Curr Diab Rep (2013) 13:56–62
DOI 10.1007/s11892-012-0331-2

Metabolic Syndrome in Youth: Chimera or Useful Concept?

M. Loredana Marcovecchio · Francesco Chiarelli

Published online: 6 October 2012

Abstract Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors associated with an increased risk for the development of cardiovascular diseases and type 2 diabetes. The prevalence of the MetS is not particularly high in the overall pediatric population (3 %–4 %) but it is as high as 30 %–50 % among overweight youth. Several definitions of the MetS have been used, thus, generating confusion and difficulties in defining the true prevalence of this syndrome. The recent definition of the International Diabetes Federation has tried to standardize the diagnostic criteria. However, there are still some concerns about use of cut-offs values and dichotomous variables, and some debate as to whether a continuous cardiometabolic risk score could be more appropriate for the pediatric population. Although there are some studies that have shown the association between childhood and adolescent MetS with long-term outcomes, further prospective studies are needed to clarify the true value of diagnosing MetS in youth.

Keywords Adolescents · Cardiometabolic · Cardiovascular disease · Children · Definition · Insulin resistance · Metabolic syndrome · Obesity · Prevalence · Type 2 diabetes · Youth

Introduction

Obesity is a growing problem that has reached epidemic proportions around the world [1]. Excess body fat has been associated with several metabolic and cardiovascular complications that significantly contribute to the overall morbidity and mortality [2].

Alarmingly, obesity-related complications can be detected already in children and adolescents and they track over time [2]. Of note, metabolic and cardiovascular complications can cluster together in what is known as the metabolic syndrome (MetS).

Over the last few years, there have been a growing number of publications addressing the dimensions and relevance of this syndrome in both youth and adults. This review offers an overview of the MetS, with a particular reference to its prevalence and significance in obese youth.

What is Metabolic Syndrome?

In 1988 Reaven first introduced the concept of 'Syndrome X' (later renamed MetS), defined as a cluster of metabolic abnormalities associated with a risk of cardiovascular disease (CVD) and type 2 diabetes (T2D) greater than that of its individual components [3]. Reaven hypothesized that insulin resistance could be the central mechanism linking this cluster of metabolic abnormalities [3]. Epidemiological studies suggest that the MetS is common among adults, particularly among obese individuals, and its incidence is increasing in parallel with the epidemics of obesity [4, 5]. In addition, there is clear evidence suggesting that, in adults, the MetS significantly increases cardiovascular morbidity and mortality [4, 5].

Since Reaven's first introduction of the concept of the MetS, a growing interest has emerged around this new entity and additional diagnostic criteria have been added, such as microalbuminuria, chronic inflammation, endothelial dysfunction, and alterations in the hemostatic system. In addition, there has been a lot of discussion as to whether non-

M. L. Marcovecchio · F. Chiarelli (✉)
Department of Paediatrics, University of Chieti and Center of Excellence on Aging, "G. D'Annunzio" University Foundation, University of Chieti,
Via dei Vestini 5,
66100 Chieti, Italy
e-mail: chiarelli@unich.it

alcoholic fatty liver disease, a common finding in obese subjects, should be another key diagnostic criterion [4, 5]. Several definitions have been developed over the years in adults, including those from the World Health Organization (WHO), the Adult Treatment Panel III (ATP III), the European Group for the Study of Insulin Resistance, the American College of Endocrinology, the American Heart Association/National Heart, Lung, and Blood Institute, and, more recently, the International Diabetes Federation (IDF) [4–6]. The main differences among the different definitions are the set of specific metabolic parameters taken into account and differences in 'pathological levels' for the included risk variables.

Pathogenesis of the Metabolic Syndrome

The pathogenesis of the MetS is not completely understood, although 2 factors appear to play a key role: obesity and insulin resistance [5]. Obesity is the main determinant of insulin resistance both in adults and in children [7]. Interestingly, several lines of evidence have suggested that visceral and/or ectopic fat distribution (ie muscle, liver) play a more important role in the development of insulin resistance than the overall body adiposity in both obese adults and children [8]. Studies conducted in the pediatric population have shown that the amount of visceral fat was directly correlated with basal and glucose-stimulated insulin levels and inversely correlated with insulin sensitivity and the rate of glucose uptake [8]. In contrast, no correlation was found between abdominal subcutaneous fat and these metabolic indexes [8]. Based on the 'portal theory', this could be related to a higher lipolytic activity of visceral compared with subcutaneous fat, and therefore to more free fatty acids and glycerol delivered directly to the liver [9].

Ectopic deposition of fat in the liver or muscle can also be responsible for insulin resistance in obese subjects, as the accumulation of fat in these sites impairs insulin signaling, with reduced glucose uptake in the muscle and decreased insulin-mediated suppression of hepatic glucose production [10]. Intramyocellular lipid (IMCL) accumulation has been associated with decreased insulin sensitivity [11, 12]; obese insulin-resistant children and adolescents have higher levels of visceral fat and IMCL when compared with obese insulin-sensitive peers [13]. Accumulation of fat in the liver has also been associated with insulin resistance, independently of total adiposity [14, 15]. In obese youth, the decrease in insulin sensitivity, imbalance between anti- and proinflammatory markers, and increased prevalence of MetS parallels the severity of liver fat accumulation [16]. Thus, nonalcoholic fatty liver disease has been suggested as an additional core component of Mets [16].

In addition to insulin resistance and obesity, other factors that have been implicated in the pathogenesis of MetS are maternal obesity, gestational diabetes, ethnicity, birth weight, and family history of diabetes, together with genetic factors [5]. Additional factors that may have a role in the pathogenesis of the MetS are the immune system, chronic stress and dysregulation of the hypothalamic-pituitary-adrenal axis, and autonomic nervous system, increases in cellular oxidative stress, renin-angiotensin-aldosterone system activity, and intrinsic tissue glucocorticoid actions [5].

The Metabolic Syndrome in Children

The MetS has been reported to be common among obese children and adolescents, where depending on the definition used, the prevalence ranges from 26 %–49.7 %. In contrast the prevalence of the MetS is quite low among normal weight youth (3 %–4 %).

In the pediatric population, several distinct definitions have been applied, thus leading to some confusion in terms of characterizing the true epidemiology of the syndrome. The initial approach has been to apply adult definitions to the pediatric population. However, the use of adult criteria in youth is hampered by several problems, including the need of adopting specific age and sex cut-offs, due to the well-known age and sex-dependent variation in anthropometric parameters, such as BMI, waist circumference, as well as in metabolic and cardiovascular parameters, such as lipids and blood pressure. This has led to several definitions being proposed over the years. The definition of MetS in children is also complicated by lack of specific normal values for some metabolic and cardiovascular measurements, and by well-known variations associated with different ethnic groups and pubertal stage.

One of the first definitions of MetS for the pediatric population was proposed by Cook et al in 2003 [17] and it was applied to a large population of American adolescents (n=2430), aged 12–19 years. This definition was based on a pediatric adaptation of the NCEP/ATP-III criteria, including waist circumference over the 90th percentile, blood pressure above the specific age and sex 90th percentiles, whereas for glycemia, triglycerides, and HDL cholesterol absolute values were used (>110 mg/dL, >110 mg/dL, and <40 mg/dL, respectively). The reported prevalence of the Mets was 4.2 % when considering the whole study population, but increased to 28.7 % when restricting the analysis to subjects who were obese [17]. In 2004, Weiss et al [18] highlighted the key association between the degree of adiposity and an increasing prevalence of the Mets, reporting an alarming prevalence of 38.7 % in moderately obese and 49.7 % in severely obese American children and adolescents (aged 8–13 years). In this study a direct association was also found

between a higher degree of insulin resistance and prevalence of the MetS. In 2004 Duncan et al [19] reported a comparison between the prevalence of the MetS over time among US adolescents, aged 12–19 years, by comparing data from the NHANES III (1988–1994) vs NHANES 1999–2000. A significant increase in the prevalence of the syndrome was reported when analyzing the whole study population (6.4 vs 4.2 %), as well as when repeating the analysis by sex (male: 9.1 vs 6.1 %; female: 3.7 vs 2.1 %) and ethnic groups.

With regards to European children, Invitti et al [20] assessed the prevalence of the MetS in 588 Italian obese children and adolescents (aged 6–16 years) by applying a modified WHO definition. The prevalence of MetS was 23.3 %, and it significantly increased across tertiles of BMI (16 % vs 23 % vs 31 %). Interestingly, in both sexes the frequency of MetS gradually increased from Tanner stage I to stage IV and declined at stage V.

The prevalence of MetS clearly varies according to the criteria used and to the age, sex and ethnicity of the studied populations [21]. In 2008, Lee et al [22] assessed the prevalence of the MetS among 251 children and adolescents (122 African Americans/129 Caucasians, aged 8–19 years), using 5 different pediatric definitions reported in the literature. Interestingly, the authors found a significant variability in the prevalence of the MetS when applying different definitions. Specifically, the prevalence was 18.7 % based on Weiss's definition, 21 % accordingly with Cook's criteria, 13.4 % using Cruz's criteria, 25.1 % using Ford's criteria. Independently of the definition applied, in the same study the prevalence of MetS was significantly higher in obese than in normal weight children and adolescents: 42.9 % vs 2.8 % for Caucasians and 31.3 % vs 0.8 % for African Americans [22]. A similar comparison was performed by Goodman et al [23], where the prevalence of MetS among adolescents was assessed by comparing the definitions from the NCEP III and WHO. The prevalence of the MetS varied from 4.2 % to 8.4 % based on the criteria used. Furthermore, Reinehr et al [24] compared eight proposed MetS definitions in 1205 Caucasian overweight children and adolescents aged 4 to 16 years. The prevalence of the MetS varied significantly between 6 % and 39 % depending on the definition used, and only 2 % of the children fulfilled the criteria of MetS in all definitions. In accordance with previous studies, the authors observed an association between the degree of obesity and insulin resistance and MetS; in contrast, pubertal stage did not significantly influence the occurrence of the MetS.

A valuable attempt to unify the diagnosis of MetS in children is represented by the IDF definition (Table 1) [25]. The authors divided children into 3 age groups: 6 to <10, 10–16, and >16 years. For children under the age of 10 years, no specific diagnosis of MetS is proposed, whereas the definition for those aged 10–16 years is based on the presence of adiposity, defined as waist circumference values above the 90th percentile, while the other metabolic alterations were defined on the basis of specific absolute cut-off values: triglycerides ≥150 mg/dL, HDL cholesterol below 40 mg/dL, fasting glucose levels ≥100 mg/dL, systolic blood pressure ≥130, or diastolic blood pressure ≥85 mm Hg. The adult IDF criteria have been proposed to define MetS in the group aged >16 years [25].

Although, the IDF definition represents a valid attempt to limit the confusion around MetS in children and adolescents, this definition is not free of limitations. In particular, 3 main issues need to be considered: (1) Is it true that MetS cannot be diagnosed in prepubertal children? (2) Is waist circumference a parameter easily and reliably applicable to the pediatric population? (3) Are there other important parameters to be included in the definition of MetS?

In the IDF definition, waist circumference is the condition "sine qua non" to define MetS. This is related to the observation that, although BMI represents an important measure of adiposity, the degree of obesity per se is not a sufficient marker to identify children at risk of MetS, while central obesity represents a key component in the development of metabolic complications [26, 27]. Waist circumference has been associated with several cardio-metabolic alterations in the pediatric population [26, 27]. However, the use of waist circumference in the pediatric population is limited by the fact that reference values exist only for some populations. Another important point is the controversy on how to measure waist circumference in children and adolescents. By comparing 4 commonly recommended waist circumference measurement sites, Johnson et al [28] have recently demonstrated that the different sites are not equivalently associated with metabolic risk and that waist circumference measured at the narrowest waist and midpoint between the floating rib and iliac crest represents the measurement site most closely associated with metabolic risk in overweight youth.

Another limitation of the IDF definition is the statement that below the age of 10 years MetS is not definable. This is in contrast with a large body of evidence showing that many of the metabolic and cardiovascular complications of obesity are already detectable in prepubertal children [29–31]. Our research group assessed the prevalence of MetS among a group of 89 prepubertal children, aged 6 to 10 years [32]. According to Weiss criteria, MetS was diagnosed in 13.5 % of prepubertal children, underlining the importance of screening for metabolic complications of obesity even in very young children. Finally, there are probably other variables not included in the IDF definition but which could be invaluable to identify children and adolescents 'at risk', such as liver steatosis [32].

The several definitions applied to the pediatric population have generated confusion and difficulties in understanding

Table 1 MetS definition: International Diabetes Federation criteria

Age <10 years					
Obesity (WC) ≥90th percentile. Metabolic syndrome cannot be diagnosed, but further measurements should be made if family history of metabolic syndrome, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, hypertension, or obesity					
Age 10–16 years					
Obesity (WC)	Plus 2 of the following:	Triglycerides	HDL-C	Blood pressure:	Glucose
≥90th percentile		≥1.7 mmol/L	<1.03 mmol/L	SBP ≥130 mm Hg DBP ≥85 mm Hg	≥5.6 mmol/L or known diabetes
Age >16 years: use IDF adult criteria					
WC:	Plus 2 of the following:	Triglycerides	HDL-C	Blood pressure:	Impaired fasting glucose or type 2 diabetes
≥94 cm (men) ≥80 cm (women)		≥1.7 mmol/L	<1.03 mmol/L (M); <1.29 mmol/L (F) or treatment	SBP ≥130 mm Hg DBP ≥85 mm Hg or previously diagnosed hypertension	

WC waist circumference, *HDL-C* high density lipoprotein-cholesterol, *M* males, *F* females

the epidemiology of MetS in children and adolescents. In addition, there have been some concerns about the stability of the MetS during childhood and adolescence [33, 34]. In a cohort of 1098 teenagers followed up over a 3-year period, Goodman et al [34] found that a categorical diagnosis of MetS in adolescents was unstable, with up to half of the children with MetS at baseline, failing to meet the criteria at follow-up.

Although there is a significant difference in the prevalence of MetS observed among different studies and there are concerns about the stability of the MetS over time in children, studies agree that there has been an increasing prevalence of MetS in children and adolescents, paralleling the epidemics of obesity in this age group. This observation is alarming and should lead to a wider application of screening and intervention programs. This is further supported by the reported association between the presence of MetS and early signs of CVD during childhood and adolescence. In particular, MetS during adolescence has been shown to be significantly associated with increased carotid intima media thickness and reduced brachial artery distensibility [35•].

Long-Term Consequences of Metabolic Syndrome in Children

The effect of being diagnosed with the MetS during childhood and adolescence on the risk for MetS in adult life is important for understanding the long-term impact on overall morbidity and mortality. Up to now there are limited but significant longitudinal studies, which have attempted to answer this question. Burns et al [36••] assessed childhood predictors of MetS during adult life and they found that subjects with MetS during adulthood had higher BMI, blood pressure, and triglycerides during childhood. A BMI above the 75th percentile was significantly associated with the risk of developing MetS, thus identifying BMI as the strongest predictor. In addition, they found that the combination of high BMI and high triglycerides levels played an additive effect on the risk of developing the MetS.

Morrison et al prospectively assessed the association of the MetS in childhood (age of the study population: 5–19 years) with adult MetS and T2D 25 to 30 years later. Their study showed that the presence of MetS and a family history of diabetes during childhood and adolescence could identify children at increased risk of adult MetS and T2D, allowing prospective primary prevention of these outcomes [37••]. Similarly, adolescents with MetS who were followed up for 14–27 years in the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study, were found to be at two- to three-fold increased risk of having MetS, increased intima media thickness and T2D during adulthood compared with those free of MetS during adolescence [38••].

Data from 3 major studies, the Fels Longitudinal Study, the Muscatine Study, and the Princeton Follow-up Study have also been combined to assess thresholds of metabolic components during childhood influencing adult risk of MetS and T2D. Interestingly, from these studies it emerged that MetS components, when examined during childhood, had a high negative predictive value for adult outcomes, thus suggesting that they may provide a useful screening approach to identifying children not at risk, so that further attention can be focused on those who more at risk [39•].

How to Prevent and Treat the MetS During Childhood and Adolescence?

The epidemiologic data available so far strongly suggest that the prevalence of the MetS is particularly high among obese

children and adolescence. Therefore, screening for the syndrome should be directed to this group of people instead of the whole pediatric population. Screening should identify the underlying insulin resistance characterizing the syndrome and the single abnormalities. Therefore, together with an anthropometric assessment (including not only BMI but also waist circumference), obese youths should undergo blood pressure measurements, assessment of lipid profile, serum glucose determination and, if indicated, an oral glucose tolerance test. Additional risk factors should also be considered, such as birth weight, gestational diabetes, accelerated growth during infancy, and a potential family history for obesity, diabetes, and cardiovascular diseases. In fact, although these factors are not included in the definition of MetS, they can contribute to the overall cardio-metabolic risk of young people and identify a group of youth requiring more intensive treatment strategies. Interestingly, a recent study has indicated that the coexistence of low birth weight, small head circumference, and parental history of overweight or obesity may be helpful in targeting children at risk for developing MetS in adolescence [40•].

Preventing obesity and insulin resistance are the key strategies to be applied early in life [41••]. However, when required, treatment should be aimed at reducing the degree of adiposity and the associated status of insulin resistance. At the present time, there is no specific treatment for the clustering of risk factors characterizing the MetS in children and treatment should focus on reducing obesity, increasing physical activity, and treating the individual components of the syndrome when necessary [41••]. Lifestyle changes, including a balanced diet appropriate for age, together with regular physical activity, should be strongly recommended [41••]. Even in the absence of weight loss, lifestyle interventions can help improve insulin sensitivity and the cardiovascular profile of obese youth. Decreases in body weight have been associated with a significant improvement in insulin sensitivity [42].

In children and adolescents, there is limited experience with weight loss medications or insulin sensitizers. Metformin has been shown to improve insulin sensitivity and BMI in non-diabetic obese adolescents with fasting hyperinsulinemia and a family history of T2D [43]. A similar efficacy of metformin on insulin sensitivity and BMI has been found in 2 other small studies conducted in obese normoglycemic adolescents [44, 45]. On the other hand, limited effect of metformin on weight and insulin sensitivity was found in a larger study of obese, insulin-resistant minority adolescents [46]. Sibutramine reduces body weight in children when used in conjunction with behavioral intervention and, in some studies, a positive effect on glucose and lipid metabolism has also been shown [47]. However, this drug has been associated to an increase in blood pressure and heart rate, thereby posing limitations for its wide use in the pediatric population [47]. Orlistat has been investigated in children and has been associated with a significant weight loss, even though several side effects have been associated with its use [48]; mainly gastrointestinal disturbances, but also multiple vitamins deficiencies [48]. No significant effects on glucose metabolism have been reported with this drug [48]. In adults, thiazolidinediones have also been shown to have a good efficacy in improving insulin sensitivity [49], but have not been well studied in the pediatric age-group and have been recently associated with a variety of concerning side effects in adults.

Further controlled trials are required to have a better assessment of the safety and efficacy of drugs to address obesity and insulin resistance in children and adolescents, and to clarify which group of subjects really needs them.

Should We Keep Talking About MetS in Youth or Just Consider Its Individual Components?

The evidence available so far strongly indicates that MetS is a reality among obese youth. Even more alarming is the observation of tracking of the single components of the syndrome as well the predictive value of the presence of MetS during adolescence on the persistence of the same during adult life. However, there are still several concerns on this entity in children and adolescence and, at present it is difficult to answer the question as to whether MetS is 'just a chimera or a useful clinical concept.' Although there has been an attempt to create a unique MetS definition for the pediatric population, there is still a lot of debate on which are the best components to consider and there is still a lot to do to have specific normative values reflecting age, gender, and race specific changes in cardiometabolic risk factors. In addition, the effect of growth and puberty seriously complicates the definition of the MetS in youth, requiring definitions that remain discriminatory over time. One major limitation of all MetS definitions applied to the pediatric population has been the use of dichotomous 'normal-abnormal' variable categorization. These are difficult to define in a clear and unbiased way due to lack of specific normative values for all criteria included in the syndrome and for all populations. In addition, strict cut points are difficult to apply in pediatrics due to the well-known fluctuations associated with growth and puberty. It has been suggested that using a continuous risk score, instead of dichotomous variables could improve the value and clinical utility of diagnosing MetS [50].

Longitudinal studies across different ethnic groups are strongly required to understand the true value of the constellation of cardio-metabolic abnormalities characterizing

the MetS during childhood and adolescence. In addition, the true clinical value of defining the syndrome in childhood will be better defined once a specific treatment for the syndrome has been identified.

Conclusions

Several definitions of the MetS have been applied to the pediatric population over the years, thus generating confusion and difficulties in defining the true prevalence of this syndrome. The recent definition from the IDF has tried to standardize the diagnostic criteria. However, there are still some concerns about use of cut-off values and dichotomous variables, and some debate as to whether a continuous cardio-metabolic risk score might be more appropriate for the pediatric population. Although there are some longitudinal studies that have shown the association between childhood and adolescence MetS with long-term outcomes, further prospective studies are needed to clarify the true value of diagnosing MetS in youth.

Disclosure No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. JAMA. 2012;307:483–90.
2. Han JC, Lawlor DA, Kimm SY. Childhood obesity. Lancet. 2010;375:1737–48.
3. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37:1595–607.
4. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005;365:1415–28.
5. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, et al. The metabolic syndrome. Endocrine Rev. 2008;29:777–822.
6. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640–5.
7. Chiarelli F, Marcovecchio ML. Insulin resistance and obesity in childhood. Eur J Endocrinol. 2008;159 Suppl 1:S67–74.
8. Caprio S, Hyman LD, Limb C, McCarthy S, Lange R, Sherwin RS, et al. Central adiposity and its metabolic correlates in obese adolescent girls. Am J Physiol. 1995;269:E118–26.
9. Matthaei S, Stumvoll M, Kellerer M, Haring HU. Pathophysiology and pharmacological treatment of insulin resistance. Endocrine Rev. 2000;21:585–618.
10. Weiss R, Kaufman FR. Metabolic complications of childhood obesity: identifying and mitigating the risk. Diabetes Care. 2008;31 Suppl 2:S310–6.
11. Jacob S, Machann J, Rett K, Brechtel K, Volk A, Renn W, et al. Association of increased intramyocellular lipid content with insulin resistance in lean nondiabetic offspring of type 2 diabetic subjects. Diabetes. 1999;48:1113–9.
12. Thamer C, Machann J, Bachmann O, Haap M, Dahl D, Wietek B, et al. Intramyocellular lipids: anthropometric determinants and relationships with maximal aerobic capacity and insulin sensitivity. J Clin Endocrinol Metab. 2003;88:1785–91.
13. Weiss R, Taksali SE, Dufour S, Yeckel CW, Papademetris X, Cline G, et al. The "obese insulin-sensitive" adolescent: importance of adiponectin and lipid partitioning. J Clin Endocrinol Metab. 2005;90:3731–7.
14. Tiikkainen M, Tamminen M, Hakkinen AM, Bergholm R, Vehkavaara S, Halavaara J, et al. Liver-fat accumulation and insulin resistance in obese women with previous gestational diabetes. Obesity Res. 2002;10:859–67.
15. Kelley DE, McKolanis TM, Hegazi RA, Kuller LH, Kalhan SC. Fatty liver in type 2 diabetes mellitus: relation to regional adiposity, fatty acids, and insulin resistance. Am J Physiol. 2003;285: E906–16.
16. Burgert TS, Taksali SE, Dziura J, Goodman TR, Yeckel CW, Papademetris X, et al. Alanine aminotransferase levels and fatty liver in childhood obesity: associations with insulin resistance, adiponectin, and visceral fat. J Clin Endocrinol Metab. 2006;91:4287–94.
17. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988–1994. Arch Pediatr Adolesc Med. 2003;157:821–7.
18. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004;350:2362–74.
19. Duncan GE, Li SM, Zhou XH. Prevalence and trends of a metabolic syndrome phenotype among U.S. Adolescents, 1999–2000. Diabetes Care. 2004;27:2438–43.
20. Invitti C, Maffeis C, Gilardini L, Pontiggia B, Mazzilli G, Girola A, et al. Metabolic syndrome in obese Caucasian children: prevalence using WHO-derived criteria and association with nontraditional cardiovascular risk factors. Int J Obes. 2006;30:627–33.
21. De Ferranti SD, Osganian SK. Epidemiology of paediatric metabolic syndrome and type 2 diabetes mellitus. Diabetes Vasc Dis Res. 2007;4:285–96.
22. Lee S, Bacha F, Gungor N, Arslanian S. Comparison of different definitions of pediatric metabolic syndrome: relation to abdominal adiposity, insulin resistance, adiponectin, and inflammatory biomarkers. J Pediatr. 2008;152:177–84.
23. Goodman E, Daniels SR, Morrison JA, Huang B, Dolan LM. Contrasting prevalence of and demographic disparities in the World Health Organization and National Cholesterol Education Program Adult Treatment Panel III definitions of metabolic syndrome among adolescents. J Pediatr. 2004;145:445–51.
24. Reinehr T, de Sousa G, Toschke AM, Andler W. Comparison of metabolic syndrome prevalence using eight different definitions: a critical approach. Arch Dis Child. 2007;92:1067–72.
25. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr Diabetes. 2007;8:299–306.

26. Lee S, Bacha F, Arslanian SA. Waist circumference, blood pressure, and lipid components of the metabolic syndrome. J Pediatr. 2006;149:809–16.
27. Lee S, Bacha F, Gungor N, Arslanian SA. Waist circumference is an independent predictor of insulin resistance in black and white youths. J Pediatr. 2006;148:188–94.
28. Johnson ST, Kuk JL, Mackenzie KA, Huang TT, Rosychuk RJ, Ball GD. Metabolic risk varies according to waist circumference measurement site in overweight boys and girls. J Pediatr. 2010;156:247–52e1.
29. Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Engl J Med. 2002;346:802–10.
30. Marcovecchio ML, Patricelli L, Zito M, Capanna R, Ciampani M, Chiarelli F, et al. Ambulatory blood pressure monitoring in obese children: role of insulin resistance. J Hypertens. 2006;24:2431–6.
31. D'Adamo E, Impicciatore M, Capanna R, Loredana Marcovecchio M, Masuccio FG, Chiarelli F, et al. Liver steatosis in obese prepubertal children: a possible role of insulin resistance. Obesity. 2008;16:677–83.
32. D'Adamo E, Marcovecchio ML, Giannini C, Capanna R, Impicciatore M, Chiarelli F, et al. The possible role of liver steatosis in defining metabolic syndrome in prepubertal children. Metab Clin Exp. 2010;59:671–6.
33. Gustafson JK, Yanoff LB, Easter BD, Brady SM, Keil MF, Roberts MD, et al. The stability of metabolic syndrome in children and adolescents. J Clin Endocrinol Metab. 2009;94:4828–34.
34. Goodman E, Daniels SR, Meigs JB, Dolan LM. Instability in the diagnosis of metabolic syndrome in adolescents. Circulation. 2007;115:2316–22.
35. • Toledo-Corral CM, Ventura EE, Hodis HN, Weigensberg MJ, Lane CJ, Li Y, et al. Persistence of the metabolic syndrome and its influence on carotid artery intima media thickness in overweight Latino children. Atherosclerosis. 2009;206:594–8. *This study shows the association between MetS and subclinical signs of atherosclerosis in youth wth MetS.*
36. •• Burns TL, Letuchy EM, Paulos R, Witt J. Childhood predictors of the metabolic syndrome in middle-aged adults: the Muscatine study. J Pediatr. 2009;155(S5):e17–26. *This study indicates that childhood BMI is the strongest predictor of MetS during adulthood In addition, there is an additive effect of high BMI and triglycerides in predicting risk.*
37. •• Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. J Pediatr. 2008;152:201–6. *This study indicates the predictive value of MetS during childhood on the same syndrome during adulthood.*
38. •• Magnussen CG, Koskinen J, Chen W, Thomson R, Schmidt MD, Srinivasan SR, et al. Pediatric metabolic syndrome predicts adulthood metabolic syndrome, subclinical atherosclerosis, and type 2 diabetes mellitus but is no better than body mass index alone: the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study. Circulation. 2010;122:1604–11. *Data from these 2 large longitudinal studies indicate a 2–3 fold increased risk of adult MetS for adolescents with the syndrome.*
39. • Schubert CM, Sun SS, Burns TL, Morrison JA, Huang TT. Predictive ability of childhood metabolic components for adult metabolic syndrome and type 2 diabetes. J Pediatr. 2009;155:S6 e1–7. *In line with reference 36, this study highlights the predictive value of MetS in youth on future cardiometabolic outcomes during adulthood.*
40. • Efstathiou SP, Skeva II, Zorbala E, Georgiou E, Mountokalakis TD. Metabolic syndrome in adolescence: can it be predicted from natal and parental profile? The Prediction of Metabolic Syndrome in Adolescence (PREMA) study. Circulation. 2012;125:902–10. *This study highlights that the coexistence of low birth weight, small head circumference, and parental history of overweight or obesity may be helpful in targeting children at risk for developing MetS during adolescence.*
41. •• Steinberger J, Daniels SR, Eckel RH, Hayman L, Lustig RH, McCrindle B, et al. 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. Circulation. 2009;119:628–47. *This is a nice update on the current state of the art on the MetS in children and adolescents.*
42. Reinehr T, Kiess W, Kapellen T, Andler W. Insulin sensitivity among obese children and adolescents, according to degree of weight loss. Pediatrics. 2004;114:1569–73.
43. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Pediatrics. 2001;107:E55.
44. Srinivasan S, Ambler GR, Baur LA, Garnett SP, Tepsa M, Yap F, et al. Randomized, controlled trial of metformin for obesity and insulin resistance in children and adolescents: improvement in body composition and fasting insulin. J Clin Endocrinol Metab. 2006;91:2074–80.
45. Kay JP, Alemzadeh R, Langley G, D'Angelo L, Smith P, Holshouser S. Beneficial effects of metformin in normoglycemic morbidly obese adolescents. Metab Clin Exp. 2001;50:1457–61.
46. Love-Osborne K, Sheeder J, Zeitler P. Addition of metformin to a lifestyle modification program in adolescents with insulin resistance. J Pediatr. 2008;152:817–22.
47. Berkowitz RI, Wadden TA, Tershakovec AM, Cronquist JL. Behavior therapy and sibutramine for the treatment of adolescent obesity: a randomized controlled trial. JAMA. 2003;289:1805–12.
48. Chanoine JP, Hampl S, Jensen C, Boldrin M, Hauptman J. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. JAMA. 2005;293:2873–83.
49. Yki-Jarvinen H. Thiazolidinediones. N Engl J Med. 2004;351:1106–18.
50. Eisenmann JC. On the use of a continuous metabolic syndrome score in pediatric research. Cardiovasc Diabetol. 2008;7:17.