In search for a definition of the metabolic syndrome in pre-adolescent children – a population-based approach

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Leibniz Institute for Prevention Research and Epidemiology, Bremen, Germany
- on behalf of the IDEFICS consortium -

Consensus Workshop on the Metabolic Syndrome in Children – the IDEFICS results

CIP 2015 – 4th Global Congress for Consensus in Pediatrics & Child Health
Budapest, 20 – 22 March 2015
Complications of obesity in children

- Psychosocial: Poor self-esteem, Depression, Eating disorders
- Neurological: Pseudotumor cerebri
- Pulmonary: Sleep apnoea, Asthma, Exercise intolerance
- Cardiovascular: Dyslipidaemia, Hypertension, Coagulopathy, Chronic inflammation, Endothelial dysfunction
- Gastrointestinal: Gallstones, Steatohepatitis
- Renal: Glomerulosclerosis
- Musculoskeletal: Slipped capital femoral epiphysis, Blount’s disease, Forearm fracture, Flat feet

Ebbeling CB et al. Lancet 2002; 360: 473-482
Metabolic syndrome in children

- **Cardiovascular risk factors tend to cluster**
  

- **Factor analysis of metabolic syndrome components show 2-4 factors**
  
  Chen W et al. Am J Epidemiol 1999; 150: 667-674  
  Moreno LA et al. Horm Metab Res 2002; 34: 394-399

- **8.9 % of obese children have the metabolic syndrome**
  
The most frequent components of the metabolic syndrome (MetS)

- Obesity
- Hypertension
- Dyslipidaemia (high triglyceride and low HDL-C concentrations)
- Insulin resistance – hyperinsulinemia – glucose intolerance and/or type 2 diabetes

What are the appropriate physiological parameters to be measured?
Correlation between waist circumference and visceral fat assessed by magnetic resonance imaging

\[ Y = 1.1X - 52.9 \]

\[ R^2 = 0.64, \ p < 0.0001 \]

RMSE = 14 cm² (33%)
Different reference standards for waist circumference (90th percentile)
Lipoprotein metabolism

**Natural history of type 2 diabetes**

- Obesity
- Diet
- Sedentary lifestyle
- Genetics
- Perinatal factors

**Insulin sensitive**

- Insulin resistance
- Compensatory hyperinsulinaemia

**β-cell decompensation**

- Relative insulin deficiency

**β-cell failure**

- **Diabetes Mellitus**
- Vascular complications

**Normoglycemia**

- Postprandial hyperglycemia

- Impaired fasting glucose
Insulin resistance

- **Homeostatic model assessment (HOMA):** the product of the fasting plasma insulin level (µU/ml) and the fasting plasma glucose level (mmol/l), divided by 22.5.

- Lower insulin-resistance values indicate a higher insulin sensitivity, whereas higher values indicate a lower insulin sensitivity.
**Definitions of paediatric metabolic syndrome (MetS) in children**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Excess adiposity</th>
<th>Blood pressure</th>
<th>Blood lipids</th>
<th>Blood glucose/ insulin</th>
</tr>
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<tr>
<td><strong>Cook et al.</strong></td>
<td>WC ≥ 90&lt;sup&gt;th&lt;/sup&gt; percentile</td>
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<td>SBP ≥ 95&lt;sup&gt;th&lt;/sup&gt; percentile</td>
<td>Triacylglycerols ≥ 150 mg/dl or HDL cholesterol &lt; 35 mg/dl or High total cholesterol ≥ 95&lt;sup&gt;th&lt;/sup&gt; percentile</td>
<td>Hyperinsulinemia ≥ 15 mU/l or Impaired fasting glucose ≥ 110 mg/dl</td>
</tr>
<tr>
<td><strong>IDF</strong></td>
<td>WC ≥ 90&lt;sup&gt;th&lt;/sup&gt; percentile or DBP ≥ 85 mmHg</td>
<td>SBP ≥ 130 mmHg or DBP ≥ 85 mmHg</td>
<td>Triacylglycerols ≥ 150 mg/dl or HDL cholesterol &lt; 40 mg/dl</td>
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*IDF=International Diabetes Federation*
Metabolic syndrome in children?

**PEDIATRIC HIGHLIGHT**

Metabolic risk-factor clustering estimation in children: to draw a line across pediatric metabolic syndrome

P Brambilla, A Pietrobelli

**Background:**

The diagnostic criteria for obesity, even though on those studies the values chosen.

**Objectives:**

To discuss concerns regarding the use of the existing definition of the metabolic syndrome (as defined in adults) in children and adolescents, analyzing the scientific evidence needed to detect a clustering of cardiovascular risk factors. Finally, we propose a new methodological approach for estimating metabolic risk-factor clustering in children and adolescents.

**Results:**

Major concerns were the lack of information on the background derived from a child's family and personal history; the lack of consensus on insulin levels, lipid parameters, markers of inflammation or steatohepatitis; the lack of an additive relevant effect of the metabolic syndrome definition to obesity per se. We propose the adoption of 10 evidence-based items from which to quantify metabolic risk-factor clustering, collected in a multilevel Metabolic Individual Risk-factor And CLustering Estimation (MIRACLE) approach, and thus avoiding the use of the current metabolic syndrome term in children.

**Conclusion:**

Pediatricians should consider a novel and specific approach to assessing children/adolescents and should not simply derive or adapt definitions from adults. Evaluation of insulin and lipid levels should be included only when specific references for the relation of age, gender, pubertal status and ethnic origin to health risk become available.

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Prevalence of each component of MetS according to different definitions (1 of 5)

Cook et al.\textsuperscript{32}

Ahrens W & Moreno LA et al. Int J Obes 2014; 38: S4-S14
Prevalence of each component of MetS according to different definitions (2 of 5)

Viner et al. 33

Ahrens W & Moreno LA et al. Int J Obes 2014; 38: S4-S14
Prevalence of each component of MetS according to different definitions (3 of 5)

Ahrens W & Moreno LA et al. Int J Obes 2014; 38: S4-S14
### Definitions of paediatric metabolic syndrome (MetS)

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<td><strong>IDF</strong>*</td>
<td>WC ≥ 90th percentile</td>
<td>SBP ≥ 130 mmHg or DBP ≥ 85 mmHg</td>
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</tr>
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<td><strong>IDEFICS-</strong></td>
<td>WC ≥ 90th percentile</td>
<td>SBP ≥ 90th percentile or DBP ≥ 90th percentile</td>
<td>Triacylglycerols ≥ 90th percentile or HDL cholesterol ≤ 10th percentile</td>
<td>HOMA-insulin resistance ≥ 90th percentile or Fasting glucose ≥ 90th percentile</td>
</tr>
<tr>
<td><strong>monitoring</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>level</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
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*IDF=International Diabetes Federation
Prevalence of each component of MetS according to different definitions (4 of 5)

Ahrens W & Moreno LA et al. Int J Obes 2014; 38: S4-S14
Prevalence of each component of MetS according to different definitions (5 of 5)

Ahrens W & Moreno LA et al. Int J Obes 2014; 38: S4-S14
Prevalence of MetS in normal weight/thin, overweight and obese children

MetS monitoring level = 5.5%

MetS action level = 1.8%

Ahrens W & Moreno LA et al. Int J Obes 2014; 38: S4-S14
Are the cut-offs chosen to define the MetS too arbitrary?
Number of MetS risk variables and elasticity of common carotid artery

Bogalusa Study

Ep = Peterson's elastic modulus
YEM = relative wall thickness-adjusted Young's elastic modulus

Continuous MetS score calculated according to Eisenmann as the sum of component z-scores:

- **Adiposity**: WC (waist circumference (cm))
- **Blood pressure**: mean of SBP and DBP (systolic / diastolic blood pressure (mm Hg))
- **Blood lipids**: mean of TRG and negative HDL (triglycerides / HDL cholesterol (mg/dl))
- **Insulin resistance**: HOMA (homeostasis model assessment)

\[
\text{MetS score} = z_{WC} + \frac{z_{SBP} + z_{DBP}}{2} + \frac{z_{TRG} - z_{HDL}}{2} + z_{HOMA}
\]
## Calculation of a MetS score: four examples

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>WC</th>
<th>SBP</th>
<th>DBP</th>
<th>TRG</th>
<th>HDL</th>
<th>HOMA</th>
<th>zWC</th>
<th>zSBP</th>
<th>zDBP</th>
<th>zTRG</th>
<th>zHDL</th>
<th>zHOMA</th>
<th>MetS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>6.5</td>
<td>59.5</td>
<td>109.0</td>
<td>67.5</td>
<td>48</td>
<td>38</td>
<td>0.65</td>
<td>1.66</td>
<td>0.85</td>
<td>0.72</td>
<td>0.29</td>
<td>-1.22</td>
<td>-0.15</td>
<td>3.05</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>5.8</td>
<td>60.4</td>
<td>92.0</td>
<td>52.5</td>
<td>50</td>
<td>52</td>
<td>1.59</td>
<td>2.20</td>
<td>-0.96</td>
<td>-1.77</td>
<td>0.17</td>
<td>0.10</td>
<td>1.39</td>
<td>2.26</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>5.2</td>
<td>53.0</td>
<td>94.0</td>
<td>58.0</td>
<td>45</td>
<td>61</td>
<td>1.00</td>
<td>0.58</td>
<td>-0.51</td>
<td>-0.81</td>
<td>-0.73</td>
<td>0.88</td>
<td>0.68</td>
<td>-0.07</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>5.5</td>
<td>57.5</td>
<td>99.0</td>
<td>66.0</td>
<td>78</td>
<td>45</td>
<td>0.99</td>
<td>1.64</td>
<td>-0.13</td>
<td>0.59</td>
<td>1.15</td>
<td>-0.54</td>
<td>0.71</td>
<td>3.43</td>
</tr>
</tbody>
</table>

Ahrens W & Moreno LA et al. Int J Obes 2014; 38: S4-S14
Age-specific reference curves for MetS in girls and boys

Ahrens W & Moreno LA et al. Int J Obes 2014; 38: S4-S14
Conclusions

- We propose sex- and age-specific standards for the most frequent cardio-metabolic features associated with obesity in children under 11 years.
- We propose a new definition of MetS to support clinical decision making.
- According to different definitions of paediatric MetS, we classify a non-negligible proportion of mostly pre-pubertal children as being affected.
- **NOTE:** The proposed cut-offs are based on a statistical definition that does not yet allow to quantify the risk of subsequent disease.
- We propose a continuous MetS score to improve quantitative risk assessment for various clinical endpoints.
The IDEFICS Consortium

Thank you!
Previous achievements
## Agreement MetS score – action level: 95th percentile

<table>
<thead>
<tr>
<th>IDEFICS MetS-Score</th>
<th>No MetS (0,1,2)</th>
<th>MetS (3,4)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;95%-Percentile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9,166</td>
<td>43</td>
<td>9,209</td>
<td></td>
</tr>
<tr>
<td>94.01</td>
<td>0.44</td>
<td></td>
<td>94.45%</td>
</tr>
<tr>
<td>99.53</td>
<td>0.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>96.32</td>
<td>18.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥95%-Percentile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>350</td>
<td>191</td>
<td>541</td>
<td></td>
</tr>
<tr>
<td>3.59</td>
<td>1.96</td>
<td></td>
<td>5.55%</td>
</tr>
<tr>
<td>64.70</td>
<td>35.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.68</td>
<td>81.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9,516</td>
<td>234</td>
<td>9,750</td>
<td></td>
</tr>
<tr>
<td>97.60%</td>
<td>2.40%</td>
<td>100.00%</td>
<td></td>
</tr>
</tbody>
</table>
### Agreement MetS score – action level: 90\textsuperscript{th} / 97.5\textsuperscript{th} percentile

<table>
<thead>
<tr>
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<th>IDEFICS action level</th>
<th></th>
<th></th>
<th></th>
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<tr>
<td>No MetS (0,1,2)</td>
<td>MetS (3,4)</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90%-perc.</td>
<td>8,671</td>
<td>6</td>
<td>8,677</td>
<td>88.99%</td>
</tr>
<tr>
<td></td>
<td>88.93</td>
<td>0.06</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>99.93</td>
<td>2.56</td>
<td>2.56</td>
<td>2.56</td>
</tr>
<tr>
<td>≥90%-perc.</td>
<td>845</td>
<td>228</td>
<td>1,073</td>
<td>11.01%</td>
</tr>
<tr>
<td></td>
<td>8.67</td>
<td>2.34</td>
<td>2.34</td>
<td>2.34</td>
</tr>
<tr>
<td></td>
<td>78.75</td>
<td>21.25</td>
<td>21.25</td>
<td>21.25</td>
</tr>
<tr>
<td></td>
<td>9.88</td>
<td>97.44</td>
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### IDEFICS MetS-Score

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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;97.5%-perc.</td>
<td>9,389</td>
<td>105</td>
<td>9,494</td>
<td>97.37%</td>
</tr>
<tr>
<td></td>
<td>96.30</td>
<td>1.08</td>
<td>1.08</td>
<td>1.08</td>
</tr>
<tr>
<td></td>
<td>98.89</td>
<td>1.11</td>
<td>1.11</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>98.67</td>
<td>44.87</td>
<td>44.87</td>
<td>44.87</td>
</tr>
<tr>
<td>≥97.5%-perc.</td>
<td>127</td>
<td>129</td>
<td>256</td>
<td>2.63%</td>
</tr>
<tr>
<td></td>
<td>1.30</td>
<td>1.32</td>
<td>1.32</td>
<td>1.32</td>
</tr>
<tr>
<td></td>
<td>49.61</td>
<td>50.39</td>
<td>50.39</td>
<td>50.39</td>
</tr>
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<td></td>
<td>1.33</td>
<td>55.13</td>
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Youden index for MetS score
(Youden-Index = Sensitivity + Specificity -1)

Max at 1.283 ≈ 90%-percentile  (Sensitivity: 97.4%, Specificity: 91.1%, Youden-Index: 0.88)
ROC for MetS score vs. action level

ROC Curve for Model
Area Under the Curve = 0.9793

Sensitivity

1 - Specificity

0.00 0.25 0.50 0.75 1.00

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Prevalence of MetS in normal weight/thin, overweight and obese children

Ahrens W & Moreno LA et al. Int J Obes 2014; 38: S4-S14
International Obesity Task Force (IOTF) body mass index cut-offs for overweight and obesity in youth

(Cole TJ et al. BMJ 2000; 320: 1240-1243)