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Metabolic syndrome burden in apparently healthy adolescents is adversely associated with cardiac autonomic modulation—Penn State Children Cohort

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ABSTRACT

Background. Reduced cardiac autonomic modulation (CAM) has been associated with metabolic syndrome (MetS) in adults. However, the association between MetS component cluster and CAM has not been examined in adolescents.

Methods. We conducted a cross-sectional analysis using data from the Penn State Child Cohort follow-up examination. CAM was assessed by heart rate variability (HRV) analysis of 39-h RR intervals, including frequency (high frequency, HF; low frequency, LF; and LF/HF ratio) and time (SDNN, standard deviation of all RR intervals; RMSSD, square root of the mean of the sum of the squares of differences between adjacent RR intervals; and HR, heart rate) domain variables. To assess the MetS burden, we used continuous MetS score (cMetS)—sum of the age and sex-adjusted standardized residual (Z-score) of five established MetS components. Linear mixed-effect models were used to analyze the association between cMetS and CAM in the entire population and stratified by gender.

Results. After adjusting for age, sex, and race, cMetS was significantly associated with reduced HRV and higher HR. With 1 standard deviation increase in cMetS, there was a significant decrease in HF (−0.10 (SE = 0.02)), LF (−0.07 (SE = 0.01)), SDNN (−1.97 (SE = 0.50)), and RMSSD (−1.70 (SE = 0.72)), and increase in LF/HF (0.08 (SE = 0.02)) and HR (1.40 (SE = 0.26)). All cMetS components, with the exception of high-density lipoprotein (HDL), were associated with significantly decreased HRV and increased HR. High blood pressure (MAP) and triglyceride (TG) levels were also associated with an increase in LF/HF and decrease in

Abbreviations: BMI, body mass index; CAM, cardiac autonomic modulation; cMetS, continuous metabolic syndrome score; CVD, cardiovascular diseases; ECG, electrocardiography; HDL, high-density lipoprotein; HF, high frequency range; HR, heart rate; HRV, heart rate variability; LF, low frequency range; LF/HF, the ratio of LF to HF; MAP, mean arterial pressure; MetS, metabolic syndrome; PSCC, Penn State Children Cohort; RMSSD, square root of the mean of the sum of the squares of differences between adjacent RR intervals; SDNN, standard deviation of all RR intervals; TG, triglycerides; WC, waist circumference.

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RMSSD. An increase in high-density lipoprotein was only associated with higher LF and SDNN. Moreover, cMetS and HRV associations were more pronounced in males than in females. The associations between HRV and. MAP, TG, and HDL were more pronounced in females.

Conclusions. cMetS score is associated with lower HRV, suggesting an adverse impact on CAM, even in apparently healthy adolescents.

1. Introduction

The metabolic syndrome (MetS) is a constellation of adverse cardiovascular disease (CVD) and metabolic risk factors that include central obesity, elevated blood pressure, elevated triglycerides, hyperglycemia or insulin resistance, and low levels of high-density lipoprotein-cholesterol [1]. The prevalence of MetS in adults in the United States is 40.1% [2]. However, in children and adolescents, the prevalence of MetS is considerably lower. Comparing data in adolescents from the 1988–1994 to 2001–2006 U.S. National Health and Nutrition Examination Survey, the prevalence of MetS increased from 4% to 9% [3]. And for those who are obese, the prevalence of MetS varies from 30% to 50% [4]. Although MetS has been well-defined in the adult population, there is no current universal definition for Mets in adolescents. Therefore, these results were not comparable. In addition, due to the low MetS prevalence reported, a large sample size is required to assess the MetS burden and study the risk factors in the youth. Several epidemiological studies have attempted to define MetS in children and adolescents and have suggested the use of a continuous MetS score (cMetS) [5–9]. Given the higher statistical power of a continuous score compared to categorical MetS criteria; it is more practical to investigate the association between cMetS and different health outcomes in adolescents.

In adults, MetS increases the risk of CVD and diabetes [10,11] and alters the function of the cardiovascular system [12]. The autonomic nervous system plays an important role in the cardiovascular regulation [13]. Heart rate variability (HRV), a noninvasive measurement of cardiac autonomic modulation (CAM) [14], is regulated by the balance of sympathetic and parasympathetic modulation. An imbalance between the these two results in impairment of CAM [13,15], which has been reported as an independent risk factor for CVD [13,15,16]. Lower HRV calculated from short-term normal RR intervals has been associated with CVD mortality and CVD morbidity in various adults populations [11,16–22]. Several studies in adults have examined the association between MetS and HRV [22–26]. However most of these studies analyzed the clustering of MetS disorders, which is not applicable in young populations due to the lack of binary defintion of MetS. A number of other studies have evaluated the association between each individual MetS component and HRV indices in children [27–34]. Only one particular study examined the relationships between each component of MetS, as continuous variable, and the change of HRV in young adults (18–21 years) [27]. However, to our knowledge, no study has examined the association between MetS component cluster and HRV in children/adolescents. Several methods, including principle component analysis [7], Z scores [5,8], and rankings [6], have been used to derive a cMetS score and represent an aggregated burden for MetS in adolescents. This cMetS score enables examinations of preclinical MetS burden in children and adolescents, much earlier than the development of clinical symptoms of MetS. Thus, the main objective of the study is to investigate the association between cMetS score and the CAM as measured by HRV in a population-based sample of adolescents.

2. Material and methods

2.1. Study population

We used data from 421 adolescents who completed the follow-up examination of the Penn State Children Cohort (PSCC) study. The recruitment and examination procedures for the baseline study have been published elsewhere [35,36]. During 2010–2013, a follow-up examination for 700 participants from phase II of PSCC was conducted. Among these subjects, 421 of them completed the follow-up with a response rate of 60% and a mean follow-up time of 7.7 years. The loss to follow-up was mainly due to subjects moving out of central Pennsylvania. However, no major difference in baseline characteristics was observed between subjects who did or did not participate. During the study period, participants were evaluated overnight in the Clinical Research Center at the Pennsylvania State University College of Medicine (COM) including a complete physical examination, a whole body dual-energy x-ray absorptiometry, a 9-h fixed-time polysomngraphy (PSG) recording, and overnight fasting blood, saliva, and urine samples. The study protocol was approved by Pennsylvania State University COM IRB. Written informed consents were obtained from participants and their parents if participant was a minor (<18 years old).

2.2. Continuous metabolic syndrome score (cMetS)

MetS burden was assessed by the cMetS—the sum of the age and sex adjusted standardized residual (Z-score) of the following parameters: waist circumference (WC), mean arterial pressure (MAP), homeostasis model assessment of insulin resistance (HOMA-IR), triglycerides (TG), and high-density lipoprotein (HDL). WC and seated blood pressure (BP) were assessed during physical exam by a trained investigator. The average of the 2nd and 3rd BP was used in the analysis. MAP was calculated as diastolic pressure + 1/3 systolic pressure. Glucose, insulin, and lipid profiles were obtained from venous blood drawn from subjects in fasted status. HOMA-IR was calculated as the product of fasting insulin level (in μU/ml) and fasting glucose level (in mmol/L) divided by 22.5. Because HDL level is inversely related to metabolic risk, it was