Heritability of the Severity of the Metabolic Syndrome in Whites and Blacks in 3 Large Cohorts

Solomon K. Musani, PhD; Lisa J. Martin, PhD; Jessica G. Woo, PhD; Michael Olivier, PhD; Matthew J. Gurka, PhD; Mark D. DeBoer, MD, MSc, MCR

Background—Although dichotomous criteria for the metabolic syndrome (MetS) appear heritable, it is not known whether MetS severity as assessed by a continuous MetS score is heritable and whether this varies by race.

Methods and Results—We used SOLAR (Sequential Oligogenic Linkage Analysis Routines) to evaluate heritability of Adult Treatment Panel-III MetS and a sex- and race-specific MetS severity Z score among 3 large familial cohorts: the JHS (Jackson Heart Study, 1404 black participants), TOPS (Take Off Pounds Sensibly, 1947 white participants), and PLRS (Princeton Lipid Research Study, 229 black and 527 white participants). Heritability estimates were larger for Adult Treatment Panel-III MetS among black compared with white cohort members (JHS 0.48; 95% confidence interval [CI], 0.28–0.68 and PLRS blacks 0.93 [95% CI, 0.73–1.13] versus TOPS 0.21 [95% CI, −0.18 to 0.60] and PLRS whites 0.27 [95% CI, −0.04 to 0.58]). The difference by race narrowed when assessing heritability of the MetS severity score (JHS 0.52 [95% CI, 0.38, 0.66] and PLRS blacks 0.64 [95% CI, 0.13–1.15] versus TOPS 0.23 [95% CI, 0.15–0.31] and PLRS whites 0.60 [95% CI, 0.33–0.87]). There was a high degree of genetic and phenotypic correlation between MetS severity and the individual components of MetS among all groups, although the genetic correlations failed to reach statistical significance among PLRS blacks. Meta-analyses revealed a combined heritability estimate for Adult Treatment Panel-III MetS of 0.24 (95% CI, 0.11–0.36) and for the MetS severity score of 0.50 (95% CI, −0.05 to 0.99).

Conclusions—MetS severity seems highly heritable among whites and blacks. This continuous MetS severity Z score may provide a more useful means of characterizing phenotypic MetS in genetic studies by minimizing racial differences.

See Clinical Perspective

There is potential that the genetic basis of MetS may differ between white and black populations because MetS seems to be manifested differently by race. Blacks as a group have a low prevalence of MetS despite having high prevalence of insulin resistance, type 2 diabetes mellitus, and CVD. This seems to be because of low rates of dyslipidemia among blacks, who have low levels of triglycerides that are nevertheless positively correlated with insulin resistance. It is for this reason that we developed a MetS severity Z score that is specific to sex and race/ethnicity. This score is correlated with insulin resistance and predicted future type 2 diabetes mellitus and CVD events in cohorts with white and black participants. Additionally, as a linear score, this provides a more powerful way to assess genetic underpinnings than traditional binary criteria.

The goal of this study was to evaluate the heritability of the MetS severity score and its individual components, as well as underlying factors. However, direct comparisons between cohorts with white and black participants are lacking.
the genetic and phenotypic correlations between MetS severity and these components, in cohorts composed of white and black participants. For this, we used data from the JHS (Jackson Heart Study; a cohort of black individuals from the area around Jackson, MS), the TOPS study (Take Off Pounds Sensibly; a cohort of white individuals from Minnesota), and the PLRS cohort (Princeton Lipid Research Study; a cohort of white and black individuals in the Cincinnati area). We were particularly interested in potential differences in the heritability of MetS severity between groups, both to help guide future efforts at risk identification and to assess whether heritability differences have been minimized in the use of the continuous MetS Z score.

Methods

Cohorts Evaluated

Jackson Heart Study

JHS is the largest longitudinal, single-site study of cardiovascular risk in black individuals in and around Jackson, MS. JHS was approved by the Institutional Review Board of the University of Mississippi Medical Center, and participants provided informed consent. The cohort consists of 5301 participants aged 21 to 95 years, of whom 1500 are part of a family component of the study. They were recruited by identifying index participants who provided extensive family information. We used data from JHS visit 1 (2000–2004). MetS components measured using standardized protocols as described previously.23–25

Take-Off-Pounds-Sensibly Study

Families were recruited from the TOPS (Take Off Pounds Sensibly, Inc) membership. In 1994, TOPS provided mailing membership on material attending its chapters in 10 states (Wisconsin, Illinois, Michigan, Iowa, Minnesota, Ohio, West Virginia, Missouri, Kentucky, and Indiana). Questionnaire data received from 60000 respondents were verified and entered into the TOPS Obesity and Metabolic Research Center databases at the Medical College of Wisconsin. Families with at least 2 obese siblings (body mass index ≥30 mg/kg2), availability of one (preferably both) parents, and at least 1 non-obese sibling or parent (body mass index <27 mg/kg2) were identified and contacted for ascertainment. Families were scheduled to visit satellites (4–6 per state), where an experienced team undertook the phenotypic procedures. Research protocols were approved by the Institutional Review Board of the Medical College of Wisconsin, and participants provided informed consent. Data for the genetic analyses presented here included 2209 individuals distributed across 507 white families of predominantly northern European ancestry and residing in the United States. MetS-associated data were collected via standard protocols published previously.26

Princeton Lipid Research Study

Participants were originally recruited as part of the Cincinnati Clinic of the National Heart Lung and Blood Institute Lipid Research Clinic Prevalence Program (1972–1978), a multistage survey of lipids and other CVD risk factors.27–28 In 1973 to 1976, the Lipid Research Clinic enrolled students in grades 1 to 12 in the Princeton City School District near Cincinnati, OH, and a random sample of their parents. The Institutional Review Boards of National Heart Lung and Blood Institute, the University of Cincinnati, and Cincinnati Children’s Hospital Medical Center approved the study and its analysis, and participants provided informed consent. The PFS (Princeton Follow-up Study, 2000–2004) was a 25- to 30-year follow-up of these student and parent participants to prospectively assess changes in CVD risk factors from childhood to the fourth to fifth decades of life.29 PFS visit eligibility required participation in Lipid Research Clinic visits where lipoproteins were measured and participation of at least one first-degree relative at those same visits. In this analysis, the family-based data from the PFS visit was used. MetS-associated data were collected at the PFS visit via standard protocols as published previously.30

MetS Determination

Traditional MetS was defined using the ATP-III criteria for adults.1 Participants had to meet ≥3 of the following 5 criteria: concentration of triglycerides ≥1.69 mmol/L (150 mg/dL); HDL cholesterol <1.04 mmol/L (40 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women; WC ≥102 cm for men and 88 cm for women; glucose concentration ≥5.55 mmol/L (100 mg/dL); and systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure ≥85 mmHg. Traditional MetS is classified as meeting versus not meeting the established criteria. MetS severity Z score was calculated using formulas published previously by our group.6,17 Briefly, these scores were formed using confirmatory factor analysis of the 5 traditional components of MetS (as above) 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 on data from the National Health and Nutrition Examination Survey for adults aged 20 to 64 years17 divided into 6 subgroups based on sex and the following self-identified race/ethnicities: non-Hispanic white, non-Hispanic black, and Hispanic. For each of these 6 population subgroups, loading coefficients for the 5 MetS components were determined toward a single MetS factor. The loading coefficients were then used to generate scores for each subgroup (http://mets.health-outcomes-policy.ufl.edu/calculator/).31 These MetS severity scores are Z scores (with mean=0 and SD=1, with 99.75% of values ranging from −3 to 3) of relative MetS severity on a sex- and race-ethnicity-specific basis, with higher scores indicating worse MetS severity. These scores correlate with other coronary heart disease risk factors, including high-sensitivity C-reactive protein, uric acid, insulin,17 and adiponectin,32 and with long-term disease risk.20,21

Correlations and Heritability Analysis

We used a variance component approach implemented in SOLAR (Sequential Oligogenic Linkage Analysis Routines)32 to estimate heritability for MetS severity score and its phenotypic and genetic correlations with its components (blood pressure, HDL, triglycerides, WC, and fasting glucose). Although the genetic correlation was directly estimated from the bivariate modeling, the phenotypic correlation was derived from the estimated proportion of variance attributed to genetic and nongenetic factors as well as the correlation because of genetic and nongenetic factors.33 We did not include dominance deviations. Although dominance deviations can be estimated, the contribution of dominance deviations apart from siblings is low; thus, most studies such as this, which include nuclear and extended pedigrees, rarely estimate this component.34 Heritability analysis on MetS as defined in the ATP-III guidelines was also conducted to allow for comparison purposes. Because of the non-normal distribution of most continuous phenotypes, we applied the t-distribution option. Covariates included age, age*age, sex, age*sex, and age*age*sex interactions. Heritability estimates for each study were computed independently, which were then meta-analyzed across racial groups using a random-effects model based on inverse variance weighting approach to reduce bias associated with meta-analysis of few studies.

Results

We evaluated data from 4107 individuals: 1404 from JHS, 756 from PLRS, and 1947 from TOPS. Participant characteristics are shown in Table 1. There was a high proportion of obesity in each of the cohorts, consistent with US population data.35 The prevalence of ATP-III MetS was higher in TOPS (48.2% of women and 41.3% of men) and white male PLRS participants (37.1%) than that in JHS (31.0% of women and 28.3% of men) and black PLRS participants (31.6% of women and 34.5% of men). MetS severity scores were generally higher in men than in women (except in JHS) and were highest in TOPS.

Table 2 shows heritability estimates for the MetS severity score and ATP-III MetS for each of the cohorts, with the PLRS cohort divided into white and black participants. MetS severity score had a significantly (P<0.001) high heritability (>0.50)
Musani et al Heritability of MetS Severity by Race

Table 1. Participant Characteristics by Cohort

<table>
<thead>
<tr>
<th></th>
<th>JHS</th>
<th>PLRS</th>
<th>TOPS*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>n</td>
<td>935</td>
<td>469</td>
<td>142</td>
</tr>
<tr>
<td>Race (% black)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Age, y</td>
<td>51±14</td>
<td>49±15</td>
<td>38.9±4.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33.5±8.2</td>
<td>30.0±6.8</td>
<td>31.0±8.4</td>
</tr>
<tr>
<td>WC</td>
<td>100.8±17.7</td>
<td>100.4±16.0</td>
<td>100.6±20.4</td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
<td>63.7</td>
<td>38.8</td>
<td>45.1</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>124.9±19.1</td>
<td>126.4±17.3</td>
<td>122.3±18.2</td>
</tr>
<tr>
<td>DBP mmHg</td>
<td>78.1±10.3</td>
<td>81.3±10.4</td>
<td>80.2±11.5</td>
</tr>
<tr>
<td>High BP, n (%)</td>
<td>59.6</td>
<td>51.5</td>
<td>38.8</td>
</tr>
<tr>
<td>Triglycerides, mg/dL†</td>
<td>85.0</td>
<td>96.5</td>
<td>72</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>53.8±14.1</td>
<td>45.2±12.1</td>
<td>50.6±14.9</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>197.5±40.7</td>
<td>195.2±39.4</td>
<td>182.6±30.2</td>
</tr>
<tr>
<td>Fasting glucose†</td>
<td>90.0</td>
<td>91.0</td>
<td>86</td>
</tr>
<tr>
<td>MetS Z score‡</td>
<td>0.04</td>
<td>−0.53</td>
<td>−0.95</td>
</tr>
<tr>
<td>MetS (ATP-III criteria)</td>
<td>31.0</td>
<td>28.3</td>
<td>31.6</td>
</tr>
</tbody>
</table>

ATP-III indicates Adult Treatment Panel-III; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; JHS, Jackson Heart Study; MetS, metabolic syndrome; PLRS, Princeton Lipid Research Study; SBP, systolic blood pressure; TOPS, Take Off Pounds Sensibly; and WC, waist circumference.

Table 2. Estimated Heritability for MetS Severity Score and ATP-III MetS for all Cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>MetS Score h²±SE</th>
<th>P Value</th>
<th>Phenotypic Variance</th>
<th>ATP-III MetS h²±SE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>JHS</td>
<td>0.52 (0.05)</td>
<td>&lt;0.001</td>
<td>0.09</td>
<td>0.48 (0.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLRS blacks</td>
<td>0.64 (0.26)</td>
<td>0.005</td>
<td>0.21</td>
<td>0.93 (0.10)</td>
<td>0.001</td>
</tr>
<tr>
<td>PLRS whites</td>
<td>0.60 (0.14)</td>
<td>&lt;0.001</td>
<td>0.00</td>
<td>0.27 (0.16)</td>
<td>0.085</td>
</tr>
<tr>
<td>TOPS</td>
<td>0.23 (0.04)</td>
<td>&lt;0.001</td>
<td>0.28</td>
<td>0.21 (0.20)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

h² is heritability estimate. ATP-III indicates Adult Treatment Panel-III; JHS, Jackson Heart Study; MetS, metabolic syndrome; PLRS, Princeton Lipid Research Study; and TOPS, Take Off Pounds Sensibly.

The heritability estimate in all cohorts except in TOPS where the estimate (±SE) was lower 0.23 (±0.04). ATP-III MetS demonstrated similar or lower heritability estimates in most cohorts (0.21 in TOPS, 0.27 in PLRS whites, and 0.48 in JHS; P<0.01 for JHS and TOPS), but a higher heritability estimate among PLRS blacks (0.93; P<0.001).

Table 3 presents heritability of the individual MetS components by cohort. Each of the individual components of MetS had a significant degree of heritability, with the exception of SBP and fasting glucose among blacks in the PFS cohort. Of the individual MetS components, SBP and fasting glucose had lower heritability estimates (<0.40), whereas WC, HDL, and log triglycerides showed higher heritability (>0.47) estimates across all cohorts except in TOPS, where all estimates were <0.35. Heritability estimates did not differ consistently by race, although blacks in PLRS showed greater variability, likely because of the smaller sample size.

Genetic correlations between the individual components and MetS severity were overall similar between cohorts, with high correlation coefficients for each of the individual components (Table 4). SBP had the lowest correlation coefficients, particularly among black cohorts (0.39 and 0.27 for JHS and the black participants of PLRS), whereas WC had the highest correlation coefficients (0.74 in TOPS to 0.87 in JHS). With the exception of SBP, there were no consistent differences in genetic correlation coefficients by race, although genetic correlations among blacks in PLRS were not significant.

Phenotypic correlations between the individual components and MetS severity were again overall similar between cohorts, with high correlation coefficients for each of the...
individual components with the overall MetS severity score (Table 4). There were no consistent differences in phenotypic correlation coefficients by race.

**Meta-Analysis**

Figure (A) and (B) displays the heritability estimates of ATP-III MetS and MetS severity score both by cohort and combined across races. Because of the small number of studies within each group, we pooled the estimates across groups using a random-effects model based on inverse variance weighting. The heterogeneity among the studies was significant for h² of both MetS phenotypes, suggesting that the studies are significantly different. We obtained the 95% confidence intervals by ignoring heterogeneity, and forest plots are presented in Figure (A) for ATP-III MetS and Figure (B) for MetS severity score. Confidence intervals were estimated assuming that the studies were similar, which is a major assumption.

Using traditional MetS criteria, blacks often have a lower prevalence of MetS than whites despite higher rates of type 2 diabetes mellitus and CVD, raising the potential that there could be differences between races in the genetics and environmental factors associated with MetS.10–12 We evaluated data from 3 large familial cohorts of whites and blacks. We indeed found a separation in heritability of ATP-III MetS by race, with a higher degree of heritability among blacks (estimates of 0.48 and 0.93 for JHS and PLRS, respectively) compared with whites (0.21 and 0.27 for TOPS and PLRS, respectively). Interestingly, in evaluating heritability of a sex- and race-specific MetS severity score, we report a much smaller difference, with blacks (estimates 0.52 and 0.64) and whites (0.23 and 0.60) exhibiting significant overlap in heritability estimates. It is important to note that heritability estimates are inherently variable by population, but this study demonstrated that the use of the MetS severity scoring reduced the degree of variability among studies and also reduced the racial disparities that were seen in heritability estimates for the ATP-III MetS definition. This score further exhibited a relatively consistent and high degree of genetic correlation with the individual components of MetS for each of the cohorts, supporting the presence of strong genetic underpinnings that are not race specific. Taken together, this score may be able to overcome some of the racial/ethnic discrepancies that are noted in MetS and potentially provide a more useful means of characterizing phenotypic MetS in genetic studies by minimizing these racial/ethnic differences.

The high degree of heritability of ATP-III MetS among the cohorts of black individuals may be surprising given that previous studies have suggested lower-than-expected prevalence of MetS among blacks. Previous research has suggested that by the time blacks are categorized with ATP-III MetS, there is

<table>
<thead>
<tr>
<th>Cohort</th>
<th>SBP</th>
<th>WC</th>
<th>LnTG</th>
<th>HDL</th>
<th>FG</th>
</tr>
</thead>
<tbody>
<tr>
<td>JHS</td>
<td>0.09 (0.05)</td>
<td>0.55 (0.07)</td>
<td>0.48 (0.07)</td>
<td>0.58 (0.20)</td>
<td>0.22 (0.06)</td>
</tr>
<tr>
<td>PLRS blacks</td>
<td>0.39 (0.28)*</td>
<td>0.51 (0.21)</td>
<td>0.61 (0.25)</td>
<td>0.85 (0.21)</td>
<td>0.33 (0.25)*</td>
</tr>
<tr>
<td>PLRS whites</td>
<td>0.35 (0.14)</td>
<td>0.49 (0.14)</td>
<td>0.54 (0.14)</td>
<td>0.47 (0.14)</td>
<td>0.49 (0.15)</td>
</tr>
<tr>
<td>TOPS</td>
<td>0.32 (0.05)</td>
<td>0.26 (0.04)</td>
<td>0.33 (0.05)</td>
<td>0.28 (0.04)</td>
<td>0.20 (0.03)</td>
</tr>
</tbody>
</table>

All heritability estimates are significant (P<0.05) unless otherwise noted. FG indicates fasting glucose; HDL, high-density lipoprotein; JHS, Jackson Heart Study; LnTG, natural logarithm of triglycerides; MetS, metabolic syndrome; PLRS, Princeton Lipid Research Study; SBP, systolic blood pressure; TOPS, Take Off Pounds Sensibly; and WC, waist circumference.

*Not significant (P>0.05).

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**Discussion**

Using traditional MetS criteria, blacks often have a lower prevalence of MetS than whites despite higher rates of type 2 diabetes mellitus and CVD, raising the potential that there could be differences between races in the genetics and environmental factors associated with MetS.10–12 We evaluated data from 3 large familial cohorts of whites and blacks. We indeed found a separation in heritability of ATP-III MetS by race, with a higher degree of heritability among blacks (estimates of 0.48 and 0.93 for JHS and PLRS, respectively) compared with whites (0.21 and 0.27 for TOPS and PLRS, respectively). Interestingly, in evaluating heritability of a sex- and race-specific MetS severity score, we report a much smaller difference, with blacks (estimates 0.52 and 0.64) and whites (0.23 and 0.60) exhibiting significant overlap in heritability estimates. It is important to note that heritability estimates are inherently variable by population, but this study demonstrated that the use of the MetS severity scoring reduced the degree of variability among studies and also reduced the racial disparities that were seen in heritability estimates for the ATP-III MetS definition. This score further exhibited a relatively consistent and high degree of genetic correlation with the individual components of MetS for each of the cohorts, supporting the presence of strong genetic underpinnings that are not race specific. Taken together, this score may be able to overcome some of the racial/ethnic discrepancies that are noted in MetS and potentially provide a more useful means of characterizing phenotypic MetS in genetic studies by minimizing these racial/ethnic differences.

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**Table 3. Estimated Heritability for Individual Components of MetS**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>SBP</th>
<th>WC</th>
<th>LnTG</th>
<th>HDL</th>
<th>FG</th>
</tr>
</thead>
<tbody>
<tr>
<td>JHS</td>
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<td>0.55 (0.07)</td>
<td>0.48 (0.07)</td>
<td>0.58 (0.20)</td>
<td>0.22 (0.06)</td>
</tr>
<tr>
<td>PLRS blacks</td>
<td>0.39 (0.28)*</td>
<td>0.51 (0.21)</td>
<td>0.61 (0.25)</td>
<td>0.85 (0.21)</td>
<td>0.33 (0.25)*</td>
</tr>
<tr>
<td>PLRS whites</td>
<td>0.35 (0.14)</td>
<td>0.49 (0.14)</td>
<td>0.54 (0.14)</td>
<td>0.47 (0.14)</td>
<td>0.49 (0.15)</td>
</tr>
<tr>
<td>TOPS</td>
<td>0.32 (0.05)</td>
<td>0.26 (0.04)</td>
<td>0.33 (0.05)</td>
<td>0.28 (0.04)</td>
<td>0.20 (0.03)</td>
</tr>
</tbody>
</table>

All heritability estimates are significant (P<0.05) unless otherwise noted. FG indicates fasting glucose; HDL, high-density lipoprotein; JHS, Jackson Heart Study; LnTG, natural logarithm of triglycerides; MetS, metabolic syndrome; PLRS, Princeton Lipid Research Study; SBP, systolic blood pressure; TOPS, Take Off Pounds Sensibly; and WC, waist circumference.

*Not significant (P>0.05).

**Table 4. Estimated Genetic and Phenotypic Correlations Between MetS Severity Score and Individual Components**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>SBP</th>
<th>WC</th>
<th>LnTG</th>
<th>HDL</th>
<th>FG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JHS</td>
<td>0.39 (0.17)</td>
<td>0.87 (0.04)</td>
<td>0.71 (0.06)</td>
<td>−0.56 (0.07)</td>
<td>0.90 (0.05)</td>
</tr>
<tr>
<td>PLRS blacks</td>
<td>0.27 (0.38)*</td>
<td>0.83 (0.12)*</td>
<td>0.47 (0.25)*</td>
<td>−0.69 (0.24)*</td>
<td>1.0*</td>
</tr>
<tr>
<td>PLRS whites</td>
<td>0.67 (0.16)</td>
<td>0.77 (0.08)</td>
<td>0.90 (0.05)</td>
<td>−0.71 (0.10)</td>
<td>0.61 (0.13)</td>
</tr>
<tr>
<td>TOPS</td>
<td>0.56 (0.10)</td>
<td>0.74 (0.06)</td>
<td>0.71 (0.06)</td>
<td>−0.51 (0.10)</td>
<td>0.49 (0.10)</td>
</tr>
</tbody>
</table>

Phenotypic† | | | | | |
| JHS | 0.15 | 0.77 | 0.54 | −0.43 | 0.80 |
| PLRS blacks | 0.53 | 0.82 | 0.46 | −0.50 | 0.65 |
| PLRS whites | 0.47 | 0.74 | 0.82 | −0.67 | 0.51 |
| TOPS | 0.43 | 0.74 | 0.68 | −0.45 | 0.55 |

All correlations are significant (P<0.05) unless otherwise noted. FG indicates fasting glucose; HDL, high-density lipoprotein; JHS, Jackson Heart Study; LnTG, natural logarithm of triglycerides; MetS, metabolic syndrome; PLRS, Princeton Lipid Research Study; SBP, systolic blood pressure; TOPS, Take Off Pounds Sensibly; and WC, waist circumference.

*Not significant (P>0.05).

†Phenotypic correlations are estimated in SOLAR (Sequential Oligogenic Linkage Analysis Routines) without SE, so SE is not presented. All correlation coefficients were significant (P<0.01).
already a more advanced condition of metabolic abnormalities, with more extreme levels of inflammation, insulin resistance, and oxidative stress than that seen in other racial/ethnic groups.\textsuperscript{10,13,36–38} Much of this potential underdiagnosis of MetS among blacks has been because of a lower prevalence of lipid abnormalities.\textsuperscript{10,14,15} The lower overall prevalence of ATP-III MetS among blacks may have resulted in more family-level clustering of genetic factors of disease, increasing the within-family similarity and thus the high heritability estimate, with particularly high heritability estimates for lipid abnormalities among PLRS individuals (low HDL: 0.85 and high ln(triglyceride): 0.61). It is unclear whether this characteristic of ATP-III MetS contributed to the higher degree of heritability of ATP-III MetS among the cohorts of black individuals in this study and whether a different threshold for determining the presence of MetS would yield different estimates. Unique MetS-associated gene variants have been identified in black populations, providing potential mechanisms for genetic contribution to heritability.\textsuperscript{39} The higher heritability estimate of ATP-III among PLRS black individuals may also have been attributable to chance alongside a smaller sample size.

One key reason for the low prevalence of ATP-III MetS among blacks is the lower rates of dyslipidemia compared with that among whites.\textsuperscript{14,15} Blacks are less likely to have hypertriglyceridemia and, in adolescence, less likely to have low HDL.\textsuperscript{10} This raised the possibility that there may be differences in how triglyceride levels relate to MetS overall. However, we noted that although the black cohorts had lower triglycerides overall, the genetic correlation coefficients for triglycerides and MetS severity were similar between white and black cohorts, suggesting a similar link between relative elevations in triglycerides and MetS, especially when using a race-specific severity score. This is consistent with a study of white, black, and Hispanic individuals, which did not find racial/ethnic differences in the relationship between triglycerides and insulin resistance.\textsuperscript{14}

One MetS component that did seem to differ by race in its genetic correlation with MetS was SBP, for which black cohorts had correlation coefficients approximately half that of the white cohorts. Blacks have a high prevalence of high blood pressure, much of which may not be related to the pathophysiologic processes underlying MetS. Interestingly, participants of JHS had a low heritability of SBP overall (0.09), suggesting a lower contribution of genetic factors in the development of SBP in this cohort.

Previous twin studies from European and Asian cohorts had revealed overall similar heritability of MetS between racial/ethnic groups, with heritability estimates for the individual MetS components among Chinese\textsuperscript{6} and Korean\textsuperscript{7} individuals of 0.45 to 0.71 compared with estimates among Dutch\textsuperscript{8} and Hungarian\textsuperscript{9} individuals of 0.36 to 0.76—and without a clear difference between cohorts. Similarly, Povel et al\textsuperscript{2} performed a meta-analysis of MetS components using data from white, Asian, and Hispanic populations, reporting a high degree of genetic correlation between components but without clear racial/ethnic
difference. This supports the concept of overall similarity of MetS heritability between other racial/ethnic groups.

We noted some variability in heritability estimates for MetS severity between studies irrespective of race. In particular, the TOPS study had lower heritability of MetS (0.23) compared with the other cohorts (0.52–0.60). This may relate to the selection criteria for participants of TOPS, which specifically targeted families with both obese and nonobese members, possibly contributing to lower within-family correlations. Nevertheless, a previous analysis did not reveal significant concerns for selection bias in this cohort, and these results may also relate to the greater geographical (and possibly genetic) diversity in TOPS compared with the JHS and PLRS, which were regionally based and may have a higher degree of shared lifestyle factors.

Because heritability is the proportion of variation that can be attributed to genetics and shared behavior/environment, these differences could be driven by differences in the overall phenotypic variability. The Princeton black participants had some of the highest heritability estimates. This may be because the families attended the same school district, and 30 years later, many still resided within the same geographic area. In contrast, the JHS participants were located in the region around a single city and the TOPS participants primarily were sampled from a single state. These findings may overall illustrate that although genes clearly play a strong role in relationships between factors, environment also plays a sizable role. Whereas previous investigators had questioned the use of performing genetic studies among different groups by race/ethnicity, this study showed that cohorts of blacks can provide data that are highly informative. In this case, the black cohorts had a strong inheritance pattern that was overall similar to the white cohorts. Thus, although initial discovery for association studies must stratify by race to control for population stratification, attention should be paid toward inclusion of cohorts of all backgrounds.

This study had several weaknesses. Foremost, the high degree of heterogeneity between these cohorts—in terms of racial differences and measurement methods—limits the conclusions one can make from direct comparisons of heritability between the groups. In addition, there was variation in the dichotomous and continuous MetS measures that may have further contributed to the differences in heritability estimates by racial group. The MetS severity score we used was formulated to reflect how MetS severity was manifested among each sex and racial/ethnic subgroup by using differential weights related to reflect how MetS severity was manifested among each group, thus lacking a common measure. Nevertheless, this did not create an obvious bias, as it resulted in both increases and decreases of metabolic syndrome traits that may have a higher degree of shared lifestyle factors.

In conclusion, although heritability estimates differed, the largest differences were not because of race, rather were study specific. Furthermore, the current study found overall similar degrees of genetic correlation between MetS and its individual components in a diverse group of cohorts, suggesting that the biological relationships among genes may not differ significantly by race. For gene discovery efforts, this suggests that the identification of how genes influence multiple traits is likely to persist across races. Understanding the unique and shared contributions of genes across traits may provide critical insight on how to manage the sequelae associated with metabolic dysregulation.

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**Disclosures**

None.

**References**

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**CLINICAL PERSPECTIVE**

The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors that is associated with insulin resistance and an increased risk of cardiovascular disease and type 2 diabetes mellitus. Previous studies have demonstrated that MetS, like insulin resistance itself, is heritable, with heritability estimates of 10% to 30%, mostly from cohorts of white individuals. These studies all assessed MetS using standard dichotomous Adult Treatment Panel-III MetS criteria, which has been shown to exhibit some racial discrepancies, with black individuals less likely to be diagnosed with MetS despite having more type 2 diabetes mellitus and death from cardiovascular disease. We evaluated 3 large cohorts of white and black individuals for the heritability of MetS as assessed both by Adult Treatment Panel-III criteria and by a continuous sex- and race-ethnicity-specific MetS severity Z score. We found that using the Adult Treatment Panel-III criteria, MetS had a higher heritability among black (estimates of 0.48 and 0.93 in the cohorts with black participants) compared with white individuals (estimates of 0.21 and 0.27 in the cohorts with white participants). However, using the sex- and race-ethnicity-specific severity score, there was less of a difference between blacks (estimates of 0.52 and 0.64) compared with whites (estimates of 0.23 and 0.60). This demonstrates that among blacks, similar to whites, there is a high degree of heritability of MetS. This heritability of MetS seemed to be more similar between groups when assessed using a race-ethnicity-specific Z score. Because this score is continuous, it also provides improved power for statistical comparisons and may be a better way of following MetS within families.
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