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Correlation of metabolic syndrome severity with cardiovascular health markers in adolescents

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ABSTRACT

Background and Objectives. The presence of metabolic syndrome (MetS) in childhood is a significant risk factor for later cardiovascular disease (CVD). Recent data showed temporal decreases in a sex- and race/ethnicity-specific MetS severity z-score among U.S. adolescents. Our goal was to characterize the relationship of this MetS z-score with other CVD risk indicators and assess their temporal trends and lifestyle influences.

Methods. We analyzed 4837 participants aged 12–20 years from the National Health and Nutrition Examination Survey by 2-year waves from 1999 to 2012. We used linear regression to compare MetS z-score and dietary factors with serum levels of low-density lipoprotein (LDL), apolipoprotein-B (ApoB), high-sensitivity C-reactive protein (hsCRP) and uric acid.

Results. MetS severity z-score was positively correlated with LDL, ApoB, hsCRP, and uric acid measurements ($p < 0.0001$ for all). These correlations held true among individual racial/ethnic groups. LDL, ApoB, and hsCRP measurements decreased over time among U.S. adolescents ($p = 0.002$, $p < 0.0001$, and $p = 0.024$, respectively). Saturated fat consumption was positively correlated with LDL ($p = 0.005$) and ApoB ($p = 0.012$) and inversely related to serum uric acid ($p = 0.001$). Total caloric intake was inversely related to LDL ($p = 0.003$) and serum uric acid ($p = 0.003$). Unsaturated fat, carbohydrate, and protein consumption were not related to LDL, ApoB, hsCRP, or serum uric acid.

Conclusions. There is a positive correlation between MetS severity and all four CVD risk indicators studied. LDL, ApoB, and hsCRP showed favorable temporal trends, which could be related to similar trends in MetS z-score. These data support the importance of considering multiple inter-related factors in clinical CVD risk assessment.

1. Introduction

The metabolic syndrome (MetS) is a cluster of clinical abnormalities characterized by: increased waist circumference (or increased BMI z-score in pediatrics), elevated blood pressure, hypertriglyceridemia, hyperglycemia, and low HDL cholesterol [1–3]. MetS has traditionally been defined based on abnormalities in at least three of these topics. The presence of MetS in childhood is a significant risk factor for developing cardiovascular disease (CVD) in adulthood [4–6]. The MetS severity score (MetS z-score) was developed as a continuous score to assess severity of metabolic derangement and account for sex and racial/ethnic differences in MetS [7–10]. We recently demonstrated that in adults, this MetS severity score remained a significant predictor of future coronary heart disease, even in models that included all of the individual components of MetS – suggesting that MetS was indeed worth more than the sum of its parts [11].

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Childhood manifestations of CVD are rare; however, the pathogenesis can begin in adolescence [12–14]. Thus, it is a priority to characterize possible risk indicators in young patients. It has been previously shown that elevated childhood MetS z-score correlates with increased risk of adulthood CVD and type 2 diabetes mellitus (T2DM) [15–17]. Additionally, the MetS z-score had been shown to correspond with abnormalities in serum uric acid and high-sensitivity C-reactive protein (hsCRP) measurements in adolescents, which are considered CVD risk indicators, though this was only performed in the population sample from which the MetS z-score was derived and has not been further confirmed among additional adolescents [7]. Low-density lipoprotein cholesterol (LDL) and apolipoprotein-B (ApoB) are additional CVD risk indicators [2,18]; it remains unclear how these relate to the severity of MetS.

We recently reported that the MetS z-score declined among U.S. adolescents from 1999 to 2012, and this change was correlated with decreasing total caloric consumption, decreasing carbohydrate consumption, and increasing unsaturated fat consumption [19]. The goals of the current project were to (1) assess whether MetS severity correlated with these additional markers of CVD risk, (2) analyze whether these markers exhibited a similar decrease over the same study period and (3) assess whether these other CVD risk markers were associated with dietary changes, as MetS severity had been. We hypothesized that elevated MetS z-scores would correspond with higher levels of LDL, ApoB, uric acid and hsCRP measurements in adolescents. We subsequently hypothesized that those CVD biochemical risk indicators would also show a decreasing temporal trend and would be related to dietary trends. Such links between CVD risk factors may have implications for the MetS z-score as an overall metabolic health marker and societal trends of other biochemical markers more specifically related to CVD risk.

2. Materials and Methods

We examined participant data from the Centers for Disease Control and Prevention National Health and Nutrition Examination Survey (NHANES 1999–2012). NHANES is a national, stratified, multistage probably, cross-sectional survey conducted in two-year waves, recruiting randomly selected non-institutionalized U.S. civilians. Racial/ethnic minority groups and those at or below 130% of the federal poverty level were oversampled. Calculated sample weights accounted for this oversampling in addition to correcting for different response rates among groups to ensure nationally representative estimates. The National Center for Health Statistics ethics review board approved this study. Laboratory and clinical measurements were obtained using controlled equipment and protocols [20].

The protocols for obtaining measurements for MetS assessment have been previously cited [19,21,22]. Fasting blood samples were obtained from participants who attended the morning session at CDC NHANES mobile examination centers. HDL was measured by direct immunoassay. Fasting glucose was measured using an enzyme-linked hexokinase method. Triglycerides measurement used a timed-endpoint method. BMI z-scores were calculated in accordance with the U.S. CDC 2000 growth reference adjusting for age and sex [23]. Elevated blood pressure (BP) was defined as systolic or diastolic BP exceeding the 90th percentile for sex, age, and height [24]. MetS z-score was calculated using the Pediatric MetS z-score (http://mets.health-outcomes-policy.ufl.edu/calculator/) [7].

The biochemical CVD markers of interest were measured in accordance with CDC NHANES protocol [20]. LDL was calculated according to the Friedewald calculation. ApoB was measured with an immunochemical light spectrometry method. Serum uric acid was measured with a timed-endpoint method. High-sensitivity CRP was quantified with latex-enhanced nephelometry; levels of hsCRP were only available for 1999–2010.

Dietary intake and physical activity were determined as previously cited [19]. Dietary intake was determined from a 24-hour food recall administered by trained dietary interviewers using a 4-step multi-pass approach on examination day at the mobile examination centers. Data were processed and coded based on individual foods and portion sizes to determine specific nutrient intake in accordance with the U.S. Department of Agriculture's National Nutrient Database for Standard Reference [25]. Food group consumption was reported as percentage of total calories accounted for by specific food group [26]. The equations were: % total energy from carbohydrates = (4 × grams of carbohydrates)/total calories, % total energy from fats (saturated or unsaturated) = (9 × grams of fat)/total calories, and % total energy from protein = (7 × grams of protein)/total calories.

Additionally, we used Food Frequency Questionnaire data from 2003 to 2006 and from 2009 to 2010 (years for which data were made available) to assess intake of high-fructose foods. NHANES participants were questioned on how often they ate a specific food. High-fructose foods included juices, sugar-sweetened beverages, and desserts such as cookies and ice cream [27]. Notably, this questionnaire did not include information about serving sizes. These data were compiled to create a daily frequency of high-fructose food consumption. This value was then log transformed given the skewed distribution.

From 2007 to 2012, physical activity was assessed as weekly minutes of moderate-to-vigorous physical recreational activity. Participants were initially asked if they participated in any moderate-to-vigorous-intensity sports, fitness, or recreational activities. If they answered yes, they were further questioned how many minutes per typical day they do these activities.

Participants were excluded due to the following conditions that may introduce confounding factors in correlating their MetS z-score with biochemical CVD markers: non-fasting status (n = 993), pregnancy (n = 242), active hepatitis-B infection (n = 8), physician-diagnosed diabetes (n = 66), or current use of antidiabetic or antihyperlipidemic medication (n = 42). Participants taking antihypertensives (n = 69) were not excluded but instead classed as having elevated BP.

Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using SAS (version 9.4, Cary, NC). Survey procedures were used to account for the NHANES survey design and obtain population-based estimates. Linear regression was used to create models correlating the different CVD indicators with MetS z-score. Initial comparison of MetS and CVD factors was unadjusted to generate Pearson's R for