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A Diagnosis of the Metabolic Syndrome in Youth That Resolves by Adult Life Is Associated With a Normalization of High Carotid Intima-Media Thickness and Type 2 Diabetes Mellitus Risk

The Bogalusa Heart and Cardiovascular Risk in Young Finns Studies

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Objectives The aim of this study was to examine the effect of resolution from metabolic syndrome (MetS) between youth and adulthood on carotid artery intima-media thickness (IMT) and type 2 diabetes mellitus (T2DM).

Background Published findings demonstrate that youth with MetS are at increased risk of cardio-metabolic outcomes in adulthood. It is not known whether this risk is attenuated in those who resolve their MetS status.

Methods Participants (n = 1,757) from 2 prospective cohort studies were examined as youth (when 9 to 18 years of age) and re-examined 14 to 27 years later. The presence of any 3 components (low high-density lipoprotein cholesterol, high triglycerides, high glucose, high blood pressure, or high body mass index) previously shown to predict adult outcomes defined youth MetS; the harmonized MetS criteria defined adulthood MetS. Participants were classified according to their MetS status at baseline and follow-up and examined for risk of high IMT and T2DM.

Results Those with MetS in youth and adulthood were at 3.4 times the risk (95% confidence interval: 2.4 to 4.9) of high IMT and 12.2 times the risk (95% confidence interval: 6.3 to 23.9) of T2DM in adulthood compared with those that did not have MetS at either time-point, whereas those that had resolved their youth MetS status by adulthood showed similar risk to those that did not have MetS at either time-point ($p > 0.20$ for all comparisons).

Conclusions Although youth with MetS are at increased risk of adult high IMT and T2DM, these data indicate that the resolution of youth MetS by adulthood can go some way to normalize this risk to levels seen in those who have never had MetS. (J Am Coll Cardiol 2012;60:1631–9) © 2012 by the American College of Cardiology Foundation

The metabolic syndrome (MetS) is considered as a clustering of multiple interrelated metabolic irregularities often including obesity (particularly central), insulin resistance, dyslipidemia, hypertension, and hyperglycemia (1). The impor-

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Abbreviations and Acronyms

BMI = body mass index
cMetS = continuous metabolic syndrome score
HDL = high-density lipoprotein
IMT = intima-media thickness
MetS = metabolic syndrome
T2DM = type 2 diabetes mellitus

tance of the diagnosis above and beyond identification and treatment of its component parts, however, is controversial in children and adolescents (herein termed youth) (2,3) as well as adults (4,5). A recent consensus statement (2) has called for more research, particularly in longitudinal studies from youth to adulthood, on a number of areas relating to pediatric MetS before a definition for the clinical diagnosis of MetS among youth is considered. Some of the unwillingness to issue a definite definition is due to concerns over the demonstrated short-term instability of a categorical diagnosis of MetS in the pediatric setting (6,7). Further to this, however, is that—irrespective of instability—the ability to predict future disease status is critically important. We and others have shown that a number of pediatric MetS definitions predict important outcomes later in life, including carotid intima-media thickness (IMT), type 2 diabetes mellitus (T2DM), and cardiovascular morbidity (3,8–11). We have also shown that 6-year spontaneous resolution from MetS in young to middle adulthood has a beneficial impact on structural and functional markers of preclinical atherosclerosis, compared with those who had persistent MetS (12). A necessary extension of this work that has not previously been reported would be to examine the impact of resolution of the MetS during the life-course on adult disease outcomes. With the current absence of data from long-term clinical trials that span youth and adulthood on this issue (13), these types of analyses would significantly contribute to the published data and provide insight into whether or not interventions to tackle pediatric MetS might be clinically relevant. Therefore we sought to determine whether resolution of the MetS between youth and adult life is associated with changes in carotid IMT and T2DM risk.

Methods

The analysis sample included participants from the Bogalusa Heart Study (14) and the Cardiovascular Risk in Young Finns Study (15) where MetS risk factor variables were measured in youth (baseline) and again in adulthood (follow-up). For the Bogalusa study, data related to 376 youth 9 to 18 years of age who had participated in either the 1984 to 1985 or 1987 to 1988 youth surveys and attended either the 2001 to 2002 or 2003 to 2007 adult surveys (then 25 to 41 years of age). For the Young Finns study, this represented 1,381 youth 9 to 18 years of age who attended the 1986 youth survey and either the 2001 or 2007 adult follow-ups (then 24 to 39 years of age). These baseline and follow-up samples were selected because: 1) glucose screening first commenced in the Young Finns study in the 1986 survey and in the Bogalusa study from the 1984–85 survey; 2) the youngest participant in the 1986 Young Finns study was 9 years old, so for consistency, we limited the baseline Bogalusa sample to those 9 years of age or older; and 3) in the case of the adult follow-ups, they were the most consistent between studies and minimized differences in length of follow-up. For individuals that participated in multiple baseline (Bogalusa) or follow-up surveys, we used those measures that provided the longest period between baseline and follow-up. All analyses were restricted to those that did not have type 1 diabetes and female subjects who were not pregnant at follow-up. Both studies received ethical approval, and written informed consent was obtained from participants. Study details have been previously described in detail (14,15). We encourage readers to view the Online Appendix for more comprehensive Methods.

Definition of youth MetS. In the absence of a consensus pediatric MetS definition (6), we used the definition that we have previously shown to predict adult outcomes (3). Body mass index (BMI) was used as the measure of adiposity, because waist circumference was not measured at baseline in either cohort. Briefly, we generated age-, sex-, race- (Bogalusa only), cohort-, and study-year-specific *z*-scores of BMI, systolic and diastolic blood pressures, high-density lipoprotein (HDL) cholesterol, triglycerides, and glucose from each of the complete cohorts. A participant was categorized as having MetS if they had any 3 of the following 5 components: BMI ≥75th percentile, systolic or diastolic blood pressure ≥75th percentile, HDL-cholesterol ≤25th percentile, triglycerides ≥75th percentile, or glucose ≥75th percentile. We note that use of other pediatric MetS definitions that we have previously found to predict adult outcomes (3) did not modify the conclusions drawn.

Definition of adulthood MetS. Adult MetS was classified according to the "harmonized" definition proposed in 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 (1). MetS was identified when 3 or more of the following 5 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

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