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The severity of the metabolic syndrome increases over time within individuals, independent of baseline metabolic syndrome status and medication use: The Atherosclerosis Risk in Communities Study

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ABSTRACT

Background and aims: The severity of the metabolic syndrome (MetS) is linked to future cardiovascular disease. However, it is unclear whether MetS severity increases among individuals followed over time.
Methods: We assessed changes in a sex- and race/ethnicity-specific MetS severity Z-score over a 10-year period (visits 1–4) among 9291 participants of the Atherosclerosis Risk in Communities study cohort. We compared sex- and racial/ethnic subgroups for the rate of change in the MetS severity score and MetS prevalence as assessed using traditional ATP-III MetS criteria. We further examined effects of use of medications for hypertension, diabetes and dyslipidemia.
Results: Over the 10 years of follow-up, MetS severity Z-scores increased in 76% of participants from an overall mean of 0.08 ± 0.77 at baseline to 0.48 ± 0.96 at visit 4 with the greatest progression in scores observed among African-American women. Baseline MetS severity scores predicted the time until ATP-III MetS diagnosis, with a model-predicted 77.5% of individuals with a visit 1 MetS severity score of 0.75 progressing to ATP-III MetS within 10 years. The rate of increase in MetS severity score was higher among those younger at baseline but was independent of baseline MetS status or the use of medications to treat blood pressure, lipids and diabetes.
Conclusion: The severity of metabolic derangements as measured using this MetS severity score increases over time within individuals and predicts diagnosis of ATP-III MetS. These data may have implications for tracking MetS related risk within individuals over time.

1. Introduction

The metabolic syndrome (MetS) is a cluster of metabolic risk factors that are associated with increased risk for cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) [1]. MetS is typically classified based on a person exhibiting abnormalities beyond specific cut-off levels for the individual MetS components of waist circumference, blood pressure (BP), fasting glucose, fasting triglycerides, and HDL-cholesterol. There is an overall tendency for these component levels to worsen in an individual over time [2]; thus, it is not surprising that in longitudinal cohorts there is an increase in the prevalence of MetS over time as more individuals exceed the cut off levels for the individual components [3]. Based on current criteria such as that of the Adult Treatment Panel III (ATP-III), an individual must have abnormalities in at least 3 of these 5 components to be classified as having MetS [4]. Nevertheless, use of medications to treat specific components such as elevated fasting glucose and dyslipidemia may contribute to overall reductions in these values [5,6]. Because of the binary nature of traditional MetS criteria, other longitudinal studies have shown the propensity of some individuals to toggle back and forth between a MetS classification over time [7]—which has been seen as a limitation to current criteria [8].

An additional limitation to the current MetS criteria is that they appear to exhibit racial/ethnic discrepancies in that African-Americans are less likely to be classified as having MetS [9–13], despite having higher rates of T2DM [14] and death from CVD [15]—conditions with which MetS is closely associated. Similarly, use of ATP-III MetS definition in other populations has been questioned

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[16]. We have formulated a MetS severity score that is sex- and race/ethnicity-specific and can follow changes in MetS characteristics within a given individual [17,18]. We recently reported use of this score in predicting future CVD based on MetS severity in childhood and mid-adulthood [19,20]. While there was a strong correlation between MetS severity in childhood and adulthood, it remains unclear how MetS severity tracks within an individual, as related to race/ethnicity and medical treatment.

Our goal in the current study was to evaluate for variation in MetS severity within individuals over time using this sex- and race/ethnicity-specific MetS severity score. We hypothesized that use of this score would reveal a gradual worsening of MetS severity in a population over time—and that this worsening would itself vary by sex and race/ethnicity and by treatment with MetS-related medications. In addition, we wished to determine the ability of this MetS severity score to predict ATP-III defined MetS. We hypothesized that this score would provide a more sensitive early measure of a person's risk of MetS. We evaluated longitudinal data from the Atherosclerosis Risk in Communities Study (ARIC), with potential implications to tracking MetS clinically over time in an individual.

2. Methods

2.1. Study population

ARIC study is a large community-based epidemiological cohort study that started in 1987–89 across 4 field centers in the US. A total of 15,792 participants aged 45–64 years were recruited. Of these 15,397 consented to be included in this study – 5359 white men, 5943 white women, 1585 African-American men, and 2464 African-American women and 46 participants of other races. Details of the study design and objectives are published elsewhere [21]. From this sample, we excluded those who reported presence of CVD or DM at the baseline visit, who missed any of the follow-up visits up to visit 4 (1996–98), participants other than African Americans and whites, or those with missing data on any of the components of MetS. Thus, a total of 9291 participants were included in the current analyses.

2.2. Measurement of metabolic syndrome components

Previous reports have published details of procedures for blood collection and analysis for lipids [22] and serum glucose [23]. Briefly, participants fasted overnight for 12 h before the examination. Phlebotomy was performed, blood sample was centrifuged and serum was sent to a central laboratory for examination. Triglycerides were measured by enzymatic methods, and HDL cholesterol was measured after dextran-magnesium precipitation. LDL cholesterol was calculated using the Friedewald equation. Serum glucose was measured by the hexokinase –6 phosphate dehydrogenase method [24]. Trained clinical staff measured waist circumference at the umbilical level to the nearest cm. BP was examined in sitting position with a random-zero sphygmomanometer – of the three measurements performed, the average of the last two measurements were used for analysis. Similar procedures were followed at all study sites over the 4 visits.

MetS severity was calculated as a Z-score for participants at all four visits using sex and race based formulae. As described elsewhere [17], these scores were derived using a confirmatory factor analysis approach for the 5 traditional components of MetS to determine the weighted contribution of each of these components to a latent MetS "factor" on a sex- and race/ethnicity-specific basis. Confirmatory factor analysis was performed among adults 20–64 years from the National Health and Nutrition Examination Survey (NHANES) with categorization into six sub-groups based on sex and the following self-identified race/ethnicities: non-Hispanic white, non-Hispanic black and Hispanic. For each of these six population sub-groups, loading coefficients for the 5 MetS components were determined toward a single MetS factor. These loading coefficients were used to generate equations to calculate a standardized MetS severity score for each sub-group (http://publichealth.hsc.wvu.edu/biostatistics/metabolic-syndrome-severity-calculator/). The resulting MetS severity scores are Z-scores (ranging from theoretical negative infinity to theoretical positive infinity) of relative MetS severity on a sex- and race/ethnicity-specific basis. These scores are highly correlated to other surrogate markers of MetS risk, including hsCRP, uric acid and the homeostasis model of insulin resistance [17] and were recently shown to correlate with long-term CVD and T2DM risk in the Princeton Lipid Research Cohort Study [19,20].

MetS was defined using the criteria established by the Adult Treatment Panel III (ATP III), i.e. presence of three or more of the following criteria – elevated waist circumference ($\geq$102 cm for men, $\geq$88 cm for women), elevated triglycerides ($\geq$150 mg/dl or drug treatment for elevated triglycerides), reduced HDL (<40 mg/dl for men, <50 mg/dl for women or drug treatment for reduced HDL), elevated BP ($\geq$130 mmHg systolic or $\geq$85 mmHg diastolic or drug treatment for hypertension) and elevated blood glucose ($\geq$100 mg/dl or drug treatment for elevated glucose) [4]. Leisure time physical activity was self-reported at baseline using questionnaire designed by Baecke [25].

2.3. Statistical analysis

All analyses were performed using SAS Version 9.4 (Cary, NC) with statistical significance set to $\alpha = 0.05$. Descriptive statistics on baseline characteristics were calculated for all included participants and compared with those that were excluded from the current study. Prevalence of MetS and mean MetS severity scores were calculated across the four visits, and by age group (<50, 50–59, and $\geq$60 years), sex, and race (white vs. African-American). For trends that appeared linear, generalized estimating equations (GEE's) were fit to model linear trends over time to compare prevalence (MetS) and mean (MetS severity score) as well as the linear increases across the four sex/race groups of interest (white males, white females, African-American males, African-American females) by age category stated above. An unstructured working correlation matrix was used to account for the repeated observations across individuals.

To determine the sensitivity of the MetS severity score in changing prior to actual development of traditionally defined MetS, mean MetS severity scores were modeled using GEE's, separately by categories defined by the timing of initial diagnosis of MetS (visit 1, 2, 3, or 4), adjusting for baseline age. This analysis only looked at those individuals who were consistently classified as having MetS in subsequent visits, eliminating those individuals whose diagnosis changed repeatedly during the study (n = 1,974, 21.2%). Further insight into the discriminative ability of the MetS severity score was determined by using an accelerated failure time model (assuming a Weibull distribution) to model "time to MetS" as a function of baseline MetS severity score (excluding those individuals with MetS at visit 1), again adjusting for baseline age. This model accounts for the interval censoring that occurred in this study (i.e., there is not a specific date of definitive diagnosis of MetS, only that we know it developed between two visits).

Finally, to determine the impact of medication use on MetS severity, mean MetS scores were modeled across visits using GEE's, as a function of medication status. Separate analyses were performed for blood pressure medications, lipid medications, and diabetes medications, and categories were defined by the start of medication use, again limiting to those individuals who remained