The metabolic syndrome in pediatrics: do we have a reliable definition? A systemic review

Angelo Tropeano, Domenico Corica, Alessandra Li Pomi, Giorgia Pepe, Letteria Anna Morabito, Selenia Lorenza Curatola, Celeste Casto, Tommaso Aversa and **Malgorzata Wasniewska**

Department of Human Pathology of Adulthood and Childhood, Unit of Pediatrics, University of Messina, Messina, Italy

Correspondence should be addressed to M Wasniewska
Email malgorzata.wasniewska@unime.it

Abstract

Objective: Metabolic syndrome is a cluster of cardio-metabolic risk factors associated with an increased risk of cardiovascular disease and type 2 diabetes. In the last two decades, several definitions of metabolic syndrome have been proposed for the pediatric population; all of them agree on the defining components but differ in the suggested criteria for diagnosis. This review aims to analyze the current diagnostic criteria of metabolic syndrome in pediatrics with reference to their feasibility and reliability in clinical practice.
Methods: The systemic research was conducted from January 2003 to June 2020 through MEDLINE via PubMed, Cochrane Library and EMBASE databases.
Results: After the selection phase, a total of 15 studies (182 screened) met the inclusion and exclusion criteria and hence they were reported in the present review. Twelve studies were cross-sectional, two were longitudinal and one was a consensus report. The sample population consisted of multiethnic group or single ethnic group, including Turkish, European, Asian and Hispanic subjects.
Conclusions: To date, there is not a univocal, internationally accepted pediatric definition of metabolic syndrome, which guarantees a high sensitivity and stability of the diagnosis. The definition proposed by IDF results the most straightforward and easy to use in clinical practice, having the unquestionable advantage of requiring measurements quickly accessible in clinical practice, without the adoption of multiple reference tables. Further research is needed to validate a new version of such definition which includes the diagnostic cut-off points recently suggested by published guidelines.

European Journal of Endocrinology (2021) **185**, 1–15

European Journal of Endocrinology

Introduction

Over the last decades, the increasing prevalence of obesity in childhood has become a matter of concern for public health. During childhood, excessive body fat increases five-fold the risk of obesity in adult life and is associated with cardio-metabolic complications, including hypertension, dyslipidemia and impaired glucose metabolism (1). The clustering of these risk factors defines the metabolic syndrome (MetS) and increases the risk of future cardiovascular disease (CVD) and type 2 diabetes (T2DM) beyond the risk related to its individual components.

Although there is an agreement on the features defining MetS, no univocal international diagnostic criteria in the pediatric population exist. Each of the definitions of MetS applied in children has a different set of cut-off values and, even when they are applied to the same population, the estimated prevalence of MetS results

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-21-0238

Published by Bioscientifica Ltd.

differently. As a consequence, up to the present time, the prevalence of MetS in childhood is not definite and, thus, its clinical implication in youth is not clear.

The aim of this review is to evaluate the current diagnostic criteria of MetS in children and adolescents focusing on their feasibility and reliability in clinical practice.

Methods

The literature included in the review was identified by two independent investigators (AT and DC) principally using an automated literature search for English language papers published from January 2003 to June 2020. The systematic research was conducted according to the EQUATOR statement (2), through MEDLINE via PubMed, Cochrane Library and EMBASE databases identifying studies that reported criteria to diagnose MetS in children and adolescents. The research was based on the combinations of three or more of the following keywords, in order to generate a wide search: ('Metabolic syndrome OR MetS') AND ('children OR adolescent') AND ('diagnosis OR definition') AND ('obesity OR overweight'). Besides the automated search, a manual search for additional relevant publications was made of the bibliographies of the papers identified automatically. The assessment of eligibility was guided by a flow diagram as reported in Fig. 1. The inclusion criteria comprised: articles written in English, which belonged to the categories of Clinical Study, Clinical Trial, Clinical Trial Protocol, Multicenter Study, Randomized Controlled Trial, Observational studies suggesting a pediatric definition of MetS; study population consisting in children and/or adolescents regardless of the pubertal stage, belonging to multiethnic or single ethnic population but not to ethnic minorities. The exclusion criteria comprised: studies with a small study population comprising less than 100 subjects; narrow age-range (inferior to 5 years) cohorts; research in which the entire study population did not undergo the same investigations; studies proposing diagnostic criteria for MetS other than the following: obesity, hypertension, dyslipidemia, abnormal glucose homeostasis and insulin resistance; studies proposing previously published diagnostic criteria or identical to the adulthood ones. Consequently, it was considered as eligible the suggested MetS definition that (1) included only the diagnostic criteria provided by Reaven's original description of 'syndrome X', (2) was applied to a sufficient wide study population and (3) in an age-range that allowed to evaluate the diagnostic reliability in different growth stages.

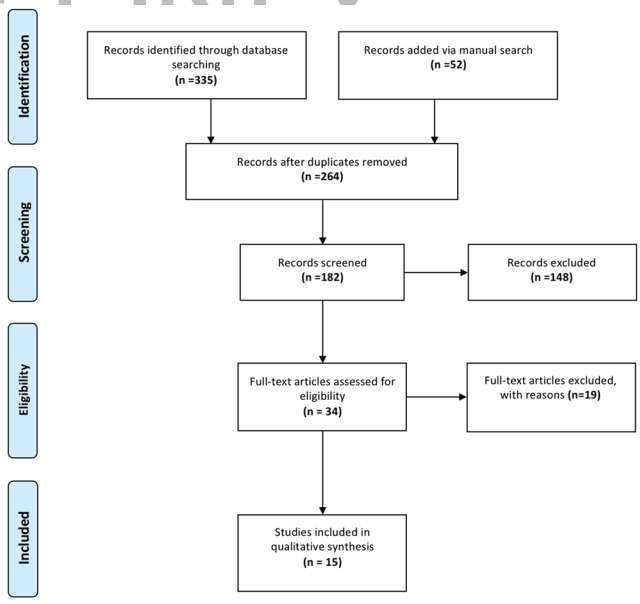

Figure 1
Flow diagram summarizing study selection process.

Quality analysis

Quality analysis for each study included was conducted by two independent investigators (AT and DC) using the Critical Appraisal Checklist for Studies Reporting Prevalence Data and the Checklist for Text and Opinion Papers developed by the Joanna Briggs Institute (3, 4).

Results

Publications included

Using the search strategy described above (Fig. 1) a total of 355 publications were found. A manual search considering the bibliographies of the review articles retrieved 52 additional papers. A total of 264 papers were found to be duplicated and were therefore excluded. Following the assessment of the titles and abstracts, 148 papers were excluded, because they were not related to the subject. The analyses of the remaining 34 articles by reading the full texts resulted in the exclusion of 19 papers for the following reasons: small study population (n= 5); narrow age-range cohorts (n= 6); research in which the entire study population did not undergo the same investigations (n= 4); studies proposing diagnostic criteria other than

the original ones (see 'Methods' section) (n= 2); studies proposing previously published diagnostic criteria (n= 2). Therefore, a total of 15 studies were included in the review.

Description of the studies and demographic analysis

Fifteen papers published from 2003 to 2014 were included in this review. Twelve studies were cross-sectional, two were longitudinal (5, 6) and one was a consensus report (7). The sample population consisted of multiethnic group (5, 6, 8, 9, 10) or single ethnic group including Turkish (11, 12), European (13, 14), Asian (15, 16, 17) and Hispanic (18, 19) subjects. The number of subjects analyzed in each study varied from 126 to 18 745 in an age range between 2 and 20 years. The prevalence of MetS ranged from 1.8 to 49.7%, with a higher prevalence among obese subjects than lean ones. This enormous variability in the disease prevalence may in part be explained by the nutritional status of the children enrolled in the study cohorts, indeed four studies (11, 13, 15, 18) included only overweight and/or obese children and adolescents, one included almost exclusively obese children (5), the remnant ones included subjects with variable BMI.

The stability of the MetS diagnosis

The two studies (5, 6) with a longitudinal design provided information about the stability of MetS diagnosis. In the study by Weiss *et al.* (5), 77 subjects (15.7% of the entire cohort) underwent a second assessment after 2 years of follow-up: 24 of 34 subjects with MetS diagnosis at baseline met the MetS criteria at the time of the second evaluation, on the other hand, 16 of 43 children without MetS diagnosis at baseline developed MetS over time. In the research by Goodman *et al.* (6) the study cohort returned for reassessment 3 years later and the authors determined the instability of the MetS diagnosis (defined as the percentage of MetS-positive youth at baseline which will become negative at follow-up) and the cumulative incidence (the proportion of new MetS cases at follow-up). They found a baseline MetS prevalence of 5.2% (CIs 95%, CI 4.0–6.7) and a follow-up MetS prevalence of 5.9% (CI 4.6–7.5), with an instability of 56.1% (CI 42.4–69.3) and a cumulative incidence of 3.8% (CI 2.8–5.2); thus, approximately half of subjects with MetS diagnosis at the baseline lost the diagnosis at the follow-up, while others gained the diagnosis over time. Moreover, the pediatric MetS definition showed a higher degree of instability than two other adult definitions (49 and 53%) applied to the same study population. Goodman *et al.* (6) also demonstrated a significant within-person variability across the diagnostic thresholds during growth and development, although the overall clustering of metabolic risks did not change during adolescence.

Components of MetS definition

Obesity

Nine (6, 7, 8, 9, 10, 14, 15, 16, 18) studies suggested the waist circumference (WC) as a criterion for obesity definition, four studies (5, 11, 12, 19) used the BMI and two studied (13, 17) proposed both WC and BMI. Goodman *et al.* (6) and Cruz *et al.* (18) suggested a set of age-, sex- and ethnicity-specific WC percentile (20) based on the NHANES III data. The International Diabetes Federation (IDF) (7) proposed a set of WC percentile according to the American (20, 21) Canadian (22), British (23) and Australian (24) nationality and two age- and sex-specific absolute values (Table 2). Ahrens *et al.* (14) adopted the WC percentile (25) based on a large cohort of normal weight European children aged 2–10.9 years enrolled in the Dietary-and lifestyle-induced health Effect in children and Infants (IDEFICS) study (26). Cook *et al.* (8) and Park *et al.* (16) used the recorded data of their own cohort to derive a WC percentile distribution, which, however, was not available for the reader. Ford *et al.* (9) and de Ferranti *et al.* (10) did not suggest the used reference WC percentiles. The abovementioned authors classified subjects having a WC at or above 90th percentile as having abdominal obesity, except de Ferranti *et al.* (10), who proposed the 75th percentile as diagnostic threshold (Tables 1 and 2). Conversely, Yoshinaga *et al.* (15) suggested some age- and sex-specific WC absolute values derived from a study including only Japanese obese and non-obese children (27). Among the authors who proposed the BMI as obesity index, Atabek *et al.* (11) and Weiss *et al.* (5) adopted the standards of the Centers for Disease Control and Prevention, suggesting, however, two different diagnostic cut-offs (Table 1), while Agirbasli *et al.* (12) proposed a set of BMI cut-off points obtained by averaging data from six large nationally representative cross-sectional surveys (28). Rodriguez-Moran *et al.* (19) used a diagnostic percentile threshold different from the previous ones (Table 5), but they did not suggest the reference percentile. Finally, Invitti *et al.* (13) and Vikram *et al.* (17) (Tables 3 and 4) used both WC and BMI for obesity diagnosis; however, only the latter suggested the BMI reference percentile derived from a cohort of Asian Indians youth (29).

Table 1 Comparison of suggested diagnostic criteria for metabolic syndrome in childhood and adolescence. Metabolic syndrome is defined by the presence of three or more criteria described in the table (each category counts as one risk criterion).

		Diagnostic criteria						
Reference	**Study population**	Obesity	Dyslipidemia	Glucose homeostasis	Blood pressure	**Overall MetS prevalence in study population**	**Most commonly met criteria**	**Least common criteria**
(8)	2430 White, Black and Mexican American adolescents aged 12–19 years (NHANES III 1988–1994 data)	WC ≥ 90th pct.	TG ≥ 110 mg/dL OR HDL-c ≤ 40 mg/dL	FG ≥ 110 mg/dL	SBP OR DBP ≥ 90th pct. adjusted for age, sex and height	4.2% (6.1% in males, 2.1% in females) – Mexican Americans: 5.6%; – Whites: 4.8%; – African Americans: 2%	Hypertriglyceridemia and low HDL-c	High FG
(18)	126 overweight Hispanic children and adolescents aged 8–13 years with a family history of T2DM	WC ≥ 90th pct. specific for age, sex and Hispanic ethnicity	TG ≥ 90th pct. specific for age, sexOR HDL-c ≤ 10th pct. specific for age and sex	IGT: 2 h glucose ≥ 140 mg/dL	SBP OR DBP ≥ 90th pct. adjusted for age, sex and height	30%	Low HDL and central obesity	Hypertension
(10)	1960 multiethnic USA adolescents aged 12–19 years (NHANES III 1988–1994 data)	WC > 75th pct. specific for age, sex	TG ≥ 97.35 mg/dL OR HDL-c < 45.17 mg/dL (boys) and < 50.19 mg/dL (girls)	FG ≥ 110 mg/dL	BP > 90th pct. adjusted for age, sex and height	9.2% (9.5% in males and 8.9% in females) – Mexican Americans: 12.9%; – non-Hispanic whites: 10.9%; – non-Hispanic blacks: 2.5%	Low HDL-c	High FG
(5)	490 white, black and Hispanic American children and adolescents aged 4–20 years (89.5% of the cohort was moderately and severe obese)	BMI z score ≥ 2 specific for age, sex	TG > 95th pct. OR HDL-c < 5th pct. specific for age, sex and ethnicity	IGT: 2 h glucose >140 and <200 mg/dL	SBP OR DBP > 95th pct. adjusted for age, sex and height	38.7% in subjects with moderate obesity (BMI z score: 2.0–2.5); 49.7% in subjects with severe obesity (BMI z score > 2.5)	NA	

(9)	1366 multiethnic USA adolescents aged 12–17 years (NHANES 1999–2000 data)	WC ≥ 90th pct.	TG ≥ 110 mg/dL OR HDL-c ≤ 40 mg/dL	FG ≥ 110 mg/dL OR FG ≥ 100 mg/dL	SBP OR DBP ≥ 90th pct. adjusted for age, sex and height	– 5.8% according to the threshold of FG ≥ 110 mg/dL; – 6.2% according to the threshold of FG ≥ 100 mg/dL	Abdominal obesity	High FG
(15)	471 overweight and obese Japanese children aged 6–11 years	6–8 years old: boys WC ≥ 65.1 cm; girls WC ≥ 58.5 cm; 9–11 years old boys and girls: WC ≥ 70.2 cm	TG > 120 mg/dLOR HDL-c < 40 mg/dL	FG > 100 mg/dL	– 1st to 3rd grades: SBP ≥ 120 OR DBP ≥ 70 mmHg; – 4th to 6th grades: SBP≥ 130 OR DBP ≥ 80 mmHg	14.5%	Abdominal obesity	High FG
(16)	1594 South Korean adolescents aged 10–19 years	WC ≥ 90th pct.	TG ≥ 140 mg/dL OR HDL-c ≤ 40 mg/dL	FG ≥ 110 mg/dL	SBP OR DBP ≥ 90th pct. adjusted for age and sex	3.3%	NA	
(11)	169 obese Turkish children and adolescents aged 7–18 years	BMI > 95th pct. specific for age, sex	TG > 105 mg/dL (in children < 10 years) and >136 mg/dL (children ≥10 years) OR HDL-c < 35 mg/dL OR Tc >95th pct.	FH* OR IFG ≥ 110 mg/dL OR IGT: 2 h glucose ≥ 140 mg/dL	SBP >95th pct. adjusted for age, sex	27.2%	Hypertriglyceridemia	IFG
(12)	1385 Turkish children and adolescents aged 10–17 years (enrolled between 1992 and 1994)	BMI corresponding to overweight or obese state	TG ≥ 90th pct. OR HDL-c ≤ 10th pct.	IFG > 100 mg/dL	SBP ≥ 95th pct.	2.2%	Hypertriglyceridemia	IFG

(6)	1098 non-Hispanic white, non-Hispanic black and Hispanic adolescents aged 12–19 years	WC ≥ 90th pct. specific for age, sex and race/ethnicity	TG ≥ 110 mg/dL OR HDL-c ≤ 10th pct. specific for race and sex	FG ≥ 100 mg/dL	SBP OR DBP ≥ 90th pct. adjusted for age, sex and height	– 5.2% at baseline and – 5.9% after 3 years of follow-up	Low HDL-c	High FG
(14)	18 745 European children aged 2–10.9 years	WC ≥ 90th pct; #WC ≥ 95th pct. specific for sex and age	TG ≥ 90th pct. OR HDL-c ≤ 10th pct.; TG ≥ 95th pct. specific for sex and age	FG ≥ 90th pct. OR HOMA-IR ≥ 90th pct.#FG ≥ 95th pct. #HOMA-IR ≥ 95th pct.	SBP OR DBP ≥ 90th pct; #SBP or DBP ≥ 95th pct. adjusted for age, sex and height	– 5.5% according to the monitoring level definition – 1.8% according to the action level definition	Abdominal obesity	Impaired glucose homeostasis

*Expressed according to the pubertal stage: prepuberal >15 mU/L, mid-puberty (tanner stages 2–4]) >30 mU/L; # Ahrens *et al.* (14) proposed two different cut-offs to guide medical decision: when at least three of the MetS components exceeded the 90th percentile, close monitoring was suggested (monitoring level) but if they were above the 95th percentile, an intervention was requested (action level).

DBP, diastolic blood pressure; FG, fasting glucose level; FH, fasting hyperinsulinemia; HDL-c, high-density lipoprotein cholesterol; HOMA-IR. Homeostatic model assessment insulin resistance; IDEFICS, Identification and prevention of Dietary-and lifestyle-induced health Effect in children and Infants; IGT, impaired glucose tolerance; NA, not applicable; pct., percentile; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; Tc, total cholesterol; TG, triglycerides; WC, waist circumference.

Table 2 Definition of metabolic syndrome according to the International Diabetes Federation (IDF) (7) (year 2007). Metabolic syndrome is defined by the presence of central obesity plus any of the other four criteria.

Age group (years)	**Obesity** (WC)	**Triglycerides**	**HDL-c**	**Glucose homeostasis**	**Blood pressure**
6 to <10	≥90th pct.				
10 to <16	≥90th pct. OR adult cut-off if lower	≥150 mg/dL	<40 mg/dL	FG ≥ 100 mg/dL OR known T2DM	SBP ≥ 130 OR DBP ≥ 85 mmHg
16+ (adult criteria)	≥94 cm for Europid males and ≥ 80 cm for Europid females	≥ 150 mg/dL OR specific treatment for high triglycerides	< 40 mg/dL in males and < 50 mg/dL in females	FG ≥ 100 mg/dL OR known T2DM	SBP ≥ 130 OR DBP ≥ 85 mmHg OR treatment for hypertension

DBP, diastolic blood pressure; FG, fasting glucose level; HDL-c, high-density lipoprotein cholesterol; pct., percentile; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; WC, waist circumference.

Impaired glucose homeostasis

Nine (6, 7, 8, 9, 10, 12, 15, 16, 19) studies proposed impaired fasting glycemia (IFG) as a diagnostic criterion with a threshold at 100 mg/dL or 110 mg/dL. In addition to IFG, Invitti *et al.* (13) also suggested the use of impaired glucose tolerance (IGT), based on a 2 h glucose tolerance test, and the homeostasis model assessment insulin resistance (HOMA-IR) values adjusted for Tanner stages (Table 3). Ahrens *et al.* (14) advocated FG and HOMA-IR index expressed as percentile threshold according to the reference values provided by a study enrolling a large cohort of normal weight prepubertal children (30). Weiss *et al.* (5) and Cruz *et al.* (18) suggested only the use of IGT. Vikram *et al.* (17) used the criterion of IFG and/or fasting hyperinsulinemia (FH) expressed as absolute values. Finally, Atabek *et al.* (11) provided the absolute values for FH, IFG or IGT as diagnostic criteria. Only the definitions suggested by Invitti *et al.* (13) (Table 3) and Vikram *et al.* (17) (MetS-D3, Table 4) requested the mandatory presence of the glucose intolerance and/or insulin resistance for MetS diagnosis.

Dyslipidemia

Dyslipidemia was defined as low HDL-c level and/or high triglyceride level by all the authors except Atabek *et al.* (11) who included also hypercholesterolemia. Seven MetS definitions (7, 8, 9, 10, 15, 16, 17) suggested several absolute values as diagnostic thresholds (Tables 1, 2 and 4). Cook *et al.* (8) used the following methodology to select their criteria: in a first step, the authors selected a range of values, considered as 'borderline low HDL-c levels' and 'borderline high triglyceride levels', from a review by Styne (31) summarizing, in a table, the lipid values of the *National Cholesterol Education Program* (NCEP) *Report* (32) and then they used the midpoint value of each range to derive the suggested absolute thresholds (Table 1). The unavailability of the summary table in the web version of the review by Styne (31) does not allow the reader to have a global vision of the methodological process used by the authors. Yoshinaga *et al.*'s (15) (Table 1) cut-off values were obtained by a consensus on the definition of the obesity comorbidities in Japanese children (33). De Ferranti *et al.* (10) derived the suggested lipid thresholds (Table 1) from a study dated from 1970s (34) enrolling American youth. The IDF group (7) (Table 2) suggested the same lipid thresholds of adult MetS definition (35). Finally, Ford *et al.* (9), Park *et al.* (16) and Vikram *et al.* (17) (Table 4) did not declare the methodological approach to derive their reference cut-off values. Among the authors who proposed a percentile threshold, Ahrens *et al.* (14) adopted the reference percentiles (36) based on the European cohort of children enrolled in the IDEFICS study, Cruz *et al.* (18) suggested the reference percentiles based on the NHANES III data (37), while Weiss *et al.* (5) used the reference percentile extrapolated by a longitudinal study enrolling only girls from 9 to 19 years (38). Invitti *et al.* (13) Agirbasli *et al.* (12) and Rodriguez-Moran *et al.* (19) did not suggest the reference percentiles. Finally, two authors used both percentile and absolute values as diagnostic thresholds: absolute value for hypertriglyceridemia proposed by Goodman *et al.* (6) was inspired by Cook *et al.*'s (8) study, as declared by the authors, while the reference percentiles for HDL-c were derived from the NHANES III data (37); Atabek *et al.* (11) did not clarify the selection of the methodological approach to derive reference curves and cut-off values.

Hypertension

Twelve studies used the 90th or 95th percentile adjusted for height, age and gender as a diagnostic threshold: six of them (5, 6, 8, 10, 12, 18) proposed the reference percentile of the *National High Blood Pressure Education Program* (39, 40), five authors (9, 11, 13, 16, 19) did not suggest the

Table 3 Definition of metabolic syndrome according to Invitti *et al.* (13) (year 2006). Metabolic syndrome is defined by the presence of glucose intolerance (IFG, IGT or diabetes) and/or insulin resistance plus two or more criteria described in the table (each category counts as one risk criterion).

	Diagnostic criteria									
Study population	Glucose intolerance	AND/OR	Insulin resistance	+	Obesity	TG	HDL-c	BP	Prevalence in study population	Most commonly met criteria	Least common criteria
588 Italian children and adolescents with obesity aged 6–16 years	IFG, FG ≥ 110 mg/dL < 126 mg/dL OR IGT 2 hglucose ≥ 140 mg/dL < 200 mg/dL OR diabetes	HOMA-IR >2.4 (Tanner stage I) >2.8 (Tanner stage II) > 3.0 (Tanner stage III) > 4.1 (Tanner stage IV) > 3.0 (Tanner stage V)	—	BMI AND WC ≥ 97th pct.	≥95th pct.	≤5th pct.	≥95 pct.	23.3%	Insulin resistance	IFG and diabetes

IFG, impaired fasting glucose; FG, fasting glucose level; IGT, impaired glucose tolerance; WC, waist circumference; pct., percentile; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; BP, blood pressure..

reference percentile, while Ahrens *et al.* (14) provided the reference values in non-overweight European children participating in the IDEFICS study (41). Conversely, three authors suggested absolute values as a diagnostic threshold: Yoshinaga *et al.* (15) derived the cut-off values from a consensus on the obesity comorbidities in Japanese children (33); the IDF group proposed the same criteria of adult MetS definition (35); Vikram *et al.* (17) did not provide a reference for the selection of own suggested criteria.

Degree of agreement between the various MetS definitions

Ahrens *et al.* (14) applied the definitions proposed by Cook *et al.* (8) and IDF Group (7) to their own study cohort with the aim of assessing the degree of agreement between them (kappa coefficient, K). This agreement was classified as 'moderate' (K 0.41–0.60), 'fair' (K 0.21–0.40) and 'slight' (K0–0.20) agreement. The best result was observed between Ahrens *et al.*'s definitions (monitoring and action level definitions, K 0.48 (CI 0.44–0.52)) while the lowest agreement was reported between Ahrens *et al.*'s and IDF group's definitions (K 0.11 (CI 0.08–0.14)), in turn the definition by IDF group showed the best agreement with Cook *et al.*'s definition (K 0.25 (CI 0.18–0.33)) while a fair agreement was showed between Cook *et al.* and Ahrens *et al.*'s definitions (monitoring level, K 0.29 (CI 0.25–0.33) and action level, K 0.35 (CI 0.28–0.41)). In addition, Ahrens *et al.* showed that the contribution of the various components used for the MetS diagnosis varied substantially between the different definitions: the cut-offs proposed by Cook *et al.* resulted in a near negligible number of children classified as hyperglycemic; likewise, the cut-off for hypertension in the definition by IDF was exceeded by a small fraction of children. Conversely, the definitions (monitoring level and action level) suggested by Ahrens *et al.* (Table 1) showed a fair balance between each criterion in the contribution to the overall prevalence of the MetS.

Discussion

Obesity rates in children and adolescents increased from less than 1% in 1975 to nearly 6% in girls (50 million) and nearly 8% in boys (74 million) in 2016, with an additional 213 million of overweight children (42). Excessive body fat during childhood increases five-fold the risk of obesity in adult life and is associated with cardio-metabolic complications, including hypertension, dyslipidemia and

Table 4 Definition of metabolic syndrome according to Vikram *et al.* (17) (year 2006). The table reports three sets of definitions (MetS-D1, D2 and D3) that differ for the presence of fasting hyperinsulinemia as diagnostic criterion. According to the sets of definitions MetS-D1 and D2 the metabolic syndrome is defined by the presence of three or more criteria described in the table (each category counts as one risk criterion), while according the MetS-D3 the metabolic syndrome is defined in the presence of fasting hyperinsulinemia plus any 2 or more of the other criteria.

		Diagnostic criteria					
Study population	**Definitions**	Obesity	Triglycerides	HDL-c	Glucose homeostasis	Blood pressure	**Overall MetS prevalence** (%)
793 Asian Indian adolescents aged 14–19 years	MetS-D1						
	Definition A	WC > 82.5 cm in males and > 76 cm in females	≥128 mg/dL	<40 mg/dL	FG ≥ 110 mg/dL	SBP ≥ 124 OR DBP ≥ 82 mmHg	0.8
	Definition B	BMI > 23 kg/m^2	≥128 mg/dL	<40 mg/dL	FG ≥ 110 mg/dL	SBP ≥ 124 OR DBP ≥ 82 mmHg	0.9
	Definition C	WC > 82.5 cm in males and >76 cm in females OR BMI >23 kg/m^2	≥128 mg/dL	<40 mg/dL	FG ≥ 110 mg/dL	SBP ≥ 124 OR DBP ≥ 82 mmHg	4.3
	MetS-D2						
	Definition A	WC > 82.5 cm in males and > 76 cm in females	≥128 mg/dL	<40 mg/dL	FG ≥ 110 mg/dL OR FH ˃ 20 µU/mL	SBP ≥ 124 OR DBP ≥ 82 mmHg	4.2
	Definition B	BMI > 23 kg/m^2	≥128 mg/dL	<40 mg/dL	FG ≥ 110 mg/dL OR FH > 20 µU/mL	SBP ≥ 124 OR DBP ≥ 82 mmHg	5.2
	Definition C	WC > 82.5 cm in males and > 76 cm in females OR BMI > 23 kg/m^2	≥128 mg/dL	<40 mg/dL	FG ≥ 110 mg/dL OR FH > 20 µU/mL	SBP ≥ 124 OR DBP ≥ 82 mmHg	10.2
	MetS-D3						
	Definition A	WC > 82.5 cm in males and > 76 cm in females	≥128 mg/dL	<40 mg/dL	FH > 20 µU/mL	SBP ≥ 124 OR DBP ≥ 82 mmHg	3.4
	Definition B	BMI > 23 kg/m^2	≥128 mg/dL	<40 mg/dL	FH > 20 µU/mL	SBP ≥ 124 OR DBP ≥ 82 mmHg	4.4
	Definition C	WC > 82.5 cm in males and > 76 cm in females OR BMI >23 kg/m^2	≥ 128 mg/dL	< 40 mg/dL	FH > 20 µU/mL	SBP ≥ 124 OR DBP ≥ 82 mmHg	8.2

DBP, diastolic blood pressure; FG, fasting glucose level; FH, fasting hyperinsulinemia; HDL-c, high-density lipoprotein cholesterol; SBP, systolic blood pressure; WC, waist circumference.

impaired glucose metabolism (1). The clustering of these risk factors defines MetS and increases the risk of future CVD and T2DM beyond the risk related to its individual components. Thus, the diagnosis of MetS in pediatric population could allow pediatrician to promptly identify and treat the children with an increased risk of future adverse outcomes, providing with the opportunity to test the efficacy of an early treatment on the incidence of CVD and T2DM in adult life. Because of the ongoing obesity epidemic, the comparison between the prevalence of MetS according to the analyzed definitions is difficult. Indeed, Cook *et al.*'s (8) and de Ferranti *et al.*'s (10) study cohorts

Table 5 Definition of metabolic syndrome according to Rodriguez-Moran *et al.* (19) (year 2004). The diagnosis of metabolic syndrome lies on a score system with two steps of evaluation: each item is computed as 1 point. After an anamnestic and clinical evaluation (1st step), eligible subjects (in presence of 2 point at least) undergo a laboratory workup (2nd step). Metabolic syndrome is defined by the presence of three or more points.

Study population	Scoring system for MetS diagnosis				Overall MetS prevalence	Most commonly met criteria	Least common criteria
	First step (anamnestic and clinical evaluation)		Second sep (laboratory workup)				
965 Mexican subjects aged 10–18 years	Family history of T2DM, obesity or hypertension	1 point	Triglycerides (serum TG ≥ 90th pct.)	1 point	7.8%	Obesity	Hypertension
	Low or high birth weight	1 point	HDL-c (threshold not clarified by the authors)	1 point			
	Diagnosis of obesity (BMI ≥ 90th pct.)	1 point	Glucose homeostasis (FG ≥ 110 mg/dL)	1 point			
	Diagnosis of hypertension (SBP/DBP ≥ 90th pct.)	1 point					

DBP, diastolic blood pressure; FG, fasting glucose level; HDL-c, high-density lipoprotein cholesterol; pct., percentile; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TG, triglycerides.

belonged to NHANES III 1988–1994 data; conversely, the cohorts of the majority of other studies were collected in the early 2000s. Consequently, the temporal changes in childhood obesity may be in part accountable for the differences in prevalence between the various definitions (Tables 1, 2, 3, 4 and 5). In addition, the use of different diagnostic cut-offs and the enrollment of youth with a variable nutrition status are non-negligible reasons which do not allow a precise estimate of the overall MetS prevalence in childhood. These considerations may explain the high MetS prevalence in the studies by Cruz *et al.* (18), Atabek *et al.* (11) and Weiss *et al.* (5) (Table 1).

Furthermore, the concept of the stability of MetS during childhood and adolescence has become an important concern in the last decade. As discussed above, Goodman *et al.* (6) showed that up to half of the children with MetS at baseline failed to meet the same criteria for MetS after a follow-up period. Gustafson *et al.* (43) confirmed this finding with a less large study population and underlined the importance of the pubertal onset as a possible influence factor on the incidence of MetS. Undeniably, a major limitation of some MetS definitions is the use of rigid cut-points, which do not consider the fluctuations associated with puberty. Nevertheless, it is common knowledge that puberty is characterized by a physiologic reduction of insulin sensitivity, which returns to normal levels by the end of puberty (44). Moreover, some research showed a deterioration of cardiovascular risk factors (BP, plasma lipids and fasting glucose levels) at the onset of puberty, with an improvement during the transition from mid to late puberty, independently from changes in the weight status (45). These considerations undermine the reliability of a single MetS definition for pre- and post-pubertal stage. An alternative approach is the development of a risk score that describes the cardio-metabolic risk of the patient with a continuous value. This method overcomes the limitation of rigid cut-off values of the classical definitions, but the complexity of its calculation makes it inapplicable in clinical practice.

Another important issue is the selection of components of MetS definition. Obesity, especially abdominal obesity, plays a key role in MetS pathogenesis. Indeed, Weiss *et al.* (5) showed in their study population a significant increase in the risk of MetS for each half-unit increase in BMI z score. Although BMI is a widely used index with good performance as a predictor of MetS, in certain situations, its use can be misleading. Because of its high specificity and low false-positive rate, BMI is able to correctly identify the fattest children in a study sample, but it can misclassify large numbers of children with a high body fat content because of its low sensitivity and moderate-high false-negative rate (46). In addition, BMI is unable to distinguish between fat and lean tissue and, consequently, cannot provide information about fat distribution. It is well known that insulin resistance (IR) is related to visceral and/or ectopic fat distribution (i.e. liver and muscle) rather than to the overall body adiposity (47). Thus, it would be more appropriate to use an anthropometric index that is more closely associated with central obesity and easy to obtain in clinical practice. WC measurement addressed in part these

limitations being a surrogate index of abdominal obesity. Although WC relates to both subcutaneous abdominal fat and intra-abdominal fat, consolidate, and recent evidence suggests an association with obesity-related morbidity (48, 49, 50). The main disadvantages in WC use are: (1) the absence of a universal agreement on WC landmark. Some authors used the mid-way between the last rib and the top of the iliac crest, others the superior border of the iliac crest or the level of the umbilicus, consequently, a comparison between different sets of WC percentile becomes difficult; (2) Ethnic difference in visceral adipose tissue (VAT). Asian Indians have more VAT, despite a lower body mass compared with the white Europeans; similarly, white youth have more VAT than African American youth at a given BMI (51); (3) Body shape during puberty. Boys develop a more android shape by depositing more fat in the abdomen, whereas girls deposit it in the hips and limbs forming a gynoid shape. These considerations indicate the importance of population-, sex- and age-specific WC cut-off points to identify the cardio-metabolic risk associated with weight gain. The waist-to-height ratio (WHtR), calculated by dividing WC by height, has several advantages if compared to BMI or WC. First, a WHtR value of 0.5 is suggested as a universal cut-off for abdominal obesity and health risks in children and adults without differences for gender, ethnicity and age, thus it does not require reference percentiles for diagnosis. Moreover, the message: 'Keep your waist circumference to less than half your height' is simple to understand and very useful in terms of public health. A recent meta-analysis in children (52) showed that WHtR was comparable to both WC and BMI for cardio-metabolic risk screening power.

Another key component of Mets is IR. IR plays a pivotal role in the development and progression of cardiometabolic risk factors, being strongly correlated with hypertension, low HDL-c, hypertriglyceridemia and T2DM (53). IR is a decreased tissue response to insulin action and, as abovementioned, it is associated with the excess of adipose tissue. In pediatric age, IR is a physiological condition that favors body accretion, reaching the zenith at the time of puberty and then declining to prepubertal values. Another unchangeable risk factor for IR, other than puberty, is ethnicity. African American, Hispanic, Pima Indian and Asian children are less insulin sensitive compared with Caucasian children. For this reason, the recognition of physiological and not physiological condition of IR has a substantial importance for identifying young individuals at increased cardiovascular risk. From a diagnostic point of view, although the fasting plasma insulin is the most used marker in clinical practice, it is not considered an adequate test because it does not evaluate insulin concentration regarding fasting glucose values; therefore, it is a poor measure of insulin sensitivity (53). HOMA is a widely used tool based on the relationship between fasting glucose and insulin levels. Although several HOMA indexes formulas have been proposed and different studies have tried to identify the normal values in youth, the reliable reference range of HOMA is not available yet (53). In the absence of strong surrogate age-, gender- and ethnic-specific biomarkers of IR, the Insulin Resistance Consensus Group (54) does not suggest the screening for IR in the clinical setting for children, including those with obesity. Conversely, the American Diabetes Association(ADA) (55) advises a risk-based screening (fasting plasma glucose test, oral glucose tolerance test and A1C test are equally appropriate) for prediabetes and/or T2DM in children with overweight, obesity or additional risk factors. In addition, ADA has lowered the defining value for IFG to 100 mg/dL.

Obesity is commonly associated with a combined dyslipidemia pattern, including mild elevation in total cholesterol (Tc) and LDL levels, moderate-to-severe elevation in triglyceride level and low HDL-c level. Considering that abnormal lipid levels in childhood predispose to accelerated atherosclerosis, identification of lipid abnormalities become crucial for the prevention of future CVD. The analyzed MetS definitions proposed several absolute cut-off values or percentile values which have been extrapolated from national surveys or identified from the authors with or without a clear methodological approach. The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk reduction in Children and Adolescents (56) proposes some absolute values as diagnostic cut points: ≥ 130 mg/dL for high LDL levels; ≥ 100 mg/dL for high triglyceride level in children aged 0 to 9 years and ≥ 130 mg/dL in those aged 10–19 years; < 40 mg/dL for low HDL-c level. In addition, the expert panel recognizes the non-HDL cholesterol level (calculated by subtracting HDL-c to Tc plasma level) as a more predictive index of persistent dyslipidemia compared with Tc, LDL or HDL-c levels alone.

Hypertension is the last component of MetS definition. Over the past 20 years, the prevalence of hypertension and prehypertension are increasing because of the rise in obesity rates and, although elevated BP is the least common abnormal health factor in youth, its treatment may reduce the future CVD (57). The BP levels suggested in the analyzed MetS definitions are extremely variable and derived typically from cross-sectional data frequently based on a single BP measurement session, on a specific ethnicity and on different nutrition state of the

study cohort. Currently, there are still no data to identify a specific level of BP in childhood which leads to adverse CV outcome in adulthood; however, Flynn *et al*. (57) recently published the pediatric hypertension guideline, which is an update to the 2004 Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. One of the most significant changes in this guideline is the inclusion of only normal weight youth which allow us to obtain more reliable normative BP tables. Therefore, the authors define 'elevate BP' as a BP value ≥ 90th percentile to < 95th percentile in children aged 1–13 years while 120/<80 mmHg to 129/<80 mmHg in adolescents aged ≥ 13 years. In addition, this guideline includes a simplified table for initial BP screening proposing a set of age- and gender-specific absolute values of BP with a negative predictive value > 99%.

In the last two decades, several definitions of MetS have been proposed for the pediatric population; all of them agree on the defining components but differ in the suggested criteria for diagnosis. To date, there is not a univocal, internationally accepted pediatric MetS definition which is easily accessible in clinical practice and that guarantees a high and stability of the diagnosis. Contrary to adult definitions of MetS, every set of diagnostic criteria for childhood contains at least one cut-off value expressed as a percentile value. For this reason, the feasibility of a MetS definition in clinical practice relies on the availability of reference percentiles, while its reliability depends on the methodological approach to derive the reference curves or the cut-off values. Frequently, those reference percentiles are not provided by the authors or, when suggested, they are usually not specific for the patient's nationality/ethnicity or higher than those of adults.

Currently, the pediatrician and the pediatric endocrinologist look for a clear and easily accessible definition, which, however, guarantees a high sensitivity and specificity in diagnosis. On the contrary, many of the analyzed MetS definitions have a common feature: the scarce practicality and applicability in the clinical setting. In fact, the search for reference percentiles of each criterion is the first difficulty for the clinician. Ahrens *et al.* (14) tried to address this issue by providing the age-specific (2–10.9 years) reference percentiles for all the components of MetS (25, 30, 36, 41). Consequently, their definition seems more homogenous and balanced than the other ones but less handy too, although the authors proposed an online tool (https://www.bips-institut.de/en/research/software/mets-score.html. Accessed February 03, 2021) to assist the clinician in the diagnosis. However, this definition is inapplicable to adolescents due to the absence of age-specific reference percentile.

In a context where there is no age-, sex- and ethnic-specific reference percentiles and/or values, the set of diagnostic criteria defined by the IDF result in the most straightforward and easy to use in clinical practice. The IDF definition (7) has the unquestionable advantage of requiring measurements quickly accessible in clinical practice, without the adoption of multiple reference tables. That definition has the drawback to use modified adult criteria to assess the MetS prevalence in childhood; therefore, it would be desirable to validate a new version of the definition which includes the diagnostic cut-off points recently suggested by published guidelines (55, 56, 57) and that introduces the WHtR in place of the 90th percentile for WC.

Limitations and future directions

To our knowledge this review represents the first attempt to systematically analyze the diagnostic criteria for MetS, the methodology to select them and their feasibility and reliability in clinical practice. However, there are also some limitations. Despite performing a comprehensive search strategy, we included only two longitudinal study; consequently, we are unable to evaluate the long-term diagnostic stability of each MetS definition. In addition, as widely discussed above, the intrinsic ethnic differences in included studies populations make it difficult to compare the generic diagnostic performance of each definition. Further research is needed to propose age-, gender- and ethnic-specific reference values for each component of MetS and to clarify the predictive value of MetS, attaching major importance to the family history for obesity, diabetes or CVD (58).

Conclusion

In the last two decades, several definitions of MetS have been proposed for the pediatric population; all of them agree on the defining components but differ in the suggested criteria for diagnosis. Besides, frequently the reference values for these criteria are scarcely representative for the general pediatric population and are not enough to establish the global cardio-metabolic risk. To date, there is not a univocal internationally accepted definition of MetS that guarantees high sensitivity and stability of the diagnosis. The definition proposed by IDF results in the most

straightforward and easy to use in clinical practice, having the unquestionable advantage of requiring measurements quickly accessible in clinical practice, without the adoption of multiple reference tables. Further research is needed to validate a new version of such definition, which includes the diagnostic cut-off points recently suggested by published guidelines (55, 56, 57). Waiting for a definition that addresses these limitations, the pediatrician should focus the attention on the screening and treatment of the cardio-metabolic risk factors in each child with obesity, bearing in mind that failing to meet the criteria for Mets is not a synonym of healthy obesity (59, 60).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

The authors thank Dr Maria Pia Zangari for professional English editing.

References

1 Gregory JW. Prevention of obesity and metabolic syndrome in children. *Frontiers in Endocrinology* 2019 **10** 669. (https://doi.org/10.3389/fendo.2019.00669)

2 Moher D, Liberati A, Tetzlaff J, Altman DG & PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009 **6** e1000097. (https://doi.org/10.1371/journal.pmed.1000097)

3 Munn Z, Moola S, Lisy K, Riitano D & Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *International Journal of Evidence Based Healthcare* 2015 **13** 147–153. (https://doi.org/10.1097/XEB.0000000000000054)

4 McArthur A, Klugarova J, Yan H & Florescu S. Innovations in the systematic review of text and opinion. *International Journal of Evidence Based Healthcare* 2015 **13** 188–195. (https://doi.org/10.1097/XEB.0000000000000060)

5 Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J *et al*. Obesity and the metabolic syndrome in children and adolescents. *New England Journal of Medicine* 2004 **350** 2362–2374. (https://doi.org/10.1056/NEJMoa031049)

6 Goodman E, Daniels SR, Meigs JB & Dolan LM. Instability in the diagnosis of metabolic syndrome in adolescents. *Circulation* 2007 **115** 2316–2322. (https://doi.org/10.1161/CIRCULATIONAHA.106.669994)

7 Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J, Caprio S *et al*. The metabolic syndrome in children and adolescents – an IDF consensus report. *Pediatric Diabetes* 2007 **8** 299–306. (https://doi.org/10.1111/j.1399-5448.2007.00271.x)

8 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. *Archives of Pediatrics and Adolescent Medicine* 2003 **157** 821–827. (https://doi.org/10.1001/archpedi.157.8.821)

9 Ford ES, Ajani UA, Mokdad AH & National Health and Nutrition Examination. The metabolic syndrome and concentrations of C-reactive protein among U.S. youth. *Diabetes Care* 2005 **28** 878–881. (https://doi.org/10.2337/diacare.28.4.878)

10 de Ferranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW & Rifai N. Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. *Circulation* 2004 **110** 2494–2497. (https://doi.org/10.1161/01.CIR.0000145117.40114.C7)

11 Atabek ME, Pirgon O & Kurtoglu S. Prevalence of metabolic syndrome in obese Turkish children and adolescents. *Diabetes Research and Clinical Practice* 2006 **72** 315–321. (https://doi.org/10.1016/j.diabres.2005.10.021)

12 Agirbasli M, Cakir S, Ozme S & Ciliv G. Metabolic syndrome in Turkish children and adolescents. *Metabolism: Clinical and Experimental* 2006 **55** 1002–1006. (https://doi.org/10.1016/j.metabol.2006.03.009)

13 Invitti C, Maffeis C, Gilardini L, Pontiggia B, Mazzilli G, Girola A, Sartorio A, Morabito F & Viberti GC. Metabolic syndrome in obese Caucasian children: prevalence using WHO-derived criteria and association with nontraditional cardiovascular risk factors. *International Journal of Obesity* 2006 **30** 627–633. (https://doi.org/10.1038/sj.ijo.0803151)

14 Ahrens W, Moreno LA, Marild S, Molnar D, Siani A, De Henauw S, Bohmann J, Gunther K, Hadjigeorgiou C, Iacoviello L *et al*. Metabolic syndrome in young children: definitions and results of the IDEFICS study. *International Journal of Obesity* 2014 **38** (Supplement 2) S4–S14. (https://doi.org/10.1038/ijo.2014.130)

15 Yoshinaga M, Tanaka S, Shimago A, Sameshima K, Nishi J, Nomura Y, Kawano Y, Hashiguchi J, Ichiki T & Shimizu S. Metabolic syndrome in overweight and obese Japanese children. *Obesity Research* 2005 **13** 1135–1140. (https://doi.org/10.1038/oby.2005.134)

16 Park HS, Han JH, Choi KM & Kim SM. Relation between elevated serum alanine aminotransferase and metabolic syndrome in Korean adolescents. *American Journal of Clinical Nutrition* 2005 **82** 1046–1051. (https://doi.org/10.1093/ajcn/82.5.1046)

17 Vikram NK, Misra A, Pandey RM, Luthra K, Wasir JS & Dhingra V. Heterogeneous phenotypes of insulin resistance and its implications for defining metabolic syndrome in Asian Indian adolescents. *Atherosclerosis* 2006 **186** 193–199. (https://doi.org/10.1016/j.atherosclerosis.2005.07.015)

18 Cruz ML, Weigensberg MJ, Huang TT, Ball G, Shaibi GQ & Goran MI. The metabolic syndrome in overweight Hispanic youth and the role of insulin sensitivity. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 108–113. (https://doi.org/10.1210/jc.2003-031188)

19 Rodriguez-Moran M, Salazar-Vazquez B, Violante R & Guerrero-Romero F. Metabolic syndrome among children and adolescents aged 10–18 years. *Diabetes Care* 2004 **27** 2516–2517. (https://doi.org/10.2337/diacare.27.10.2516)

20 Fernandez JR, Redden DT, Pietrobelli A & Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. *Journal of Pediatrics* 2004 **145** 439–444. (https://doi.org/10.1016/j.jpeds.2004.06.044)

21 Katzmarzyk PT, Srinivasan SR, Chen W, Malina RM, Bouchard C & Berenson GS. Body mass index, waist circumference, and clustering of cardiovascular disease risk factors in a biracial sample of children and adolescents. *Pediatrics* 2004 **114** e198–e205. (https://doi.org/10.1542/peds.114.2.e198)

22 Katzmarzyk PT. Waist circumference percentiles for Canadian youth 11–18y of age. *European Journal of Clinical Nutrition* 2004 **58** 1011–1015. (https://doi.org/10.1038/sj.ejcn.1601924)

23 McCarthy HD, Jarrett KV & Crawley HF. The development of waist circumference percentiles in British children aged 5.0–16.9 y. *European*

Journal of Clinical Nutrition 2001 **55** 902–907. (https://doi.org/10.1038/sj.ejcn.1601240)
24 Eisenmann JC. Waist circumference percentiles for 7- to 15-year-old Australian children. *Acta Paediatrica* 2005 **94** 1182–1185. (https://doi.org/10.1111/j.1651-2227.2005.tb02071.x)
25 Nagy P, Kovacs E, Moreno LA, Veidebaum T, Tornaritis M, Kourides Y, Siani A, Lauria F, Sioen I, Claessens M *et al*. Percentile reference values for anthropometric body composition indices in European children from the IDEFICS study. *International Journal of Obesity* 2014 **38** (Supplement 2) S15–S25. (https://doi.org/10.1038/ijo.2014.131)
26 Ahrens W, Bammann K, Siani A, Buchecker K, De Henauw S, Iacoviello L, Hebestreit A, Krogh V, Lissner L, Marild S *et al*. The IDEFICS cohort: design, characteristics and participation in the baseline survey. *International Journal of Obesity* 2011 **35** (Supplement 1) S3–S15. (https://doi.org/10.1038/ijo.2011.30)
27 Asayama K, Hayashi K, Kawada Y, Nakane T, Uchida N, Hayashibe H, Kawasaki K & Nakazawa S. New age-adjusted measure of body fat distribution in children and adolescents: standardization of waist-hip ratio using multivariate analysis. *International Journal of Obesity and Related Metabolic Disorders* 1997 **21** 594–599. (https://doi.org/10.1038/sj.ijo.0800447)
28 Cole TJ, Bellizzi MC, Flegal KM & Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000 **320** 1240–1243. (https://doi.org/10.1136/bmj.320.7244.1240)
29 Vikram NK, Misra A, Dwivedi M, Sharma R, Pandey RM, Luthra K, Chatterjee A, Dhingra V, Jailkhani BL, Talwar KK *et al*. Correlations of C-reactive protein levels with anthropometric profile, percentage of body fat and lipids in healthy adolescents and young adults in urban North India. *Atherosclerosis* 2003 **168** 305–313. (https://doi.org/10.1016/s0021-9150(03)00096-0)
30 Peplies J, Jimenez-Pavon D, Savva SC, Buck C, Gunther K, Fraterman A, Russo P, Iacoviello L, Veidebaum T, Tornaritis M *et al*. Percentiles of fasting serum insulin, glucose, HbA1c and HOMA-IR in pre-pubertal normal weight European children from the IDEFICS cohort. *International Journal of Obesity* 2014 **38** (Supplement 2) S39–S47. (https://doi.org/10.1038/ijo.2014.134)
31 Styne DM. Childhood and adolescent obesity. Prevalence and significance. *Pediatric Clinics of North America* 2001 **48** 823–854, vii. (https://doi.org/10.1016/s0031-3955(05)70344-8)
32 American Academy of Pediatrics. National Cholesterol Education Program: report of the expert panel on blood cholesterol levels in children and adolescents. *Pediatrics* 1992 **89** 525–584.
33 Asayama K, Ozeki T, Sugihara S, Ito K, Okada T, Tamai H, Takaya R, Hanaki K & Murata M. Criteria for medical intervention in obese children: a new definition of 'obesity disease' in Japanese children. *Pediatrics International* 2003 **45** 642–646. (https://doi.org/10.1046/j.1442-200x.2003.01795.x)
34 Plasma lipid distributions in selected North American populations: the Lipid Research Clinics Program Prevalence Study. The Lipid Research Clinics Program Epidemiology Committee. *Circulation* 1979 **60** 427–439. (https://doi.org/10.1161/01.cir.60.2.427)
35 Alberti KG, Zimmet P & Shaw J. Metabolic syndrome – a new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabetic Medicine* 2006 **23** 469–480. (https://doi.org/10.1111/j.1464-5491.2006.01858.x)
36 De Henauw S, Michels N, Vyncke K, Hebestreit A, Russo P, Intemann T, Peplies J, Fraterman A, Eiben G, de Lorgeril M *et al*. Blood lipids among young children in Europe: results from the European IDEFICS study. *International Journal of Obesity* 2014 **38** (Supplement 2) S67–S75. (https://doi.org/10.1038/ijo.2014.137)
37 Hickman TB, Briefel RR, Carroll MD, Rifkind BM, Cleeman JI, Maurer KR & Johnson CL. Distributions and trends of serum lipid levels among United States children and adolescents ages 4–19 years: data from the Third National Health and Nutrition Examination Survey. *Preventive Medicine* 1998 **27** 879–890. (https://doi.org/10.1006/pmed.1998.0376)
38 NGHS Coordinating Center. *NHLBI Growth and Health Study (NGHS) Data Monitoring Report*. Baltimore: Maryland Medical Research, 1998.
39 Update on the 1987 Task Force Report on high blood pressure in children and adolescents: a working group report from the National High Blood Pressure Education Program. National High Blood Pressure Education Program Working Group on hypertension control in children and adolescents. *Pediatrics* 1996 **98** 649–658.
40 National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004 **114** (2 Supplement 4th Report) 555–576. (https://doi.org/10.1542/peds.114.2.S2.555)
41 Barba G, Buck C, Bammann K, Hadjigeorgiou C, Hebestreit A, Marild S, Molnar D, Russo P, Veidebaum T, Vyncke K *et al*. Blood pressure reference values for European non-overweight school children: the IDEFICS Study. *International Journal of Obesity* 2014 **38** (Supplement 2) S48–S56. (https://doi.org/10.1038/ijo.2014.135)
42 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* 2017 **390** 2627–2642. (https://doi.org/10.1016/S0140-6736(17)32129-3)
43 Gustafson JK, Yanoff LB, Easter BD, Brady SM, Keil MF, Roberts MD, Sebring NG, Han JC, Yanovski SZ, Hubbard VS *et al*. The stability of metabolic syndrome in children and adolescents. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 4828–4834. (https://doi.org/10.1210/jc.2008-2665)
44 Goran MI & Gower BA. Longitudinal study on pubertal insulin resistance. *Diabetes* 2001 **50** 2444–2450. (https://doi.org/10.2337/diabetes.50.11.2444)
45 Reinehr T. Metabolic syndrome in children and adolescents: a critical approach considering the interaction between pubertal stage and insulin resistance. *Current Diabetes Reports* 2016 **16** 8. (https://doi.org/10.1007/s11892-015-0695-1)
46 McCarthy HD. Body fat measurements in children as predictors for the metabolic syndrome: focus on waist circumference. *Proceedings of the Nutrition Society* 2006 **65** 385–392. (https://doi.org/10.1017/s0029665106005143)
47 Marcovecchio ML & Chiarelli F. Metabolic syndrome in youth: chimera or useful concept? *Current Diabetes Reports* 2013 **13** 56–62. (https://doi.org/10.1007/s11892-012-0331-2)
48 Freedman DS, Serdula MK, Srinivasan SR & Berenson GS. Relation of circumferences and skinfold thicknesses to lipid and insulin concentrations in children and adolescents: the Bogalusa Heart Study. *American Journal of Clinical Nutrition* 1999 **69** 308–317. (https://doi.org/10.1093/ajcn/69.2.308)
49 Spolidoro JV, Pitrez Filho ML, Vargas LT, Santana JC, Pitrez E, Hauschild JA, Bruscato NM, Moriguchi EH, Medeiros AK & Piva JP. Waist circumference in children and adolescents correlate with metabolic syndrome and fat deposits in young adults. *Clinical Nutrition* 2013 **32** 93–97. (https://doi.org/10.1016/j.clnu.2012.05.020)
50 Trandafir LM, Russu G, Moscalu M, Miron I, Lupu VV, Leon Constantin MM, Cojocaru E, Lupu A & Frasinariu OE. Waist circumference a clinical criterion for prediction of cardio-vascular complications in children and adolescences with overweight and obesity. *Medicine* 2020 **99** e20923. (https://doi.org/10.1097/MD.0000000000020923)
51 Staiano AE & Katzmarzyk PT. Ethnic and sex differences in body fat and visceral and subcutaneous adiposity in children and adolescents. *International Journal of Obesity* 2012 **36** 1261–1269. (https://doi.org/10.1038/ijo.2012.95)
52 Lo K, Wong M, Khalechelvam P & Tam W. Waist-to-height ratio, body mass index and waist circumference for screening paediatric cardio-metabolic risk factors: a meta-analysis. *Obesity Reviews* 2016 **17** 1258–1275. (https://doi.org/10.1111/obr.12456)

53 Tagi VM, Giannini C & Chiarelli F. Insulin resistance in children. *Frontiers in Endocrinology* 2019 **10** 342. (https://doi.org/10.3389/fendo.2019.00342)

54 Levy-Marchal C, Arslanian S, Cutfield W, Sinaiko A, Druet C, Marcovecchio ML, Chiarelli F, ESPE-LWPES-ISPAD-APPES-APEG-SLEP-JSPE & Insulin Resistance in Children Consensus Conference Group. Insulin resistance in children: consensus, perspective, and future directions. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 5189–5198. (https://doi.org/10.1210/jc.2010-1047)

55 American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in Diabetes-2020. *Diabetes Care* 2020 **43** S14–S31. (https://doi.org/10.2337/dc20-S002)

56 Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents & National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics* 2011 **128** (Supplement 5) S213–S256. (https://doi.org/10.1542/peds.2009-2107C)

57 Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK *et al*. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 2017 **140** e20171904. (https://doi.org/10.1542/peds.2017-1904)

58 Corica D, Aversa T, Valenzise M, Messina MF, Alibrandi A, De Luca F & Wasniewska M. Does family history of obesity, cardiovascular, and metabolic diseases influence onset and severity of childhood obesity? *Frontiers in Endocrinology* 2018 **9** 187. (https://doi.org/10.3389/fendo.2018.00187)

59 Corica D, Aversa T, Ruggeri RM, Cristani M, Alibrandi A, Pepe G, De Luca F & Wasniewska M. Could AGE/RAGE-related oxidative homeostasis dysregulation enhance susceptibility to pathogenesis of cardio-metabolic complications in childhood obesity? *Frontiers in Endocrinology* 2019 **10** 426. (https://doi.org/10.3389/fendo.2019.00426)

60 Corica D, Oreto L, Pepe G, Calabro MP, Longobardo L, Morabito L, Pajno GB, Alibrandi A, Aversa T & Wasniewska M. Precocious preclinical cardiovascular sonographic markers in metabolically healthy and unhealthy childhood obesity. *Frontiers in Endocrinology* 2020 **11** 56. (https://doi.org/10.3389/fendo.2020.00056)

Received 3 March 2021
Revised version received 22 May 2021
Accepted 1 June 2021

Author Queries

JOB NUMBER: 210238

JOURNAL: EJE

Q1 Please check and approve the title.
Q2 AQ: Please check and approve the author list.
Q3 AQ: Please check and approve the affiliation details.
Q4 AQ: Please check that only approved HUGO, MGI or ZFIN gene and protein nomenclature is used in your paper. For more details, see https://eje.bioscientifica.com/page/author/author-guidelines#genes and correct if necessary.
Q5 AQ: Please check and approve the identification of the section level headings.
Q6 AQ: Tables MUST be cited in strict sequential order, in the text the tables are cited out of order: please choose whether to re-number the tables or remove this citation.
Q7 AQ: We have been unable to find the DOI for these references; please provide if possible.