Metabolic Syndrome in Adolescence
Can It Be Predicted From Natal and Parental Profile?
The Prediction of Metabolic Syndrome in Adolescence (PREMA) Study

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Background—There are well-established predisposing factors for the development of metabolic syndrome (MetS) in childhood or adolescence, but no specific risk profile has been identified as yet. The Prediction of Metabolic Syndrome in Adolescence (PREMA) study was conducted (1) to construct a classification score that could detect children at high risk for MetS in adolescence and (2) 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 6 to 8 years of age were used to detect independent predictors of MetS at 13 to 15 years of age 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 adolescents in the derivation phase (8%), whereas birth weight <10th percentile (odds ratio, 6.02; 95% confidence interval, 2.53–10.12, $P<0.001$), birth head circumference <10th percentile (odds ratio, 4.15; 95% confidence interval, 2.04–7.14, $P<0.001$), and parental overweight or obesity (in at least 1 parent; odds ratio, 3.22; 95% confidence interval, 1.30–5.29, $P<0.01$) were independently associated with diagnosis of MetS in adolescence. Among adolescents in the validation cohort (86 [8%] with MetS), the presence of all these 3 predictors predicted MetS with a sensitivity of 91% and a specificity of 98%.

Conclusions—The coexistence 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. **(*Circulation*. 2012;125:902-910.)**

Key Words: metabolic syndrome ■ adolescence ■ prediction

The metabolic syndrome (MetS), a cluster of disturbed glucose and insulin metabolism, abdominal obesity, dyslipidemia, and hypertension, is observed in 35% to 40% of adults in developed countries.[1] Its prevalence in childhood and adolescence has increased from approximately 2% in the mid-1990s to a current estimate of 10% in the United States 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 nonadult individuals, and the growing criticism regarding the practical value of the overall MetS concept 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 adult MetS, subclinical atherosclerosis, and type 2 diabetes mellitus, independent of other known predictors.[2]

Clinical Perspective on p 910

Several studies have investigated predisposing factors for MetS in childhood/adolescence, but no specific risk profile has been identified as yet. Although accumulating research suggests that both light[4–7] and heavy[4,8–10] newborns have a higher probability of MetS before adulthood, the exact association between birth weight and MetS in childhood/adolescence remains unclear. Moreover, maternal obesity,[10,11] gestational diabetes,[10] family history of diabetes,[4,12] and attendance at schools of lower academic grading[12] have been linked to offspring's MetS in American[4,10,11] and Asian[12] populations, but such data from Europe are lacking. The PREdiction of Metabolic syndrome in Adolescence (PREMA) study was conducted (1) to construct a risk score for MetS in adolescence using natal, parental, and childhood characteristics and (2) to test the predictive accuracy of this score via its application to an independent population of adolescents.

Methods

Design

The PREMA study was a 10-year investigation conducted in 2 phases: (1) Phase 1 was a prospective study (derivation cohort) in which data from natal, parental, and clinical/laboratory profile in

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childhood were used for the construction of a risk score for MetS in adolescence. At baseline (year 2000), children 6 to 8 years old underwent anthropometric, blood pressure (BP), fasting plasma glucose, and lipid measurements, and their natal and parental histories were recorded. Parents were informed about their children's status and were given typical lifestyle recommendations. At follow-up (2007), all adolescents 13 to 15 years of age who had attended the first session were invited to participate in a survey evaluating the prevalence of MetS in Greek adolescents. (2) 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 12 to 15 years of age (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, the capital of Greece with 3.5 million 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, which consisted of 1270 children 6 to 8 years old reassessed in adolescence (derivation cohort) and 1091 adolescents 12 to 15 years old (validation cohort), represented approximately 2‰ of each of these 2 age population categories in Greece. Children with known major cardiovascular, endocrinal, nutritional, or renal problems, with secondary obesity, or taking drugs that influence metabolic profile were excluded.

Parents/caretakers who had used the preventive medicine program before the PREMA study were informed by telephone of the scope and procedures of this investigation before their children's scheduled annual checkup 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 the study visit. This questionnaire was used to collect separate paternal and maternal information regarding age, history of cardiovascular 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 cross-checked 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 before 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 after 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.[13] Status as small for gestational age was defined as birth weight and/or length that was 2 SD below the mean for each gestational age (equivalent to the 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).[13] The midwife (E.Z.) who conducted participants' assessment and the 2 physicians (S.P.E. and I.I.S.) who made the 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 at both baseline and follow-up of phase 1 and on 1 occasion during phase 2. Weight was measured to the nearest 0.1 kg with a portable electronic scale (model 68987; Befour Inc, Saukville, WI), and height was measured to the nearest centimeter with 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 weight (kg)/height $(m)^2$. Waist circumference (WC) was measured to the nearest 0.1 cm with a flexible, nonelastic tape midway between the lowest portion of the 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 or maternal BMI $\geq$25 and $<$30 kg/m^2, whereas parental obesity was defined as paternal or maternal BMI $\geq$30 kg/m^2.

Plasma total cholesterol and triglycerides were determined by enzymatic methods adapted to a Hitachi 705 analyzer (Boehringer Mannheim, Mannheim, Germany); high-density lipoprotein was measured in the supernatant after sodium phosphotungstate/magnesium chloride precipitation. The intra-assay and interassay coefficients of variation were approximately 2% and 3% for triglycerides and 1% and 3%, respectively, for high-density lipoprotein. Low-density lipoprotein was determined by the Friedewald formula. Fasting plasma glucose was measured by the hexokinase/glucose-6-phosphate dehydrogenase method, with intra-assay and interassay coefficients of variation of approximately 2% and 4%, respectively. Supine BP measurements were performed in the right arm with a standard mercury sphygmomanometer (Baumanometer; W.A. Baum, Copiague, NY) with appropriate cuff size according to arm size, ie, cuff with inflatable bladder width $\geq$40% and length $\geq$80% of the arm circumference at the midway point between the olecranon and acromion. Korotkoff phase I sounds were used for determination of systolic BP and phase V for diastolic BP. After a 5-minute rest period, BP was measured 3 times to the nearest 2 mm Hg with a 1-minute interval between measurements, and the average of the last 2 measurements was used in the analysis.

Because we assessed adolescent populations 12 to 15 years of age, we used the International Diabetes Federation consensus definition of MetS for ages 10 to 16 years,[14] which is currently the most widely recognized until more outcome data are available. MetS was defined as abdominal obesity (WC $\geq$90th percentile) plus $\geq$2 of the following: BP $\geq$130 mm Hg (systolic) or $\geq$85 mm Hg (diastolic); triglyceride $\geq$150 mg/dL; high-density lipoprotein $<$40 mg/dL; and fasting plasma glucose $\geq$100 mg/dL.[14] Despite the limitations of this definition imposed by the absolute cutoffs, the major component (abdominal obesity) is defined by age-, sex-, and ethnic-specific WC percentiles as recommended by the International Diabetes Federation.[14] Percentiles of birth measurements and of childhood/adolescence characteristics were based on national data provided by the First University Department of Pediatrics of Agia Sophia Hospital of Athens[13] and the Hellenic Medical Association for Obesity.[15–17]

Statistical Analysis

Statistical analysis was performed via Statistical Package for the Social Sciences software (SPSS Inc; Chicago, IL; release 17.0). Normality of data distribution was assessed by Kolmogorov-Smirnov test. Intergroup comparisons were made by χ^2 or Fisher exact test for categorical data and unpaired Student t test for continuous variables, whereas Spearman coefficient (ρ) was used to assess correlations. We calculated z scores in the derivation cohort for BMI and BP at 6 to 8 years and 13 to 15 years, as well as for weight at birth, during childhood, and during adolescence on the basis of the respective age- and sex-specific mean values and SDs derived from national data.[15–18] In addition, we used the widely accepted international age- and sex-specific BMI cutoff points for definition of overweight/obesity in children/adolescents,[19] according to the recommendations of the International Obesity Task Force[19] and the Hellenic Medical Association for Obesity,[15,17] to estimate the prevalence of overweight/obesity at age 6 to 8 and 13 to 15 in the MetS and non-MetS groups 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 κ concordance test was used to assess agreement between provisional MetS diagnosis at 6 to 8 years of age and diagnosis of MetS at 13 to 15 years of age. Ninety-five percent confidence intervals (95% CIs) were calculated, tests of significance were 2-tailed, and $P<0.05$ was considered significant.

Table 1. Newborn and Parental Characteristics of the Derivation Cohort

Newborn and Parental Characteristics	Subjects With Normal Metabolic Profile in Adolescence (n=1165)	Subjects Who Developed MetS in Adolescence (n=105)	*P*	Odds Ratio or Mean Difference	95% CI
Birth weight, g	3447±644	2941±349	<0.001	−506±103	−982 to −202
Birth length, cm	51.2±2.4	50.8±1.9	0.658	−0.4±0.3	−1.1 to 0.4
Birth head circumference, cm	36.1±1.9	33.1±1.4	<0.001	−3.0±0.8	−5.0 to −1.5
Parental history of CVD*	81 (7)	23 (22)	0.002	3.8	2.2–6.3
Parental history of diabetes*	35 (3)	11 (11)	0.003	3.8	1.9–7.7
Parental overweight or obesity*	408 (35)	84 (80)	<0.001	7.4	4.5–12.2
Paternal history of diabetes mellitus	24 (2)	8 (8)	0.002	3.9	1.7–8.9
Paternal overweight	248 (21)	54 (51)	0.013	3.9	2.6–5.9
Paternal obesity	130 (11)	25 (24)	0.022	2.5	1.5–4.1
Maternal history of diabetes	19 (2)	6 (6)	0.009	3.7	1.4–9.4
Maternal overweight	184 (16)	43 (41)	0.010	3.7	2.4–5.6
Maternal obesity	103 (9)	27 (26)	0.007	3.6	2.2–5.7
Maternal age, y	27±7	29±9	0.188	2±1	−1.8 to 4.4
Pregnancy smoking	193 (17)	20 (19)	0.081	1.2	0.7–1.9
Pregnancy alcohol consumption	87 (8)	13 (12)	0.072	1.8	0.9–3.3
Premature delivery	91 (8)	11 (11)	0.091	1.4	0.7–2.7
Small for gestational age	45 (4)	6 (6)	0.104	1.5	0.6–3.6
Large for gestational age	31 (3)	5 (5)	0.097	1.8	0.7–4.8
Gestational duration, wk	39±2	38±2	0.179	−1±1	−4 to 1
Gestational diabetes	42 (4)	7 (7)	0.083	1.9	0.8–4.4
Gestational hypertension	30 (3)	6 (6)	0.059	2.3	0.9–5.6
Cesarean section	526 (45)	52 (50)	0.117	1.2	0.8–1.8
First pregnancy	463 (40)	40 (38)	0.433	0.9	0.6–1.4
Breast-feeding for at least 4 wk (exclusive/predominant)	454 (39)	20 (19)	0.009	0.4	0.2–0.6

MetS indicates metabolic syndrome; CI, confidence interval; and CVD, cardiovascular disease.
Values are expressed as No. of subjects (%) or mean±pooled SD.
*At least in 1 parent.

Logistic regression analysis was applied to identify independent predictors of MetS and to investigate the association between birth weight percentiles and odds of MetS by calculating the respective odds ratios. A stepwise selection procedure was used, with entry and removal criteria of $P=0.05$ and $P=0.10$, respectively, whereas the presence of multicollinearity was examined by calculating the variance inflation factor and tolerance. A Hosmer-Lemeshow test was used to assess model fitting. We selected the 10th and 90th percentiles as cutoffs for dichotomizing continuous variables such as birth measurements because these thresholds (1) offered a simple, easily interpretable risk classification in the context of a prediction score; (2) gave the largest difference between individual outcomes in the resulting 2 groups and consequently the largest sensitivity, specificity, and positive and negative predictive values; (3) created a binary split of continuous covariates to 2 relatively distinct but homogeneous, clinically meaningful, and sufficiently large groups so that differences could reach statistical significance; and (4) have been used successfully in previous large-scale investigations, thus allowing comparability.[20,21]

Results

Phase 1: Derivation Cohort (2000–2007)

The initial database of the 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 also had higher prevalence of parental history of cardiovascular disease and diabetes, parental overweight/obesity, paternal history of diabetes, paternal overweight/obesity, maternal history of diabetes, and maternal overweight/obesity and lower prevalence of breast-feeding for at least 4 weeks. Participants' characteristics at age 6 to 8 years are illustrated in Table 2. Children 6 to 8 years of age who subsequently developed MetS had higher weight, height, BMI, WC, BP, total cholesterol, low-density lipoprotein, and triglycerides and lower high-density lipoprotein. The above differences persisted at 13 to 15 years of age (Table 3), whereas a greater proportion of smokers were additionally found in the MetS group.

Table 2. Characteristics of the Derivation Cohort at 6 to 8 Years of Age

Participant Characteristics at Age 6–8 y	Subjects With Normal Metabolic Profile in Adolescence (n=1165)	Subjects Who Developed MetS in Adolescence (n=105)	*P*	Odds Ratio or Mean Difference	95% CI
Age, y	7.1±1.0	7.0±0.8	0.638	−0.1±0.1	−0.6 to 0.4
Males	579 (50)	51 (49)	0.941	0.9	0.6–1.4
Weight, kg	26±7	29±7	0.012	3±2	1–6
Height, cm	124±5	127±7	0.041	3±2	2–6
Body mass index, kg/m^2	16.7±2.2	17.4±2.4	0.014	0.7±0.5	0.3–1.6
Body mass index (*z* score)	−0.2±0.4	0.3±0.3	0.011	0.5±0.5	0.2–1.0
Waist circumference, cm	54±9	59±10	0.003	5±4	3–8
Waist/height ratio	0.42±0.06	0.47±0.05	0.028	0.05±0.01	0.02–0.09
Systolic BP, mm Hg	96±10	108±10	0.002	12±2	6–20
Systolic BP *z* score	−0.1±0.4	0.9±0.5	<0.001	1.0±0.6	0.4–1.7
Diastolic BP, mm Hg	63±7	69±5.8	0.005	6±1	2–10
Diastolic BP *z* score	−0.2±0.2	0.7±0.5	0.002	0.9±0.4	0.3–1.6
Fasting plasma glucose, mg/dL	76±10	89±11	0.004	13±4	4–20
Cholesterol, mg/dL	169±27	176±26	0.013	7±2	3–10
LDL, mg/dL	99±21	109±20	0.034	10±3	4–18
HDL, mg/dL	56±10	46±9	<0.001	−10±3	−18 to −3
Triglycerides, mg/dL	70±25	101±29	<0.001	31±10	11–53
Non-HDL cholesterol, mg/dL	113±18	130±20	<0.001	17±8	6–26
Total/HDL cholesterol ratio	3±1	3.8±2	0.031	0.8±0.5	0.3–2

MetS indicates metabolic syndrome; CI, confidence interval; BP, blood pressure; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.
Values are expressed as No. of subjects (%) or mean±pooled SD.

The plotted association between birth weight percentiles and odds ratio for MetS in the derivation cohort is shown in the Figure. Birth weight percentile showed a significant inverse relationship with BMI both at ages 6 to 8 years (Spearman correlation coefficient $\rho=-0.412$, $P=0.005$) and 13 to 15 years ($\rho=-0.631$, $P<0.001$) 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 years and $\rho=-0.817$ [$P<0.001$] at age 13–15 years) and in those without MetS ($\rho=-0.433$ [$P=0.008$] at age 6–8 years and $\rho=-0.599$ [$P<0.001$] at age 13–15 years). 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 to 8 years of age to 1.6±1.1 at 13 to 15 years of age. Comparable values in those who did not develop MetS were 0.2±0.5, −0.2±0.3, and −0.1±0.6, respectively. Furthermore, only 38 (36%) of the 105 children who developed MetS were already overweight or obese at 6 to 8 years of age according to International Obesity Task Force criteria,[19] compared with 94 (90%) of 105 in adolescence. Among those who did not develop MetS, the proportions of overweight or obese were 228 (20%) of 1165 at 6 to 8 years of age and 286 (25%) of 1165 in adolescence.

There were 38 children in the overall derivation cohort (3%) with provisional MetS according to International Diabetes Federation (ie, WC ≥90th age-, sex-, and ethnic-specific percentile at age 6–8 years and family history of MetS, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, hypertension, or obesity).[14] Thus, 28 participants had MetS both in childhood and in adolescence, 10 only in childhood, 77 only in adolescence, and 1155 neither in childhood nor in adolescence ($\kappa=0.27$, which indicates only fair agreement between diagnosis of provisional MetS and MetS in adolescence). Provisional MetS at 6 to 8 years of age predicted MetS at 12 to 15 years of age with a sensitivity of 27%, specificity of 99%, positive predictive value of 74%, and negative predictive value of 94%. Multiple logistic regression analysis identified 3 independent predictors of MetS (Table 4): Birth weight <10th percentile, birth head circumference <10th percentile, and parental overweight or obesity (in at least 1 parent). No indication of multicollinearity was found for any of the variables considered in the regression analysis (tolerance >0.40 and variance inflation factor <2.5). The Hosmer-Lemeshow test showed good model fitting ($\chi^2=6.642$, 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 coexistence of all 3 factors was used for MetS prediction, the score showed a sensitivity of 91% (95% CI, 83%–95%), specificity of 98% (95% CI, 97%–99%), positive predictive value of 81% (95% CI, 72%–87%), negative predictive value of 99% (95% CI, 98%–99%), positive likelihood ratio of 46 (95% CI, 30–69), negative likelihood ratio of 0.1 (95% CI, 0.05–0.18), and accuracy of 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

Table 3. Characteristics of the Derivation Cohort in Adolescence

Participants' Characteristics in Adolescence	Subjects With Normal Metabolic Profile (n=1165)	Subjects With MetS (n=105)	*P*	Odds Ratio or Mean Difference	95% CI
Age, y	13.9±1.2	14.4±0.9	0.895	0.5±0.2	−0.4 to 1.1
Males, %	579 (50)	51 (49)	0.941	0.9	0.6–1.4
Weight, kg	51±10	71±14	<0.001	20±5	9–31
Height, cm	163±5	167±5	0.041	4±2	2–8
Body mass index, kg/m^2	19.2±3.2	25.6±2.9	<0.001	6.4±1.6	2.3–10.4
Body mass index *z* score	−0.1±0.5	1.5±0.4	<0.001	1.6±0.6	0.5–2.8
Waist circumference, cm	75±9	90±7	<0.001	15±5	5–25
Waist/height ratio	0.45±0.06	0.54±0.07	<0.001	0.09±0.01	0.05–0.13
Active smoking*	82 (7)	16 (15)	0.019	2.4	1–4
Systolic BP, mm Hg	110±10	130±13	<0.001	20±3	10–32
Systolic BP *z* score	−0.1±0.4	1.3±0.7	<0.001	1.4±0.6	0.4–2.4
Diastolic BP, mm Hg	69±8	85±9	<0.001	16±2	4–25
Diastolic BP *z* score	−0.2±0.3	1.2±0.5	<0.001	1.4±0.7	0.5–2.3
Fasting plasma glucose, mg/dL	84±12	102±13	0.006	18±5	6–27
Cholesterol, mg/dL	162±23	175±30	0.012	13±4	4–24
LDL, mg/dL	90±20	106±20	0.002	16±4	5–26
HDL, mg/dL	54±10	39±8	<0.001	−15±5	−28 to −5
Triglycerides, mg/dL	88±40	152±42	<0.001	64±20	30–102
Non-HDL cholesterol, mg/dL	108±19	136±21	<0.001	28±9	12–51
Total/HDL cholesterol ratio	3±1	4.5±2	0.009	1.5±0.5	0.6–3.3

MetS indicates metabolic syndrome; CI, confidence interval; BP, blood pressure; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.
Values are expressed as No. of subjects (%) or mean±pooled SD.
*As reported confidentially by adolescents themselves.

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 odds ratio for MetS in the validation cohort is illustrated in the Figure, whereas the application of the classification tool to the validation database is shown in Table 5. When the coexistence of all 3 predictors was considered for MetS prediction, the score showed a sensitivity of 91% (95% CI, 83%–95%), specificity of 98% (95% CI, 97%–98%), positive predictive value of 77% (95% CI, 67%–84%), negative predictive value of 99% (95% CI, 98%–99%), positive likelihood ratio of 38 (95% CI, 25–57), negative likelihood ratio of 0.09 (95% CI, 0.05–0.19), and accuracy of 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

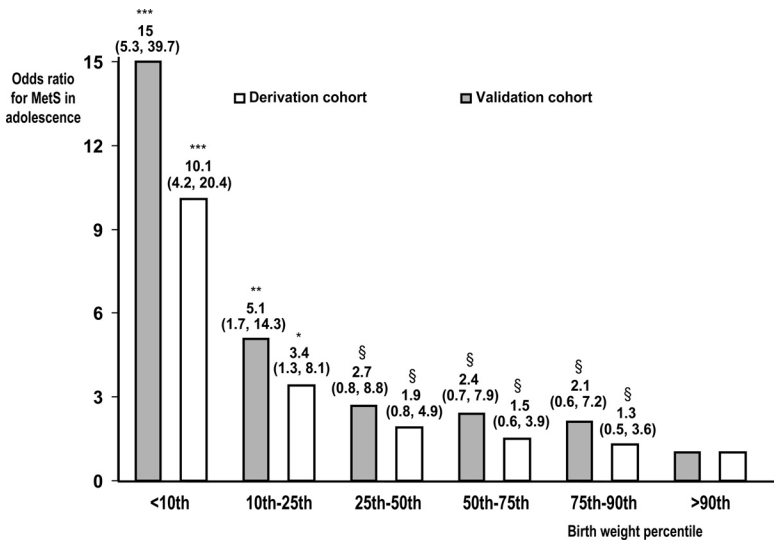

Figure. Odds ratio for metabolic syndrome (MetS) in adolescence according to percentiles of birth weight. Birth weight more than the 90th percentile was considered the reference level, ie, with the lowest probability for MetS. §Nonsignificant; *P<0.05; **P<0.01; ***P<0.001. 95% Confidence intervals are given in parentheses.

Table 4. Multiple Logistic Regression Analysis for Diagnosis of MetS in the Derivation Cohort

Variables	β-Coefficient	Standard Error	P	OR	95% CI
Birth weight <10th percentile	1.795	0.59	<0.001	6.02	2.53, 10.12
Birth head circumference <10th percentile	1.423	0.44	<0.001	4.15	2.04, 7.14
Parental overweight or obesity	1.171	0.39	0.008	3.22	1.30, 5.29

MetS indicates metabolic syndrome; OR, odds ratio; and CI, confidence interval.

possible. The prevalence of MetS in adolescents in the present study (≈8%) was comparable to that observed in similar recent investigations,[2] thus corroborating the alarming increase in the rate of MetS at the age of 12 to 18 years,[2] which converges with the respective increase in the adult population during the last decade.[1] In both the derivation and validation cohorts, the positive predictive value of the proposed score suggested that >75% of children with all 3 factors are expected to develop MetS, whereas its very high negative predictive value practically excluded the probability of MetS among children with a negative score result (ie, not fulfilling all 3 criteria). Because 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 (eg, with marginally abnormal WC, weight, BP, fasting plasma glucose, and/or lipids), although 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 the present study is in line with the notion expressed initially 20 years ago in the United Kingdom by Barker and colleagues,[22] who showed that slow rates of prenatal growth predicted cardiovascular mortality, which indicates that cardiovascular disease may originate from programming in fetal life and infancy. Subsequently, a large body of literature has been added that confirms that birth weight is inversely associated with coronary heart disease,[23,24] stroke,[23] BP,[25] insulin resistance,[26] MetS, type 2 diabetes mellitus, dyslipidemia, and nonalcoholic fatty liver.[27] Nevertheless, the association between birth weight percentiles and odds ratio for MetS in the present study was closer to a log relationship (Figure) than the U-shaped association found by several research groups.[4–10] Small head circumference has also been associated with elevated adult BP,[28] reduced arterial compliance,[28] impaired glucose tolerance,[29] increased prevalence of coronary heart disease,[30] and mortality due to coronary heart disease[31] in large-scale investigations that included Indian[30] and Scandinavian[31] populations, independent of known cardiovascular risk factors. These observations offered an 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 that result in increased adult susceptibility to cardiovascular and metabolic diseases.[22] It has been suggested that alterations in cortisol and growth hormone,[32] insulin-like growth factors,[33] or the sympathetic nervous system[34] could mediate the observed associations between birth size and later central obesity.

The children of obese/overweight parents repeatedly have been found to be at increased risk of obesity, the parents' BMI being a more powerful independent predictor of offspring's BMI than nutrition habits and sedentary behavior.[35–40] The present analysis is in accord with the above data, yielding a relative risk of 3.2 for MetS in adolescents with overweight/obese parents compared with those with normal-weight parents, the lower boundary of the 95% CIs ruling out

Table 5. Performance of the Proposed Diagnostic Score in Derivation and Validation Cohorts

No. of Factors	Adolescents With MetS, n	Adolescents With Normal Metabolic Profile, n	Proportion of Adolescents With MetS Among Adolescents With the Respective Factors, %
Derivation cohort (n=1270)			
No factors	0	778	0
1 Factor	5	353	1
2 Factors	5	11	31
3 Factors	95	23	81
Validation cohort (n=1091)			
No Factors	0	798	0
1 Factor	5	174	3
2 Factors	3	9	25
3 Factors	78	24	77

MetS indicates metabolic syndrome.

Table 6. Characteristics of the Overall Validation Cohort

Demographics, natal characteristics and family history	
Age, y	14.1±1.6
Males	557 (51)
Birth weight, g	3402±517
Birth length, cm	52.1±2.2
Birth head circumference, cm	35.9±1.8
Parental history of cardiovascular disease	98 (9)
Parental history of diabetes mellitus	55 (5)
Parental overweight/obesity	293 (27)
Clinical characteristics	
Body mass index, kg/m^2	19.5±3.9
Waist circumference, cm	75±10
Active smoking	88 (8)
Systolic BP, mm Hg	110±10
Diastolic BP, mm Hg	69±8
Laboratory characteristics	
Fasting plasma glucose, mg/dL	84±13
Cholesterol, mg/dL	161±25
LDL, mg/dL	90±21
HDL, mg/dL	53±10
Triglycerides, mg/dL	88±31
Non-HDL cholesterol, mg/dL	108±15
Total/HDL cholesterol ratio	3±1
Gestational history	
Maternal age, y	28±6
Pregnancy smoking	197 (18)
Pregnancy alcohol consumption	99 (9)
Premature delivery	110 (10)
Cesarean section	524 (48)
First pregnancy	403 (37)
Breast-feeding for at least 4 wk	382 (35)
Gestational duration, wk	38±2
Gestational diabetes mellitus	54 (5)
Gestational hypertension	22 (2)

BP indicates blood pressure; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.

Values are expressed as No. of subjects (%) or mean±pooled SD.

an increase in risk less than 30%. This particular predictor of MetS, which encompassed a wide range of conditions, ie, from only 1 overweight parent to 2 obese parents, was detected in 80% of children with MetS, thus underscoring 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' nutritional preferences and physical activity patterns are shaped early in childhood[41] and are largely influenced by parental practices and familial environment.[42]

It is noteworthy that although characteristics of participants at 6 to 8 years of age were candidates for the multivariate model, none of them entered the model when the birth characteristics were included; this finding suggests that birth weight/head circumference and parental overweight/obesity are more important for MetS risk than children's weight at age 6 to 8 years in the population studied. The latter interpretation appears to be further supported by the timing of weight gain, which we can speculate about on the basis of our observations regarding the derivation cohort. Although a greater proportion of overweight or obese children already existed at age 6 to 8 years among participants who developed MetS (36%) than among those who did not (20%), the prevalence of overweight/obesity increased in the time interval between 6 to 8 and 13 to 15 years to 90% in the MetS group compared with 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.

The proposed score identifies a high-risk group, whereas the finding that ≈75% of children who met the International Diabetes Federation provisional definition of MetS developed MetS in adolescence reveals an important target for individual intervention that applies to a small group of younger children. However, although weight z score at 6 to 8 years of age did not track well enough (at least in the Greek children studied) to identify future weight, the increase in obesity was 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, per se, but rather should be focused on the underlying central disorder of overweight and abdominal obesity and considered as a matter that involves the entire family.[41] With regard to intervention, the prevention of excess weight gain in preadolescence (ie, between early childhood and adolescence) may be recommended on the basis of the above data. Furthermore, specially designed research is required to identify with appropriate methodology the critical period for subsequent MetS development, because this may be more important than having a predictive risk score.

Several limitations of the present study should be taken into account. Although a fully independent validation can only be performed in studies that use data from different institutions, the probability of bias is limited in our report because physicians assessing outcome were blinded to predictors, whereas the midwife who assessed 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 blacks[43] and more in Asians[44] than in whites for a given WC. Hence, our findings should be replicated in other settings with varying dietary habits, physical activity, and 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 the statistical significance of associations, it can be argued that the present 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 that includes 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 cause of small birth size. This is relevant for the exact determination of cardiovascular risk, inasmuch as the effect of low birth weight on cardiovascular risk could be different in children of mothers who had smoked during pregnancy, presented with preeclampsia, or experienced placental insufficiency. Lastly, the score described in our observational study predicted MetS under presumably stable developmental conditions in the context of a noninterventional investigation, because no specific dietary/exercise guidelines were adopted by high-risk subjects in either the derivation or the validation cohort.

Disclosures

None.

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CLINICAL PERSPECTIVE

The prevalence of metabolic syndrome in adolescence has gradually increased to approximately 10% in the United States and Western Europe. Because it is strongly associated with adult metabolic syndrome, subclinical atherosclerosis, and type 2 diabetes mellitus, the early detection of children at high risk may have potential clinical impact. After assessment of an overall urban population of 2361 white children and adolescents over a 10-year period, the present study showed that birth measurements and family history can be helpful for the practicing clinician in classifying children according to risk of metabolic syndrome in adolescence. The coexistence of low birth weight (<10th percentile) and small birth head circumference (<10th percentile) together with parental (in at least 1 parent) overweight or obesity was found to predict metabolic syndrome in adolescence with a sensitivity of 91% and a specificity of 98%. Thus, the coexistence of low birth weight, small head circumference, and parental history of overweight or obesity may be helpful in targeting children at risk for developing metabolic syndrome in adolescence who may benefit especially from early institution of heart-healthy behaviors.

Metabolic Syndrome in Adolescence: Can It Be Predicted From Natal and Parental Profile?The Prediction of Metabolic Syndrome in Adolescence (PREMA) Study

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