SUPPLEMENTAL MATERIAL

Supplemental Methods

For the BHS, youth aged 9-18 years who participated in either the 1984-85 or 1987-88 surveys and participated in either the 2001-02 or 2003-07 adult surveys (then aged 25-41 years) were included in the analyses. To harmonize the study designs, we included from Young Finns those who participated in the 1986 survey when aged 9, 12, 15, or 18 years and in either the 2001 or 2007 adult follow-ups (then aged 24-39 years). We selected these baseline and follow-up samples for the following reasons: first, glucose screening only commenced in Young Finns in 1986; second, Young Finns participants in 1986 were aged from 9 years, so for consistency, we limited the baseline BHS sample to those aged 9 years or older; third, we chose the adult follow-ups because they were the most consistent time-points between the two studies and served to minimize differences in length of follow-up. For individuals that participated in multiple baseline (in the case of BHS) or follow-up surveys, we used those measures that provided the longest time-period between baseline and follow-up. For all analyses, we excluded women who were pregnant at the time of follow-up or participants with type 1 diabetes mellitus. Each study received ethical approval, and obtained written informed consent from participants. Participant numbers with available data and the measures relevant to the aims of this report follow.

United States Data: The Bogalusa Heart Study

Study sample

The Bogalusa Heart study sample has been described in detail elsewhere.[1] For this study, 374 participants aged 9-18 years at baseline (11% of those eligible, 42% male, 34% Black) were included.

Clinic measurements

Height and weight were measured at all time points and body mass index (BMI) calculated as weight(kg)/[height(m)]^2. Waist circumference was only measured at adult follow-ups. Blood pressure measurements at baseline and follow-up were obtained from the right arm of seated participants by two randomly assigned nurses using mercury sphygmomanometers. The first and fifth Korotkoff sounds were used to define systolic and diastolic blood pressures, with the means of replicate readings used in all analyses. Venous blood samples were taken after a 12-hour fast. At the 1984-85 baseline survey, 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.[2] These variables were determined by enzymatic procedures using the Hitachi 902-Automatic Analyzer (Roche Diagnostics, Indianapolis, IN) at follow-up. Serum lipoprotein cholesterols were analyzed using a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures.[3] Plasma glucose was measured enzymatically using the Beckman Instant Glucose Analyzer (Beckman Instruments, Palo Alto, CA).

Carotid artery ultrasound studies

B-mode ultrasound examinations were performed according to established protocols.[4-6] Maximum cIMT measurements of 3 right and 3 left far walls for common carotid, carotid bifurcation, and internal carotid segments were recorded according to strict protocols.[5] Seventy-five participants underwent repeat ultrasound examinations 10-12 days after their initial visit to determine intra-individual reproducibility. The average absolute difference and standard deviation (SD) between measurements for all cIMT segments was 0.05±0.03 mm.

Finnish Data: The Cardiovascular Risk in Young Finns Study

Study sample

The Young Finns sample is described in detail elsewhere.[7] For this study, 1407 participants aged 9-18 years at baseline (79% of those eligible from baseline, 44% male) were included.

Clinic measurements

Height and weight were measured at baseline and follow-up and BMI calculated. Waist circumference was measured in 2001 and 2007 only. Blood pressure measurements were obtained from the right arm using a random zero sphygmomanometer at baseline and follow-up. The first and fifth Korotkoff sounds were used to define systolic and diastolic pressures, with the average of three measurements used in the analyses. Venous blood samples were taken after a 12-hour fast. At baseline (1986), serum cholesterol and triglycerides were measured using fully enzymatic Boehringer CHOD-PAP kits with an OLLI 3000 analyzer. Since this time, Olympus System reagent analyzer in a clinical chemistry analyzer (AU400, Olympus), was used to determine lipid levels. Serum HDL-cholesterol was measured by the dextran sulphate 500,000 method. Glucose concentration was determined using β-D-glucose: nicotinamide adenine dinucleotide oxidoreductase method in 1986 and enzymatically (Olympus, Diagnostica GmbH, Germany) at follow-up. Due to changes in determination methods and kits during study years, biochemistry for 1986 has been corrected to follow-up levels, as previously detailed.[8]

Carotid artery ultrasound studies

B-mode ultrasound studies of the left carotid artery were performed at both 2001 and 2007 follow-ups using standardized protocols.[9] At least four measurements of the far wall were taken approximately 10 mm proximal to the bifurcation to derive mean and maximum cIMT. To assess intra-individual reproducibility of ultrasound measurements, 57 subjects were re-

examined 3 months after their initial visit. The average absolute difference and SD between measurements was 0.05±0.04 mm.

Classification of the metabolic syndrome in childhood

Because there is no universal definition of pediatric MetS, we took an approach used in previous reports that characterize pediatric MetS using multiple alternate definitions.[10] We used BMI as the measure of adiposity since waist circumference was not available for either cohort at baseline. For the first two definitions, we generated age-, sex-, race- (Bogalusa), cohort-, and study-year-specific z-scores of BMI, systolic and diastolic blood pressures, HDL-cholesterol, triglycerides, and glucose. For the modified National Cholesterol Education Program (modNCEP) definition, a participant was categorized as having MetS if he/she had any three of the following five components: BMI $\geq 75^{th}$ percentile, systolic or diastolic blood pressure $\geq 75^{th}$ percentile, HDL-cholesterol $\leq 25^{th}$ percentile, triglycerides $\geq 75^{th}$ percentile, or glucose $\geq 75^{th}$ percentile. For the modified International Diabetes Federation (modIDF) definition, the same cut-points as those for the modNCEP definition were used but the combination of the components differed. The modIDF required elevated BMI plus any two of the remaining four components to be classified as having MetS. The third and fourth definitions utilized age- and sex-standardized pediatric cut-points available in the literature to denote each component risk factor. For example, overweight or obesity was defined according to the Cole classification;[11] 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;[12, 13] low HDL-cholesterol and high triglycerides were defined using cut-points recently proposed from growth-curve data that were linked to adult definitions;[14] and hyperglycemia was defined as plasma glucose ≥5.60 mmol/L (100 mg/dL), as growth-curve data linking youth glucose levels to adult hyperglycemia have

shown levels to remain consistent in the pediatric setting.[15] Pediatric NCEP (pedNCEP) definition required any three of these five criteria whereas the pediatric IDF (pedIDF) required overweight or obesity plus any two of the remaining four components. To complement the dichotomous definitions, a continuous metabolic syndrome risk score (cMetS) was created using the methods described by Wijndaele et al.[16, 17] Briefly, principal component analysis with varimax rotation was applied separately by cohort to the normalized MetS components (age-, sex-, race [Bogalusa], cohort-, and study-year-specific z-scores of BMI, systolic and diastolic blood pressure, HDL-cholesterol, triglycerides, and fasting plasma glucose) to derive the principal components that account for the greater proportion (eigenvalue ≥ 1.0) of MetS variance. Similar to previous studies using this method,[16, 18] two principal components were identified (see Table I on the online-only data supplement for details). The principal components were then summed, with weights determined by the relative proportion of variance explained, in order to compute cMetS where a higher score is indicative of a less favorable MetS profile.[16]

Classification of the metabolic syndrome in adulthood

To classify adult MetS, we used the recent definition proposed in a joint statement of the IDF Task Force on Epidemiology and Prevention, National Heart, Lung and Blood Institute (NHLBI), the AHA, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity that attempts to harmonize the multiple MetS classifications that have been proposed for adult populations in the literature into a single definition.[19] MetS was therefore identified when three or more of the following five criteria were present: waist circumference ≥102 cm in men or ≥88 cm in women, triglycerides ≥1.695 mmol/l (≥150 mg/dL, or specific drug treatment for elevated triglycerides), HDL-cholesterol <1.036 mmol/l (<40 mg/dL) in men or <1.295 mmol/l (<50

mg/dL) in women (or specific drug treatment for reduced HDL-cholesterol), blood pressure ≥130/≥85 mmHg (or antihypertensive drug treatment in persons with a history of hypertension), fasting plasma glucose ≥5.6 mmol/l (≥100 mg/dL or specific drug treatment of elevated glucose). At this stage, the joint statement concedes that further work is needed before the definition of central adiposity is finalized but suggests that either the former (lower threshold) IDF or (higher threshold) AHA/NHLBI cut-points be used. We chose the higher threshold for waist circumference in our data as these cut-points are more consistent with the thresholds generally used in the United States[20] and Europe.[21]

Classification of high carotid IMT in adulthood

As previously detailed,[22] the most consistent cIMT measurement recorded across study centers was the maximum measurement at the far wall of the left common carotid artery. We defined high cIMT in adulthood as a maximum cIMT ≥90th percentile for age-, sex-, race-(Bogalusa), study-year-, and cohort-specific values to account for any method, secular, or cohort differences. We however acknowledge that no consensus clinical definition of high cIMT currently exists for young adults.

Classification of type 2 diabetes in adulthood

Participants were classified as having T2DM if they: (1) had a fasting plasma glucose ≥7.0 mmol/L (≥125 mg/dL); or (2) reported receiving oral hypoglycaemic agents and/or insulin injections and did not have type 1 diabetes; or (3) reported a history of physician-diagnosed T2DM, which is consistent with the WHO definition.[23] Women who reported having physician-diagnosed diabetes only during the term of their pregnancy were considered to have had gestational diabetes, and were classified as not currently having T2DM provided their plasma glucose levels were not ≥7.0 mmol/L (≥125 mg/dL).

Statistical analyses

Data have been pooled where appropriate, but cohort stratified data have also been provided. All analyses were performed using STATA 10.

Stability of MetS between youth and adulthood

Stability of MetS definitions between youth and adulthood are presented according to three groups: (1) *persistent* MetS (MetS positive youth who were also MetS positive as adults); (2) *instable* (those MetS positive at baseline but MetS negative at follow-up); and (3) *incident* MetS (MetS negative youth who were MetS positive as adults). The number of participants in each of these three groups is expressed as a proportion of the total MetS cases identified (total cases from youth and adulthood) and are presented graphically, which is consistent with previous reports on short-term stability.[10, 24]

Utility of pediatric MetS in predicting adult outcomes

Relative risks and 95% confidence intervals estimated using log binomial regression or Poisson regression with robust standard errors were used to examine associations between MetS phenotypes (number of MetS components in youth; youth MetS status; cMetS score) and outcomes of: (1) adult MetS; (2) adult high cIMT; and (3) adult T2DM. Analyses were performed for both cohort-stratified and cohort-pooled data. All estimates were adjusted for length of follow-up (continuous variable determined as follow-up clinic date minus baseline clinic date expressed in days) to account for any within-cohort differences observed between length of follow-up and risk of outcome.[22] Race was also included as a covariate for BHS analyses. For pooled estimates, we included a two-level variable for cohort to account for possible differences between cohorts. Because all predictor variables were standardized for

age and sex, these variables were not included as covariates. Interactions between cohort and the predictor variables were assessed by including product terms as additional covariates. The association between each MetS component (high BMI, high blood pressure, low HDL-cholesterol, high triglycerides, or high glucose) and outcomes of adult MetS, adult high cIMT, and adult T2DM were also examined in pooled data using two models. Model 1 adjusted for length of follow-up and cohort; model 2 included length of follow-up, cohort, and all MetS components in the same multivariable model. In all of the above models, pubertal status was considered as a covariate but its inclusion had minimal effect on the coefficients and as such was not retained for final models.

The ability of each MetS definition in youth to predict MetS, high cIMT, and T2DM in adulthood was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under receiver-operating characteristic curves (AUC). These statistics were calculated as follows: sensitivity = true positives/(true positives + false negatives) X 100; specificity = true negatives/(true negatives + false positives) X 100; NPV = true negatives/(true negatives + false negatives) X 100; and PPV = true positives/(true positives + false positives) X 100. The AUC was determined from the logistic model and represents an estimate of the probability that the model assigns a higher risk to those who have the outcome compared with those who do not have the outcome. The AUC has a range of 0 to 1, where a value of 0.5 represents no discrimination, and a value of 1 would indicate perfect discrimination. Because we found high BMI in youth to be the major contributing component in the prediction of adult outcomes, we also provide these data for high BMI. In addition we performed comparisons between three models: (A) high youth BMI (referent model); (B) modNCEP (or pedNCEP) MetS definition; and (C) modIDF (or pedIDF) MetS definition to predict adult outcomes of MetS, high cIMT, and T2DM. Differences in AUC between model B or model C compared with model A were estimated using the DeLong

algorithm.[25] Net reclassification improvement (NRI) was also calculated to determine the extent to which MetS definitions reassigned participants to a risk status that better reflected their final outcome (case or control).[26, 27] The proportions of participants reclassified to either higher- or lower-risk categories using models B, or C were compared with model A. Risk classification is improved if an individual with the outcome in adulthood (case) is placed in a higher risk category in youth or if an individual without the outcome in adulthood (control) is moved to a lower risk category in youth. The NRI is the sum of improvements for both case and control participants determined from youth BMI and MetS status.

Supplemental Tables

eTable 1. Rotated factor loadings from principal components factor analysis to derive the continuous MetS score at baseline in the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study

	Factor 1	Factor 2
Bogalusa (1984-5)		
BMI	0.539	0.271
Systolic BP	0.137	0.827
Diastolic BP	-0.029	0.817
HDL cholesterol	-0.794	0.059
Triglycerides	0.837	-0.045
Glucose	0.005	0.224
Variance explained, %	27.3	24.7
Total variance explained, %	52.0	
Bogalusa (1987-8)		
BMI	0.672	0.289
Systolic BP	0.097	0.802
Diastolic BP	-0.099	0.769
HDL cholesterol	-0.706	0.132
Triglycerides	0.697	0.090
Glucose	0.130	0.195
Variance explained, %	24.5	23.0
Total variance explained, %	47.5	

Young Finns (1986)		
BMI	0.552	0.404
Systolic BP	0.819	0.031
Diastolic BP	0.722	-0.083
HDL cholesterol	0.067	-0.814
Triglycerides	0.211	0.746
Glucose	0.216	0.101
Variance explained, %	26.5	23.3
Total variance explained, %	49.8	

eTable 2. Unadjusted* and adjusted† relative risks (RR) and 95% confidence intervals (95%CI) of adult MetS, high cIMT, and T2DM according to each component of the youth MetS definitions as well as insulin

	MetS				High cIMT				T2DM			
	Model 1*		Model 2†		Model 1*		Model 2†		Model 1*		Model 2†	
	RR	(95%CI)	RR	(95%CI)	RR	(95%CI)	RR	(95%CI)	RR	(95%CI)	RR	(95%CI)
modNCEP/IDF												
BMI ≥75th percentile	3.0	(2.5-3.7)	2.4	(1.9-3.0)	2.2	(1.7-2.9)	2.1	(1.5-2.8)	3.4	(1.8-6.4)	2.9	(1.6-5.5)
BP ≥75th percentile	1.5	(1.2-1.8)	1.2	(1.0-1.5)	1.4	(1.0-1.8)	1.3	(1.0-1.6)	1.0	(0.5-2.0)	0.9	(0.5-1.8)
HDL-C ≤25th percentile	1.9	(1.6-2.4)	1.5	(1.2-1.8)	1.3	(1.0-1.8)	1.1	(0.8-1.6)	1.8	(0.9-3.4)	1.5	(0.7-3.1)
TG ≥75th percentile	2.0	(1.6-2.5)	1.3	(1.0-1.6)	1.3	(1.0-1.7)	1.0	(0.7-1.4)	1.3	(0.6-2.6)	0.9	(0.4-1.8)
Glucose ≥75th percentile	1.5	(1.2-1.9)	1.2	(1.0-1.5)	1.1	(0.8-1.6)	1.0	(0.7-1.4)	1.8	(0.9-3.4)	1.5	(0.8-2.8)
Insulin ≥75th percentile	2.0	(1.7-2.5)	1.3	(1.0-1.6)	1.4	(1.1-1.9)	1.1	(0.8-1.5)	1.9	(1.0-3.7)	1.1	(0.6-2.1)

eTable 3. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the curve (AUC), and net reclassification index (NRI) values for youth MetS definitions in predicting adult MetS, high cIMT, and T2DM

Adult outcome	Child MetS definition	N	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC	(95%CI)	P-value	NRI, %	P-value
MetS											
	Overweight or obese*	1708	33.7	88.8	39.6	86.0	0.612	(0.585-0.640)	-	-	-
	pedsNCEP	1708	8.2	98.6	56.8	83.1	0.534	(0.518-0.550)	<0.001	-15.4	<0.001
	pedsIDF	1708	7.2	98.9	57.9	83.0	0.530	(0.515-0.545)	<0.001	-15.9	<0.001
High cIMT											
	Overweight or obese*	1696	28.1	86.8	19.9	91.1	0.574	(0.540-0.608)	-	-	-
	pedsNCEP	1696	5.1	97.9	22.0	89.8	0.515	(0.498-0.531)	<0.001	-19.4	0.005
	pedsIDF	1696	3.9	98.2	20.0	89.7	0.510	(0.496-0.525)	<0.001	-19.3	0.005
T2DM											
	Overweight or obese*	1720	48.6	85.5	6.5	98.8	0.670	(0.586-0.755)	-	-	-
	pedsNCEP	1720	8.6	97.6	6.8	98.1	0.531	(0.484-0.578)	0.001	-9.1	0.23
	pedsIDF	1720	8.6	97.9	7.9	98.1	0.533	(0.485-0.580)	0.001	-9.1	0.23

*Overweight or obese according to Cole definition.[11]

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