Epidemiology of paediatric metabolic syndrome and type 2 diabetes mellitus

SARAH D DE FERRANTI, STAVROULA K OSGIANIAN

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 of 6–19-year-olds have tripled since the 1960s and up to 50% of people in select racial/ethnic groups may have a body mass index (BMI) at or above the 85th percentile. Obesity plays a significant role in the development of metabolic syndrome and type 2 diabetes in children and adults, and central adiposity predisposes children to multiple metabolic risk factors.

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. Clustering of the major metabolic components has been demonstrated in youth, 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. For adults, three national expert committees, The World Health Organization (WHO), the National Cholesterol Education Program–Third Adult Treatment Panel (NCEP ATP III) and the International Diabetes Federation (IDF) 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). 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). 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. 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, Jolliffe and Janssen formalised this approach, by
Table 1. Major definitions of metabolic syndrome in adults

<table>
<thead>
<tr>
<th>World Health Organization</th>
<th>International Diabetes Federation</th>
<th>National Cholesterol Education Panel Adult Treatment Panel III</th>
<th>National Heart, Lung and Blood Institute/American Heart Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 of the following:</td>
<td>Central obesity:</td>
<td>Any 3 of the following:</td>
<td>Any 3 of the following:</td>
</tr>
<tr>
<td>● Type 2 diabetes (fasting plasma glucose ≥ 126 mg/dL or 2 hour post glucose load ≥ 200 mg/dL)</td>
<td>● Waist circumference &gt; 94 cm in Europoid men or &gt; 80 cm in Europoid women with gender-specific values for other groups</td>
<td>● Fasting glucose ≥ 110 mg/dL or drug treatment for elevated glucose</td>
<td>● Fasting glucose ≥ 100 mg/dL or treatment for elevated glucose</td>
</tr>
<tr>
<td>● Impaired fasting glucose (fasting glucose from 110–125 mg/dL)</td>
<td>● Systolic BP ≥ 130 or DBP ≥ 85 mmHg or treatment for previously diagnosed type 2 diabetes</td>
<td>● SBP ≥ 130 or DBP ≥ 85 mmHg and/or drug treatment for hypertension</td>
<td>● SBP ≥ 130 or DBP ≥ 85 mmHg and/or treatment for hypertension</td>
</tr>
<tr>
<td>● Impaired glucose tolerance (2 hour post glucose load from 140–199 mg/dL)</td>
<td>● Fasting triglycerides ≥ 150 mg/dL or treatment with medication for this abnormality</td>
<td>● Fasting triglycerides ≥ 150 mg/dL or treatment with medication for this abnormality</td>
<td>● Triglycerides ≥ 150 mg/dL or treatment for hypertriglyceridaemia</td>
</tr>
<tr>
<td>● Insulin resistance (glycose uptake below the lower quartile for the background population under investigation under hyperinsulinaemic, euglycemic conditions.)</td>
<td>● HDL cholesterol &lt; 40 mg/dL in men or &lt; 50 mg/dL in women or drug treatment for this abnormality</td>
<td>● HDL cholesterol &lt; 40 mg/dL in men or &lt; 50 mg/dL in women or drug treatment for this abnormality</td>
<td>● HDL cholesterol &lt; 40 mg/dL in men or &lt; 50 mg/dL in women or drug treatment for low HDL</td>
</tr>
<tr>
<td>And any 2 of the following:</td>
<td>● Waist circumference &gt; 100 mg/dL in men or previously diagnosed type 2 diabetes</td>
<td>● Waist circumference ≥ 102 cm in men or ≥ 88 cm in women with lower thresholds for individual or ethnic groups prone to insulin resistance</td>
<td>● Waist circumference ≥ 102 cm in men or ≥ 88 cm in women</td>
</tr>
<tr>
<td>● SBP ≥ 140 mmHg or DBP ≥ 90 mmHg and/or antihypertensive medication</td>
<td>● Fasting triglycerides ≥ 150 mg/dL in men and/or HDL Cholesterol &lt; 35 mg/dL in men or HDL Cholesterol &lt; 39 mg/dL in women</td>
<td>● Triglycerides or drug treatment for this abnormality</td>
<td>● Triglycerides or drug treatment for low HDL</td>
</tr>
<tr>
<td>● Fasting triglycerides ≥ 150 mg/dL and/or HDL Cholesterol &lt; 35 mg/dL in men or HDL Cholesterol &lt; 39 mg/dL in women</td>
<td>● BMI &gt; 30 kg/m² and/or waist:hip ratio &gt; 0.9 in men or &gt; 0.85 in women</td>
<td>● Fasting glucose ≥ 100 mg/dL in men or &lt; 50 mg/dL in women or specific treatment for this abnormality</td>
<td>● Fasting glucose ≥ 100 mg/dL in men or &lt; 50 mg/dL in women or specific treatment for this abnormality</td>
</tr>
<tr>
<td>● BMI &gt; 30 kg/m² and/or waist:hip ratio &gt; 0.9 in men or &gt; 0.85 in women</td>
<td>● Urinary albumin excretion rate ≥ 20 µg/min or albumin:creatinine ratio ≥ 30 mg/g</td>
<td>● BMI &gt; 30 kg/m² and/or waist:hip ratio &gt; 0.9 in men or &gt; 0.85 in women</td>
<td>● BMI &gt; 30 kg/m² and/or waist:hip ratio &gt; 0.9 in men or &gt; 0.85 in women</td>
</tr>
</tbody>
</table>

Key: SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; 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

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. 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, 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. 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, 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. 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Study population</th>
<th>Risk factor cut-offs</th>
<th>Definition</th>
<th>Prevalence</th>
</tr>
</thead>
</table>
| de Ferranti*             | Nationally representative sample of 12–19-year-old US adolescents 1,960 participants | ● ≥ 75th percentile WC for age and sex of study cohort  
● ≥ 90th percentile SBP or DBP for age, sex and height 
● ≥ 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                                                                 | NHANES 1988–1994  
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%  
NHANES 1999–2000  
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% |
| Duncan*                 | Nationally representative sample of 12–19-year-old US adolescents 991 participants | ● ≥ 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: 9.1%  
Females: 3.7%  
Non-Hispanic white: 7.2%  
Non-Hispanic black: 5.1%  
Mexican American: 8.5%  
Overweight: 32.1% |
| Cook                    | Nationally representative sample of 12–19-year-old US adolescents 2,430 participants | ● ≥ 90th percentile WC for age and sex of study cohort  
● ≥ 90th percentile SBP or DBP for age, sex and height  
● ≥ 110 mg/dL TG  
● ≥ 110 mg/dL LDL  
● ≥ 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*              | Population-based cohort of 3–18-year-old Finnish children and adolescents 3,457 participants | ● ≥ 75th percentile sum of biceps, subscapular and triceps skinfolds  
● ≥ 75th percentile SBP  | 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% |
● ≥ 75th percentile WC for age and sex  
● ≥ 75th percentile SBP  
● ≥ 75th percentile of sum of biceps, subscapular and triceps skinfolds  
● ≥ 75th percentile of sum of biceps, subscapular and triceps skinfolds  
● ≥ 75th percentile of sum of biceps, subscapular and triceps skinfolds  | 3 of 5 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%  |

*Extrapolated adult IDF definition

**NHANES 1999–2002**

**NHANES 1988–1994**

**NHANES III 1988–1994**

**ATP III**

**IDF**
<table>
<thead>
<tr>
<th>Author</th>
<th>Study population</th>
<th>Risk factor cut-offs</th>
<th>Definition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retnakaran37</td>
<td>Community-based sample of Oji-Cree Canadian children aged 10–19-years-old</td>
<td>• ≥ 90th percentile WC for age and sex</td>
<td>3 or more criteria</td>
<td>Overall: 18.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 90th percentile SBP or DBP for age, sex and height</td>
<td></td>
<td>Males: 14.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 1.1 mmol/L TG</td>
<td></td>
<td>Females: 21.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HDL &lt; 1.2 mmol/L in boys 15–19 years and HDL&lt; 1.3 mmol/L&lt; in all others</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 110 mg/dL fasting glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morrison29</td>
<td>School-based cohort of US black and white girls aged 9 and 10 years followed for 10 years</td>
<td>• &gt; 88 cm WC</td>
<td>3 or more criteria</td>
<td>Ages 9–10 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &gt;130 mmHg SBP or &gt; 85 mmHg DBP</td>
<td></td>
<td>Black girls: 0.2%</td>
</tr>
<tr>
<td>National Heart, Lung and Blood Institute Growth and Health Study</td>
<td>2,270 participants</td>
<td>• &gt; 150 mg/dL TG</td>
<td></td>
<td>White girls: 0.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &lt; 50 mg/dL HDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Braunschweig33</td>
<td>School-based US sample of urban African American children in grades 3–6</td>
<td>• ≥ 90th percentile WC for age and sex</td>
<td>3 or more criteria</td>
<td>Overall: 5.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 90th percentile DBP or SBP for age, sex and height</td>
<td></td>
<td>Males: 5.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 40 mg/dL HDL</td>
<td></td>
<td>Females: 4.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 110 mg/dL fasting glucose</td>
<td></td>
<td>Overweight: 13.8%</td>
</tr>
<tr>
<td>Rodriguez-Moran30</td>
<td>Community-based sample of 10–18 year old Mexican children and adolescents</td>
<td>• ≥ 90th percentile BMI</td>
<td>3 or more criteria</td>
<td>Overall: 6.5%</td>
</tr>
<tr>
<td>Goodman31</td>
<td>School-based sample of white, black and Hispanic US adolescents aged 12–19 years</td>
<td>• ≥ 102 cm WC in males and • ≥ 88 cm WC in females or</td>
<td>NCEP definition</td>
<td>Overall NCEP: 4.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 95th percentile BMI for age and sex (WHO)</td>
<td>used any 3 or more criteria</td>
<td>WHO: 8.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 130 mmHg SBP</td>
<td></td>
<td>Males: 3.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 40 mg/dL HDL</td>
<td></td>
<td>Females: 7.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 50 mg/dL HDL in females (NCEP)</td>
<td></td>
<td>NCP: 4.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 35 mg/dL HDL in males or</td>
<td></td>
<td>WHO: 9.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 39 mg/dL HDL in females (WHO)</td>
<td></td>
<td>OBSE: 3.0%</td>
</tr>
<tr>
<td>Lambert27</td>
<td>School-based sample of Canadian youth aged 9, 13 and 16 years</td>
<td>• ≥ 85th percentile BMI</td>
<td>Hyperinsulinemia Overall</td>
<td>11.5%</td>
</tr>
<tr>
<td>The Quebec Child and Adolescent Health and Social Survey</td>
<td>1,369 participants</td>
<td>• ≥ 75th percentile SBP or DBP</td>
<td>plus 2 or more risk factors</td>
<td>Males: Age 9 years: 10.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 75th percentile TG</td>
<td></td>
<td>Females: Age 13 years: 11.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 25th percentile HDL</td>
<td></td>
<td>Definition 2:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 75th percentile fasting insulin of study cohort (WHO)</td>
<td></td>
<td>Any 3 or more risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 110 mg/dL fasting glucose</td>
<td></td>
<td>Age 16 years: 12.2%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Study population</th>
<th>Risk factor cut-offs</th>
<th>Definition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katzmarzyk et al.</td>
<td>School-based US cohort of 5–18-year-old children and adolescents</td>
<td>Study cohort percentiles for age</td>
<td>3 or more criteria</td>
<td>Males: White: 18.2%</td>
</tr>
<tr>
<td>Bogalusa Heart Study</td>
<td>School-based cohort of 5–18-year-old black and white children</td>
<td>● = &gt; 80th percentile SBP or DBP</td>
<td>Overall: 4.0%</td>
<td></td>
</tr>
<tr>
<td>Srinivasan et al., 2002</td>
<td>School-based US cohort of 8–17-year-olds</td>
<td>● = &gt; 75th percentile BMI</td>
<td>Students with all 4 criteria</td>
<td>Overall: 3.6%</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>School-based cohort of 5–17-year-old US black and white children</td>
<td>● = &gt; 90th percentile SBP or DBP</td>
<td>Overall: 3.0%</td>
<td></td>
</tr>
<tr>
<td>Freedman et al.</td>
<td>School-based US cohort of 5–17-year-old black and white children and adolescents</td>
<td>● = &gt; 90th percentile BMI</td>
<td>Overall: 2.0%</td>
<td></td>
</tr>
<tr>
<td>Chu et al.</td>
<td>School-based sample of 12–16-year-old Chinese adolescents from Taiwan</td>
<td>● = &gt; 90th percentile SBP or DBP</td>
<td>Overall: 2.0%</td>
<td></td>
</tr>
<tr>
<td>Viner et al.</td>
<td>Clinic-based sample of 2–18-year-old youth undergoing obesity evaluation in the UK</td>
<td>● = &gt; 95th percentile BMI for age and sex</td>
<td>Obese: 33%</td>
<td></td>
</tr>
</tbody>
</table>

III. School or clinic-based samples of overweight or obese children and adolescents

● Abnormal glucose homeostasis (fasting hyperinsulinaemia prepubertal = > 15 µU/mL, mid puberty = > 30 µU/mL; post pubertal = > 20 mU/L; impaired glucose tolerance min = > 140 mg/dL)

● Dyslipidaemia (elevated triglycerides > = 1.75 mM/L, low HDL < = 0.9 mM/L, high TC > = 95th percentile)
<table>
<thead>
<tr>
<th>Author</th>
<th>Study population</th>
<th>Risk factor cut-offs</th>
<th>Definition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invitti38</td>
<td>Clinic-based sample of 6–16-year-old obese Italian youth undergoing an evaluation in Italy</td>
<td>● Glucose intolerance (fasting glucose ≥ 100 mg/dL and/or 2 hour post load glucose ≥ 140 mg/dL) and/or insulin resistance defined by being the median of the Tanner stage (L-V) specific HOMA-IR values (2.4, 2.8, 3.0, 3.4, 3.0) or BMI tertiles &lt; 97th percentile of a control population</td>
<td>Glucose intolerance/insulin resistance I z score 2.0–3.5: 16% II z score 3.6–4.1: 23% III z score 4.2–6.2: 31% of the other factors</td>
<td>Obese: 23.3%</td>
</tr>
<tr>
<td>Yoshinaga35</td>
<td>School-based sample of 6–11-year-old Japanese overweight or obese youth</td>
<td>● WC ≥ 90th percentile for age and sex of study cohort or SBP ≥ 120 mmHg for grades 1–3 or ≥ 130 mmHg for grades 4–6 or &lt; 40 mg/dL HDL</td>
<td>BMI plus any criteria 3 or more factors</td>
<td>Obese: 17.7% Overweight: 8.7%</td>
</tr>
<tr>
<td>Sherry36</td>
<td>Clinic-based sample of obese 2–10-year-old US children of Dominican ancestry</td>
<td>● Z score &gt; 2.0 for BMI in study cohort or BMI plus any criteria 2 of the other risk factors</td>
<td>Obese: 14.3%</td>
<td></td>
</tr>
<tr>
<td>Cruz43</td>
<td>Clinic-based US sample of obese 8–13-year-old Hispanic youth with a family history of type 2 diabetes</td>
<td>● WC ≥ 90th percentile for age, gender and ethnicity or SBP ≥ 90th percentile or DBP for age, sex and height or TG ≥ 90th percentile or HDL for age and sex or OGTT 2 hour glucose 140–199 mg/dL</td>
<td>Obese: 30% No sex differences</td>
<td></td>
</tr>
<tr>
<td>Weiss42</td>
<td>Clinic-based US sample of obese 4–20-year-old children and adolescents</td>
<td>● BMI ≥ 97th percentile or Z score ≥ 2.0 in study cohort or BMI plus any criteria 3 or more factors</td>
<td>Moderately obese: 38.7% Severely obese: 49.7%</td>
<td></td>
</tr>
<tr>
<td>Csabi45</td>
<td>Hospital-based sample of 8–18-year-old Hungarian children and adolescents</td>
<td>● OGTT 2 hour glucose 140–200 mg/dL</td>
<td>Obese: 8.9%</td>
<td></td>
</tr>
</tbody>
</table>

**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.

the prevalence is higher in overweight youth (table 2). 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.27 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,31,41-43 and the more severely obese16,42 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.34,36,40 Studies that do not include a measure of adiposity42-44 report a lower prevalence; the use of internal study percentiles leads to higher estimates.

### Table 3. International Diabetes Foundation definition of paediatric metabolic syndrome19

<table>
<thead>
<tr>
<th>Ages 6–&lt; 10 years</th>
<th>Ages 10–&lt; 16 years</th>
<th>Age &gt; 16 years:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity =&gt; 90th percentile by waist circumference</td>
<td>Obesity =&gt; 90th percentile by waist circumference</td>
<td>Central obesity</td>
</tr>
<tr>
<td>Metabolic syndrome not diagnosed, but heightened clinical suspicion for family history of:</td>
<td>Any 2 or more of the following:</td>
<td>Waist circumference &gt; 94 cm in Europoid men or &gt; 80 cm in Europoid women with ethnicity-specific values for other groups</td>
</tr>
<tr>
<td>● Metabolic syndrome</td>
<td>● Fasting glucose =&gt; 100 mg/dL (OGTT recommended) or known type 2 diabetes</td>
<td>And any 2 of the following:</td>
</tr>
<tr>
<td>● Type 2 diabetes mellitus</td>
<td>● SBP =&gt; 130 or DBP =&gt; 85 mmHg</td>
<td>● Fasting glucose =&gt; 100 mg/dL or previously diagnosed type 2 diabetes</td>
</tr>
<tr>
<td>● Dyslipidaemia</td>
<td>● Fasting triglycerides =&gt; 150 mg/dL</td>
<td>● Systolic BP =&gt; 130 or DBP =&gt; 85 mmHg or treatment of previously diagnosed hypertension</td>
</tr>
<tr>
<td>● Cardiovascular disease</td>
<td>● HDL cholesterol &lt; 40 mg/dL</td>
<td>● Fasting triglycerides =&gt; 150 mg/dL or specific treatment for this abnormality</td>
</tr>
<tr>
<td>● Hypertension</td>
<td></td>
<td>● HDL cholesterol &lt; 40 mg/dL in men or &lt; 50 mg/dL in women or specific treatment for this abnormality</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
adults.\textsuperscript{10,15-22} 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.\textsuperscript{40} Waist circumference showed the most consistent and the strongest association with insulin levels and adverse lipid levels.\textsuperscript{42,43} In a sample of younger children, Maffeis found similar associations with adiposity, as measured by waist circumference, but – interestingly – independent of BMI.\textsuperscript{44} This supports the association between central adiposity and cardiometabolic risk factors, probably due to excess visceral fat.\textsuperscript{45,46} 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.\textsuperscript{7} Another study found a three-fold increase in adult metabolic syndrome in those who were overweight as children.\textsuperscript{46}

It is not clear whether the influence of obesity is entirely or only in part accounted for by insulin resistance.\textsuperscript{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,\textsuperscript{57} and also in a group of obese adolescents (BMI \( \geq \) 97th percentile).\textsuperscript{46} 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.\textsuperscript{4}

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/m\(^2\)), 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.\textsuperscript{10}

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 a six-year follow-up, even after adjusting for baseline obesity and changes in obesity status over time.\textsuperscript{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.\textsuperscript{7} 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.\textsuperscript{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 \( \geq \) 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.\textsuperscript{60} This testing is used for children, although the precise paediatric dose for provocative glucose testing is not well validated.\textsuperscript{61,62} 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,\textsuperscript{63} yet the use of these adults cut-off points has not been demonstrated by outcomes-based research in children.\textsuperscript{64}

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 diabetes 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.\textsuperscript{65-70} 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;\textsuperscript{69} 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.\textsuperscript{71} 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,\textsuperscript{72} and Native Americans.\textsuperscript{73}

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. 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. 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. 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. Smaller studies taking participants from clinical practice demonstrate higher rates of paediatric type 2 diabetes than the population-based surveys. Pinhas-Hamiel 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. 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%. 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, 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.

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 syndrome 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. 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 as well summarised by a recent meta-analysis, and confers a nearly seven-fold increased risk of type 2 diabetes. 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.

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, and NAFLD has been estimated to affect 22.5% to 52.8% of obese children. 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 Pathologic Determinants of Atherosclerosis in Youth (PDAY) study and the Bogalusa study. 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-media thickness (IMT), a subclinical marker of atherosclerosis and predictor of adult coronary artery events, was greater in young adulthood than in those with worse childhood cardiovascular risk factor profiles in the Bogalusa Heart Study. 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. 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). Carotid stiffness has been shown to be significantly higher in obese children with metabolic syndrome compared to those without metabolic syndrome. 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. 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). The Princeton Lipid Research Clinics Prevalence Study demon-
stated that children with metabolic syndrome\textsuperscript{17} were six times more likely to have metabolic syndrome as adults and more than 14 times more likely to develop cardiovascular disease.\textsuperscript{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.\textsuperscript{64,84} 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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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. 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\textsubscript{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.\textsuperscript{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\textsubscript{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).\textsuperscript{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.\textsuperscript{2,4,10} 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, 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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