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Epidemiology of paediatric metabolic syndrome and type 2 diabetes mellitus

SARAH D DE FERRANTI, STAVROULA K OSGANIAN

Abstract

The epidemic in childhood obesity is a driving force behind the increase in paediatric metabolic syndrome, a collection of abnormalities that is associated in adults with increased risk for cardiovascular disease and type 2 diabetes mellitus. Although there is no clear consensus about the paediatric definition for metabolic syndrome, the prevalence of this syndrome is clearly rising. Children with metabolic syndrome are at increased risk for metabolic syndrome in adulthood. A late consequence of metabolic syndrome is type 2 diabetes, which increasingly affects adolescents. The rise in metabolic syndrome and type 2 diabetes in children is almost sure to lead to an increase in associated complications in young adulthood, including early cardiovascular disease. This epidemic will bear fruit in forthcoming decades, putting further stress on the healthcare system and probably leading to increased morbidity and a shorter lifespan for future generations.

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Key words: childhood, definitions, metabolic syndrome, obesity, type 2 diabetes mellitus, youth.

Introduction

The rise in rates of obesity in children has been accompanied by an increase in a number of associated metabolic abnormalities, known collectively as the metabolic syndrome, and in turn by an increase in adolescent type 2 diabetes. United States obesity rates in 6–19-year-olds have tripled since the 1960s¹ and up to 50% of people in select racial/ethnic groups may have a body mass index (BMI) at or above the 85th percentile.² Obesity plays a significant role in the development of metabolic syndrome and type 2 dia-

betes in children and adults,^{3–5,6} and central adiposity predisposes children to multiple metabolic risk factors.⁷

Metabolic syndrome is defined as a constellation of risk factors, including obesity, dyslipidaemia, impaired glucose metabolism and elevated blood pressure; all are major predictors for cardiovascular disease.^{8,9} Clustering of the major metabolic components has been demonstrated in youth,^{3,4,10} and a number of estimates of the prevalence of metabolic syndrome show a higher prevalence among obese youth. The adverse consequences of the obesity epidemic are beginning to manifest themselves as an increase in paediatric metabolic syndrome and the parallel and disturbing rise in the prevalence of adolescent type 2 diabetes. The epidemiology of paediatric metabolic syndrome, and of its worrying sequel, type 2 diabetes, are described below.

Epidemiology of paediatric metabolic syndrome

Definition

The metabolic syndrome was first identified by Reaven as Syndrome X; he described it as the co-existence of multiple metabolic derangements, including hyperinsulinaemia, glucose intolerance, hypertension, decreased levels of high-density lipoprotein (HDL) cholesterol and elevated levels of triglycerides.¹¹ For adults, three national expert committees, The World Health Organization (WHO),¹² the National Cholesterol Education Program–Third Adult Treatment Panel (NCEP ATP III)^{9,13,14} and the International Diabetes Federation (IDF)¹⁵ have developed clinical definitions of the metabolic syndrome (table 1). The American Heart Association (AHA) and National Heart, Lung, and Blood Institute (NHLBI) modified the original NCEP definition to conform with more recent standards on abnormal fasting glucose, lowering the criteria from 110 mg/dL to ≥ 100 mg/dL (6.1 mmol/L to > 5.6 mmol/L).¹³ All definitions include Reaven's original elements, yet the threshold values and the number and combinations of the risk factors required vary considerably, reflecting debate about metabolic syndrome among adult researchers.

There is no consensus definition for metabolic syndrome in childhood. Most commonly, modifications of the adult WHO and NCEP ATP III definitions (table 1) have been used in paediatric research (table 2).^{3,4} The majority of researchers agree that the paediatric definition should require the same risk factors as adults because of their basis in hard outcome data.^{4,16,17} However, the appropriate risk factor cut-offs for children remain uncertain. Most paediatric studies use age- and gender-specific percentiles from national reference data or study-specific distributions to define thresholds for abnormalities of the metabolic components. In a recent publication, Joffe and Janssen formalised this approach, by

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Table 1. Major definitions of metabolic syndrome in adults

World Health Organization ¹²	International Diabetes Federation ¹⁵	National Cholesterol Education Panel Adult Treatment Panel III ⁹	National Heart, Lung and Blood Institute/American Heart Association ¹⁹
<p>1 of the following:</p> <ul style="list-style-type: none"> ● Type 2 diabetes (fasting plasma glucose \geq 126 mg/dL or 2 hour post glucose load \geq 200 mg/dL) ● Impaired fasting glucose (fasting glucose from 110–125 mg/dL) ● Impaired glucose tolerance (2 hour post glucose load from 140–199 mg/dL) ● Insulin resistance (glucose uptake below the lowest quartile for the background population under investigation under hyperinsulinaemic, euglycemic conditions.) <p>And any 2 of the following:</p> <ul style="list-style-type: none"> ● SBP \geq 140 mmHg or DBP \geq 90 mmHg and/or antihypertensive medication ● Fasting triglycerides \geq 150 mg/dL and/or HDL Cholesterol $<$ 35 mg/dL in men or HDL Cholesterol $<$ 39 mg/dL in women ● BMI $>$ 30 kg/m² and/or waist:hip ratio $>$ 0.9 in men or $>$ 0.85 in women ● Urinary albumin excretion rate $= >$ 20 μg/min or albumin:creatinine ratio $= >$ 30 mg/g 	<p>Central obesity:</p> <ul style="list-style-type: none"> ● Waist circumference $>$ 94 cm in Europoid men or $>$ 80 cm in Europoid women with ethnicity-specific values for other groups <p>And any 2 of the following:</p> <ul style="list-style-type: none"> ● Fasting glucose \geq 100 mg/dL or previously diagnosed type 2 diabetes ● Systolic BP \geq 130 or DBP \geq 85 mmHg or treatment of previously diagnosed hypertension ● Fasting triglycerides \geq 150 mg/dL or specific treatment for this abnormality ● HDL cholesterol $<$ 40 mg/dL in men or $<$ 50 mg/dL in women or specific treatment for this abnormality 	<p>Any 3 of the following:</p> <ul style="list-style-type: none"> ● Fasting glucose \geq 110 mg/dL or drug treatment for elevated glucose ● SBP \geq 130 or DBP \geq 85 mmHg and/or drug treatment for hypertension ● Fasting triglycerides \geq 150 mg/dL or treatment with medication for this abnormality ● HDL cholesterol $<$ 40 mg/dL in men or $<$ 50 mg/dL in women or drug treatment for this abnormality ● Waist circumference \geq 102 cm in men or \geq 88 cm in women with lower thresholds for individual or ethnic groups prone to insulin resistance 	<p>Any 3 of the following:</p> <ul style="list-style-type: none"> ● Fasting glucose \geq 100 mg/dL or treatment for elevated glucose ● SBP \geq 130 or DBP \geq 85 mmHg or drug treatment for hypertension ● Triglycerides \geq 150 mg/dL or treatment for hypertriglyceridaemia ● HDL cholesterol $<$ 40 mg/dL for men, $<$ 50 mg/dL for women or drug treatment for low HDL ● Waist circumference \geq 102 cm for men, \geq 88 cm for women
<p>Key: SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; HDL = high-density lipoprotein</p> <p>To convert to mg/dL multiply by 0.0113 for triglycerides, 0.0555 for glucose, 0.0259 for total cholesterol, HDL and LDL</p>			

combining all National Health and Nutrition Examination Survey (NHANES) datasets (1988–1994, 1999–2000 and 2001–2002) to generate metabolic syndrome component growth curves that were then linked to adult cut-off points from the NCEP ATP III and the IDF definitions.¹⁸ Values of each element of metabolic syndrome for every survey participant were plotted along the gender-specific curves to determine whether they met criteria. Recently, the International Diabetes Federation (IDF) proposed its own paediatric definition of metabolic syndrome (table 3). It closely follows the adult IDF definition and cut-off points are identical to those used for adults,¹⁹ despite the more favourable distribution of lipid profiles and blood pressure normally found in childhood.

Regardless of the definition used, there is substantial instability in the designation for the individual adolescent: follow-up data from the Princeton School District Study revealed that approximately half of the adolescents diagnosed with metabolic syndrome at baseline no longer qualified for the diagnosis at later follow-up, regardless of

whether the IDF, ATP III or paediatric ATP III definition was met originally.²⁰ This may reflect the changes children go through during pubertal development; it may also indicate that our debated paediatric definitions of metabolic syndrome do not yet reliably reflect even mid-term cardiometabolic risk. Despite the nearly 30 years since Reaven's lecture on Syndrome X, there remains substantial controversy about metabolic syndrome as an independent clinical entity,^{21,22} and whether it is more informative to consider each risk factor individually. Paediatric metabolic syndrome is perhaps more heavily debated because of the issues outlined above, and because there are limited data linking paediatric metabolic syndrome directly to the development of adverse cardiovascular health outcomes.²³ However, some evidence supports the existence of metabolic syndrome in childhood.

Prevalence

Epidemiological studies in youth suggest that the syndrome does develop during childhood and adolescence and that

Table 2. Summary of epidemiologic studies of metabolic syndrome or risk factor clustering in youth

Author	Study population	Risk factor cut-offs	Definition	Prevalence
I. Population-based samples of children and adolescents				
de Ferranti ¹⁶ NHANES (1988–1994) NHANES (1999–2000)	Nationally representative sample of 12–19-year-old US adolescents 1,960 participants	<ul style="list-style-type: none"> ● => 75th percentile WC for age and sex of study cohort ● => 90th percentile SBP or DBP for age, sex and height¹²⁸ ● => 100 mg/dL TG ● < 45 mg/dL HDL in boys 15–19 years and < 50 mg/dL HDL for all others ● => 110 mg/dL fasting glucose 	3 or more criteria	<p><i>NHANES 1988–1994</i> Overall: 9.2% Males: 9.5% Females: 8.9% Non-Hispanic white: 10.9% Non-Hispanic black: 2.5% Mexican American: 12.9% At risk /overweight: 31.2%</p> <p><i>NHANES 1999–2000</i> Overall: 12.7% Males: 13.8% Females: 11.6% Non-Hispanic white: 12.5% Non-Hispanic black: 10.2% Mexican American: 16.9% At risk/overweight: 38.6%</p>
Duncan ²⁶ NHANES (1999–2000)	Nationally representative sample of 12–19-year-old US adolescents 991 participants	<ul style="list-style-type: none"> ● => 90th percentile WC for age and sex of study cohort ● => 90th percentile SBP or DBP for age, sex and height ● => 110 mg/dL TG ● => 40 mg/dL HDL ● => 110 mg/dL fasting glucose 	3 or more criteria	Overall: 6.4% Males: 9.1% Females: 3.7% Non-Hispanic white: 7.2% Non-Hispanic black: 5.1% Mexican American: 8.5% Overweight: 32.1%
Cook ¹⁷ NHANES III (1988–1994)	Nationally representative sample of 12–19-year-old US adolescents 2,430 participants	<ul style="list-style-type: none"> ● => 90th percentile WC for age and sex of study cohort ● => 90th percentile SBP or DBP for age, sex and height ● => 110 mg/dL TG ● => 40 mg/dL HDL ● => 110 mg/dL fasting glucose 	3 or more criteria	Overall: 4.2% Males: 6.1% Females: 2.1% Non-Hispanic white: 4.8% Non-Hispanic black: 2.0% Mexican American: 5.6% Overweight: 28.7%
Raitakari ²⁸ Cardiovascular Risk in Young Finns Study	Population-based cohort of 3–18-year-old Finnish children and adolescents 3,457 participants	Study cohort percentiles for age and sex <ul style="list-style-type: none"> ● => 75th percentile of sum of biceps, subscapular and triceps skinfolds ● => 75th percentile SBP ● => 75th percentile of LDL 	All 3 criteria	Overall: 3.1% Males: 3.56% Females: 2.64% Ages 3–6 Males: 2.69% Females: 2.21% Ages 9–12 Males: 3.48% Females: 2.80% Ages 15–18 Males: 4.49% Females: 2.92%
Jolliffe and Janssen, 2007 ¹⁸ NHANES (1999–2002)	Nationally representative sample of 12–20-year-old US adolescents	Extrapolated ATP III Extrapolated adult IDF definition	3 of 5 criteria High WC, plus 2 of 4 criteria	All: 7.6% Male: 8.2% Female: 7.0% Age 12–15: 7.7% Age 16–19: 7.7% Non-Hispanic white: 8.0% Non-Hispanic black: 6.4% Hispanic: 8.0% All: 9.6% Male: 9.4% Female: 9.7% Age 12–15: 9.0% Age 16–19: 10.2% Non-Hispanic white: 10.2% Non-Hispanic black: 6.9% Hispanic: 10.1%

continued

Table 2. Summary of epidemiologic studies of metabolic syndrome or risk factor clustering in youth (continued)

Author	Study population	Risk factor cut-offs	Definition	Prevalence
II. Community- or clinic-based samples of children and adolescents				
Retnakaran ³⁷	Community-based sample of Oji-Cree Canadian children aged 10–19-years-old 236 participants	<ul style="list-style-type: none"> ● => 90th percentile WC for age and sex ● => 90th percentile SBP or DBP for age, sex and height ● => 1.1 mmol/L TG ● HDL < 1.2 mmol/L in boys 15–19 years and HDL < 1.3 mmol/L in all others ● => 110 mg/dL fasting glucose 	3 or more criteria	Overall: 18.6% Males: 14.3% Females: 21.4%
Morrison ²⁹ National Heart, Lung and Blood Institute Growth and Health Study	School-based cohort of US black and white girls aged 9 and 10 years followed for 10 years 2,270 participants	<ul style="list-style-type: none"> ● > 88 cm WC ● >130 mmHg SBP or > 85 mmHg DBP ● >150 mg/dL TG ● < 50 mg/dL HDL-C ● => 110 mg/dL fasting glucose 	3 or more criteria	Ages 9–10 years Black girls: 0.2% White girls: 0.2% Ages 18–19 years Black girls: 3.5% White girls: 2.3%
Morrison ⁹⁷	School-based cohort, Princeton Lipid Research Clinic 1973–76 771 participants	<ul style="list-style-type: none"> ● BMI => 90th percentile ● => 110 mg/dL TG ● => 50 mg/dL HDL females ● => 40 mg/dL HDL males ● => 90th percentile SBP, DBP ● => 110 mg/dL fasting glucose 	3 or more criteria	Ages 6–19 years Overall: 4.0%
Braunschweig ³³	School-based US sample of urban African American children in grades 3–6 90 participants	<ul style="list-style-type: none"> ● => 90th percentile WC for age and sex ● => 90th percentile DBP or SBP for age, sex and height ● => 40 mg/dL HDL ● => 110 mg/dL TG ● => 110 mg/dL fasting glucose 	3 or more criteria	Overall: 5.6% Males: 5.0% Females: 4.0% Overweight: 13.8%
Rodriguez-Moran ³⁰	Community-based sample of 10–18 year old Mexican children and adolescents 965 participants	Study cohort percentiles for age and sex <ul style="list-style-type: none"> ● => 90th percentile BMI ● => 90th percentile TG ● => 90th percentile SBP or DBP ● => 110 mg/dL fasting glucose 	3 or more criteria	Overall: 6.5%
Goodman ³¹	School-based sample of white, black and Hispanic US adolescents aged 12–19 years 1,513 participants	<ul style="list-style-type: none"> ● => 102 cm WC in males and => 88 cm WC in females or => 95th percentile BMI for age and sex (WHO) ● => 85 mmHg DBP or => 130 mmHg SBP ● => 40 mg/dL HDL in males or => 50 mg/dL HDL in females (NCEP) ● => 35 mg/dL HDL in males or => 39 mg/dL HDL in females (WHO) ● => 150 mg/dL TG ● => 110 mg/dL fasting glucose ● => 75th percentile fasting insulin of study cohort (WHO) 	NCEP definition used any 3 or more criteria WHO definition required impaired fasting glucose, type 2 diabetes, or hyperinsulinaemia or plus any 2 of the other criteria	<i>Overall</i> NCEP: 4.2% WHO: 8.4% <i>Males</i> NCEP: 3.8% WHO: 7.5% <i>Females</i> NCEP: 4.7% WHO: 9.5% <i>OBESE</i> NCEP: 19.5% WHO: 38.9%
Lambert ²⁷ The Quebec Child and Adolescent Health and Social Survey	School-based sample of Canadian youth aged 9, 13 and 16 years 1,369 participants	Study cohort percentiles for age and sex (and height for BP) <ul style="list-style-type: none"> ● => 85th percentile BMI ● => 75th percentile SBP or DBP ● => 75th percentile TG ● => 25th percentile HDL ● => 75th percentile fasting insulin ● => 110 mg/dL fasting glucose 	Definition 1: Hyperinsulinaemia plus 2 or more risk factors Definition 2: Any 3 or more risk factors	<i>Definition 1</i> Overall: 11.5% <i>Males</i> Age 9 years: 10.7% Age 13 years: 11.9% Age 16 years: 12.2% <i>Females</i> Age 9 years: 12.0%

continued

Table 2. Summary of epidemiologic studies of metabolic syndrome or risk factor clustering in youth (continued)

Author	Study population	Risk factor cut-offs	Definition	Prevalence
				Age 13 years: 11.8% Age 16 years: 10.8% <i>Definition 2</i> Overall: 14.0% <i>Males</i> Age 9 years: 13.1% Age 13 years: 14.3% Age 16 years: 15.2% <i>Females</i> Age 9 years: 14.4% Age 13 years: 14.7% Age 16 years: 12.4%
Katzmarzyk ³⁹ Bogalusa Heart Study	School-based US cohort of 5–18-year-old children and adolescents 2,597 participants	Study cohort percentiles for age ● => 80th percentile SBP or DBP ● => 80th percentile LDL ● => 80th percentile TG ● => 20th percentile HDL ● => 80th percentile fasting insulin ● => 80th percentile fasting glucose	3 or more criteria	<i>Males</i> White: 18.2% Black: 17.3% <i>Females</i> White: 16.5% Black: 16.6%
Srinivasan <i>et al.</i> , 2002 ⁷ Bogalusa Heart Study	School-based US cohort of 8–17-year-old black and white children 745 participants	Study cohort percentiles for age, sex, race and study year ● => 75th percentile BMI ● => 75th percentile SBP or MAP ● => 75th percentile cholesterol to HDL ratio or TG to HDL ratio ● => 75th percentile fasting insulin	All 4 criteria	Overall: 3.6% No race or sex differences
Chen ³⁴ Bogalusa Heart Study	School-based cohort of 5–17-year-old US black and white children and adolescents 2,515 participants	Study cohort percentiles for age, race and sex ● => 75th percentile ponderal index (weight/height ³) ● => 75th percentile SBP or DBP ● => 75th percentile TG and/or HDL ● => 75th percentile fasting insulin	All 4 criteria	Ages 5–11 years White: 4.8% Black: 3.7% Ages 12–17 years White: 3.0% Black: 2.7%
Freedman ⁴⁰ Bogalusa Heart Study	School-based US cohort of 5–17-year-old black and white children and adolescents 9,167 participants	Study cohort percentiles for age, race and sex ● => 95th percentile SBP or DBP ● => 130 mg/dL TG ● => 130 mg/dL LDL ● < 35 mg/dL HDL ● => 95th percentile fasting insulin	3 or more criteria	Ages 5–10 years Overall: 2% Overweight: 11% Ages 11–17 years Overall: 2% Overweight: 10% No race differences
Chu ³² Taipei Children's Heart Study	School-based sample of 12–16-year-old Chinese adolescents from Taiwan 1,366 participants	Study cohort percentiles for age and sex ● => 90th percentile of SBP or DBP ● => 90th percentile TG or TC ● => 90th percentile of fasting glucose	All 3 criteria	<i>Non-obese</i> Males: 0.5% Females: 0.3% <i>Obese</i> Males: 2.0% Females: 4.0%
III. School or clinic-based samples of overweight or obese children and adolescents				
Viner ⁴¹	Clinic-based sample of 2–18-year-old youth undergoing obesity evaluation in the UK 103 participants	● => 95th percentile BMI for age and sex ¹³⁰ ● Abnormal glucose homeostasis (fasting hyperinsulinaemia prepubertal => 15 µU/mL, mid puberty => 30 µU/mL; post pubertal => 20 mU/L; impaired fasting glucose => 110 mg/dL; impaired glucose tolerance min => 140 mg/dL) ● => 95th percentile SBP or DBP for age and sex ¹³¹ ● Dyslipidaemia (elevated triglycerides >= 1.75 mM/l, low HDL <=0.9 mM/l, high TC >=95th percentile)	3 or more criteria	Obese: 33% Males: 34% Females: 33% 12–18 years: 36% 2–11 years: 30% White: 37% Black: 13% Asian: 22%

continued

Table 2. Summary of epidemiologic studies of metabolic syndrome or risk factor clustering in youth (continued)

Author	Study population	Risk factor cut-offs	Definition	Prevalence
Invitti ³⁸	Clinic-based sample of 6–16-year-old obese Italian youth undergoing an evaluation in Italy 588 participants	<ul style="list-style-type: none"> ● Glucose intolerance (fasting glucose \geq 100 mg/dL and/or 2 hour post load glucose \geq 140 mg/dL) and/or insulin resistance defined by being \geq the median of the Tanner stage (I-V) specific HOMA-IR values (2.4, 2.8, 3.0, 4.1, or 3.0) ● BMI or waist circumference \geq 97th percentile of a control population ● HDL cholesterol \geq 5th percentile of a control population ● triglycerides \geq 95th percentile of a control population ● blood pressure \geq 95th percentile of a control population 	Glucose intolerance/ Insulin resistance plus 2 or more of the other factors	Obese: 23.3% BMI tertiles I z= 2.0–3.5: 16% II z= 3.6–4.1: 23% III z= 4.2–6.2: 31% No sex differences
Yoshinaga ³⁵	School-based sample of 6–11-year-old Japanese overweight or obese youth 471 participants	<ul style="list-style-type: none"> ● \geq 90th percentile WC for age and sex of study cohort ● \geq 120 SBP or \geq 70 mmHg DBP for grades 1–3 or \geq 130 SBP or \geq 80 mmHg DBP for grades 4–6 ● $<$ 40 mg/dL HDL ● $>$ 120 mg/dL TG ● $>$ 100 mg/dL fasting glucose 	3 or more criteria	Obese: 17.7% Overweight: 8.7%
Sherry ³⁶	Clinic-based sample of obese 2–10-year-old US children of Dominican ancestry 193 participants	<ul style="list-style-type: none"> ● Z score $>$ 2.0 for BMI in study cohort ● $<$ 40 mg/dL HDL ● $>$ 150 mg/dL TG ● \geq 90th percentile SBP or DBP for age, sex, height¹²² ● \geq 100 mg/dL fasting glucose 	BMI plus any 2 of the other risk factors	Obese: 14.3%
Cruz ⁴³	Clinic-based US sample of obese 8–13-year-old Hispanic youth with a family history of type 2 diabetes 126 participants	<ul style="list-style-type: none"> ● \geq 90th percentile WC for age, gender and ethnicity ● \geq 90th percentile SBP or DBP for age, sex and height ● \geq 90th percentile TG for age and sex ● \geq 10th percentile HDL for age and sex ● OGTT 2 hour glucose 140–199 mg/dL 	3 or more criteria	Obese: 30% No sex differences
Weiss ⁴²	Clinic-based US sample of obese 4–20-year-old children and adolescents 439 participants	<ul style="list-style-type: none"> ● $>$ 97th percentile BMI or Z score \geq 2.0 in study cohort ● $>$ 95th percentile TG for age, sex, race (NGHS) ● $<$ 5th percentile HDL for age, sex, race (NGHS) ● OGTT 2 hour glucose 140–199 mg/dL ● $>$ 95th percentile SBP or DBP for age, sex, height 	3 or more criteria	Moderately obese: 38.7% Severely obese: 49.7%
Csabi ⁴⁵	Hospital-based sample of 8–18-year-old Hungarian children and adolescents 180 obese children	<ul style="list-style-type: none"> ● $>$ 110 mg/dL TG ● $>$ 200 mg/dL TC ● $<$ 35 mg/dL HDL ● OGTT 2 hour glucose 140–200 mg/dL ● $>$ 18.7 μU/mL fasting insulin 	4 or more criteria	Obese: 8.9%

Key: TG = triglycerides; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TC = total cholesterol; WC = waist circumference; OGTT = oral glucose tolerance test; WHO = World Health Organization; NCEP = National Cholesterol Education Program; ATP = Adult Treatment Panel; IDF = International Diabetes Federation; HOMA = homeostasis model assessment

CDC growth charts were used to define percentiles of body mass index for age and sex unless otherwise noted.

Adapted from Osganian SK, de Ferranti SD. Complications of Obesity: Metabolic Syndrome. Nutrition in Pediatrics 4th ed. Eds. Walker WA, Watkins JB, Duggan C. Hamilton: BC Becker, in press.

Table 3. International Diabetes Foundation definition of paediatric metabolic syndrome¹⁹

Ages 6–< 10 years	Ages 10–< 16 years	Age > 16 years: Use adult criteria of International Diabetes Federation ²⁰
Obesity => 90th percentile by waist circumference Metabolic syndrome not diagnosed, but heightened clinical suspicion for family history of: <ul style="list-style-type: none"> ● Metabolic syndrome ● Type 2 diabetes mellitus ● Dyslipidaemia ● Cardiovascular disease ● Hypertension ● Obesity 	Obesity => 90th percentile by waist circumference Any 2 or more of the following: <ul style="list-style-type: none"> ● Fasting glucose => 100 mg/dL (OGTT recommended) or known type 2 diabetes ● SBP => 130 or DBP => 85 mmHg ● Fasting triglycerides => 150 mg/dL ● HDL cholesterol < 40 mg/dL 	Central obesity <ul style="list-style-type: none"> ● Waist circumference > 94 cm in Europoid men or > 80 cm in Europoid women with ethnicity-specific values for other groups And any 2 of the following: <ul style="list-style-type: none"> ● Fasting glucose => 100 mg/dL or previously diagnosed type 2 diabetes ● Systolic BP => 130 or DBP => 85 mmHg or treatment of previously diagnosed hypertension ● Fasting triglycerides => 150 mg/dL or specific treatment for this abnormality ● HDL cholesterol < 40 mg/dL in men or < 50 mg/dL in women or specific treatment for this abnormality
Key: OGTT = oral glucose tolerance test; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high-density lipoprotein To convert to mg/dL multiply by 0.0113 for triglycerides, 0.0555 for glucose, 0.0259 for total cholesterol, HDL and LDL		

the prevalence is higher in overweight youth (table 2).^{3,4} Several analyses of NHANES, a nationally representative sample of US adolescents and adults, describe the prevalence of metabolic syndrome in adolescents as substantially lower than the prevalence in adults.^{17,24,25} Estimates of prevalence vary necessarily depending on the definition used. Using the 1988–1994 dataset, we estimated that the prevalence of metabolic syndrome was 9.2% overall, with a higher prevalence in males compared to females, and in Mexican-Americans and whites compared to non-Hispanic blacks.²⁵ In the more recent 1999–2000 dataset, we found a 38% increase in prevalence; 12.7% of 12–19-year-olds had metabolic syndrome, with similar subgroup distributions to the earlier study.¹⁶ Cook, Duncan and colleagues analysed the NHANES data using more restrictive cut-offs for waist circumference, triglycerides and HDL, and reported a lower overall prevalence of the syndrome and for subgroups, with similar subgroup patterns (table 2).^{17,26} The prevalence estimates of Jolliffe and Janssen generated using their extrapolated NHANES risk factor curves showed similar estimates, and also found a nearly two-fold increase from the earlier to later dataset.¹⁸ National survey data have shown a higher prevalence of metabolic syndrome in overweight or obese children of all ages: the prevalence is 32.1% among adolescents with a BMI at or above the 95th percentile for age and gender, compared to 7.1% among those with BMI 85th–< 95th percentile, and 0.1% among those with a BMI < 85th percentile.²⁶

In addition to national survey data, a number of reports of community- and school-based samples describe paediatric metabolic syndrome. Although variability exists between studies (table 2), the overall prevalence of metabolic syndrome or risk factor clustering is generally low;^{7,27–36}

the higher prevalence (18.6%) of metabolic syndrome in a community-based sample of Oji-Cree children is thought to be consistent with an excess burden of cardiovascular risk factors in Native Canadian children.³⁷ Younger children have a similar prevalence of metabolic syndrome or risk factor clustering when compared to older adolescents;^{27,28,34} gender and racial/ethnic differences are not consistently observed in smaller studies.^{17,26–29,31,34,37–40} Overweight adolescents are affected strikingly more often in community-based and clinic-based samples,^{38,41–43} and the more severely obese^{38,42} are the most affected (nearly 50% among youth with BMI z-score > 2.5).

The variability in the prevalence across studies is due, at least in part, to differences in the definition used. In a school-based adolescent sample the prevalence was approximately twice as high when the WHO definition was used, compared to the NCEP definition in the group as a whole, and for subgroups, although missing data on blood pressure probably affected the analysis.³¹ Another comparison of different definitions using community- and school-based cohorts of preadolescent girls demonstrated poor agreement among the definitions.⁴⁴ The Bogalusa Heart Study also reported large differences in the prevalence of risk factor clustering, depending on the type and number of criteria used.^{7,34,39,40} Studies that do not include a measure of adiposity in the definition^{32,45} or that require more than three criteria^{7,34,45} report a lower prevalence; the use of internal study percentiles leads to higher estimates.

Obesity as a risk factor for paediatric metabolic syndrome

Obesity is an accepted major risk factor for metabolic abnormalities^{40,46–49} and metabolic syndrome in both children and

adults.^{10,50-53} In the Bogalusa Heart Study, children with BMI \geq 85th percentile were more likely to have elevated systolic and diastolic blood pressure, triglycerides and insulin, and depressed HDL, as well as more than one risk factor, compared to non-overweight children.⁴⁰ Waist circumference showed the most consistent and the strongest association with insulin levels and adverse lipid levels.^{48,49} In a sample of younger children, Maffeis found similar associations with adiposity, as measured by waist circumference, but – interestingly – independent of BMI.⁴⁷ This supports the association between central adiposity and cardiometabolic risk factors, probably due to excess visceral fat.^{54,55} Longitudinal studies confirm the importance of childhood obesity in predicting metabolic syndrome in young adulthood. The Bogalusa Heart Study demonstrated that childhood obesity was the strongest predictor of adult metabolic syndrome: youth in the highest versus lowest quartile of BMI were 11.7 times (95% confidence intervals [CI] 3.4–39.7) more likely to develop risk factor clustering in adulthood.⁷ Another study found a three-fold increase in adult metabolic syndrome in those who were overweight as children.⁵⁶

It is not clear whether the influence of obesity is entirely or only in part accounted for by insulin resistance.⁵ Many studies support the importance of insulin resistance. Serum insulin correlated with the typical metabolic components in a cohort of Finnish children and young adults,⁵⁷ and also in a group of obese adolescents (BMI > 97th percentile).⁴² Among Hispanic children, insulin sensitivity decreased with increasing numbers of metabolic components, while fat mass by dual energy X-ray absorptometry (DEXA) did not change.⁴³

Similar associations have been observed in prospective studies. Bogalusa Study subjects with insulin levels consistently in the highest quartile compared to those in the lowest quartile showed higher BMI (+9 kg/m²), triglycerides (+58 mg/dL [0.7 mmol/L]), LDL cholesterol (+11 mg/dL [0.3 mmol/L]), systolic blood pressure (+7 mmHg) and diastolic blood pressure (+3 mmHg) and lower levels of HDL cholesterol (-4 mg/dL [0.1 mmol/L]) compared to adults.⁵⁸

In the Young Finns cohort, fasting insulin at baseline predicted the subsequent identification of the combination of high triglycerides, low HDL-cholesterol and high systolic blood pressure at six years of follow-up, even after adjusting for baseline obesity and changes in obesity status over time.⁵⁹

In contrast, other studies have found that adiposity has a stronger contribution to clustering of risk factors than insulin resistance, and the effect of insulin resistance is accounted for by obesity. In a school-based sample, both insulin and BMI were strongly associated with clustering when analysed individually: however, the independent contribution of adiposity defined by BMI (odds ratio [OR]=2.8; 95% CI 1.9–3.2) was stronger than that of fasting insulin (OR=1.4; 95% CI 1.0–2.0) when these measures were modelled simultaneously.²⁷ The Bogalusa Heart Study found that the increased risk for developing clustering as an adult was independently associated with childhood BMI but not with fasting insulin.⁷ These findings suggest that more than one pathophysiological process may account for the development of paediatric metabolic syndrome.

Epidemiology of type 2 diabetes mellitus

Definition

Type 2 diabetes is a serious adverse consequence of obesity and paediatric metabolic syndrome, more likely to manifest in adolescence and early adulthood than clinical atherosclerotic disease. In contrast to paediatric metabolic syndrome, there is less controversy about the definition of type 2 diabetes. The American Diabetes Association defines diabetes as being present if one of three criteria are present: 1) a casual plasma glucose of > 200 mg/dL (11.1 mmol/L) in someone with symptoms of diabetes; 2) fasting (eight-hour) plasma glucose of \geq 126 mg/dL (7.0 mmol/L); or 3) two-hour plasma glucose of \geq 200 mg/dL (11.1 mmol/L) as part of an oral glucose tolerance test, with a glucose load of 1.75 g/kg to a maximum of 75 gm.⁶⁰ This dosing is used for children, although the precise paediatric dose for provocative glucose testing is not well validated.⁶¹ In most cases, type 2 diabetes does not, at least initially, require insulin therapy for survival; it involves insulin resistance and only relative insulin deficiency, and does not demonstrate autoimmune damage to the islet cells. The diagnostic criteria for type 2 diabetes are the same for children and adults,⁶² yet the use of these adults cut-off points has not been demonstrated by outcomes-based research in children.⁶¹

Although diagnosing diabetes is relatively straightforward, determining the type of diabetes is clinically important and not entirely evident. Diabetic ketoacidosis (DKA), the classic presentation of type 1 diabetes, is increasingly seen in type 2 diabetics of all ages, including adolescents; this presentation may run in families. Some type 1 diabetics are overweight, the classic body habitus for type 2 diabetes. The most reliable way to determine type is to perform blood testing: children with elevated fasting C-peptide and negative antibodies to islet cells or glutamic acid decarboxylase are generally designated as type 2 diabetics, although the absence of antibodies can be deceptive in non-white populations.

Prevalence

Obesity is a major risk factor for the development of type 2 diabetes in adults and children, and recent epidemiological investigations suggest an increase in type 2 diabetes in youth concomitant with the rise in obesity,^{6,62-65} both as a proportion of childhood diabetes, and overall. The prevalence of all types of diabetes in US adolescents was estimated at 0.41% (95% CI 0–0.86%) from the NHANES III (1988–1994) dataset;⁶⁶ this survey took place early in the increase in paediatric obesity, and before the rise in case reports of type 2 diabetes. A similar trend has been observed among Japanese schoolchildren; the prevalence in school-aged children increased 10-fold, and among adolescents nearly doubled, between 1976–1980 and 1991–1995.⁶⁷ The rate of type 2 diabetes was high in US adolescents compared to younger children, making up 33% of incident diabetes, and was disproportionately greater among African American youth, Mexican Americans,⁶⁸ and Native Americans.⁶⁹

Type 2 diabetes had previously been thought to account for less than 5% of all childhood diabetes; however, recent case series suggest a higher incidence of 29% of all diabetes

diagnoses.⁶³ United States data from NHANES 1999–2002 identified 0.5% of 12–19-year-olds as having diabetes, and reported that 29% of these adolescents probably had type 2.⁷⁰ Estimates from National Health Interview Survey data suggested 0.22% of the 2005 United States population aged 2–20 years (176,500 paediatric-aged patients) had type 1 or type 2 diabetes.⁷¹ Because of concerns about the accuracy of estimates based on the National Health Interview Survey data, a population-based study was initiated to estimate the incidence of paediatric type 2 diabetes in the US in 2002–2003; this demonstrated an incidence of 8.1/100,000 in 10–14-year-olds and 11.8/100,000 in 15–19-year-olds.⁷²

Smaller studies taking participants from clinical practice demonstrate higher rates of paediatric type 2 diabetes than the population-based surveys. Pinhas-Hamiel⁷³ found a 10-fold increase in the diagnosis of type 2 diabetes at the Children's Hospital Medical Center of Cincinnati, from 2–4% prior to 1992 to 16% of all patients in 1994. A clinic-based report of 112 obese adolescents (BMI > 95th percentile) aged 11–18 years who had an OGTT, found that 21% had impaired glucose tolerance and 4% had silent type 2 diabetes.⁷⁴ In that study, all children with type 2 diabetes were black or Hispanic, whereas about half of children with impaired glucose tolerance were black or Hispanic and half were white. Results from a school-based survey of Canadian Native youths showed an overall prevalence of newly diagnosed type 2 diabetes of 3.6%.^{75,76} The available data are limited because of an inability to detect asymptomatic diabetes (present in up to 50% of children with diabetes) in series in which children are not actively screened,⁶² or because studies have been conducted with single race/ethnic groups, primarily Native American youth. Thus, the prevalence estimates vary from 0.05% to 5%, with a higher prevalence among older adolescents and obese youth.^{77,78}

The smaller studies demonstrate the following characteristics of paediatric patients with type 2 diabetes: they are likely to be female and obese, to have polycystic ovary syndrome⁷⁹ and a family history of diabetes – between 74% and 100% of children with type 2 diabetes have a first- or second-degree relative with the diagnosis.⁷⁴ The overall prevalence of type 2 diabetes in the paediatric age range is low relative to the prevalence in adults, but is probably increasing, particularly in at-risk populations.

Adverse health outcomes

The adverse health outcomes associated with metabolic syndrome and type 2 diabetes in adults are well known. Several large prospective cohort studies have shown that metabolic syndrome doubles the relative risk for atherosclerotic cardiovascular disease events,^{80–85} as well summarised by a recent meta-analysis,⁸⁶ and confers a nearly seven-fold increased risk of type 2 diabetes.⁸² Diabetes mellitus is associated with serious microvascular and macrovascular complications, leading to chronic disability from blindness, renal disease, amputations, stroke and ischaemic heart disease, and premature death.^{6,70}

The longer-term health implications of paediatric metabolic syndrome and type 2 diabetes are still unknown. Short-term co-morbidities for children and adolescents as well as

for adults with metabolic syndrome include polycystic ovary syndrome (PCOS) and non-alcoholic fatty liver disease (NAFLD). PCOS is being diagnosed at higher rates in children with the metabolic syndrome and metabolic abnormalities,^{87,88} and NAFLD has been estimated to affect 22.5% to 52.8% of obese children.⁸⁹ The available data also suggest that metabolic syndrome in youth can have significant long-term health consequences, with potential for an earlier presentation of cardiovascular disease and type 2 diabetes.

Pathology and pre-clinical disease studies support the association between metabolic syndrome and cardiovascular disease. Obesity, a major abnormality underlying metabolic syndrome and obesity, is associated with early pathological evidence of atherosclerotic lesions. This is demonstrated by the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study⁹⁰ and the Bogalusa study.⁹¹ The extent of lesions in the aorta and coronary arteries was greater with increasing number of metabolic risk factors and with the presence of the metabolic syndrome ($r=0.70$; $p<0.001$). Carotid artery intima-medial thickness (IMT), a subclinical marker of atherosclerosis and predictor of adult coronary artery events, was greater in young adulthood in those with worse childhood cardiovascular risk factor profiles in the Bogalusa Heart Study.⁹² The odds ratio of being in the highest quartile of carotid IMT compared to the lower three quartiles was 1.25 (95% CI 1.01–1.54) for every unit increase in BMI, while higher HDL levels were protective. The Cardiovascular Risk in Young Finns Study, similarly, found that childhood cardiovascular risk factor levels were significantly associated with increased carotid IMT in young adulthood.⁹³ Likewise, having more favourable levels of metabolic syndrome variables in childhood can be beneficial in adulthood: mean carotid IMT values in adulthood decreased significantly as the number of risk variables in the lowest quartiles in childhood increased (p for trend = 0.013).⁹⁴ Carotid stiffness has been shown to be significantly higher in obese children with metabolic syndrome compared to those without metabolic syndrome.⁹⁵

The occurrence of risk factor clustering in childhood is also more likely to be maintained into adulthood. Limited prospective data have also shown that clustering of metabolic risk factors in childhood tracks into adulthood and predicts the development of metabolic syndrome in adulthood. In the Bogalusa Heart Study, a multiple risk index was shown to track significantly over an eight-year follow-up period in all race-sex groups (correlations ranged from 0.54 to 0.67). The magnitude of the overall multiple risk index tracking correlation ($r=0.64$) was significantly stronger than the individual risk factor correlations ($r=0.34$ to 0.57). Among subjects who were in the highest quintile of the multiple risk index at baseline, 61% remained there eight years later.⁹⁶ Furthermore, after an average follow-up period of 15.8 years, there was a significant positive relationship between childhood and adulthood clustering of cardiovascular risk factor variables. Children with clustering of three or more versus fewer than three risk factor variables had a nearly three-fold higher prevalence of metabolic syndrome in adulthood (12.9% vs. 4.6%, respectively; $p=0.005$).⁹⁴ The Princeton Lipid Research Clinics Prevalence Study demon-

strated that children with metabolic syndrome¹⁷ were six times more likely to have metabolic syndrome as adults and more than 14 times more likely to develop cardiovascular disease.⁹⁷

As described above, the increase in type 2 diabetes appears to be quite strongly linked to overweight, and to the physiological conditions present in the metabolic syndrome. In fact, the majority of youth with type 2 diabetes are overweight or obese at diagnosis.^{62,63} Although much is known about the cardiovascular risk for adults with type 2 diabetes, comparatively little is known about the long-term health of children with this diagnosis. Several studies have demonstrated that vascular function is compromised in children with type 1 diabetes.^{98,99} One study of Hispanic children with type 2 diabetes demonstrated increased flow velocity compared to lean children in response to vascular testing, although the percent increase in brachial artery diameter did not differ between the two groups.¹⁰⁰ According to limited data, adults diagnosed with type 2 diabetes in childhood may have poor outcomes: one small study found 9% mortality, along with significant morbidity (6% on dialysis).¹⁰¹ Large long-term follow-up studies of adults diagnosed with type 2 diabetes in childhood are needed.

Screening

Although paediatric metabolic syndrome and type 2 diabetes are more frequently found in association with excess weight, fortunately not all overweight adolescents develop these conditions. However, because of the risks associated with metabolic syndrome and type 2 diabetes (described above), obese youth are a high-risk population who should be the target for screening, prevention and intervention.^{3,4,10} Guidelines comparable to those for adults (NCEP ATP III) have not been agreed upon. Yet the available data suggest that overweight and obese children, as well as those with other risk factors (family history, chronic steroid use etc), should be carefully evaluated for components of the metabolic syndrome, and for the short-term consequence of metabolic syndrome, type 2 diabetes mellitus. Clinicians should assess metabolic risk factors, including blood pressure, fasting glucose and possibly insulin and HbA_{1C}, fasting lipids, and should assess the subject for the complications of obesity, including liver enzymes for NAFLD and a history of irregular menstrual periods, acne and hirsutism for PCOS in adolescent girls.¹⁰²

Screening for diabetes should generally be performed in children with a BMI > 85th percentile in the presence of a family history of type 2 diabetes and the following risk factors: 1) signs of insulin resistance (acanthosis nigricans) or conditions associated with insulin resistance; 2) ethnic background at high risk such as African American, Hispanic, Native American; and 3) clinical suspicion. Screening should occur every two years, beginning at puberty or age 10 years, and probably can be accomplished with fasting glucose; it may be investigated further with fasting insulin, haemoglobin A_{1C} and two-hour glucose tolerance testing, depending on clinical suspicion. The exact method by which to screen for type 2 diabetes is complicated by the fact that 30% of adults with diabetes evident on oral glucose tolerance testing do

not have fasting glucose levels that would indicate frank diabetes by non-provocative testing (fasting serum glucose).¹⁰³

Summary and future directions

The high prevalence of metabolic syndrome and type 2 diabetes in obese youth, the tendency for risk factors in childhood to track into adulthood and the increased association of metabolic risk factors with subclinical markers of atherosclerotic disease underscore the importance of defining and better understanding the longer-term health implications of these conditions in children and adolescents. A clinically useful consensus definition of paediatric metabolic syndrome and national guidelines are needed for proper screening, evaluation and treatment of children at risk for metabolic syndrome and type 2 diabetes.^{3,4,10} Additional research is also needed to understand the pathophysiology of the syndrome, including why some overweight children do not go on to develop metabolic syndrome or type 2 diabetes, and to identify and evaluate new treatment strategies. Improved understanding of the pathophysiology may provide insights into a single therapy that can target a common aetiological factor and affect multiple risk factors simultaneously,⁵ and prevent progression to type 2 diabetes. Better understanding of the risks associated with a childhood diagnosis of type 2 diabetes is crucial in order to help with primary prevention of diabetes and secondary prevention of cardiovascular complications. The single most effective therapy for prevention and treatment, and the one most difficult to implement, is likely to be lifestyle modification aimed at weight loss and improving cardiovascular risk factors.

Conflicts of interest statement

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