ORIGINAL RESEARCH

Childhood Age and Associations Between Childhood Metabolic Syndrome and Adult Risk for Metabolic Syndrome, Type 2 Diabetes Mellitus and Carotid Intima Media Thickness: The International Childhood Cardiovascular Cohort Consortium

Juha Koskinen, MD, PhD; Costan G. Magnussen, PhD; Alan Sinaiko, MD; Jessica Woo, MHSA, PhD; Elaine Urbina, MD, MS; David R. Jacobs, Jr, PhD; Julia Steinberger, MD, MS; Ronald Prineas, MB, BS, PhD; Matthew A. Sabin, MD, PhD; Trudy Burns, MPH, PhD; Gerald Berenson, MD; Lydia Bazzano, MD, PhD; Alison Venn, PhD; Jorma S.A. Viikari, MD, PhD; Nina Hutri-Kähönen, MD, PhD; Olli Raitakari, MD, PhD; Terence Dwyer, MD, MPH; Markus Juonala, MD, PhD

Background—There is paucity of knowledge concerning the specific age in youth when the associations of metabolic syndrome (MetS) begin to be operative. Thus, we investigated the relation of age to the associations of childhood MetS with adult MetS, type 2 diabetes mellitus and high carotid intima-media thickness.

Methods and Results—Five thousand eight-hundred three participants were analyzed in 4 cohort studies (Cardiovascular Risk in Young Finns, Bogalusa Heart Study, Princeton Lipid Research Study, Insulin Study). International cutoffs and previously used 75th percentile cutoffs were used for children to define MetS and its components. Mean follow-up period was 22.3 years. Logistic regression was used to calculate risk ratios and 95% confidence intervals. Childhood MetS and overweight were associated with over 2.4-fold risk for adult MetS from the age of 5 years onward. Risk for type 2 diabetes mellitus was increased from the age of 8 (risk ratio, 2.6–4.1; 95% confidence interval, 1.35–6.76 and 1.12–7.24, respectively) onward for the 2 childhood MetS criteria based on international cut-off values and for childhood overweight. Risk for high carotid intima-media thickness was significant at ages 11 to 18 years in relation to childhood MetS or overweight (risk ratio, 2.44–4.22; 95% confidence interval, 1.55–3.55 and 2.55–5.66, respectively). Continuous childhood MetS score was associated with adult MetS from the age of 5, with type 2 diabetes mellitus from the age of 14 and with high carotid intima-media thickness from the age of 11 years onward.

Conclusions—Adult MetS was predicted by MetS in childhood beginning at age 5. However, adult type 2 diabetes mellitus and subclinical atherosclerosis were not predicted by childhood data until after age 8. Body mass index measurement alone at the same age points provided similar findings. **(*J Am Heart Assoc*. 2017;6:e005632. DOI: 10.1161/JAHA.117.005632.)**

Key Words: carotid intima-media thickness • metabolic syndrome • obesity • type 2 diabetes mellitus

From the Research Centre of Applied and Preventive Cardiovascular Medicine (J.K., C.G.M.) and Department of Medicine (J.S.A.V., M.J.), University of Turku, Finland; Heart Center (J.K.) and Division of Medicine (J.S.A.V., M.J.), Turku University Hospital, Turku, Finland; Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia (C.G.M., A.V.); Department of Pediatrics (A.S.) and Division of Epidemiology and Community Health, School of Public Health (D.R.J.), University of Minnesota, Minneapolis, MN; Division of Biostatistics and Epidemiology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, OH (J.W.); Division of Cardiology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH (E.U.); Department of Pediatrics, University of Minnesota Masonic Children's Hospital, Minneapolis, MN (J.S.); Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC (R.P.); Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, Australia (M.A.S., T.D.); Department of Pediatrics, University of Melbourne, Parkville, Australia (M.A.S., T.D.); Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA (T.B.); Department of Epidemiology, Tulane Center for Cardiovascular Health, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA (G.B.); Departments of Epidemiology and Biostatistics and Bioinformatics, Tulane University Health Sciences Center, Tulane University, New Orleans, LA (L.B.); Department of Pediatrics, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland (N.H.-K.); Department of Clinical Physiology and Nuclear Medicine, University of Turku and Turku University Hospital, Turku, Finland (O.R.).

Correspondence to: Juha Koskinen, MD, PhD, Research Center of Applied and Preventive Cardiovascular Medicine, University of Turku, Kiinamyllynkatu 10, FIN-20520, Turku, Finland. E-mail: jkkosk@utu.fi

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Clinical Perspective

What Is New?

- The data from this study provide help to inform the timing for initiating clinical screening of cardiovascular risk factors.

What Are the Clinical Implications?

- Evaluation of metabolic risk factor levels provide meaningful prediction of adult outcomes around the time of puberty onset.
- Using body mass index alone provides essentially similar results compared to the conventional metabolic syndrome model.

Metabolic syndrome (MetS) is a constellation of metabolically interrelated variables, including obesity, hypertension, dyslipidemia, hyperglycemia, and, in some analyses, also including hyperinsulinemia.[1] It is well known that adults with MetS are at increased risk of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).[2] The potential importance of childhood MetS has been outlined in a consensus statement from the American Heart Association[3] that noted the need for additional research in children and adolescents in order to clarify its relation to the development of adult cardiovascular risk and disease.[3]

Defining the age when childhood metabolic risk exposure begins to be associated with adult cardio-metabolic risk and atherosclerosis would help focus pediatric caregivers on preventive strategies, including evaluation and intervention. Using longitudinal data from a collaborative study, we have previously shown a relation between pediatric MetS and adult MetS, T2DM, and high carotid artery intima-media thickness (cIMT), a subclinical marker of atherosclerosis.[4] However, the study did not consider the specific age or ages in youth when the association begins to be operative or whether overweight alone in childhood predicts adult outcomes differentially according to age of measurement.

In the present study, we used data from 5803 individuals in 4 large, prospective cohort studies participating in the International Childhood Cardiovascular Cohort (i3C) Consortium[5] that have followed participants from childhood into adulthood. The objective of the study is to examine the age in childhood when the relationship of childhood MetS and overweight (according to childhood MetS criteria) is first associated with adult MetS, T2DM, and cIMT. Because there is no standard definition for pediatric MetS, we compared 3 previously published definitions.[4,6]

Methods

Detailed study characteristics and methods of the 4 cohorts are described elsewhere. These previous reports also include analyses of loss to follow-up to show that the representativeness of the cohorts was maintained.[5,7–12]

Data were analyzed in 5803 participants from 4 longitudinal cohort studies (YFS [Cardiovascular Risk in Young Finns Study], BHS [Bogalusa Heart Study], PLRS [Princeton Lipid Research Study], and IS [Minnesota Insulin Study]) that measured risk factors of MetS in childhood and adulthood. Each study was approved by the appropriate institutional review boards, and written informed consent or assent was obtained from all the study participants aged >18 or assent and consent from their parents for participants aged <18.

Data from more than 1 age (maximum, 1 visit per participant per age group) were entered into the childhood analyses from the 5803 participants (eg, in YFS, a participant examined at age 6, 9, and 12 years had data entered into the analyses from all 3 ages). For subjects with multiple follow-up visits in adulthood, data from the most recent visit were used to maximize the length to follow-up.

Details of the methods used for the measurement of weight, height, blood pressure (BP), lipid levels, glucose and insulin levels, cIMT, and other covariates in each cohort study are provided elsewhere.[5,7–12] Height and weight were measured at all time points. Body mass index (BMI) was calculated from the formula: weight (kg)/height $(m)^2$. A random zero sphygmomanometer was used to measure BP. Venous blood samples were taken after a 12-hour fast from the antecubital vein. In YFS at baseline, serum cholesterol and triglycerides were measured using fully enzymatic Boehringer CHOD-PAP kits with an OLLI 3000 analyzer. Subsequently, Olympus System reagent analyzer in a clinical chemistry analyzer (AU400; Olympus, Tokyo, Japan) was used to determine lipid levels. Serum high-density lipoprotein (HDL) cholesterol was measured by the dextran sulphate 500 000 method. Low-density lipoprotein cholesterol was calculated using the Friedewald formula.[13] In BHS, HDL-cholesterol and triglycerides were measured using chemical procedures with a Technicon Auto Analyzer II (Technicon Instrument Corp, Tarrytown, NY), according to the laboratory manual of the Lipid Research Clinics program. Since this time, these variables were determined by enzymatic procedures[14] using the Abbott VP instrument (Abbott Laboratories, North Chicago, IL). In PLRS data, all serum lipid measurements were performed with standard methods in Centers for Disease Control and Prevention–standardized laboratories.[15] Childhood glucose levels were measured with an ABA-100 system by using the hexokinase method. In adulthood, glucose levels were measured with a Dade Dimension Xpand system by using the hexokinase/glucose-6-phosphate dehydrogenase method.[15,16] In IS, serum lipids were analyzed in the University of Minnesota laboratory with a Cobas FARA. HDL-cholesterol was determined after precipitation of non-HDL lipoproteins with a magnesium/dextran precipitating reagent.

Triglycerides were determined with a standard glycerol blanked enzymatic triglyceride method. Blood samples were analyzed for glucose with a Beckman Glucose Analyzer II (Beckman Instruments Inc, Fullerton, CA). Insulin samples were determined with a radioimmunoassay kit (Equate RIA; Binax Corp, Portland, ME). B-mode ultrasound studies of the left carotid artery were performed at follow-ups using standardized protocols in each study. In YFS, to assess intraindividual reproducibility of ultrasound measurements, 57 subjects were re-examined 3 months after the initial visit. The average absolute difference and SD between measurements was 0.05±0.04 mm. In BHS, 75 participants underwent repeat ultrasound examinations 10 to 12 days after their initial visit to determine intraindividual reproducibility. The average absolute difference and SD between measurements for all cIMT segments was 0.05±0.03 mm. In IS, reproducibility of the cIMT showed a mean difference (±SD) of 0.02±0.03 for analysis separated by 1 week.

Definition of MetS and Its Components in Childhood

Table 1 lists the components and values for the 3 MetS definitions used in this study. BMI was used as the measure of adiposity because waist circumference was not available at baseline in all cohorts. Fasting insulin was used when glucose was not available for the YFS, BHS, or IS cohorts at baseline. We generated age-, sex-, race-, cohort-, and study-year–specific percentiles of BMI, systolic and diastolic BPs, HDL-cholesterol, triglycerides, insulin, and glucose.

For the modified National Cholesterol Education Program (MetSNCEP75) definition, a participant was categorized as having MetS if he or she had any 3 of the following 5 components: BMI or waist circumference ≥75th percentile; systolic or diastolic BP ≥75th percentile; HDL-cholesterol ≤25th percentile; triglycerides ≥75th percentile; or insulin/glucose ≥75th percentile.

The second childhood MetS definition used age- and sex-standardized pediatric cut points available in the literature to denote each component risk factor (MetSPed).[4] A participant was categorized as having MetS if he or she fulfilled overweight plus any 2 of 4 remaining risk component criteria. Overweight or obesity were defined according to the Cole classification.[17] Prehypertension or hypertension was defined according to the Fourth Report on High Blood Pressure in Children and Adolescents from the National High Blood Pressure Education Program.[18] Low HDL-cholesterol and high triglycerides were defined using cut points proposed from growth-curve data that were linked to adult definitions.[19] Hyperglycemia was defined as plasma glucose ≥5.60 mmol/L (100 mg/dL).[20] Hyperinsulinemia was defined when glucose was unavailable as having insulin levels above age-, sex-, race-, study-cohort–, and study-year–specific 75th percentile.

The third MetS definition (MetSCook) was described by Cook et al[21] using the National Cholesterol Education Program (Adult Treatment Panel III) definition modified for age. Overweight or obesity and elevated BP was defined as BMI or systolic or diastolic BP ≥90th percentile. Elevated values for triglycerides were defined at levels at or above 1.695 mmol/L (150 mg/dL) and for glucose levels at or above 5.6 mmol/L (100 mg/dL); decreased levels of HDL-cholesterol were defined as levels at or below 1.036 mmol/L (40 mg/dL). When glucose was not available, we used hyperinsulinemia (≥90th percentile). Finally, a continuous MetS score for children was constructed based on a sex- and race-specific algorithm derived from confirmatory factor analysis of data from the National Health and Nutrition Examination Survey.[22] Participants with missing glucose data were excluded from the continuous MetS analyses.

Table 1. MetS Definitions and Their Components Used in This Study

MetS Definition	Overweight	Elevated BP	High Triglyceride Level	Low-HDL Cholesterol	Glucose/Insulin Abnormality
MetSNCEP75 (any 3 components)	BMI ≥75th percentile	Systolic and/or diastolic BP ≥75th percentile	Triglycerides ≥75th percentile	HDL-cholesterol ≤25th percentile	Glucose or insulin level ≥75th percentile
MetSCook (any 3 components)	BMI ≥90th percentile	Systolic and/or diastolic BP ≥90th percentile or >130/85 mm Hg	≥150 mg/dL	≤40 mg/dL	Glucose ≥100 mg/dL or insulin ≥90th percentile
MetSPed (overweight+any 2 components)	Cole classification	NHBPEP-classification	Growth curve dependent*	Growth curve dependent*	Glucose ≥100 mg/dL or insulin ≥90th percentile

BP indicates blood pressure; MetS, metabolic syndrome; NCEP, National Cholesterol Education Program; NHBPEP, the National High Blood Pressure Education Program.
*Available only from age of 6 years onward.

Definition of MetS in Adulthood

MetS in adulthood was defined by the diagnostic criteria provided by a joint statement from the International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung and Blood Institute, the American Heart Association, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity.[23] MetS was diagnosed when 3 or more of the following 5 criteria were present: waist circumference cut points of ≥102 cm for men and ≥88 cm for women to define abdominal obesity; triglycerides ≥1.695 mmol/L (150 mg/dL); HDL-cholesterol <1.036 mmol/L (40 mg/dL) in men or <1.295 mmol/L (50 mg/dL) in women; BP ≥130/≥85 mm Hg or BP-lowering medication; or fasting glucose ≥5.6 mmol/L (100 mg/dL).

Definition of T2DM in Adulthood

Participants were classified as having T2DM if they: (1) had a fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL); (2) had a glycohemoglobin (A1C) level of ≥6.5% (48 mmol/mol); (3) reported receiving oral hypoglycemic agents and/or insulin injections and did not have type 1 diabetes mellitus; or (4) reported a history of physician-diagnosed T2DM. Women who reported having physician-diagnosed diabetes mellitus only during the term of their pregnancy were considered to have had gestational diabetes mellitus.

Definition of High cIMT in Adulthood

Consistent with previous reports,[24] high cIMT in adulthood was defined as a maximum cIMT ≥90th percentile for age-, sex-, race-, study-year–, and study-cohort–specific values (YFS, BHS). For IS, high cIMT in adulthood was defined as a mean value ≥90th percentile (age, sex, race, and study year) because maximum values were not available. Data on cIMT were not available for the PLRS cohort and were excluded from the analyses examining high cIMT.

Statistical Analysis

The YFS cohort examined children from specific birth cohorts with 3-year intervals (ages 3, 6, 9, 12, 15, and 18 years at baseline survey), whereas the other studies had participants varying across all ages from 3 to 18 years. Therefore, dictated by YFS being the largest cohort, individuals from BHS, PLRS, and IS at age groups of 3 to 4, 5 to 7, 8 to 10, 11 to 13, 14 to 16, and 17 to 18 years were included in the respective age groups with the 3-, 6-, 9-, 12-, 15-, and 18-year-olds from YFS. To take into account possible differences attributed to age, sex, race, and secular trends in risk factors, study cohort, and different methodology age-, sex-, race-, study-year–, and study-cohort–specific risk factor percentiles were generated for childhood risk factors. Age- and sex-adjusted ANOVA for continuous variables and logistic regression for categorical variables was used to compare characteristics among the study groups. For main analyses, different multivariate techniques (Poisson regression with time offset, multinomial regression, Cox proportional hazards ratios, and logistic regression) were used to calculate risk ratios (RR) and 95% confidence intervals (95% CI). Conclusions drawn from the results were essentially similar independent of the method used. In the Results section, the values from the logistic regression are shown, which had the lowest Akaike and Bayesian criterion information values. All regression analyses using data from both sexes were adjusted with sex and all regression models combining data from several cohorts were additionally adjusted for study cohort, and year to minimize the effect of heterogeneity of the participants attributed to geography and physiology. Because of almost no T2DM events were observed in the 2 youngest age groups, we collapsed these 2 groups (3–4 and 5–7 year olds) into 1 age group (3–7 year olds) when analyzing future risk of T2DM. Statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC). Statistical significance was inferred as $P<0.05$.

Results

Clinical Characteristics

Table 2 shows the number of childhood visits in each study cohort and the clinical characteristics of the study subjects. Mean±SD follow-up time was 22.3±9.5 years. PLRS had the oldest and IS had the youngest participants at adult follow-up. Subjects were predominantly whites (76%) and blacks (24%). Childhood insulin levels, MetSNCEP75, and adulthood MetS did not have significant differences among the groups ($P>0.16$). Otherwise statistically significant differences in clinical characteristics were observed among the study groups (P always <0.05). The normality assumptions of the residuals were assessed by examining histograms of the residuals and normal probability plots. The residuals were normally distributed.

Childhood MetS and Overweight Predicting the Risk for Adult MetS

Tables 3 and 4 show RRs and 95% CIs (sexes combined and separately, respectively) according to child age (ages 3–18, divided into 3-year intervals) for childhood MetS prediction of adult MetS. Childhood MetS was a significant predictor of adult MetS from ages 5 (RR, 2.43–3.39 with 95% CI 1.74–3.40 and 1.68–6.83, respectively) to 18 years (RR, 3.64–

Table 2. Characteristics of Study Subjects at Their First Observation in Childhood and Their Most Recent Observation in Adulthood

	BHS	IS	PLRS	YFS		All Cohorts
N	1983	322	562	2936	*P* Value*	5803
Childhood data						
Age, y	11.2±3.5	14.3±1.6	12.6±3.1	10.9±3.9	<0.0001	11.8±4.0
Age range, y	3 to 18	11 to 18	6 to 18	3 to 18		3 to 18
Ethinicity (white/black %)	62/38	78/22	71/29	100/0	<0.0001	76/24
BMI, kg/m^2	19.3±4.5	22.8±5.2	19.9±4.4	17.9±3.0	<0.0001	19.2±4.3
Systolic BP, mm Hg	102±11	108±9	104±13	111±11	<0.0001	106±12
Diastolic BP, mm Hg	50±13	56±13	63±11	65±10	<0.0001	56±14
Glucose, mmol/L	4.6±0.5	4.9±0.4	4.8±0.44	4.7±0.7	<0.0001	4.6±0.5
Insulin, mU/L	10.4±8.2	11.5±8.8	…	10.0±6.8	0.16	10.4±7.6
Triglycerides, mmol/L	0.78±0.40	1.01±0.58	0.85±0.42	0.77±0.35	<0.0001	0.79±0.40
HDL-cholesterol, mmol/L	1.50±0.44	1.13±0.25	1.39±0.32	1.60±0.32	<0.0001	1.51±0.40
Childhood MetS, %						
MetSNCEP75	20	20	20	19	0.16	19
MetSPed	9	14	4	3	<0.0001	6
MetSCook	5	9	14	3	<0.0001	5
Continuous MetS score (mean)	−0.95±0.78	−0.10±0.69	−0.71±0.78	−0.67±0.63	<0.0001	−0.83±0.80
Adulthood data						
Age, y	31.3±8.0	23.3±2.5	42.1±6.8	34.4±8.1	<0.0001	33.2±8.5
Age range, y	19 to 51	19 to 35	19 to 57	21 to 50		19 to 57
BMI, kg/m^2	27.5±7.1	26.4±6.5	28.7±6.9	25.3±4.7	<0.0001	26.5±6.2
Systolic BP, mm Hg	114±13	110±10	120±15	119±14	<0.0001	116±14
Diastolic BP, mm Hg	69±11	65±10	79±11	73±11	<0.0001	71±11
Glucose, mmol/L	4.7±0.9	4.8±0.8	5.0±1.5	5.2±0.9	<0.0001	4.9±1.0
Triglycerides, mmol/L	1.32±0.95	1.09±0.63	1.52±1.47	1.30±0.94	<0.0001	1.31±0.97
HDL-cholesterol, mmol/L	1.28±0.40	1.19±0.28	1.18±0.38	1.35±0.34	<0.0001	1.30±0.37
MetS, %	20	9	32	25	0.009	23
T2DM, %	1	0	5	2.5	0.17	2
cIMT mean, mm	…	0.443±0.057	…	0.603±0.097	<0.0001	0.591±0.104
cIMT maximum, mm	0.719±0.192		…	0.643±0.101	<0.0001	0.672±0.148

Values are mean (SD), unless otherwise mentioned. BHS indicates the Bogalusa Heart Study; BMI, body mass index; BP, blood pressure; cIMT, carotid intima-media thickness; HDL, high-density lipoprotein; IS, the Insulin Study; MetS, metabolic syndrome; PLRS, the Princeton Lipid Research Study; YFS, the Cardiovascular Risk in Young Finns Study.
*Age- and sex-adjusted *P* values from group comparisons.

5.13; 95% CI, 2.90–4.56 and 3.23–8.15, respectively) for the 3 definitions, except that the association in males using the MetSCook definition did not become significant until 8 years (RR, 4.62; 95% CI, 2.41–8.83). Next, we removed BMI from the MetSNCEP75 criteria; the results based on any 2 of the remaining components remained essentially similar to MetSNCEP75. Finally, a multivariable model including all individual MetSNCEP75 risk factors was constructed. All MetSNCEP75 components were significant predictors between ages 5 to 18 years (Table 5). When study cohorts were analyzed separately, the RRs for childhood MetS in predicting adulthood MetS were consistent with Table 3 (results shown in Table 6).

Childhood MetS Predicting the Risk for Adult T2DM

Because of low number of T2DM events, we collapsed 2 youngest age groups (3–4 and 5–7 year olds) into 1 age group (3–7 year olds). Childhood MetS became a significant

Table 3. RRs and Their 95% CIs for Childhood MetS Predicting the Risk for Adulthood MetS

	Age at Childhood Measurement in Years (No. of MetS Events in Adulthood/No. of Subjects)											
	3 to 4 (N=74/422)		5 to 7 (N=144/859)		8 to 10 (N=238/1054)		11 to 13 (N=351/1410)		14 to 16 (N=316/1334)		17 to 18 (N=275/949)	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
MetSNCEP75 (yes/no)	1.77 (0.98–3.20)	0.060	2.43 (1.74–3.40)	<0.0001	3.21 (2.51–4.11)	<0.0001	2.91 (2.37–3.58)	<0.0001	3.26 (2.66–3.99)	<0.0001	3.64 (2.90–4.56)	<0.0001
MetSPed (yes/no)*	…	…	3.17 (1.92–5.22)	<0.0001	2.76 (2.01–3.80)	<0.0001	3.18 (2.46–4.11)	<0.0001	3.68 (2.84–4.76)	<0.0001	3.20 (2.28–4.51)	<0.0001
MetSCook (yes/no)	1.50 (0.57–3.92)	0.40	3.39 (1.68–6.83)	0.0006	4.08 (2.62–6.35)	<0.0001	3.79 (2.57–5.58)	<0.0001	4.10 (2.84–5.93)	<0.0001	5.13 (3.23–8.15)	<0.0001

All models are adjusted for sex, study cohort, and year. CI indicates 95% confidence interval; MetS, metabolic syndrome, RR, risk ratio.
*MetSPed was defined only for subjects aged 6 to 18 years.

predictor of adult T2DM at age 8 years (RR, 2.85–4.14; 95% CI, 1.12–7.24 and 1.37–12.4, respectively) and continued through age 18 (RR, 7.63; 95% CI, 3.85–15.1 and 1.98–10.2, respectively) with the MetSCook, and MetSPed methods. Detailed results are shown in Table 7. Significant associations between childhood MetS and adulthood T2DM were observed from 14 years onward by the MetSNCEP75 method (RR, 3.59; 95% CI, 2.09–6.16). When sexes were analyzed separately (Table 8), the association in females between childhood MetS and adult T2DM was inconsistent and sporadic, with MetSCook significant at age 11 to 13, MetSPed and MetSNCEP75 significant at age 14 to 16, and MetSPed and MetSCook significant at age 17 to 18. Similar results with childhood MetS relation to adult T2DM were obtained by using overweight alone (Table 9). Other MetSNCEP75 risk factors did not show consistent association with adult T2DM. When study cohorts were analyzed separately, the outcome was unreliable, because of almost no outcome events (Table 10).

Childhood MetS Predicting the Risk for Adult High cIMT

Childhood MetS measured by all methods predicted adulthood high cIMT 2- to 4-fold in the 11 to 18 age groups. Detailed RR and 95% CI are presented in Table 11. The results were the same when sexes were analyzed separately (Table 12). When BMI was removed from the MetSNCEP75 criteria, the association was no longer statistically significant in the 11 to 16 female age groups ($P>0.13$). From the MetSNCEP75 risk factors, only high BMI showed consistent association with adult cIMT from the age of 11 onward (Table 13). High BP was associated with later intima-media thickness at ages 5 to 7, high insulin at ages 11 to 16, and high triglycerides and low HDL cholesterol at ages 14 to 18. When individual cohorts were analyzed (Table 14), high adult cIMT was predicted only in YFS and BHS for 11- to 18-year-olds.

Childhood Continuous MetS Score Predicting the Risk for Adult MetS, T2DM, and High cIMT

The association between childhood continuous MetS and adulthood outcomes is shown in Table 15, with the analyses limited to those with childhood glucose data. The results were similar to the 3 MetS methods (ie, significant for adult MetS at all ages and significant for T2DM and cIMT at adolescent ages). When sexes were analyzed separately, prediction of the adult MetS was significant from age 5 onward (RR, 2.14; 95% CI, 1.19–3.85 for males and RR, 3.79; 95% CI, 1.89–7.77 for females) and high cIMT from age 11 onward (RR, 2.02; 95% CI, 1.20–3.37 for males and RR, 1.82; 95% CI, 1.11–2.98 for

Table 4. Sex-Specific RRs and Their 95% CIs for Childhood MetS Predicting the Risk for Adulthood MetS

	Age in Years (No. of Subjects)											
	3 to 4 (N=44/203)		5 to 7 (N=85/376)		8 to 10 (N=119/461)		11 to 13 (N=180/655)		14 to 16 (N=171/620)		17 to 18 (N=132/438)	
Males	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
MetS variants												
MetSNCEP75 (yes/no)	1.91 (0.88–4.15)	0.10	1.85 (1.16–2.97)	0.010	3.28 (2.29–4.69)	<0.0001	3.13 (2.33–4.22)	<0.0001	3.62 (2.72–4.82)	<0.0001	3.96 (2.83–5.53)	<0.0001
MetSPed (yes/no)*	…	…	3.36 (1.54–7.30)	0.0022	3.68 (2.32–5.84)	<0.0001	4.03 (2.73–5.95)	<0.0001	4.30 (2.97–6.23)	<0.0001	3.33 (2.02–5.49)	<0.0001
MetSCook (yes/no)	0.79 (0.17–3.86)	0.77	2.19 (0.77–6.19)	0.14	4.62 (2.41–8.83)	<0.0001	4.75 (2.55–8.85)	<0.0001	3.60 (2.14–6.03)	<0.0001	4.13 (2.24–7.61)	<0.0001
MetSNCEP75† (yes/no, omitting BMI from the MetS definition)	1.48 (0.75–2.94)	0.26	1.72 (1.14–2.60)	0.009	2.21 (1.61–3.02)	<0.0001	2.59 (1.98–3.38)	<0.0001	2.52 (1.95–3.25)	<0.0001	2.88 (2.16–3.84)	<0.0001
	3 to 4 (N=30/219)		5 to 7 (N=59/483)		8 to 10 (N=119/593)		11 to 13 (N=171/755)		14 to 16 (N=145/714)		17 to 18 (N=143/511)	
Females	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
MetS variants												
MetSNCEP75 (yes/no)	1.61 (0.63–4.09)	0.31	3.22 (1.99–5.21)	<0.0001	3.17 (2.24–4.46)	<0.0001	2.78 (2.07–3.72)	<0.0001	2.94 (2.20–3.91)	<0.0001	3.46 (2.54–4.72)	<0.0001
MetSPed (yes/no)	…	…	2.93 (1.52–5.65)	0.0013	2.11 (1.35–3.32)	0.0011	2.64 (1.86–3.74)	<0.0001	3.20 (2.22–4.61)	<0.0001	3.13 (1.96–5.00)	<0.0001
MetSCook (yes/no)	2.48 (0.73–8.41)	0.15	4.65 (1.81–11.9)	0.0014	3.68 (2.00–6.77)	<0.0001	3.45 (2.07–5.73)	<0.0001	4.72 (2.80–7.97)	<0.0001	6.99 (3.41–14.3)	<0.0001
MetSNCEP75† (yes/no, omitting BMI from the MetS definition)	1.13 (0.50–2.52)	0.76	2.94 (1.85–4.67)	<0.0001	2.65 (1.93–3.65)	<0.0001	2.63 (2.01–3.43)	<0.0001	2.34 (1.82–3.01)	<0.0001	2.12 (1.62–2.77)	<0.0001

All models are adjusted for sex, study cohort, and year. BMI indicates body mass index; CI, 95% confidence interval; MetS, metabolic syndrome; RR, risk ratio.

*MetSPed was defined only for subjects aged 6 to 18 years.

†MetS status was fulfilled if he or she fulfilled any 2 of the remaining MetS components (blood pressure, triglycerides, or glucose/insulin above 75th percentile and high-density lipoprotein cholesterol below 25th percentile).

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Table 5. Multivariable RRs and Their 95% CIs for Childhood MetS Risk Factors Predicting the Risk for Adulthood MetS

Risk Factor (Yes/No)*	Age at Childhood Measurement in Years (No. of MetS Events in Adulthood/No. of Subjects)											
	3 to 4		5 to 7		8 to 10		11 to 13		14 to 16		17 to 18	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
High BMI 75	1.20 (0.67–2.13)	0.53	2.39 (1.73–3.29)	<0.0001	2.49 (1.97–3.13)	<0.0001	2.89 (2.38–3.51)	<0.0001	3.21 (2.66–3.87)	<0.0001	3.51 (2.84–4.33)	<0.0001
High BP 75	1.15 (0.69–1.92)	0.59	1.62 (1.20–2.20)	0.002	2.11 (1.70–2.64)	<0.0001	1.61 (1.34–1.93)	<0.0001	1.22 (1.02–1.45)	0.03	1.57 (1.30–1.91)	<0.0001
High insulin 75	1.14 (0.67–1.94)	0.63	2.01 (1.46–2.77)	<0.0001	1.77 (1.39–2.25)	<0.0001	2.28 (1.86–2.79)	<0.0001	2.14 (1.77–2.59)	<0.0001	1.86 (1.50–2.29)	<0.0001
High triglycerides 75	1.37 (0.78–2.41)	0.26	1.70 (1.23–2.36)	0.001	1.83 (1.44–2.33)	<0.0001	2.14 (1.75–2.61)	<0.0001	2.28 (1.89–2.75)	<0.0001	2.00 (1.62–2.46)	<0.0001
Low HDL 75	2.09 (1.23–3.55)	0.006	2.13 (1.54–2.94)	<0.0001	1.91 (1.51–2.42)	<0.0001	2.27 (1.87–2.77)	<0.0001	1.88 (1.56–2.28)	<0.0001	1.98 (1.61–2.44)	<0.0001

All models are adjusted for sex, study cohort, and year. BMI indicates body mass index; BP, blood pressure; CI, 95% confidence interval; HDL, high-density lipoprotein; MetS, metabolic syndrome; RR, risk ratio.
*High BMI, BP, insulin, triglycerides ≥age, sex, race, study cohort, and year-specific 75th percentile and low HDL ≤25th percentile.

Table 6. RRs and Their 95% CIs for Childhood MetS Predicting Risk for MetS in Adulthood Stratified by Study Cohort

	Age (y)											
	3 to 4		5 to 7		8 to 10		11 to 13		14 to 16		17 to 18	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
YFS												
MetSNCEP75 (yes/no)	1.76 (0.96–3.22)	0.063	2.25 (1.52–3.35)	<0.0001	2.89 (2.13–3.93)	<0.0001	2.61 (1.98–3.44)	<0.0001	3.06 (2.34–4.02)	<0.0001	3.27 (2.45–4.36)	<0.0001
BHS												
MetSNCEP75 (yes/no)	2.53 (0.12–93.3)	0.61	2.98 (1.52–5.85)	0.001	3.59 (2.26–5.71)	<0.0001	3.38 (2.33–4.89)	<0.0001	3.13 (2.22–4.40)	<0.0001	4.16 (2.77–6.26)	<0.0001
IS												
MetSNCEP75 (yes/no)	…	…	…	…	…	…	2.86 (0.91–9.00)	0.07	9.05 (3.51–23.4)	<0.0001	6.78 (1.88–24.0)	0.0033
PLRS												
MetSNCEP75 (yes/no)	…	…	2.17 (0.29–15.9)	0.44	6.44 (2.15–19.2)	0.0009	4.01 (1.95–8.25)	0.0002	3.37 (1.38–8.18)	0.0072	5.55 (1.76–17.5)	0.0035

Models adjusted for sex. BHS indicates the Bogalusa Heart Study; CI, 95% confidence interval; IS, the Insulin Study; MetS, metabolic syndrome; PLRS, the Princeton Lipid Research Study; RR, risk ratio; YFS, the Cardiovascular Risk in Young Finns Study.

Table 7. RRs and Their 95% CIs for Childhood MetS Predicting the Risk for Adulthood T2DM

	Age at Childhood Measurement in Years (No. of T2DM Events in Adulthood/No. of Subjects)									
	3 to 7* (N=12/1281)		8 to 10 (N=19/1054)		11 to 13 (N=26/1410)		14 to 16 (N=34/1334)		17 to 18 (N=34/949)	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
MetSNCEP75 (yes/no)	1.54 (0.58–2.50)	0.33	1.46 (0.64–3.48)	0.38	1.67 (0.86–3.23)	0.13	3.59 (2.09–6.16)	<0.0001	2.61 (1.50–4.56)	0.0007
MetSPed (yes/no)†	1.64 (0.20–13.0)	0.63	2.85 (1.12–7.24)	0.027	3.21 (1.59–6.46)	0.0011	5.15 (2.74–9.68)	<0.0001	7.63 (3.85–15.1)	<0.0001
MetSCook (yes/no)	3.73 (0.73–16.9)	0.09	4.14 (1.37–12.4)	0.011	5.57 (2.52–12.3)	<0.0001	5.54 (2.61–11.7)	<0.0001	4.50 (1.98–10.2)	0.0003

All models are adjusted for sex, study cohort, and year. CI indicates 95% confidence interval; MetS, metabolic syndrome; RR, risk ratio; T2DM, type 2 diabetes mellitus.
*Because oflow number of outcomes, 2 youngest age groups were collapsed into 1 age group.
†MetSPed was defined only for subjects aged 6 to 18 years.

females) for both males and females. Because of the small number of diabetes mellitus cases, results were inconsistent in significance but consistent in direction. The risk for T2DM was significant for 8 to 10- and 14 to 16-year-old males (RR, 4.19; 95% CI, 1.16–15.1 and RR, 3.40; 95% CI, 1.72–6.71, respectively) and for 8 to 10- and for 17 to 18-year-old females (RR, 3.43; 95% CI, 1.32–8.86 and RR, 2.99; 95% CI, 1.34–6.68, respectively).

Discussion

The results from this study demonstrate that childhood MetS and overweight in both males and females seems to predict increased risk for adult MetS from age 5 years onward. In addition, childhood MetS identifies children from ages 8 to 14 years onward who are at increased risk for adult T2DM and early subclinical atherosclerosis measured by cIMT. Similar results were found when an MetS score, using MetS components as continuous variables, was substituted for the MetS, which uses dichotomized components to define risk.

We and others have assessed pediatric MetS as a risk factor for adult MetS, T2DM, and high cIMT in cohorts consisting of both children and adolescents. A prospective study of former students from the Princeton lipid research study reported that children aged 5 to 19 years with MetS were more likely to have MetS, T2DM, and clinical CVD 25 to 30 years later as adults.[10,25] Similar associations were observed in the YFS and BHS studies concerning MetS, T2DM, and cIMT.[4,6] However, the number of participants in those studies was too small to be able to consider age-stratified analyses, and little is currently known about the age when childhood MetS exposure begins to relate to adult risk. The present study, with a cohort of 5803 individuals, shows that a significant relation between childhood MetS and adult MetS begins as early as age 5 (our data at earlier ages are sparse and we therefore do not consider them definitive), and the relation for T2DM and subclinical atherosclerosis begins in early adolescence. In contrast to the present study, a 10-year longitudinal study of 1604 Pima Indians aged 5 to 19 years with data obtained at age 26 years showed that clustering of CVD risk factors in 3 childhood age groups (5–9, 10–14, and 15–19 years) increased the risk for early T2DM.[26] The slightly younger age at which a relation to adult T2DM was recognized may be related to the known increased risk for development of diabetes mellitus in the Pima population.

A standard universal method for defining pediatric MetS is not available, and the criteria currently used have been variably adopted from adult standards.[3] In the present report, we show that the results between 3 different pediatric MetS definitions were essentially similar in predicting adult MetS, T2DM, and cIMT. In addition, the cMetS score, using risk factors as continuous variables, resulted in findings similar

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Table 8. Sex-Specific RRs and Their 95% CIs for Childhood MetS Predicting the Risk for Adulthood T2DM

	Age in Years (No. of Subjects)									
	3 to 7 (N=7/579)*		8 to 10 (N=6/461)		11 to 13 (N=10/655)		14 to 16 (N=20/620)		17 to 18 (N=17/438)	
Males	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
MetS variants										
MetSNCEP75 (yes/no)	1.39 (0.64–2.64)	0.55	1.58 (0.42–5.94)	0.49	2.98 (1.10–8.05)	0.030	4.97 (2.29–10.7)	<0.0001	3.48 (1.64–7.41)	0.0012
MetSPed (yes/no)†	3.34 (0.37–27.6)	0.28	2.41 (0.51–11.3)	0.27	6.06 (2.11–17.4)	0.0008	7.29 (3.12–17.0)	0.0001	10.1 (3.98–25.6)	<0.0001
MetSCook (yes/no)	2.94 (0.35–24.6)	0.31	5.66 (0.94–19.6)	0.060	5.41 (1.34–21.0)	0.018	8.50 (3.27–20.0)	<0.0001	5.23 (1.84–14.8)	0.0019
MetSNCEP75* (yes/no, omitting BMI from the MetS definition)	1.81 (0.51–6.35)	0.35	1.00 (0.29–3.33)	0.96	1.82 (0.69–4.82)	0.23	3.37 (1.53–7.43)	0.0026	2.72 (1.28–5.77)	0.009
	3 to 7 (N=5/702)		8 to 10 (N=13/593)		11 to 13 (N=16/755)		14 to 16 (N=14/714)		17 to 18 (N=17/511)	
Females	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
MetS variants										
MetSNCEP75 (yes/no)	5.70 (1.00–34.1)	0.057	1.41 (0.44–4.42)	0.55	1.12 (0.44–2.81)	0.80	2.62 (1.19–5.73)	0.016	1.85 (0.79–4.32)	0.15
MetSPed (yes/no)†	‡		3.35 (0.96–10.8)	0.055	2.15 (0.83–5.55)	0.11	3.25 (1.17–9.02)	0.023	5.61 (1.99–15.7)	0.0011
MetSCook (yes/no)	0.20 (0.03–1.27)	0.20	3.13 (0.66–14.7)	0.15	6.08 (3.00–16.0)	0.0003	3.03 (0.84–10.9)	0.089	4.05 (1.08–15.2)	0.038
MetSNCEP75 (yes/no, omitting BMI from the MetS definition)†	‡		0.97 (0.53–2.84)	0.97	1.05 (0.47–2.35)	0.89	1.44 (0.69–3.05)	0.33	1.43 (0.56–3.11)	0.35

All models are adjusted for sex, study cohort, and year. BMI indicates body mass index; CI, 95% confidence interval; MetS, metabolic syndrome; RR, risk ratio; T2DM, type 2 diabetes mellitus.
*Because of low number of outcomes, 2 youngest age groups were collapsed into 1 age group percentile and high-density lipoprotein cholesterol below 25th percentile).
†MetS status was fulfilled if he or she fulfilled any 2 of the remaining MetS components (blood pressure, triglycerides, or glucose/insulin above 75th.
‡Insufficient observations in the outcome variable (N≤3).

Table 9. Multivariable RRs and Their 95% CIs for Childhood MetS Risk Factors Predicting the Risk for Adulthood T2DM

	Age at Childhood Measurement in Years (No. of MetS Events in Adulthood/No. of Subjects)									
	3 to 7*		8 to 10		11 to 13		14 to 16		17 to 18	
Risk Factor (Yes/No)	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
High BMI 75	1.65 (0.60–4.50)	0.32	3.52 (1.67–7.46)	0.001	2.46 (1.35–4.50)	0.003	4.22 (2.46–7.23)	<0.0001	3.69 (2.15–6.32)	<0.0001
High BP 75	1.72 (0.66–4.50)	0.26	2.44 (1.13–5.23)	0.02	1.43 (0.78–2.59)	0.24	2.07 (1.21–3.56))	0.008	1.57 (1.30–1.91)	<0.0001
High insulin 75	7.59 (2.52–23.8)	0.005	1.30 (0.56–3.02)	0.53	1.95 (0.95–4.00)	0.07	3.28 (1.87–5.73)	<0.0001	1.95 (1.11–3.46)	0.02
High triglycerides 75	0.91 (0.29–2.82)	0.87	1.03 (0.43–2.44)	0.94	0.74 (0.55–1.55)	0.43	1.54 (0.44–2.70)	0.13	1.16 (0.64–2.10)	0.61
Low HDL 75	1.16 (0.41–3.32)	0.78	1.40 (0.63–3.12)	0.40	2.02 (0.62–3.71)	0.02	1.11 (0.34–2.03)	0.71	1.49 (0.85–2.63)	0.16

High BMI, BP, insulin, triglycerides ≥age, sex, race, study cohort, and year-specific 75th percentile and low HDL ≤25th percentile. All models are adjusted for sex, study cohort, and year. BMI indicates body mass index; BP, blood pressure; CI, 95% confidence interval; HDL, high-density lipoprotein; MetS, metabolic syndrome; RR, risk ratio; T2DM, type 2 diabetes mellitus.
*Because of low number of outcomes, 2 youngest age groups were collapsed into 1 age group.

Table 10. RRs and Their 95% CIs for Childhood MetS Predicting Risk for T2DM in Adulthood Stratified by Study Cohort

	Age (y)									
	3 to 7*		8 to 10		11 to 13		14 to 16		17 to 18	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
YFS										
MetSNCEP75 (yes/no)	5.48 (2.01–14.9)	0.0008	0.47 (0.11–2.05)	0.32	1.70 (0.74–3.91)	0.21	3.00 (1.57–5.74)	0.0009	1.94 (0.99–3.78)	0.051
BHS										
MetSNCEP75 (yes/no)	…	…	5.87 (0.96–35.6)	0.054	…	…	7.33 (2.11–25.4)	0.0017	10.8 (2.14–54.5)	0.0039
IS										
MetSNCEP75 (yes/no)	…	…	…	…	…	…	…	…	…	…
PLRS										
MetSNCEP75 (yes/no)	…	…	…	…	2.50 (0.77–8.01)	0.13	3.10 (0.49–19.6)	0.28	2.90 (0.43–19.4)	0.27

Models adjusted for sex. BHS indicates the Bogalusa Heart Study; CI, 95% confidence interval; IS, the Insulin Study; MetS, metabolic syndrome; PLRS, the Princeton Lipid Research Study; RR, risk ratio; T2DM, type 2 diabetes mellitus; YFS, the Cardiovascular Risk in Young Finns Study.
*Because oflow number of outcomes, 2 youngest age groups were collapsed into 1 age group.

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Table 11. RRs and Their 95% CIs for Childhood MetS Predicting the Risk for High cIMT (≥90th Percentile) in Adulthood

	Age at Childhood Measurement in Years (No. of High Intima-Media Thickness Events in Adulthood/No. of Subjects)											
	3 to 4 (N=32/369)		5 to 7 (N=47/550)		8 to 10 (N=45/609)		11 to 13 (N=67/824)		14 to 16 (N=69/779)		17 to 18 (N=62/576)	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
MetSNCEP75 (yes/no)	1.53 (0.65–3.59)	0.32	1.57 (0.92–2.68)	0.10	1.33 (0.83–2.11)	0.22	2.01 (1.36–2.96)	0.0004	2.50 (1.75–3.57)	<0.0001	2.18 (1.48–3.22)	<0.0001
MetSPed (yes/no)*	…	…	0.86 (0.31–2.34)	0.76	1.31 (0.72–2.37)	0.38	2.29 (1.51–3.47)	<0.0001	2.22 (1.50–3.29)	<0.0001	2.19 (1.24–3.52)	<0.0001
MetSCook (yes/no)	1.05 (0.24–4.71)	0.95	2.19 (0.61–7.78)	0.22	1.97 (0.86–4.52)	0.11	3.99 (2.11–7.54)	<0.0001	5.73 (3.31–9.90)	<0.0001	4.11 (2.19–7.72)	<0.0001

All models are adjusted for sex, study cohort, and year. CI indicates 95% confidence interval; cIMT, carotid intima-media thickness; MetS, metabolic syndrome; RR, risk ratio.
*MetSPed was defined only for subjects aged 6 to 18 years.

(slightly greater discrimination, but harder for clinicians to use) to the MetS definitions. In a previous report from YFS, the prediction of adult T2DM and high cIMT using continuous MetS scores in youth was no different to a dichotomous MetS definition.[6] However, among overweight adolescents, it has been observed that the best model for predicting increased cIMT was the sum of the quantitative components of MetS whereas the use of dichotomized MetS variable reduced the predictive accuracy.[27] Concerning the prediction of metabolic risk factors, the results from the IS study have suggested that compared to the dichotomous MetS definition, a continuous MetS score at the age of 13 years provides more-reliable prediction of young adult risk of MetS at the age of 22 years.[28] The present data suggest that a combined evaluation of metabolic risk factor levels provides meaningful prediction of adult outcomes especially after the age of 11 years, that is, around the time of the puberty onset. Based on the present age-stratified analyses, we observe that using BMI alone provides essentially similar results compared with the conventional MetS model. We have previously shown in YFS and BHS data that MetS—binary or continuous—does not seem to contain any additive information beyond the sum of its components, and it usually does not perform any better in predicting cardiometabolic risk than BMI alone.[4,6] Compared with these previous articles, we now have data from additional cohorts, with bigger sample size, and more case numbers. Therefore, we were able to perform age-stratified analyses. We found that there is not an age in youth when MetS outperforms BMI, given that the present data show that a single assessment of BMI significantly predicts adult outcomes (MetS, T2DM, and high cIMT) at the same age points compared with MetS. In addition to tracking of childhood overweight into adulthood,[29] possible explanation for why high BMI alone predicted adult outcomes similar to MetS in the present study was that BMI is more accurate than measurements of other components of MetS. It has also been shown that excess adiposity may precede the development of other risk factors.[4,30] Another explanation may be attributed to the complex nature of overlapping pathophysiological mechanisms between the components of MetS.[31] Furthermore, childhood MetS has shown to have marked short- and long-term instability in the categorical diagnosis.[3,4,32] Thus, the clinical utility of MetS definition may be limited especially when taking into account the ease and better tractability of overweight from childhood to adulthood.

An important issue in pediatric preventive care is the age during childhood when measurement of risk factors can be related to adult CVD. The data from this study provide help to inform the timing for initiating clinical screening of cardiovascular risk factors. Current pediatric guidelines from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents[33]

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Table 12. Sex-Specific RRs and Their 95% CIs for Childhood MetS Predicting the Risk for High cIMT (≥90th Percentile) in Adulthood

	Age in Years (No. of Subjects)											
	3 to 4 (N=15/178)		5 to 7 (N=23/237)		8 to 10 (N=22/276)		11 to 13 (N=26/373)		14 to 16 (N=37/365)		17 to 18 (N=31/254)	
Males	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
MetS variants												
MetSNCEP75 (yes/no)	1.53 (0.45–5.15)	0.48	1.76 (0.80–3.85)	0.16	1.19 (0.60–2.40)	0.61	3.22 (1.86–5.59)	<0.0001	2.87 (1.77–4.67)	<0.0001	2.47 (1.43–4.28)	0.0012
MetSPed (yes/no)*	…	…	1.94 (0.53–6.99)	0.31	1.56 (0.63–3.84)	0.33	2.80 (1.46–5.34)	0.0018	2.66 (1.52–4.68)	0.0006	2.09 (0.93–4.68))	0.098
MetSCook (yes/no)	3.40 (0.64–18.1)	0.16	3.36 (0.67–17.0)	0.15	1.51 (0.43–5.29)	0.51	3.74 (1.42–9.81)	0.0072	4.61 (2.09–10.1)	0.0002	3.59 (1.52–8.47)	0.0035
MetSNCEP75† (yes/no, omitting BMI from the MetS definition)	1.65 (0.57–4.80)	0.35	1.26 (0.62–2.58)	0.52	1.61 (0.91–2.83)	0.098	1.71 (1.01–2.92)	0.047	2.16 (1.35–3.45)	0.001	1.52 (0.91–2.55)	0.11
	3 to 4 (N=17/191)		5 to 7 (N=24/313)		8 to 10 (N=23/333)		11 to 13 (N=41/451)		14 to 16 (N=32/414)		17 to 18 (N=31/322)	
Females	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
MetS variants												
MetSNCEP75 (yes/no)	1.53 (0.46–5.05)	0.48	1.48 (0.71–3.09)	0.29	1.45 (0.78–2.68)	0.23	1.31 (0.74–2.31)	0.34	2.11 (1.24–3.60)	0.0058	1.94 (1.11–3.38)	0.019
MetSPed (yes/no)*	…	…	0.31 (0.04–2.36)	0.26	1.16 (0.48–2.82)	0.72	2.31 (1.24–4.33)	0.0084	2.11 (1.09–4.07)	0.042	2.44 (1.09–5.45)	0.029
MetSCook (yes/no)	…	…	2.37 (0.25–21.7)	0.45	2.53 (0.83–7.69)	0.10	4.31 (1.85–10.09	0.0007	7.03 (3.29–15.0)	<0.0001	4.96 (1.95–12.5)	0.0008
MetSNCEP75† (yes/no, omitting BMI from the MetS definition)	1.26 (0.46–3.48)	0.65	1.25 (0.65–2.42)	0.51	1.18 (0.68–2.06)	0.56	1.19 (0.73–1.95)	0.49	1.45 (0.90–2.33)	0.13	2.30 (1.39–3.80)	0.001

All models are adjusted for sex, study cohort, and year. BMI indicates body mass index; CI, 95% confidence interval; cIMT, carotid intima-media thickness; MetS, metabolic syndrome; RR, risk ratio.

*MetSPed was defined only for subjects aged 6 to 18 years.

†MetS status was fulfilled if he or she fulfilled any 2 of the remaining MetS components (blood pressure, triglycerides, or glucose/insulin above 75th percentile and high-density lipoprotein cholesterol below 25th percentile).

Table 13. Multivariable RRs and Their 95% CIs for Childhood MetS Risk Factors Predicting the Risk for Adulthood High cIMT (≥90th Percentile)

Risk Factor (Yes/No)	Age at Childhood Measurement in Years											
	3 to 4		5 to 7		8 to 10		11 to 13		14 to 16		17 to 18	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
High BMI 75 (yes/no)	1.43 (0.65–3.15)	0.37	1.41 (0.84–2.35)	0.19	1.27 (0.83–1.95)	0.26	2.13 (1.48–3.07)	<0.0001	1.90 (1.34–2.69)	0.0002	2.01 (1.38–2.91)	0.0002
High BP 75	1.05 (0.50–2.20)	0.88	1.77 (1.10–2.85)	0.02	1.22 (0.82–1.80)	0.32	1.27 (0.89–1.81)	0.18	1.36 (0.98–1.89)	0.07	1.52 (1.06–2.17))	0.02
High insulin 75	1.80 (0.86–3.77)	0.12	1.04 (0.62–1.75)	0.87	1.47 (0.97–2.23)	0.07	1.79 (1.24–2.59)	0.002	1.83 (1.29–2.57)	0.0006	1.24 (0.84–1.83)	0.27
High triglycerides 75	0.78 (0.32–1.86)	0.58	0.85 (0.48–1.50)	0.58	1.05 (0.68–1.63)	0.80	1.35 (0.92–1.99)	0.12	1.65 (1.17–2.33)	0.004	1.64 (1.13–2.39)	0.009
Low HDL 75	1.34 (0.62–2.90)	0.44	0.95 (0.55–1.64)	0.86	0.97 (0.62–1.50)	0.89	1.11 (0.75–1.66)	0.58	1.55 (1.09–2.21)	0.02	2.39 (1.66–3.44)	<0.0001

High BMI, BP, insulin, triglycerides ≥ age, sex, race, study cohort, and year-specific 75th percentile and low HDL ≤25th percentile. All models are adjusted for sex, study cohort, and year. BMI indicates body mass index; BP, blood pressure; CI, 95% confidence interval; cIMT, carotid intima-media thickness; HDL, high density lipoprotein; MetS, metabolic syndrome; RR, risk ratio.

Table 14. RRs and 95% CIs for Childhood MetS Predicting Risk for High cIMT (≥90th Percentile) in Adulthood Stratified by Study Cohort

	Age (y)											
	3 to 4		5 to 7		8 to 10		11 to 13		14 to 16		17 to 18	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
YFS												
MetSNCEP75 (yes/no)	1.53 (0.66–3.59)	0.32	1.51 (0.87–2.65)	0.15	1.35 (0.82–2.22)	0.24	1.65 (1.02–2.67)	0.04	2.15 (1.34–3.45)	0.0015	1.84 (1.12–2.99)	0.014
BHS												
MetSNCEP75 (yes/no)	…	…	3.73 (0.49–28.3)	0.20	1.23 (0.37–4.10)	0.73	2.76 (1.10–6.05)	0.011	3.30 (1.71–6.36)	0.0004	3.83 (1.76–8.35)	0.0007
IS												
MetSNCEP75 (yes/no)	…	…	…	…	…	…	4.68 (1.18–18.3)	0.027	2.59 (0.96–6.95)	0.058	1.63 (0.41–6.53)	0.48
PLRS												
MetSNCEP75 (yes/no)	…	…	…	…	…	…	…	…	…	…	…	…

Models adjusted for sex. BHS indicates Bogalusa Heart Study; CI, 95% confidence interval; cIMT, carotid intima-media thickness; IS, the Insulin Study; MetS, metabolic syndrome; PLRS, the Princeton Lipid Research Study; RR, risk ratio; YFS, the Cardiovascular Risk in Young Finns Study.

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Table 15. Associations Between Childhood Continuous MetS Score and Adulthood Outcomes

Age Group in Childhood (y)	MetS in Adulthood			T2DM in Adulthood			High cIMT (≥90th Percentile) in Adulthood		
	n/N*	RR (95% CI)	*P* Value	n/N	RR (95% CI)	*P* Value	n/N	RR (95% CI)	*P* Value
5 to 7	53/344	2.69 (1.68–4.31)	<0.0001	1/344	0.75 (0.03–12.0)	0.86	5/88	2.07 (0.47–9.07)	0.33
8 to 10	107/491	2.55 (2.00–3.25)	<0.0001	7/491	3.64 (1.73–7.62)	0.0006	13/146	1.41 (0.85–2.32)	0.17
11 to 13	179/818	3.12 (2.55–3.81)	<0.0001	15/818	1.88 (1.04–3.41)	0.036	27/355	1.90 (1.33–2.71)	0.0004
14 to 16	159/763	3.32 (2.74–4.02)	<0.0001	13/763	2.81 (1.67–4.70)	<0.0001	39/342	1.99 (1.44–2.74)	<0.0001
17 to 18	115/439	3.67 (2.90–4.65)	<0.0001	9/439	2.91 (1.58–5.36)	0.0006	21/163	2.39 (1.62–3.53)	<0.0001

Data are lacking for 3- to 4-year-olds because of missing glucose data in YFS, BHS, and IS cohorts. All models are adjusted for sex, study cohort, and year. RR values are for 1-SD change in MetS score. CI indicates confidence interval; cIMT, carotid intima-media thickness; MetS, metabolic syndrome; RR, risk ratio; T2DM, type 2 diabetes mellitus.
*n=Number of events in adulthood, N=Number subjects in each age group with available data in adulthood.

suggest that universal lipid screening in children should be started between ages 9 to 11 years and testing for fasting glucose among high-risk individuals at younger ages. The guidelines further suggest that MetS should not be considered as a separate entity in childhood or adolescence.[33] Our data are in concert with this recommendation. On the basis of this study, there seems to be no particular age range in childhood at which BMI measurements were not associated with subsequent cardiometabolic outcomes, but MetS would provide significant prediction.

This study had some potential limitations. First, waist circumference could not be used as a component of the MetS, because it was not collected at baseline in any of these cohorts. However, BMI previously has been shown to give similar results as waist circumference.[22,34] Second, heterogeneity in the methodology and especially cIMT location and ultrasound protocols existed between the cohorts. Thus, we attempted to take this heterogeneity into account by harmonizing our data for clinical characteristics[5] and defining risk factors according to age-, sex-, race-, study-year–, and study-specific values. cIMT data were available only among 3 of the cohorts and none of them had measurements available from childhood. Therefore, we were not able to analyze longitudinal cIMT data. However, we have previously shown in the YFS cohort that MetS also identifies young adults with accelerated cIMT progression between 2 time points.[35] Because the study participants were comprised of whites and blacks, the results cannot be directly generalized to other races or ethnic groups. Because of categorical age structure of the YFS and other cohorts, age could not be included as a continuous regression variable in the present study, thus limiting the ability to assess differences within the ages included in these groups. Finally, it should be noted that the power to evaluate associations at the youngest ages was low, because only the YFS and BHS study specifically included children <5 years. The main strength of this study is the vast database from all 4 studies that included similar lifestyle and biological risk factors in childhood and followed the cohorts into adulthood.

In conclusion, this study addresses the utility of MetS in youth outlined in the scientific statement from the American Heart Association[3] by providing information on the age at which childhood MetS begins to identify individuals at increased risk of developing adult CVD. On the basis of our results, adult MetS can be predicted beginning at least as young as age 5, and T2DM and cIMT at or after 8 to 14 years of age. However, the predictions obtained from the status of overweight alone were equivalent to childhood MetS definitions. Therefore, in a pediatric setting, BMI measurements alone seem to provide an easy and informative measure of subsequent cardiometabolic risk.

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Disclosures

None.

References

1. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;37:1595–1607.
2. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation*. 2005;112:3066–3072.
3. Steinberger J, Daniels SR, Eckel RH, Hayman L, Lustig RH, McCrindle B, Mietus-Snyder ML; American Heart Association Atherosclerosis, Hypertension, Council on Cardiovascular Nursing, and Council on Nutrition, Physical Activity. 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 Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2009;119:628–647.
4. Magnussen CG, Koskinen J, Chen W, Thomson R, Schmidt MD, Srinivasan SR, Kivimaki M, Mattsson N, Kahonen M, Laitinen T, Taittonen L, Ronnemaa T, Viikari JS, Berenson GS, Juonala M, Raitakari OT. Pediatric metabolic syndrome predicts adulthood metabolic syndrome, subclinical atherosclerosis, and type 2 diabetes mellitus but is no better than body mass index alone: the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study. *Circulation*. 2010;122:1604–1611.
5. Dwyer T, Sun C, Magnussen CG, Raitakari OT, Schork NJ, Venn A, Burns TL, Juonala M, Steinberger J, Sinaiko AR, Prineas RJ, Davis PH, Woo JG, Morrison JA, Daniels SR, Chen W, Srinivasan SR, Viikari JS, Berenson GS. Cohort profile: the International Childhood Cardiovascular Cohort (i3C) Consortium. *Int J Epidemiol*. 2013;42:86–96.
6. Magnussen CG, Cheriyan S, Sabin MA, Juonala M, Koskinen J, Thomson R, Skilton MR, Kahonen M, Laitinen T, Taittonen L, Hutri-Kahonen N, Viikari JS, Raitakari OT. Continuous and dichotomous metabolic syndrome definitions in youth predict adult type 2 diabetes and carotid artery intima media thickness: the Cardiovascular Risk in Young Finns Study. *J Pediatr*. 2016;171:103.e3.
7. Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Maki-Torkko N, Jarvisalo MJ, Uhari M, Jokinen E, Ronnemaa T, Akerblom HK, Viikari JS. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003;290:2277–2283.
8. Raitakari OT, Juonala M, Ronnemaa T, Keltikangas-Jarvinen L, Rasanen L, Pietikainen M, Hutri-Kahonen N, Taittonen L, Jokinen E, Marniemi J, Jula A, Telama R, Kahonen M, Lehtimaki T, Akerblom HK, Viikari JS. Cohort profile: the Cardiovascular Risk in Young Finns Study. *Int J Epidemiol*. 2008;37:1220–1226.
9. Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med*. 1998;338:1650–1656.
10. Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. *Pediatrics*. 2007;120:340–345.
11. Morrison JA, Glueck CJ, Horn PS, Yeramaneni S, Wang P. Pediatric triglycerides predict cardiovascular disease events in the fourth to fifth decade of life. *Metabolism*. 2009;58:1277–1284.
12. Sinaiko AR, Jacobs DR, Steinberger J, Moran A, Luepker R, Rocchini AP, Prineas RJ. Insulin resistance syndrome in childhood: associations of the euglycemic insulin clamp and fasting insulin with fatness and other risk factors. *J Pediatr*. 2001;139:700–707.
13. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
14. Chen W, Srinivasan SR, Li S, Xu J, Berenson GS. Metabolic syndrome variables at low levels in childhood are beneficially associated with adulthood cardiovascular risk: the Bogalusa Heart Study. *Diabetes Care*. 2005;28:126–131.
15. Morrison JA, Kelly K, Horvitz R, Khoury P, Laskarzewski PM, Mellies MJ, Glueck CJ. Parent-offspring and sibling lipid and lipoprotein associations during and after sharing of household environments: the Princeton school district family study. *Metabolism*. 1982;31:158–166.
16. Patten RL, Hewitt D, Waldman GT, Jones G, Little JA. Associations of plasma high-density lipoprotein cholesterol with clinical chemistry data. *Circulation*. 1980;62:41.
17. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320:1240–1243.
18. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114:555–576.
19. Cook S, Auinger P, Huang TT. Growth curves for cardio-metabolic risk factors in children and adolescents. *J Pediatr*. 2009;155:S6.e15-26.
20. Jolliffe CJ, Janssen I. Development of age-specific adolescent metabolic syndrome criteria that are linked to the Adult Treatment Panel III and International Diabetes Federation criteria. *J Am Coll Cardiol*. 2007;49:891–898.
21. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988–1994. *Arch Pediatr Adolesc Med*. 2003;157:821–827.
22. Gurka MJ, Ice CL, Sun SS, Deboer MD. A confirmatory factor analysis of the metabolic syndrome in adolescents: an examination of sex and racial/ethnic differences. *Cardiovasc Diabetol*. 2012;11:128.
23. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC; International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart L, American Heart Association, World Heart Federation, International Atherosclerosis Society, International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645.
24. Magnussen CG, Venn A, Thomson R, Juonala M, Srinivasan SR, Viikari JS, Berenson GS, Dwyer T, Raitakari OT. The association of pediatric low- and high-density lipoprotein cholesterol dyslipidemia classifications and change in dyslipidemia status with carotid intima-media thickness in adulthood evidence from the Cardiovascular Risk in Young Finns Study, the Bogalusa Heart Study, and the CDAH (Childhood Determinants of Adult Health) Study. *J Am Coll Cardiol*. 2009;53:860–869.
25. Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. *J Pediatr*. 2008;152:201–206.
26. Franks PW, Hanson RL, Knowler WC, Moffett C, Enos G, Infante AM, Krakoff J, Looker HC. Childhood predictors of young-onset type 2 diabetes. *Diabetes*. 2007;56:2964–2972.
27. Reinehr T, Wunsch R, Putter C, Scherag A. Relationship between carotid intima-media thickness and metabolic syndrome in adolescents. *J Pediatr*. 2013;163:327–332.
28. Kelly AS, Steinberger J, Jacobs DR, Hong CP, Moran A, Sinaiko AR. Predicting cardiovascular risk in young adulthood from the metabolic syndrome, its component risk factors, and a cluster score in childhood. *Int J Pediatr Obes*. 2011;6:e283–e289.
29. Juhola J, Magnussen CG, Viikari JS, Kahonen M, Hutri-Kahonen N, Jula A, Lehtimaki T, Akerblom HK, Pietikainen M, Laitinen T, Jokinen E, Taittonen L, Raitakari OT, Juonala M. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the Cardiovascular Risk in Young Finns Study. *J Pediatr*. 2011;159:584–590.
30. Srinivasan SR, Myers L, Berenson GS. Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood: the Bogalusa Heart Study. *Diabetes*. 2002;51:204–209.
31. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415–1428.
32. Goodman E, Daniels SR, Meigs JB, Dolan LM. Instability in the diagnosis of metabolic syndrome in adolescents. *Circulation*. 2007;115:2316–2322.
33. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128(Suppl 5):S213–S256.
34. Eisenmann JC. On the use of a continuous metabolic syndrome score in pediatric research. *Cardiovasc Diabetol*. 2008;7:17.
35. Koskinen J, Kahonen M, Viikari JS, Taittonen L, Laitinen T, Ronnemaa T, Lehtimaki T, Hutri-Kahonen N, Pietikainen M, Jokinen E, Helenius H, Mattsson N, Raitakari OT, Juonala M. Conventional cardiovascular risk factors and metabolic syndrome in predicting carotid intima-media thickness progression in young adults: the Cardiovascular Risk in Young Finns Study. *Circulation*. 2009;120:229–236.