Metabolic Syndrome in Adolescence: Can it be Predicted from Natal and Parental Profile? The Prediction of Metabolic Syndrome in Adolescence (PREMA) Study

Running title: Efthathiou et al.; Metabolic syndrome in adolescents

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Abstract:

**Background** - There are well-established predisposing factors for the development of metabolic syndrome (MetS) in childhood and/or adolescence, but no specific risk profile has been identified as yet. The **PRE**diction of **M**etabolic syndrome in **A**dolescence (PREMA) study was conducted (i) to construct a classification score that could detect children at high risk for MetS in adolescence, and (ii) to test its predictive accuracy.

**Methods and Results** - In the derivation cohort (1270 children), data from natal and parental profile, and from initial laboratory assessment at age 6-8 were used to detect independent predictors of MetS at 13-15 years according to the International Diabetes Federation definition. In the validation cohort (1091 adolescents), the discriminatory capacity of the derived prediction score was tested on an independent adolescent population. MetS was diagnosed in 105 (8%) adolescents in the derivation phase, whereas birth weight <10th percentile (odds ratio 6.02 [95% confidence intervals 2.53, 10.12]; p <0.001), birth head circumference <10th percentile (4.15 [2.04, 7.14]; p <0.001), and parental overweight or obesity (at least in one parent) (3.22 [1.30, 5.29]; p <0.01) were independently associated with diagnosis of MetS in adolescence. Among adolescents of the validation cohort (86 [8%] with MetS), the presence of all these 3 predictors predicted MetS with sensitivity 91% and specificity 98%.

**Conclusions** - The co-existence of low birth weight, small head circumference and parental history of overweight or obesity may be useful for detection of children at risk of developing MetS in adolescence.

**Key words:** Metabolic Syndrome, Adolescence, Prediction
Introduction

The metabolic syndrome (MetS), a cluster of disturbed glucose and insulin metabolism, abdominal obesity, dyslipidemia and hypertension, is observed in 35-40% of adults in developed countries\(^1\). Its prevalence in childhood and adolescence has increased from about 2% in the mid-’90s to a current estimate of 10% in US and Western Europe\(^2\). However, the applicability of MetS diagnosis in childhood/adolescence is controversial because of the classification limitations imposed by dichotomous definitions, the lack of standardized diagnostic criteria in non-adult individuals, and the growing criticism regarding the practical value of the overall “MetS concept” \textit{per se} as a distinct clinical entity\(^1-3\). On the other hand, there is robust evidence indicating that pediatric MetS is strongly associated with adults’ MetS, subclinical atherosclerosis and type 2 diabetes, independently of other known predictors\(^2\).

Several studies have investigated predisposing factors for MetS in childhood/adolescence, but no specific risk profile has been identified as yet. Accumulating research suggests that both light\(^4-7\) and heavy\(^4,8-10\) newborns have higher probability of MetS before adulthood, the exact association between birth weight and MetS in childhood/adolescence remaining unclear. Moreover, maternal obesity\(^10,11\), gestational diabetes\(^10\), family history of diabetes\(^4,12\) and attending schools of lower academic grading\(^12\) have been linked to offspring’s MetS in American\(^4,10,11\) and Asian populations\(^12\), but such data from Europe are lacking.

The \textbf{PRE}diction of \textbf{M}etabolic syndrome in \textbf{A}dolescence (\textbf{PREMA}) study was conducted (i) to construct a risk score for MetS in adolescence using natal, parental and childhood characteristics, and (ii) to test the predictive accuracy of this score via its application to an independent population of adolescents.
Patients and methods

Design

The PREMA study was a 10-year investigation conducted in two phases: (i) Phase 1 was a prospective study (derivation cohort) in which data from natal, parental, and clinical/laboratory profile in childhood were used for the construction of a risk score for MetS in adolescence. At baseline (year 2000), children aged 6-8 years underwent anthropometric, blood pressure (BP), fasting plasma glucose (FPG) and lipid measurements, and their natal and parental history was recorded. Parents were informed about their children’s status and were given typical lifestyle recommendations. At follow up (2007), all adolescents aged 13-15 years who had attended the first session were invited to participate in a survey evaluating the prevalence of MetS in Greek adolescents. (ii) Phase 2 was a cross-sectional investigation testing the predictive accuracy of the above score by its application to a new, independent population of adolescents aged 12-15 years (validation cohort) who underwent preventive medical examination from January 2008 to December 2010. No subject participated in both phases and no standardized intervention took place.

Population

Participants were recruited in Athens, capital of Greece with 3.5 x 10^6 inhabitants, from an urban population of Greek children/adolescents of Caucasian origin on the basis of a preventive medicine program provided by the National Bank of Greece Health Insurance Organization. No children/adolescents belonging to other ethnic/racial groups were included. The study sample, consisting of 1270 children 6-8 years old reassessed in adolescence (derivation cohort) and 1091 adolescents 12-15 years old (validation cohort), represented about
2% of each of these two age population categories in Greece. Children with known major cardiovascular (CV), endocrinial, nutritional or renal problems, secondary obesity or on drugs influencing metabolic profile were excluded.

Parents/caretakers who had used the preventive medicine program before PREMA study were informed by telephone for the scope and the procedures of this investigation prior to their children’s scheduled annual check-up and were invited to join the study. They were asked to bring relevant documents and medical records to the clinic for data verification and were supplied with a standardized self-administered health and lifestyle questionnaire during study visit. This questionnaire was used for collecting separate paternal and maternal information regarding age, history of CV disease or diabetes, smoking and alcohol consumption. Data on pregnancy history, fetal development, gestational age, delivery characteristics, birth measurements, breast-feeding and offspring’s medical history and current health status were also provided by mothers via the above questionnaire and crosschecked through a short interview by a trained midwife (E. Z.). Missing natal information was obtained by parents or caretakers from the Office of Vital Statistics prior to study entry. Key measurements such as birth weight and head circumference were ascertained and completed through children’s personal health insurance booklets, original birth certificates and obstetric records, which were made available to researchers following telephone request. Data regarding the validation cohort were collected with the same methodology used for the derivation cohort as described above.

**Measurements**

Premature birth was defined as delivery of an infant before 37 completed weeks of gestation. Small for gestational age status was defined as birth weight and/or length that was 2
SD below the mean for each gestational age (equivalent to 3rd percentile) as established by sex-
and gestational age-specific national charts, whereas large for gestational age status was defined
as birth weight and/or length that was 2 SD above the mean for each gestational age (equivalent
to 97th percentile)\textsuperscript{13}. The midwife (E. Z.) who conducted participants' assessment and the two
physicians (S. E. and I. S.) who made MetS diagnosis were unaware of natal characteristics and
initial measurements. Authorization from the appropriate ethics committee was obtained and all
participants and their parents/caretakers gave informed consent.

A fasting blood sample was obtained from each participant both at baseline and follow up
of phase 1 and on one occasion of phase 2. Weight was measured to the nearest 0.1 kg using a
portable electronic scale (model 68987, Befour Inc, Saukville, WI) and height was measured to
the nearest cm using a portable stadiometer (model IP0955, Invicta Plastics Limited, Leicester,
England) with subjects wearing light indoor clothing and no shoes. Body mass index (BMI) was
calculated as \(\text{weight (kg)}/\text{[height (m)]}^2\). Waist circumference (WC) was measured to the nearest
0.1 cm with a flexible, nonelastic tape at the midway between the lowest portion of rib cage and
iliac crest at minimal respiration. Parental height and weight were measured with the same
methodology and equipment used for children as described above. Parental overweight was
defined as paternal and/or maternal BMI \(\geq 25\) kg/m\(^2\) and <30 kg/m\(^2\), whereas parental obesity as
paternal and/or maternal BMI \(\geq 30\) kg/m\(^2\).

Plasma total cholesterol and triglycerides were determined by enzymatic methods
adapted to a Hitachi 705 analyser (Boehringer Mannheim, Germany), whereas high-density
lipoprotein (HDL) was measured in the supernatant after sodium phosphotungstate/magnesium
chloride precipitation. The intra- and interassay coefficients of variation were approximately 2%
and 3\% for triglycerides and 1\% and 3\%, respectively, for HDL. The low-density lipoprotein
(LDL) was determined by the Friedewald formula. FPG was measured by hexokinase-glucose-6-phosphate dehydrogenase method with intra- and interassay coefficients of variation of approximately 2% and 4%, respectively. Supine BP measurements were performed in the right arm using a standard mercury sphygmanometer (Baumanometer, W. A. Baum, Copiague, NY) with appropriate cuff size according to arm size, i.e. cuff with inflatable bladder width ≥40% and length ≥80% of the arm circumference at the midway between olecranon and acromion. Korotkoff phase I sounds were used for determination of systolic BP and phase V for diastolic BP. After a 5-min rest period, BP was measured three times to nearest 2 mmHg with a 1-min interval between measurements and the average of the last two measurements was used in the analysis.

Since we assessed adolescent populations aged 12-15 years, we used the International Diabetes Federation (IDF) consensus definition of MetS for 10-16 years\textsuperscript{14}, which is currently the most widely recognized until more outcome data are available. MetS was defined as abdominal obesity (WC ≥90\textsuperscript{th} percentile) plus ≥2 of the following: BP ≥130 mmHg (systolic) and/or ≥85 mmHg (diastolic); triglycerides ≥150 mg/dl; HDL <40 mg/dl; FPG ≥100 mg/dl\textsuperscript{14}. Despite the limitations of this definition imposed by the absolute cut-offs, the major component (abdominal obesity) is defined by age-, sex- and ethnic-specific WC percentiles as recommended by IDF\textsuperscript{14}. Percentiles of birth measurements and of childhood/adolescence characteristics were based on national data provided by the 1\textsuperscript{st} University Department of Paediatrics of Agia Sophia Hospital of Athens\textsuperscript{13} and the Hellenic Medical Association for Obesity\textsuperscript{15-17}.

**Statistical analysis**

Statistical analysis was performed via the Statistical Package for the Social Sciences
software (SPSS Inc, Chicago, Illinois, release 17.0). Normality of data distribution was assessed by Kolmogorov-Smirnov test. Inter-group comparisons were made by chi-square or Fisher’s exact test for categorical data, and unpaired Student’s t test for continuous variables, whereas Spearman coefficient (rho) was used for assessing correlations. We calculated z scores in the derivation cohort for BMI and BP at 6-8 years and 13-15 years, as well as for weight at birth, childhood and adolescence on the basis of the respective age- and gender-specific mean values and standard deviations derived from national data \(^{15-18}\). In addition, we used the widely accepted international age- and sex- specific BMI cut-off points for definition of overweight/obesity in children/adolescents \(^{19}\), according to the recommendations of the International Obesity Task Force (IOTF) \(^{19}\) and the Hellenic Medical Association for Obesity \(^{15,17}\), in order to estimate the prevalence of overweight/obesity at age 6-8 and 13-15 in the MetS and the non-MetS group of the derivation cohort. We also applied listwise deletion by excluding cases with missing values and we examined the reasons for missing data. Cohen's kappa (\(\kappa\)) concordance test was used to assess agreement between provisional MetS diagnosis at 6-8 years and diagnosis of MetS at 13-15 years. Ninety-five percent confidence intervals (95% CIs) were calculated, tests of significance were two-tailed and a p value <0.05 was considered to be significant.

Logistic regression analysis was applied to identify independent predictors of MetS as well as to investigate the association between birth weight percentiles and odds of MetS by calculating the respective odds ratios (OR). A stepwise selection procedure was used with entry and removal criteria \(p=0.05\) and \(p=0.10\), respectively, whereas the presence of multicollinearity was examined by calculating variance inflation factor (VIF) and tolerance. Hosmer-Lemeshow test was used to assess model fitting. We selected 10\(^{th}\) and 90\(^{th}\) percentiles as cut-offs for dichotomizing continuous variables such as birth measurements, because these thresholds (i)
offered a simple, easily interpretable risk classification in the context of a prediction score; (ii) gave the largest difference between individual outcomes in the resulting two groups and consequently the largest sensitivity, specificity, positive (PPV) and negative predictive values (NPV); (iii) created a binary split of continuous covariates to two relatively distinct but homogeneous, clinically meaningful and large enough groups, so that differences reach statistical significance; and (iv) have been successfully used in previous large-scale investigations, thus allowing comparability20,21.

Results

Phase 1: derivation cohort (2000-2007)

The initial database of PREMA study comprised 1380 children with full initial records, 1270 of whom also attended the follow up visit of phase 1 and had complete records in both phases (full follow-up rate 92%). Reasons for encountering missing values or cases included parents’ reluctance for offspring’s second examination (38 subjects), adolescents’ denial of venipuncture (22 subjects) and adolescents’ time constraints (50 subjects). The 1270 subjects who had adequate natal and parental information and attended both baseline and follow up visits constituted the phase 1 study population (Table 1). Birth weight and head circumference were lower in children with MetS in adolescence, whereas the latter had also higher prevalence of parental history of CV disease and diabetes, parental overweight/obesity, paternal history of diabetes, paternal overweight/obesity, maternal history of diabetes, maternal overweight/obesity, and lower prevalence of breast-feeding for at least 4 weeks. Participants’ characteristics at age 6-8 are illustrated in Table 2. Children at age 6-8 who subsequently developed MetS had higher weight, height, BMI, WC, BP, total cholesterol, LDL and triglycerides, and lower HDL. The
above differences persisted at age 13-15 (Table 3), whereas a greater proportion of smokers was additionally found in the MetS group.

The plotted association between birth weight percentiles and OR for MetS in the derivation cohort is shown in Figure 1. Birth weight percentile showed a significant inverse relationship with BMI both at ages 6-8 (Spearman correlation coefficient rho = -0.412; p = 0.005) and 13-15 (rho = -0.631; p < 0.001) in the overall derivation cohort. This negative association was found both in participants who developed MetS (rho = -0.221 [p = 0.03] at age 6-8 and rho = -0.817 [p < 0.001] at age 13-15) and in those without MetS (rho = -0.433 [p = 0.008] at age 6-8 and rho = -0.599 [p < 0.001] at age 13-15). Moreover, the correlation between BMI in childhood and in adolescence was significant in the overall population (rho = 0.508; p < 0.001) and more potent in the non-MetS (rho = 0.562; p < 0.001) than in the MetS group (rho = 0.231; p = 0.02). In the MetS group, the mean z scores increased from -1.7±1.2 for birth weight to 0.5±0.4 at 6-8 years, to 1.6±1.1 at age 13-15. Comparable values in those who did not develop MetS were 0.2±0.5, -0.2±0.3 and -0.1±0.6, respectively. Further, only 38 of the 105 children who developed MetS (36%) were already overweight or obese at age 6-8 according to IOTF criteria [19], compared to 94 out of 105 in adolescence (90%). Among those who did not develop MetS, the proportions of overweight or obese were 228 out of 1165 (20%) at age 6-8 and 286 out of 1165 (25%) in adolescence.

There were 38 children in the overall derivation cohort (3%) with provisional MetS according to IDF (i.e. WC ≥90th age-, sex- and ethnic-specific percentile at age 6-8 and family history of MetS, type 2 diabetes, dyslipidemia, CV disease, hypertension and/or obesity)14. Thus, 28 participants had MetS both in childhood and adolescence, 10 only in childhood, 77 only in adolescence and 1155 neither in childhood nor in adolescence (κ=0.27, indicating only fair
agreement between diagnosis of provisional MetS and MetS in adolescence). Provisional MetS at 6-8 years predicted MetS at 12-15 years with sensitivity 27%, specificity 99%, PPV 74% and NPV 94%. Multiple logistic regression analysis identified three independent predictors of MetS (Table 4): birth weight <10th percentile, birth head circumference <10th percentile, and parental overweight and/or obesity (at least in one parent). No indication of multicollinearity was found for any of the variables considered in regression analysis (tolerance >0.40 and VIF <2.5). The Hosmer-Lemeshow test showed good model fitting (chi-square = 6.642, significance level = 0.576). The proportion of adolescents with MetS among subjects with 0, 1, 2, and 3 of the above predictors is shown in Table 5. When the criterion of the co-existence of all 3 factors was used for MetS prediction, the score showed sensitivity 91% (95% CIs 83, 95), specificity 98% (95% CIs 97, 99), PPV 81% (95% CIs 72, 87), NPV 99% (95% CIs 98, 99), positive likelihood ratio 46 (95% CIs 30, 69), negative likelihood ratio 0.1 (95% CIs 0.05, 0.18), and accuracy 97%.

Phase 2: validation cohort (2008-2010)

The above diagnostic score was applied to the next 1091 adolescents (86 [8%] with MetS) who underwent preventive medical assessment from 2008 to 2010. The overall population of the validation cohort was comparable to the overall population of the derivation cohort (Table 6). The plotted association between birth weight percentiles and OR for MetS in the validation cohort is illustrated in Figure 1, whereas the application of the classification tool to the validation database is shown in Table 5. When the co-existence of all 3 predictors was considered for MetS prediction, the score showed sensitivity 91% (95% CIs 83, 95), specificity 98% (95% CIs 97, 98), PPV 77% (95% CIs 67, 84), NPV 99% (95% CIs 98, 99), positive
likelihood ratio 38 (95% CIs 25, 57), negative likelihood ratio 0.09 (95% CIs 0.05, 0.19), and accuracy 97%.

Discussion

This study provides additional support to the view that the roots of MetS need to be traced back as early in life as possible. The prevalence of adolescents’ MetS in our study (approximately 8%) was comparable to that observed in similar recent investigations², thus corroborating the alarming increase in the rate of Mets at the age of 12-18 years², which converges at the respective increase in the adult population during the last decade [1]. In both derivation and validation cohorts, the PPV of the proposed score suggested that more than 75% of children with all three factors are expected to develop MetS, whereas its very high NPV practically excluded the probability of MetS among children with a negative score result (i.e. not fulfilling all three criteria). Since this score gives few false negative (type II errors) and even fewer false positive results (type I errors), it may be suitable for use mainly as a confirmatory test for establishing increased risk of MetS in children with adverse clinical/laboratory trends (e.g. with marginally abnormal WC, weight, BP, FPG and/or lipids), whereas it may have a complementary role as a screening test early after birth as well.

The high predictive power of small birth size for MetS that was found in our study is in line with the notion expressed initially 20 years ago in UK by Barker and colleagues who showed slow rates of prenatal growth to predict CV mortality, indicating that CV disease may originate from programming in fetal life and infancy²². Subsequently, a large body of literature has been added confirming that birth weight is inversely associated with coronary heart disease (CHD)²³,²⁴, stroke²³, BP²⁵, insulin resistance²⁶, MetS, type 2 diabetes, dyslipidemia, and non-
alcoholic fatty liver. Nevertheless, the association between birth weight percentiles and OR for MetS in our study was closer to a log relationship (Figure 1) instead of the U-shape association found by several research groups. Small head circumference has been also associated with elevated adult BP, reduced arterial compliance, impaired glucose tolerance, increased prevalence of CHD and mortality from CHD in large-scale investigations including Indian and Scandinavian populations independently of known CV risk factors. These observations offered impetus to the concept of “developmental origins of disease”, according to which fetal undernutrition at critical periods of development in utero and during infancy leads to permanent changes in body structure and metabolism resulting in increased adult susceptibility to CV and metabolic diseases. It has been suggested that alterations in cortisol and growth hormone, insulin-like growth factors or the sympathetic nervous system could mediate the observed associations between birth size and later central obesity.

The children of obese/overweight parents have been repeatedly found at increased risk of obesity, the parents’ BMI being more powerful independent predictor of offspring’s BMI than nutrition habits and sedentary behaviour. Our analysis is in accord with the above data yielding a relative risk of 3.2 for MetS in adolescents with overweight/obese parents as compared to those with normal-weighted parents, the lower bounder of 95% CIs ruling out an increase of risk less than 30%. This particular predictor of MetS, which encompassed a wide range of conditions, i.e. from only one overweight parent to two obese parents, was detected in 80% of children with MetS, thus underlying the importance of both the genetic predisposition derived from first-degree relatives and the environmental influence as expressed by familial dietary culture. This observation may have considerable implications, inasmuch as it has been
shown that adolescents’ nutrition preferences and physical activity patterns are shaped early in childhood\textsuperscript{41} and are largely influenced by parental practices and familial environment\textsuperscript{42}.

It is noteworthy that while participants’ characteristics at age 6-8 were candidates for the multivariate model, none of them entered given the birth characteristics, this finding suggesting that birth weight/head circumference and parental overweight/obesity are more important for MetS risk than children’s weight at age 6-8 in the population studied. The latter interpretation appears to be further supported by the timing of weight gain that we can speculate on the basis of our observations regarding the derivation cohort. Although a greater proportion of overweight or obese children already existed at age 6-8 among participants who developed MetS (36\%) as compared to those who did not (20\%), the prevalence of overweight/obesity increased in the time interval between 6-8 and 13-15 years to 90\% in the MetS group as compared to 25\% in the non-MetS group. Thus, it may be argued that the period between childhood and adolescence was the most critical for the increase in the weight of children who developed MetS in adolescence.

On the other hand, the proposed score identifies a high-risk group, whereas the finding that about 75\% of children meeting the IDF provisional definition of MetS developed MetS in adolescence reveals an important target for individual intervention applying to a small group of younger children. However, although weight z score at age 6-8 does not track well enough – at least in the Greek children studied – to identify future weight, increase in obesity is critical for the remainder of the cohort. In this respect, the complementary importance of both population-based and individual prevention strategies should be taken into account when designing health policies. Prevention and management of MetS in adolescence could not be specific to the ‘syndrome’ \textit{per se}, but rather should be focused on the underlying central disorder of overweight and abdominal obesity, and be considered as a matter of the entire family\textsuperscript{41}. With regard to
intervention, the prevention of excess weight gain in pre-adolescence (i.e. between early childhood and adolescence) may be recommended on the basis of the above data. Further, specially designed research is required to identify with appropriate methodology the critical period for subsequent MetS development, since this may be more important than having a predictive risk score.

Several limitations of our study should be taken into account. Although a fully independent validation can only be performed in different institutions, the probability of bias is limited in our report because physicians assessing outcome were blinded to predictors, whereas the midwife assessing predictors was blinded to outcome. Nevertheless, birth weight and head circumference may be influenced by the level of affluence and the gestational culture of the population studied, whereas the prevalence of MetS depends heavily on definition, local epidemiology of overweight/obesity, and racial differences that could affect WC. For example, less visceral adiposity tissue has been found in African-Americans\textsuperscript{43} and more in Asians\textsuperscript{44} as compared to Caucasians for a given WC. Hence, our findings should be replicated in other settings with varying dietary habits, physical activity, socioeconomic and cultural patterns, as well as with pretest probabilities different from those of our derivation cohort in which approximately one third of parents were overweight/obese.

Likewise, the use of the score requires the widespread availability – at least to obstetricians and pediatricians – of race- or ethnic-specific charts of newborns’ weight and head circumference percentiles and of fetal growth charts, so that precise adjustments for gestational age can be made. In addition, despite statistical significance of associations, it can be argued that our analysis is insufficient for drawing clinically useful conclusions for the general population because it does not include several factors that could influence offspring’s metabolic profile,
such as attending schools of lower academic grading, parental education level and socioeconomic status, and second-hand smoke exposure at home. Therefore, large-scale validation including these parameters is needed before routine application of the score.

Because our assessments of MetS incidence were cross-sectional, causation could not be inferred. Longitudinal cohort studies would provide more concrete evidence for this purpose. Moreover, scant information was available in our investigation regarding the etiology of small birth size. This is relevant for the exact determination of CV risk, inasmuch as the effect of low birth weight on CV risk could be different in children of mothers who had smoked during pregnancy, presented with pre-eclampsia or experienced placental insufficiency. Lastly, the score described in our observational study predicted MetS under presumably stable developmental conditions in the context of a non-interventional investigation, since no specific dietary/exercise guidelines were adopted by high-risk subjects in neither the derivation nor the validation cohort.

Conflicts of Interest Disclosures: None

References:


2. Steinberger J, Daniels SR, Eckel RH, Hayman L, Lustig RH, McCrindle B, Mietus-Snyder ML. Progress and challenges in metabolic syndrome in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on


Table 1. Newborn and parental characteristics of the derivation cohort. Values are expressed as number of subjects (%) or mean±pooled standard deviation (OR, odds ratio; MD, mean difference; CI, confidence intervals; CV, cardiovascular disease; * at least in one parent).

<table>
<thead>
<tr>
<th>Newborn &amp; parental characteristics</th>
<th>Subjects with normal metabolic profile in adolescence (n=1165)</th>
<th>Subjects who developed MetS in adolescence (n=105)</th>
<th>P value</th>
<th>OR or MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (gr)</td>
<td>3447±644</td>
<td>2941±349</td>
<td>&lt;0.001</td>
<td>-506±103</td>
<td>-982, -202</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>51.2±2.4</td>
<td>50.8±1.9</td>
<td>0.658</td>
<td>-0.4±0.3</td>
<td>-1.1, 0.4</td>
</tr>
<tr>
<td>Birth head circumference (cm)</td>
<td>36.1±1.9</td>
<td>33.1±1.4</td>
<td>&lt;0.001</td>
<td>-3.0±0.8</td>
<td>-5.0, -1.5</td>
</tr>
<tr>
<td>Parental history of CV disease * (%)</td>
<td>81 (7)</td>
<td>23 (22)</td>
<td>0.002</td>
<td>3.8</td>
<td>2.2, 6.3</td>
</tr>
<tr>
<td>Parental history of diabetes * (%)</td>
<td>35 (3)</td>
<td>11 (11)</td>
<td>0.003</td>
<td>3.8</td>
<td>1.9, 7.7</td>
</tr>
<tr>
<td>Parental overweight or obesity * (%)</td>
<td>408 (35)</td>
<td>84 (80)</td>
<td>&lt;0.001</td>
<td>7.4</td>
<td>4.5, 12.2</td>
</tr>
<tr>
<td>Paternal history of diabetes (%)</td>
<td>24 (2)</td>
<td>8 (8)</td>
<td>0.002</td>
<td>3.9</td>
<td>1.7, 8.9</td>
</tr>
<tr>
<td>Paternal overweight (%)</td>
<td>248 (21)</td>
<td>54 (51)</td>
<td>0.013</td>
<td>3.9</td>
<td>2.6, 5.9</td>
</tr>
<tr>
<td>Maternal history of diabetes (%)</td>
<td>19 (2)</td>
<td>6 (6)</td>
<td>0.009</td>
<td>3.7</td>
<td>1.4, 9.4</td>
</tr>
<tr>
<td>Maternal overweight (%)</td>
<td>184 (16)</td>
<td>43 (41)</td>
<td>0.010</td>
<td>3.7</td>
<td>2.4, 5.6</td>
</tr>
<tr>
<td>Maternal obesity (%)</td>
<td>103 (9)</td>
<td>27 (26)</td>
<td>0.007</td>
<td>3.6</td>
<td>2.2, 5.7</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>27±7</td>
<td>29±9</td>
<td>0.188</td>
<td>2±1</td>
<td>-1.8, 4.4</td>
</tr>
<tr>
<td>Pregnancy smoking (%)</td>
<td>193 (17)</td>
<td>20 (19)</td>
<td>0.081</td>
<td>1.2</td>
<td>0.7, 1.9</td>
</tr>
<tr>
<td>Pregnancy alcohol consumption (%)</td>
<td>87 (8)</td>
<td>13 (12)</td>
<td>0.072</td>
<td>1.8</td>
<td>0.9, 3.3</td>
</tr>
<tr>
<td>Premature delivery (%)</td>
<td>91 (8)</td>
<td>11 (11)</td>
<td>0.091</td>
<td>1.4</td>
<td>0.7, 2.7</td>
</tr>
<tr>
<td>Small for gestational age (%)</td>
<td>45 (4)</td>
<td>6 (6)</td>
<td>0.104</td>
<td>1.5</td>
<td>0.6, 3.6</td>
</tr>
<tr>
<td>Large for gestational age (%)</td>
<td>31 (3)</td>
<td>5 (5)</td>
<td>0.097</td>
<td>1.8</td>
<td>0.7, 4.8</td>
</tr>
<tr>
<td>Gestational duration (weeks)</td>
<td>39±2</td>
<td>38±2</td>
<td>0.179</td>
<td>-1±1</td>
<td>-4, 1</td>
</tr>
<tr>
<td>Gestational diabetes (%)</td>
<td>42 (4)</td>
<td>7 (7)</td>
<td>0.083</td>
<td>1.9</td>
<td>0.8, 4.4</td>
</tr>
<tr>
<td>Gestational hypertension (%)</td>
<td>30 (3)</td>
<td>6 (6)</td>
<td>0.059</td>
<td>2.3</td>
<td>0.9, 5.6</td>
</tr>
<tr>
<td>Caesarian section (%)</td>
<td>526 (45)</td>
<td>52 (50)</td>
<td>0.117</td>
<td>1.2</td>
<td>0.8, 1.8</td>
</tr>
<tr>
<td>First pregnancy (%)</td>
<td>463 (40)</td>
<td>40 (38)</td>
<td>0.433</td>
<td>0.9</td>
<td>0.6, 1.4</td>
</tr>
<tr>
<td>Breast-feeding for at least 4 weeks (%) (exclusive/predominant) (%)</td>
<td>454 (39)</td>
<td>20 (19)</td>
<td>0.009</td>
<td>0.4</td>
<td>0.2, 0.6</td>
</tr>
</tbody>
</table>
Table 2. Characteristics of the derivation cohort at age 6-8. Values are expressed as number of subjects (%) or mean±pooled standard deviation (OR, odds ratio; MD, mean difference; CI, confidence intervals; BP, blood pressure).

<table>
<thead>
<tr>
<th>Participants characteristics at age 6-8</th>
<th>Subjects with normal metabolic profile in adolescence (n=1165)</th>
<th>Subjects who developed MetS in adolescence (n=105)</th>
<th>P value</th>
<th>OR or MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.1±1.0</td>
<td>7.0±0.8</td>
<td>0.638</td>
<td>-0.1±0.1</td>
<td>-0.6, 0.4</td>
</tr>
<tr>
<td>Males (%)</td>
<td>579 (50)</td>
<td>51 (49)</td>
<td>0.941</td>
<td>0.9</td>
<td>0.6, 1.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>26±7</td>
<td>29±7</td>
<td>0.012</td>
<td>3±2</td>
<td>1, 6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>124±5</td>
<td>127±7</td>
<td>0.041</td>
<td>3±2</td>
<td>2, 6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>16.7±2.2</td>
<td>17.4±2.4</td>
<td>0.014</td>
<td>0.7±0.5</td>
<td>0.3, 1.6</td>
</tr>
<tr>
<td>Body mass index (z score)</td>
<td>-0.2±0.4</td>
<td>0.3±0.3</td>
<td>0.011</td>
<td>0.5±0.5</td>
<td>0.2, 1.0</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>54±9</td>
<td>59±10</td>
<td>0.003</td>
<td>5±4</td>
<td>3, 8</td>
</tr>
<tr>
<td>Waist/height ratio</td>
<td>0.42±0.06</td>
<td>0.47±0.05</td>
<td>0.028</td>
<td>0.05±0.01</td>
<td>0.02, 0.09</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>96±10</td>
<td>108±10</td>
<td>0.002</td>
<td>12±2</td>
<td>6, 20</td>
</tr>
<tr>
<td>Systolic BP (z score)</td>
<td>-0.1±0.4</td>
<td>0.9±0.5</td>
<td>&lt;0.001</td>
<td>1.0±0.6</td>
<td>0.4, 1.7</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>63±7</td>
<td>69±5.8</td>
<td>0.005</td>
<td>6±1</td>
<td>2, 10</td>
</tr>
<tr>
<td>Diastolic BP (z score)</td>
<td>-0.2±0.2</td>
<td>0.7±0.5</td>
<td>0.002</td>
<td>0.9±0.4</td>
<td>0.3, 1.6</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>76±10</td>
<td>89±11</td>
<td>0.004</td>
<td>13±4</td>
<td>4, 20</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>169±27</td>
<td>176±26</td>
<td>0.013</td>
<td>7±2</td>
<td>3, 10</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>99±21</td>
<td>109±20</td>
<td>0.034</td>
<td>10±3</td>
<td>4, 18</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>56±10</td>
<td>46±9</td>
<td>&lt;0.001</td>
<td>-10±3</td>
<td>-18, -3</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>70±25</td>
<td>101±29</td>
<td>&lt;0.001</td>
<td>31±10</td>
<td>11, 53</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mg/dl)</td>
<td>113±18</td>
<td>130±20</td>
<td>&lt;0.001</td>
<td>17±8</td>
<td>6, 26</td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio</td>
<td>3±1</td>
<td>3.8±2</td>
<td>0.031</td>
<td>0.8±0.5</td>
<td>0.3, 2</td>
</tr>
</tbody>
</table>
Table 3. Characteristics of the derivation cohort in adolescence. Values are expressed as number of subjects (%) or mean±pooled standard deviation (OR, odds ratio; MD, mean difference; CI, confidence intervals; BP, blood pressure; * as reported confidentially by adolescents themselves).

<table>
<thead>
<tr>
<th>Participants’ characteristics in adolescence</th>
<th>Subjects with normal metabolic profile (n=1165)</th>
<th>Subjects with MetS (n=105)</th>
<th>P value</th>
<th>OR or MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>13.9±1.2</td>
<td>14.4±0.9</td>
<td>0.895</td>
<td>0.5±0.2</td>
<td>-0.4, 1.1</td>
</tr>
<tr>
<td>Males (%)</td>
<td>579 (50)</td>
<td>51 (49)</td>
<td>0.941</td>
<td>0.9</td>
<td>0.6, 1.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>51±10</td>
<td>71±14</td>
<td>&lt;0.001</td>
<td>20±5</td>
<td>9, 31</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163±5</td>
<td>167±5</td>
<td>0.041</td>
<td>4±2</td>
<td>2, 8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>19.2±3.2</td>
<td>25.6±2.9</td>
<td>&lt;0.001</td>
<td>6.4±1.6</td>
<td>2.3, 10.4</td>
</tr>
<tr>
<td>Body mass index z score</td>
<td>-0.1±0.5</td>
<td>1.5±0.4</td>
<td>&lt;0.001</td>
<td>1.6±0.6</td>
<td>0.5, 2.8</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>75±9</td>
<td>90±7</td>
<td>&lt;0.001</td>
<td>15±5</td>
<td>5, 25</td>
</tr>
<tr>
<td>Waist/height ratio</td>
<td>0.45±0.06</td>
<td>0.54±0.07</td>
<td>&lt;0.001</td>
<td>0.09±0.01</td>
<td>0.05, 0.13</td>
</tr>
<tr>
<td>Active smoking * (%)</td>
<td>82 (7)</td>
<td>16 (15)</td>
<td>0.019</td>
<td>2.4</td>
<td>1, 4</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>110±10</td>
<td>130±13</td>
<td>&lt;0.001</td>
<td>20±3</td>
<td>10, 32</td>
</tr>
<tr>
<td>Systolic BP (z score)</td>
<td>-0.1±0.4</td>
<td>1.3±0.7</td>
<td>&lt;0.001</td>
<td>1.4±0.6</td>
<td>0.4, 2.4</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>69±8</td>
<td>85±9</td>
<td>&lt;0.001</td>
<td>16±2</td>
<td>4, 25</td>
</tr>
<tr>
<td>Diastolic BP (z score)</td>
<td>-0.2±0.3</td>
<td>1.2±0.5</td>
<td>&lt;0.001</td>
<td>1.4±0.7</td>
<td>0.5, 2.3</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>84±12</td>
<td>102±13</td>
<td>0.006</td>
<td>18±5</td>
<td>6, 27</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>162±23</td>
<td>175±30</td>
<td>0.012</td>
<td>13±4</td>
<td>4, 24</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>90±20</td>
<td>106±20</td>
<td>0.002</td>
<td>16±4</td>
<td>5, 26</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>54±10</td>
<td>39±8</td>
<td>&lt;0.001</td>
<td>-15±5</td>
<td>-28, -5</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>88±40</td>
<td>152±42</td>
<td>&lt;0.001</td>
<td>64±20</td>
<td>30, 102</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mg/dl)</td>
<td>108±19</td>
<td>136±21</td>
<td>&lt;0.001</td>
<td>28±9</td>
<td>12, 51</td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio</td>
<td>3±1</td>
<td>4.5±2</td>
<td>0.009</td>
<td>1.5±0.5</td>
<td>0.6, 3.3</td>
</tr>
</tbody>
</table>
Table 4. Multiple logistic regression analysis for diagnosis of MetS in the derivation cohort (OR, odds ratio; CI, confidence intervals).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Beta coefficient</th>
<th>Standard error</th>
<th>P value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight &lt;10th percentile</td>
<td>1.795</td>
<td>0.59</td>
<td>&lt; 0.001</td>
<td>6.02</td>
<td>2.53, 10.12</td>
</tr>
<tr>
<td>Birth head circumference &lt;10th percentile</td>
<td>1.423</td>
<td>0.44</td>
<td>&lt; 0.001</td>
<td>4.15</td>
<td>2.04, 7.14</td>
</tr>
<tr>
<td>Parental overweight or obesity</td>
<td>1.171</td>
<td>0.39</td>
<td>0.008</td>
<td>3.22</td>
<td>1.30, 5.29</td>
</tr>
</tbody>
</table>

Table 5. Performance of the proposed diagnostic score in derivation and validation cohorts.

<table>
<thead>
<tr>
<th>Number of factors</th>
<th>Adolescents with MetS</th>
<th>Adolescents with normal metabolic profile</th>
<th>Proportion of adolescents with MetS among adolescents with the respective factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derivation cohort (N = 1270)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No factors</td>
<td>0</td>
<td>778</td>
<td>0%</td>
</tr>
<tr>
<td>1 factor</td>
<td>5</td>
<td>353</td>
<td>1%</td>
</tr>
<tr>
<td>2 factors</td>
<td>5</td>
<td>11</td>
<td>31%</td>
</tr>
<tr>
<td>3 factors</td>
<td>95</td>
<td>23</td>
<td>81%</td>
</tr>
<tr>
<td>Validation cohort (N = 1091)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No factors</td>
<td>0</td>
<td>798</td>
<td>0%</td>
</tr>
<tr>
<td>1 factor</td>
<td>5</td>
<td>174</td>
<td>3%</td>
</tr>
<tr>
<td>2 factors</td>
<td>3</td>
<td>9</td>
<td>25%</td>
</tr>
<tr>
<td>3 factors</td>
<td>78</td>
<td>24</td>
<td>77%</td>
</tr>
</tbody>
</table>
Table 6. Characteristics of the overall validation cohort. Values are expressed as number of subjects (%) or mean±pooled standard deviation (BP, blood pressure).

<table>
<thead>
<tr>
<th>Demographics, natal characteristics and family history</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>14.1±1.6</td>
</tr>
<tr>
<td>Males (%)</td>
<td>557 (51)</td>
</tr>
<tr>
<td>Birth weight (gr)</td>
<td>3402±517</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>52.1±2.2</td>
</tr>
<tr>
<td>Birth head circumference (cm)</td>
<td>35.9±1.8</td>
</tr>
<tr>
<td>Parental history of cardiovascular disease (%)</td>
<td>98 (9)</td>
</tr>
<tr>
<td>Parental history of diabetes (%)</td>
<td>55 (5)</td>
</tr>
<tr>
<td>Parental overweight/obesity (%)</td>
<td>293 (27)</td>
</tr>
<tr>
<td>Parental history of diabetes (%)</td>
<td>55 (5)</td>
</tr>
<tr>
<td>Parental overweight/obesity (%)</td>
<td>293 (27)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>84±13</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>161±25</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>90±21</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>53±10</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>88±31</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mg/dl)</td>
<td>108±15</td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio</td>
<td>3±1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gestational history</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>28±6</td>
</tr>
<tr>
<td>Pregnancy smoking (%)</td>
<td>197 (18)</td>
</tr>
<tr>
<td>Pregnancy alcohol consumption (%)</td>
<td>99 (9)</td>
</tr>
<tr>
<td>Premature delivery (%)</td>
<td>110 (10)</td>
</tr>
<tr>
<td>Caesarian section (%)</td>
<td>524 (48)</td>
</tr>
<tr>
<td>First pregnancy (%)</td>
<td>403 (37)</td>
</tr>
<tr>
<td>Breast-feeding for at least 4 weeks (%)</td>
<td>382 (35)</td>
</tr>
<tr>
<td>Gestational duration (weeks)</td>
<td>38±2</td>
</tr>
<tr>
<td>Gestational diabetes (%)</td>
<td>54 (5)</td>
</tr>
<tr>
<td>Gestational hypertension (%)</td>
<td>22 (2)</td>
</tr>
</tbody>
</table>

Figure Legend:

Figure 1. Odds ratio for MetS in adolescence according to percentiles of birth weight.
Odds ratios for MetS in adolescence according to percentiles of birth weight. Birth weight >90th percentile was considered as the reference level, i.e. with the lowest probability for MetS (§ non significant; * p<0.05; ** p<0.01; *** p<0.001; 95% confidence intervals in parentheses)
Metabolic Syndrome in Adolescence: Can it be Predicted from Natal and Parental Profile? The Prediction of Metabolic Syndrome in Adolescence (PREMA) Study
Stamatis P. Efstatiou, Irini I. Skeva, Evi Zorbala, Evangelos Georgiou and Theodore D. Mountokalakis

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