microscopic histological analysis of the aortic and coronary intima confirmed these findings.

One recent study prospectively analyzed a cohort of 276,835 children for coronary disease. The risk of a coronary event in adulthood had a positive correlation with BMI between 7 and 13 years of age for boys and between 10 and 13 years of age for girls, with a linear relationship between BMI and the rate of cardiac events.¹³ Another interesting study estimated the future consequences of the obesity epidemic observed among today's adolescents. By estimating the prevalence of obesity among 35-year-olds in the United States in 2020 (projected from current data and secular trends) and the future incidence of coronary events between 2020 and 2035 (using a computerized statistical simulation program), these researchers concluded that in 2035 the prevalence of coronary disease would have risen by 5 to 16%, with an excess of 100,000 cases being attributable to the increase in obesity.¹⁴

Components of the metabolic syndrome in the child population

Obesity

The clinical significance of visceral fat is well-established, being positively correlated with DM2, hypertension and dyslipidemia. Intra-abdominal visceral fat is best measured using imaging exams and computerized tomography (CT)

and magnetic resonance (MRI) offer the most precise estimates of intra-abdominal fat in children.¹⁵ In adults, waist circumference (WC) measured at the midpoint between the costal margin and the anterior superior iliac spine are well-correlated with the quantity of visceral fat measured by CT.¹⁶⁻¹⁸ Although there is also a correlation between these two parameters in adolescents, it is not significant and is influenced by puberty.¹⁹ The effect of puberty can be explained by the marked physiological changes that take place during this period in response to increased sex hormone levels.²⁰ It is believed that BMI and WC are not sufficiently sensitive as methods for assessing visceral adiposity in children and adolescents, possibly because of the significant changes in the distribution of body fat during this period.²¹ Nevertheless, recent studies that assess the composition of adipose tissue in children and adolescents using MRI have shown that WC measurement and BMI calculation are viable methods for estimating visceral and subcutaneous fat respectively.^{22,23}

Some years ago, our research team proposed using ultrasonography as a low-cost method of assessing visceral obesity.²⁴ Using ultrasonography with children for the same reason has recently been proposed, although the method is not yet being used universally.²⁵

Although BMI is often used in Brazil, studies with children suggest that WC has a closer relationship with other metabolic syndrome parameters than BMI does (insulin resistance, hypertension and dyslipidemia).^{26,27}

There are BMI curves adjusted for age and sex which have been based on longitudinal data from a number of countries. At our institution we use the curves published by the Centers for Disease Control and Prevention (CDC), which provide BMI broken down by age and sex for children from two to 19 years of age. Obesity is defined as a BMI above the 95th percentile and cases where BMI is between the 85th and 95th percentile defined as at risk of obesity.²⁸

There is no universal cutoff for WC measurements and there is no consensus in the literature. Figures for WC will be discussed later, in the subsection on classifying metabolic syndrome in children.

In addition to the lack of established cutoff points for waist circumference measurements, the best anatomic location to be measured is also debatable. For example, Cook et al.²⁹ measured WC at the midpoint between the costal margin and the anterior superior iliac spine, which is the procedure used with adults. De Ferranti et al.³⁰ do not describe the measurement method used, but it can be inferred that the position is similar to that adopted by Cook et al., since their criteria for diagnosing metabolic syndrome were based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP-III) for adults.

A different study, which employed NCEP/ATP-III and World Health Organization (WHO) criteria, determined

that the measurement should be taken using a measuring tape passing over the umbilical scar and the superior iliac crest.³¹

Golley et al. employed a different protocol, measuring at the midpoint between the 10th rib and the iliac crest in a study comparing different metabolic syndrome criteria in a population of girls aged 6 to 9 years.³²

The National Health and Nutrition Examination Survey (NHANES) was conducted by the CDC in the United States population and employed a WC measurement taken at the top of the iliac crest with the subject in the supine position and breathing out.³³

Although WC is a more complex parameter in children than in adults, it is nevertheless clear that the measurement should be standardized in order to avoid discordant results, whether in clinical use or epidemiological studies.

Dyslipidemia

Dyslipidemia is a risk factor that provokes many doubts among pediatricians who are assessing and treating obese children. These uncertainties spring from the fact that the literature on lipids and their complications gives priority to total cholesterol and LDL-cholesterol, but the two lipid disorders found in metabolic syndrome are low HDL cholesterol and high triglycerides.³⁴

Treatment objectives for reducing cardiovascular risk in dyslipidemic children have been published, with the following targets being set: HDL cholesterol > 35 mg/dL and triglycerides < 150 mg/dL.³⁵

There is no agreement in the literature about which values should be used to define metabolic syndrome. Some of the proposals that do exist will be presented later, in the subsection on classifying metabolic syndrome in children.

Insulin resistance

It has not yet been established whether the influence of obesity on metabolic parameters can be entirely or partially explained by insulin resistance.³⁶ There are studies in the literature which consider insulin resistance of great importance in the metabolic syndrome. Serum insulin levels have been shown to correlate with other components of the syndrome in some studies conducted with obese children and adolescents.^{37,38} Prospective studies such as the Bogalusa Heart Study³⁹ have also observed relationships between high insulin levels and increased BMI, LDL cholesterol and triglycerides, in addition to hypertension and low HDL cholesterol.

In contrast, other studies have shown that obesity has a greater influence on the other components of metabolic syndrome than does insulin resistance, meaning that the effect of insulin resistance can be explained by obesity. In one Canadian study, both BMI and insulin levels were

associated with other syndrome components when analyzed separately, but the contribution of BMI was greater in a simultaneous analysis.⁴⁰ In the Bogalusa study, the risk of developing metabolic syndrome in adulthood had an independent association with BMI but not with fasting serum insulin.⁴¹

The criteria for diagnosing diabetes mellitus type 2 are the same for both children and adults.⁴² However, there is no consensus in the literature on the criteria for assessing glycemic metabolism in order to classify children as suffering from the metabolic syndrome. The majority of classifications proposed have used fasting glycemia ≥ 110 mg/dL, but classifications based on percentile curves and postprandial measurements have also been published.⁴³

Systemic arterial hypertension

The association between arterial hypertension and obesity is valid for all age groups. In the pediatric population, obesity is the primary cause of hypertension. Systolic hypertension is positively correlated with BMI and the waist-to-hip ratio in both children and adolescents.^{44,45}

Arterial hypertension in children is defined statistically on the basis of a distribution curve from healthy children, in contrast with adults, where arterial hypertension is defined according to possible cardiovascular outcomes and mortality on the basis of the results of large-scale studies.

Body composition is the greatest determinant of arterial blood pressure in children and adolescents. For this reason,

arterial blood pressure measurements must be adjusted for height, age and sex.

Classification of metabolic syndrome in children

While classification of NAS in adults is still widely discussed, it is nevertheless well-established (Table 1). The two most important definitions are those published by the WHO in 1999,⁴⁶ and the NCEP/ATP-III,⁴⁷ which was published in 2001. The first demands that insulin resistance be present, while this is not the case with the second. Despite this difference, studies show similar prevalence among adults comparing the two classifications.⁴⁸ In 2005, the International Diabetes Federation presented a new classification proposal.⁴⁹ This system takes visceral obesity, as represented by waist circumference, as the most important marker.

When attempts were made to use these classifications with children and adolescents, conflicting results were observed. Goodman et al.³¹ tried to determine the prevalence of metabolic syndrome in adolescents using the WHO and NCEP/ATP-III definitions. They used the same cutoff points for both classifications for all risk factors, with the exception of obesity, which was defined as BMI ≥ 95 th percentile% according to an age and sex-adjusted BMI chart. Among the 1,513 people enrolled on the study, the prevalence was 4.2% according to the WHO definition and 8.4% according to the NCEP/ATP-III system. In addition to the enormous difference between the two groups, the prevalence also attracts attention by being very much lower than in adults,

Table 1 - Classification of metabolic syndrome in adults according to the WHO, NCEP/ATP-III and IDF criteria

Criteria/ components	WHO (1999)	NCEP/ATP-III (2001)	IDF (2005)
Obligatory	Insulin resistance + at least 2 criteria	At least three criteria	Central obesity defined by ethnicity + at least 2 criteria
Definition of adiposity	BMI ≥ 30 kg/m ² or WHR > 0.9 (men) or > 0.85 (women)	WC ≥ 102 cm (men) or ≥ 88 cm (women)	WC ≥ 90 cm (men) or ≥ 80 cm (women)
Metabolism glycemic	Diabetes, TDG or AFG	Fasting glycemia ≥ 100 mg/dL	Fasting glycemia ≥ 100 mg/dL
Dyslipidemia	Triglycerides ≥ 150 mg/dL or HDL ≥ 35 (men) or ≥ 40 (women) mg/dL or taking hypolipemiant	Triglycerides ≥ 150 mg/dL or HDL ≥ 40 (men) or ≥ 50 (women) mg/dL or taking hypolipemiant	Triglycerides ≥ 150 mg/dL or HDL ≥ 40 (men) or ≥ 50 (women) mg/dL or taking hypolipemiant
Arterial hypertension	PA ≥ 140 or 90 mmHg or taking antihypertensives	PA ≥ 130 or 85 mmHg or taking antihypertensives	PA ≥ 130 or 85 mmHg or taking antihypertensives
Other components	Microalbuminuria	-	-

AFG = abnormal fasting glycemia; BMI = body mass index; HDL = HDL cholesterol; IDF = International Diabetes Federation; NCEP/ATP-III = National Cholesterol Education Program/Adult Treatment Panel III; PA = arterial blood pressure; RGT = reduced glucose tolerance; WC = waist circumference; WHO = World Health Organization; WHR = waist to hip ratio.

estimated at 24%.⁴⁸ The most likely explanation for this difference is the lower prevalence of obesity in adolescents when compared with adults. It could also be postulated that not enough time had passed for central obesity to trigger the mechanisms responsible for the emergence of associated risk factors.

In response to these findings, classifications have been proposed in the last few decades based on modified versions of the criteria for adults with the objective of identifying children and adolescents with metabolic syndrome (Table 2).

Cook et al. conducted one of the first studies to analyze metabolic syndrome in children in 2003.²⁹ Using data from the Third National Health and Nutrition Examination Survey from 1988-1994 (NHANES III) the study assessed adolescents aged 12 to 19, applying the criteria for metabolic syndrome defined by the NCEP/ATP-III, with certain modifications. The first change was that obesity was defined as WC \geq 90th percentile for age and sex. The cutoff point for arterial blood pressure was extracted from figures published by the National Blood Pressure Education Program (NBPEP).⁵⁰ Additionally, the reference values for the lipid profile were taken from the National Cholesterol Education Panel.⁵¹ The results indicated a metabolic syndrome prevalence of 4.2% for the sample studied. When stratified by BMI, 28.7% of the obese adolescents (BMI \geq 95th percentile for age and sex) met the metabolic syndrome criteria. This prevalence is not surprising if one considers that approximately 7% of 20 to 29-year-old adults suffer from metabolic syndrome.⁴⁸ The author defends using the waist circumference measure rather than other obesity indicators, such as BMI, on the basis that fat distribution is strongly indicative of cardiovascular risk.

The same population was analyzed by Ferranti et al. in 2004,³⁰ but they employed different criteria to define

metabolic syndrome. In their study they also used a modified version of the NCEP/ATP-III criteria. Their results indicated a metabolic syndrome prevalence of 9.2% in the sample and 31.2% of children whose BMI was \geq the 85th percentile for age and sex. The reason for this prevalence, which was considerably greater than that calculated by Cook et al., was the cutoff points for WC and the lipid profile. The WC cutoff point chosen was $>$ 75th percentile, in contrast with Cook et al. who used the 90th. The lipid profile cutoff points used were also different. The result is a less restrictive definition, which increases the number of adolescents meeting the criteria. The authors defend these criteria stating that they are relatively closer to those used with adults. For example, setting HDL cholesterol at 40 mg/dL as employed by Cook, selects percentiles 10 to 25 for boys and 10 to 15 for girls, which is lower than the percentile that corresponds to 40 mg/dL in adults. Triglycerides at 110 mg/dL represent the pediatric percentiles of 85 to 95 - higher than the adult percentiles of 75 to 85. Finally, the WC cutoff point at the 90th percentile is very much higher than the 75th percentile used in the adult NCEP/ATP-III criteria. Therefore, de Ferranti et al. derived a pediatric definition that was strictly based on the adult criteria defined by the NCEP/ATP-III.

In a study of 429 children aged 4 to 20 and classified as obese, Weiss et al.³⁷ found a metabolic syndrome prevalence of 38.7% among those defined as moderately obese (BMI z score from 2.0 to 2.5) and 49.7% in a group defined as severely obese (BMI z score $>$ 2.5). Weiss et al. used different criteria to define metabolic syndrome. One difference was the fact that obesity was defined on the basis of BMI rather than waist circumference, as in other studies. The authors defend using BMI on the basis that it is less subject to variations due to puberty or race. They also state that BMI has a strong correlation with visceral adiposity, and correlates better with blood pressure and the lipid profile than does waist circumference.⁵²

Table 2 - Criteria for classifying metabolic syndrome in children and adolescents as proposed by Cook et al., de Ferranti et al. and Weiss et al., with at least three of five criteria present

Criteria/ components	Cook et al.	de Ferranti et al.	Weiss et al.
Definition of adiposity	WC \geq 90th percentile	WC $>$ percentile 70	z (BMI) \geq 2
Metabolism glycemica	Fasting glycemia \geq 110 mg/dL	Fasting glycemia \geq 110 mg/dL	Glycemia (OGTT) de 140 to 200 mg/dL
Dyslipidemia	Triglycerides \geq 110 mg/dL or HDL \geq 40 mg/dL	Triglycerides \geq 100 mg/dL or HDL $<$ 45 (men) or $<$ 50 (women) mg/dL	Triglycerides $>$ 95th percentile or HDL $<$ 5th percentile
Arterial hypertension	PA \geq p 90%	PA \geq p 90%	PA \geq p 95%

HDL = HDL cholesterol; OGTT = oral glucose tolerance test; PA = arterial blood pressure; WC = waist circumference; z (BMI) = z score for body mass index.

Table 3 - Classification of metabolic syndrome in children and adolescents according to the International Diabetes Federation criteria

Criteria/ components	Age		
	6 to < 10 years	10 to 16 years	> 16 years
Definition of adiposity	WC \geq 90th percentile	WC \geq 90th percentile	WC \geq 90 cm (men) or \geq 80 cm (women)
Metabolism glycemie	No set value for diagnosis of metabolic syndrome	Fasting glycemia \geq 100 mg/dL	Fasting glycemia \geq 100 mg/dL
Dyslipidemia	No set value for diagnosis of metabolic syndrome	Triglycerides \geq 150 mg/dL or HDL \geq 40 mg/dL or taking hypolipemiant	Triglycerides \geq 150 mg/dL or HDL \geq 40 (men) or \geq 50 (women) mg/dL or taking hypolipemiant
Arterial hypertension	No set value for diagnosis of metabolic syndrome	PA \geq 130 or 85 mmHg or taking antihypertensives	PA \geq 130 or 85 mmHg or taking antihypertensives

HDL = HDL cholesterol; PA = arterial blood pressure; WC = waist circumference.

Recently, the IDF has published a new definition of metabolic syndrome for children (Table 3).⁵³ Due to the fact that there are developmental differences between children and adolescents, the pediatric population was divided into the following groups: from 6 to 10 years, from 10 to 16 and over 16. Children less than 6 years old were excluded due to the lack of data for this age-group. The authors suggest that the metabolic syndrome should not be diagnosed in children less than 10 years old, but that weight loss should be strongly recommended to those with abdominal obesity. For children over 10 years old the metabolic syndrome is diagnosed according to the presence of abdominal obesity combined with two or more clinical criteria. With the exception of the WC measurement, the cut-offs for other criteria, such as blood pressure, lipid profile and glycemia, are fixed values that do not take into account percentiles age and sex. This is in contrast with a tendency observed in other classifications where figures are ever more commonly converted to percentiles, because of the changes in body and metabolism between different age groups of adolescents.

Although using percentiles for age and sex has been shown to be more appropriate, one problem is choosing the cutoff during the transition to adulthood.⁵⁴ For adults, criteria are not based on percentiles but on fixed values. Thus, whereas for children where the waist circumference cutoff point is the 90th percentile, for adults it is a fixed number (102 cm for men and 88 cm for women according to the NCEP/ATP-III criteria) which corresponds to the 75th to the 90th percentiles for men and the 75th for women. Therefore, an 18-year-old may be classified as having central

obesity according to the adult classification but not if the child classification is used.

Conclusions

Children and adolescents are becoming the victims of the obesity epidemic that has emerged in modern times. The future complications of this situation could be catastrophic if preventative interventions are not implemented. To achieve this it is necessary to identify those people who are at risk of developing complications from being overweight. Therefore, the term metabolic syndrome, habitually used for adults, may be applicable to people in younger age groups. A number of models for classifying metabolic syndrome in children have been published, but there is considerable divergence between them. Further studies and continued debate are needed in order to standardize the criteria for classifying metabolic syndrome in children.

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Correspondence:
Rafael Nardini Queiroz Pergher
Rua Cristiano Viana, 765/122 - Pinheiros
CEP 05411-001 - São Paulo, SP - Brazil
E-mail: pergherafael@hotmail.com