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Prevalence, Associated Factors and the Heritability of Metabolic Syndrome and its Individual Components in African American: The Jackson Heart Study

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Abstract

Background: Both environmental and genetic factors play important roles in development of metabolic syndrome (MetS). Studies about its associated factors and genetic contribution in African Americans (AA) are sparse. Our aim was to report the prevalence, associated factors and heritability estimates of MetS and its components in AA.

Methods: This is a cross-sectional analysis of data of 5227 individuals from the Jackson Heart Study. Multiple logistic regression analysis was used to isolate independently associated factors of MetS. Heritability was estimated from the family study subset (1636 individuals, 281 families) using variance component methods.

Results: 27% of men and 40% of women had MetS. For men, associated factors with having MetS were older age, lower physical activity, higher body mass index, higher homocysteine and adiponectin level ($p<0.05$ for all). For women, in addition, lower education, current smoking, and higher stress were also significant ($p<0.05$ for all). Heritability of MetS was 32% ($p<0.01$), and ranged from 14 to 45% for its five components. Relatively higher heritability was estimated for waist circumference (45%), high density lipoprotein-cholesterol (43%) and triglycerides (42%). Heritability for systolic blood pressure (BP), diastolic BP, and fasting blood glucose were 16%, 15%, and 14%, respectively.

Conclusion: Stress and low education were associated with having MetS in AA women, but not in men. Higher heritability estimates for lipids and waist circumference supports the hypothesis of lipid metabolism playing the central role in the development of MetS and encourages additional efforts to identify the underlying susceptibility genes for this syndrome in AA.

Strengths and limitations of this study

- African American community disproportionately suffers from metabolic syndrome, but relatively little is known about the genetic contribution and the environmental influence of this syndrome among African Americans.
- Using the data from large, community-based Jackson Heart study, this study showed a high prevalence of metabolic syndrome, and reported the associated factors and heritability estimates of metabolic syndrome and its components in African Americans.
- We are not aware of any published data that explored these issues among African American from such a big setting. The large sample size also provided a reliable statistical ground to detect heritability estimates than nuclear families, twin pair data or sib-pair data.
- Potential limitations of this study included the cross-sectional observational design, which could only confirm the associations of the factors with metabolic syndrome, but not the causality, and the absence of information on shared environmental factors like childhood environment and neighborhood factors, which might slightly overestimated the heritability results.
- This study encourages additional efforts to identify the underlying susceptibility genes for metabolic syndrome among African Americans.

BACKGROUND

Metabolic syndrome (MetS) is a clustering of different interrelated cardio-metabolic risk factors including obesity, elevated blood pressure (BP), dyslipidemia, and impaired fasting plasma glucose (IFG). These risk factors often occur together and increases cardiovascular disease (CVD) deaths almost by three to four fold.[1, 2] As MetS is the combined effect of more than one risk factor, the etiology of the MetS is complex. Factors like lifestyle, gender, ethnicity, socioeconomic status, psychosocial factors and some inflammatory markers play key roles in the pathogenesis of MetS.[1-3] Findings also suggest that MetS clusters in families[4-8] and has reasonable heritability, which is defined as the proportion of phenotypic variance in a trait that is attributable to the additive effects of genes.[9-17] Thus, the interplay of both environmental and genetic factors makes MetS a multifactorial disorder.

Though the pathogenesis, diagnosis and the treatment of MetS remain complex because of its multifactorial nature, the construct MetS is an important risk-assessment method for early detection and early intervention of CVD. In spite of steady decline in CVD mortality during recent decades, CVD is still the leading cause of death in all Americans, and is highly prevalent in persons of African ancestry.[18] It is important to note that the majority of studies that explored the associated factors and quantified the heritability of MetS almost exclusively involved Caucasians.[10-14, 19] Relatively little is known about these issues among adult African American (AA) population.[15-17] Using the Jackson Heart Study (JHS) data, this cross-sectional study reports the prevalence, risk factors and heritability estimates MetS and its components in AA.

METHODS

Data Source

Data of this analysis comes from large and community based JHS, which comprises 5301 adult AA enrolled between September 2000 and March 2004 residing in Jackson, Mississippi, metropolitan area.[20] About 24% of 5301 participated in the JHS family study component.[21] The JHS was approved by the University of Mississippi Medical Center Institutional Review Board, and the participants gave written informed consent. Details of the study design and data collection methods are described elsewhere.[21, 22] After excluding 74 participants who didn't have information on their MetS status, the current analysis had a total of 5227 participants, of which 1636 from 281 families contributed to the heritability analyses.

Measures

We collected information on participant's waist circumference (WC), systolic BP (SBP) and diastolic BP (DBP), fasting blood glucose (FPG), fasting triglyceride, and plasma high-density lipoprotein cholesterol (HDL-C). Two measures of the waist at the level of the umbilicus and in the upright position were averaged to calculate WC. Sitting BP was measured twice at 5-min intervals, and the average of two measurements was used. Fasting blood samples were collected according to standardized protocols, and the assessments of FPG and lipids were processed at the Central Laboratory, University of Minnesota.[23] Individuals were classified as having MetS if they had at least three of the following five components: (1) large WC or abdominal obesity (> 102 cm for men and > 88 cm for women); (2) hypertriglyceridemia (fasting plasma triglyceride concentration ≥ 150 mg/dL or on drug treatment); (3) low HDL-C levels (< 40 mg/dL for men and < 50 mg/dL in women or on drug treatment); (4) elevated BP

(≥ 130 mm Hg SBP or ≥ 85 mm Hg DBP or on drug treatment); or, (5) IFG (≥ 110 mg/dL or on drug treatment).[24, 25]

Data about socio-demographic (age, sex, and education); the psychosocial (stress) and lifestyle (physical activity, smoking status, and alcohol consumption) variables were also collected. Age was classified as: 20-39, 40-59, 60-79 and 80 years and above. Education status was self-reported and was divided into three categories (less than high school being the referent). Stress level was obtained from The Global Perceived Stress Scale, which is an 8-item questionnaire that measures the severity of chronic stress experienced over a prior period of twelve months.[26] The physical activity index composite score was calculated as the sum of four different domains of physical activity: active living, work, home and garden, and sport and exercise indexes.[27] Smoking status was classified as never (referent), current, and former. Alcohol consumption status was defined as "yes" if they currently consumed alcoholic beverages and "no" (referent) if they had stopped drinking more than a year back, or if they never consumed alcohol. Information on clinical factors like body mass index or BMI (weight in kg divided by height in meter square), C reactive protein or CRP (mg/dL), serum adiponectin (mg/dL), and serum homocysteine (umol/L) were also obtained.[23]

Analysis

Data from the full cohort (n= 5227) were used to explore the risk factors of MetS. Socio-demographic, psychosocial, lifestyle and clinical characteristics of participants were compared by gender and MetS status using the chi-square or independent t test. The primary outcome measure for this analysis was the presence of MetS, evaluated as a dichotomous variable.

Logistic regression analysis was used to examine the association between each independent variable (age, education level, stress level, physical activity score, smoking status, alcohol consumption status, BMI, CRP, fasting total cholesterol, serum concentration of adiponectin, and serum homocysteine) with the outcome of MetS. A multiple logistic regression model was fitted including all variables to isolate the statistically significant predictors of MetS.

Heritability Analysis

After checking the pedigree data for inconsistencies a total of 1636 individuals from 281 families were analyzed to calculate the heritabilities by variance component methods using SOLAR (Sequential Oligogenic Linkage Analysis Routines) software.[28] We estimated the heritability of individual MetS components including WC, SBP, DBP, FPG, fasting triglyceride, and plasma HDL-C with adjustment for age, education level, physical activity index composite score, smoking status, alcohol consumption status and respective medication usage. Log transformed values of FPG and triglycerides were used due to deviation from normal distribution. Heritabilities were calculated using a standard quantitative genetic variance-components model implemented in SOLAR.[28] This approach uses the maximum-likelihood estimation to a mixed-effects model that incorporates fixed covariate effects, additive genetic effects and residual error. The heritability of MetS (discrete variable) was analyzed by a threshold model in SOLAR. The method assumed that an individual belonged to a specific affected status if an underlying genetically determined risk exceeded a certain threshold.[29]

RESULTS

Out of 5227 individuals, 1909 (36.52%, mean age 53.93 years and standard deviation or SD=12.93) were men and 3318 (63.48%, mean age 55.30 years and SD=12.76) were women. According to characteristics presented in table 1, education level were similar for men and women. About 40% of men and women had college level education or beyond. A clear gender difference however, was found in alcohol use and smoking, with women being far less likely than men to consume alcohol and smoke cigarettes ($p<0.001$). Women reported greater levels of stress, but lower level of physical activity than men ($p<0.001$). Women also had higher BMI, CRP, adiponectin, and lower homocysteine level than men ($p<0.001$ for all). Table 1 also shows the prevalence of MetS and its individual components among the JHS participants. About 27.34% of the men and 38.94% of the women had MetS ($p<0.001$). In terms of individual components, women had higher abdominal obesity (75.70% versus 41.03%, $p<0.001$) and IFG (22.45% versus 19.64%, $p<0.001$), but lower hypertriglyceridemia (13.23% versus 18.39%, $p <0.001$) than men.

Table 1: Characteristics of the 1909 male and 3318 female participants of the Jackson Heart Study (N=5227)

	Men[a] n=1909	Women[a] n=3318	P value[b]
Age in years	53.93 (12.93)	55.30 (12.76)	0.0002
Education level			
Less than high school	18.73	17.88	
High school/GED or some college	42.82	41.83	
College/associate degree or higher	38.45	40.29	0.4094
Smoking Status			
Never	56.68	74.59	
Former	25.33	15.30	
Current	17.99	10.11	<.0001
Alcohol drinking status			
Yes	58.92	38.41	
No	41.08	61.59	<.0001
Total Physical Activity Score[c]	8.64 (2.63)	8.16 (2.58)	<.0001
Global Stress Total Score[d]	4.50 (4.20)	5.52 (4.45)	<.0001
Body mass index (weight in kg/height in squared meter)	29.83±6.14	32.86 (7.59)	<.0001
High Sensitivity C-Reactive Protein in mg/dL	0.35 (0.96)	0.60 (0.85)	<.0001
Homocysteine in umol/L	10.17 (3.56)	9.00 (5.20)	<.0001
Adiponectin level in µg/mL	4.15 (3.41)	6.15 (4.57)	<.0001
Abdominal obesity[e]	41.03	75.70	<.0001
Hypertriglyceridemia	18.39	13.23	<.0001
Low HDL-C[g]	33.01	39.55	<.0001
Elevated blood Pressure[h]	69.62	70.58	0.4616
impaired fasting glucose[i]	19.64	22.45	0.0171
Metabolic syndrome[k]	27.34	38.94	<.0001

[a]Data presented as mean (SD) or percentage of subjects
[b]Independent t test or Chi-square test;
[c]sum of the four different domains of physical activity;
[d] sum of 8 item questionnaire that measures the severity of chronic stress experienced over a prior period of twelve months;
[e]waist circumference > 102 cm for men and > 88 cm for women
[f]fasting plasma triglyceride concentration ≥ 150 mg/dL or on drug treatment
[g]HDL cholesterol levels <40 mg/dL for men and < 50 mg/dL in women or on drug treatment
[h]Blood pressure ≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or on drug treatment
[i]fasting glucose ≥ 110 mg/dL or on drug treatment
[k] Metabolic Syndrome defined as having at least three of the following five components: (1) abdominal obesity; (2) hypertriglyceridemia; (3) low HDL cholesterol levels; (4) elevated blood; (5) impaired fasting glucose

Table 2 shows the descriptive characteristics of participants by MetS status. Those who had MetS were older, less educated, less likely to smoke, less likely to consume alcohol, and less physically active ($p<0.001$ for all). They also had higher BMI, higher CRP and higher homocysteine level; but lower adiponectin concentration ($p<0.001$ for all). The unadjusted and the adjusted relationships of MetS with these features are displayed in table 3. After adjustment, older age remained significant for both men and women. Notably, the trend of having MetS with increasing age was clearer for women than for men. Education was only significant for women, and not for men. Women who went to high school had 24% (adjusted odds ratio or AOR: 0.76; 95% confidence interval or CI:0.59-0.97) decreased odds of having MetS compared to those who had the lowest education level. Like education, higher stress level was also a significant factor for women only (AOR: 1.02; 95% CI: 1.01-1.04). Physical activity decreased the odds of having MetS for both sexes, but alcohol consumption was associated with 26% decreased odds (AOR: 0.74; 95% CI: 0.61-0.90) of MetS for women only. Relationship between smoking and MetS was different for men and women. While current smoking only predicted women's MetS (AOR:1.43; 95% CI:1.07-1.91), former smoking had significant association with men's MetS (AOR: 1.54 ; 95% CI:1.14-2.08). Biomedical risk factors such as increased BMI (AOR:1.18; 95% CI:1.15-1.21 for men and AOR:1.08; 95% CI:1.07-1.10 for women), increased serum homocysteine (AOR:1.05; 95% CI:1.02-1.09 for men and AOR:1.06; 95% CI:1.03-1.09 for women) and decreased serum adiponectin (AOR:0.90; 95% CI:0.85-0.95 for men and AOR:0.90; 95% CI:0.87-0.92 for women) were associated with increased odds of having MetS for both sexes.

Table 2: Characteristics of Jackson Heart Study Participants by metabolic syndrome status (N=5227)

	Metabolic Syndrome[a] (n=1814)	No Metabolic Syndrome[a] (n=3413)	P value[b]
Age in years	58.04 (11.43)	53.07 (13.21)	<.0001
Gender of Participant			
Men	28.78	40.46	
Women	71.22	59.36	<.0001
Education level			
Less than high school	23.32	15.46	
High school/GED or some college	41.94	42.33	
College/associate degree or higher	34.74	42.21	<.0001
Smoking Status			
Never	66.17	69.05	
Former	21.59	17.56	
Current	12.24	13.39	0.0017
Alcohol drinking status			
Yes	37.01	50.63	
No	62.99	49.37	<.0001
Total Physical Activity Score[c]	7.74 (2.56)	8.65 (2.57)	<.0001
Global Stress Total Score[d]	5.11 (4.42)	5.17 (4.37)	0.6251
Body mass index (weight in kg/height in squared meter)	34.87 (6.92)	30.10 (6.86)	<.0001
High Sensitivity C-Reactive Protein in mg/dL	0.65 (1.13)	0.44 (0.74)	<.0001
Homocysteine: The concentration of homocysteine in umol/L	9.94 (6.37)	9.15 (3.44)	<.0001
Serum concentration of adiponectin in µg/mL	4.72 (4.02)	5.79 (4.38)	<.0001

[a]Data presented as mean (SD) or percentage of subjects
[b]Independent t test or Chi-square test;
[c]sum of the four different domains of physical activity;
[d] sum of 8 item questionnaire that measures the severity of chronic stress experienced over a prior period of twelve months;

Table 3: Association between selected factors and prevalence of metabolic Syndrome among Jackson Heart Study Participants (n=5227)

	Metabolic Syndrome Odds Ratio (95% CI)			
	Men (n=1909)		Women (n=3318)	
	Unadjusted[a]	Adjusted[a]	Unadjusted[a]	Adjusted[a]
Age				
20-39 (Ref)	1		1	
40-59	1.34(0.96-1.86)	1.55 (1.02-2.35)	2.44(1.84-3.23)	2.79 (2.00 -3.87)
60-79	1.69(1.20-2.38)	2.17 (1.34-3.51)	4.69(3.54-6.22)	5.50 (3.81-7.93)
80 and above	0.88(0.28-2.71)	2.18 (0.60-8.00)	3.43(1.89-6.24)	5.06 (2.34-10.96)
Education				
Less than High school	1		1	
High school or some College	0.95(0.72-1.25)	1.20 (0.83-1.74)	0.53(0.44-0.65)	0.76 (0.59- 0.97)
College degree or higher	0.79(0.60-1.05)	1.05 (0.72 1.55)	0.44(0.36-0.53)	0.82 (0.63-1.07)
Smoking Status				
Never	1		1	
Former	1.47(1.16-1.85)	1.54 (1.14-2.08)	1.39(1.15-1.69)	1.20 (0.95-1.52)
Current	0.92(0.69-1.22)	1.29 (0.89-1.86)	1.20(0.95-1.51)	1.43 (1.07-1.91)
Alcohol drinking				
No	1		1	
Yes	0.72(0.59-0.88)	0.85 (0.66-1.11)	0.57(0.49-0.66)	0.74 (0.61-0.90)
Physical Activity[b]	0.90(0.86-0.94)	0.93 (0.88- 0.98)	0.86(0.84-0.89)	0.94 (0.91-0.98)
Global Stress[c]	1.01(0.98-1.03)	1.02 (0.99-1.06)	0.98(0.97-1.00)	1.02 (1.01- 1.04)
Body mass index	1.18(1.15-1.20)	1.18 (1.15-1.21)	1.08(1.07-1.09)	1.08 (1.07-1.10)
C-Reactive Protein in mg/dL	1.36(1.15-1.60)	1.10 (0.96- 1.26)	1.29(1.18-1.41)	0.99 (0.89-1.09)
Homocysteine in umol/L	1.04(1.01-1.07)	1.05 (1.02 1.09)	1.07(1.05-1.10)	1.06(1.03-1.09)
Adiponectin in µg/mL	0.89(0.85-0.92)	0.90 (0.85-0.95)	0.91(0.90-0.93)	0.90 (0.87-0.92)

Metabolic Syndrome defined as having at least three of the following five components: (1) abdominal obesity or large waist circumference (> 102 cm for men and > 88 cm for women); (2) hypertriglyceridemia (fasting plasma triglyceride concentration ≥ 150 mg/dL or on drug treatment); (3) low HDL cholesterol levels (< 40 mg/dL for men and < 50 mg/dL in women or on drug treatment); (4) elevated blood pressure (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or on drug treatment); or, (5) IFG or impaired fasting glucose (110 mg/dL or or on drug treatment)

[a]Analysis done using simple and multiple logistic regression. The multivariate models are adjusted for for all other variables in the table.

[b]sum of the four different domains of physical activity;

[c]sum of 8 item questionnaire that measures the severity of chronic stress experienced over a prior period of twelve months;

Table 4 illustrates the heritability estimates along with the proportion of variation explained by covariates (σ_e^2) of MetS and its individual component in the family study subset (n=1636). All components of the MetS were significantly correlated with each other except for the pairs of blood pressure and HDL-C and blood pressure and fasting glucose (results not shown in table). After accounting for the covariates (except medication), the heritability of MetS was about 32% ($p<0.0001$, σ_e^2: 10%). The adjusted heritability of individual MetS components ranged from the lowest of 14% ($p<0.01$, σ_e^2: 33%) for FPG to the highest of 45% ($p<0.0001$, σ_e^2: 8%) for WC after adjusting for all the covariates. The adjusted estimates of DBP (15%, $p<0.01$, σ_e^2: 9%) and SBP (16%, $p<0.001$, σ_e^2: 22%) were on the lower end and similar to the estimate of FPG. Conversely, heritability of triglyceride (42%, $p<0.001$, σ_e^2: 10%) and HDL-C (43%, $p<0.001$, σ_e^2: 11%) was relatively high and similar to the heritability of WC.

Table 4: Heritability estimates of Metabolic Syndrome and its individual components of Jackson Heart Study Participants (n=1636)

	Heritability Estimate	Standard error	P value	Variations explained by covariate
Metabolic Syndrome[a]	0.32	0.08	<0.0001	0.10[e]
Fasting Plasma Glucose[b,c]	0.14	0.06	<0.01	0.33[d]
Waist Circumference[b]	0.45	0.06	<0.0001	0.08[e]
High Density Lipoprotein Cholesterol[b]	0.43	0.07	<0.0001	0.11[d]
Fasting Triglyceride[b,c]	0.42	0.05	<0.0001	0.10[d]
Systolic blood pressure[b]	0.16	0.07	<0.001	0.22[d]
Diastolic blood pressure[b]	0.15	0.05	<0.01	0.09[d]

[a]Treated as discrete trait, and defined as having at least three of the following five components: (1) abdominal obesity or large waist circumference (> 102 cm for men and > 88 cm for women); (2) hypertriglyceridemia (fasting plasma triglyceride concentration ≥ 150 mg/dL or on drug treatment); (3) low HDL cholesterol levels (< 40 mg/dL for men and < 50 mg/dL in women or on drug treatment); (4) elevated blood pressure (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or on drug treatment); or, (5) IFG or impaired fasting glucose (110 mg/dL or on drug treatment)
[b]Treated as continuous trait
[c]Log transformed
[d] Covariates are age, sex, education, smoking status, alcohol intake, physical activity and respective medication
[e] Covariates are age, sex, education, smoking status, alcohol intake, physical activity

DISCUSSION

Overall, in our study sample, the prevalence of MetS was higher among women than men. Factors independently associated with having MetS for men were older age, lower physical activity level, higher BMI, higher level of homocysteine and lower level of adiponectin. For women, in addition to these factors, low education, higher stress, current smoking and alcohol consumption were also significant. The heritability of the MetS was 32% and among its individual components, heritability ranged from 14% for FPG to 45% for WC.

The prevalence of MetS that we found (38.94% of women and 27.34% of men) was almost identical to a recent estimate from a National Survey, which reported 38.2% of AA women and 25.5% of AA men had MetS.[1] A higher prevalence of MetS in women than in men has been reported in several other Asian and Eastern European countries, as well as among Hispanic, and Native Americans.[1, 30-32] However, it is opposite for US Caucasians with higher prevalence in men.[1] This, together with our finding suggest the possibility of an increased risk of MetS for women belonging to an economically disadvantaged or a minority population group. The unfavorable condition of women was also evident from our multivatiate analysis, where we found lower education and stress to be significantly related with MetS for women, but not for men. While in the industrialized society social class and education are typically inversely related to different cardio-metabolic risk factors regardless of gender,[33-35] in our study, this was true only for women, indicating an adverse social environment of our women participants. Literature have indicated active smoking to be associated with development of MetS.[36, 37] We however found, active smoking to be associated with women's MetS only. The lack of association between current smoking and MetS among men in our study can be partly attributed to the much discussed inverse association between active smoking and obesity as the smoking prevalence was higher and abdominal obesity was relatively lower in the men than women in our analysis.[38] Further, researchers have also found smoking cessation to be frequently followed by weight gain,[39] which explains our observed association between past smoking and men's MetS.

Although lifestyle, physiological and socio-demographic factors play key roles in the pathogenesis of MetS, there is also strong evidence that the syndrome is inherited.[40-43] We evaluated the contributions of genetic factors to the phenotypic variability of MetS and its traits

by heritability estimation. According to various studies from different ethnic groups, heritability of MetS ranges from approximately 19 to 38%.[10-13] Besides the genetic effect itself, which could be different among different studied populations, the discrepancy in heritability might be attributable to other factors like different sample sizes, different structure of pedigrees or covariates included in the analysis. A Dutch study estimated a heritability of 19.2% of MetS in an isolated group of population.[11] A heritability of 24% in a Caribbean-Hispanic population has been reported by Lin et al.[12] The heritability for the Caucasian population was about 27% according to large population based study.[10] Bayoumi et al. reported a heritability of 38% of MetS in healthy Omani Arab families.[13] Compared to different ethnic groups, relatively little information is available on the heritability of MetS in AA population. The heritability of MetS in our study was 32% after taking into account the contributions of covariates, like age, sex, alcohol consumption, smoking and physical activity level, suggesting that more than one-third of the variance in MetS was attributable to the additive effects of genes in the JHS participants. This estimate is on the higher end of the heritability range reported so far, which suggests significant genetic influences on clustering of risk factors among AA.

Reported heritability from different studies for the individual traits ranges from 10% for plasma glucose to 60% for HDL-C.[10-14, 19] Our estimates correspond well with these findings. In the present study, more than 40% of the variance in HDL-C, triglyceride and WC was attributable to genetic effect. Conversely, a moderate but significant heritability were observed for BP and FPG. In different studies as well, HDL-C, obesity and lipid profiles showed the strongest heritability, and BP and FPG had the lowest heritability.[10-14] While for lipid levels and WC genetic influence remains dominant; it seems, for FPG and BP the environmental contribution

play a more prominent role, which was apparent by the remarkable covariate effect that was observed for FPG and BP (33% and 22%, respectively) not only in our findings, but also in some other studies.[10, 12] This hypothesis is further supported by some genetic association studies, where investigators have tried to find a unifying pathogenic mechanism for the different MetS components and identify genetic variants contributing to MetS. No such work among AA were found, but a meta-analysis of 4000 Asian and Caucasian participants reviewing 25 genes reported an association between MetS and single nucleotide polymorphisms in the FTO, TCFL72, IL6, APOA5, APOC3 and CETP genes. [44] Another Swedish study found that genetic variants in the PPARG and ADRB1 genes conferred an increased risk of future MetS [45]. All of these genes are mostly involved in lipid metabolism [44, 45]. These evidence indicate that lipid metabolism plays the central role in MetS development; and possibly, genetic impact FPG and BP have a relatively minor role in MetS clusters. Our finding also indirectly supports this view as we found triglyceride, HDL-C and WC to be strongly correlated with one another and a relatively weaker correlation for blood pressure and FPG with other traits. More importantly, we also found higher and similar heritability estimates for triglyceride, HDL-C and WC and relatively lower heritability estimates for BP and FPG, suggesting a possible similarity in genetic mechanism of developing MetS for AA population with other ethnic groups.

Our results should be interpreted within the context of few limitations. We acknowledge that given our cross-sectional observational design, our study can only confirm the associations of the facotors with MetS; and cannot prove the causality. Our heritability estimates were influenced by shared environmental factors like childhood environment and neighborhood

factors, and thus, our results could be slightly overestimated. Nonetheless, even if there was a possibility of slight overestimation, the complex and extended pedigree structure of JHS with a large sample provided us a reliable statistical ground to detect genetic effects than nuclear families, twin pair data or sib-pair data. Further, ascertainment of socio-demographic variables in the JHS was performed uniformly and precise techniques were used to measure all physiological and biochemical values, which makes our findings reliable. The present data although cross-sectional, comes from a large, community-based AA population, who are vastly understudied. We are not aware of any published data that reported the associated factors and quantified the heritability of MetS among AA from such a big setting.

We found a significant and independent inverse association between MetS and adiponectin; and a positive association between MetS and homocysteine. In line with our findings, a number of recent studies also have reported similar results.[46-50] These findings suggest inclusion of biomarkers like adiponectin and homocysteine to improve early identification of MetS. It was obvious from our study that social and economic context has disparate impact on women's cardiovascular health and subsequent policies and health educational programs should be particularly directed towards women for future CVD risk reduction in AA. As the causes of the MetS are reversible and the individual components are modifiable, lifestyle change such as increasing physical activity may reduce the prevalence of MetS. Our results reconfirm that MetS is a complex disease and though change in lifestyle can modify the risk of MetS, genetic background also contributes to the development of MetS. Our finding supports the hypothesis of lipid metabolism playing the central role in the development of MetS and strongly encourages additional efforts to identify the underlying susceptibility genes for this syndrome

in AA. Further exploration of the genetic and environmental factors of the MetS among AA will lead to a more comprehensive understanding and better therapeutic options for the syndrome, and ultimately lead to improved cardiovascular health.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
√**Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
√**Introduction**		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
√**Methods**		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
√**Results**		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

√Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
√Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence, Associated Factors and the Heritability of Metabolic Syndrome and its Individual Components in African Americans: The Jackson Heart Study

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Abstract

Objective: Both environmental and genetic factors play important roles in development of metabolic syndrome (MetS). Studies about its associated factors and genetic contribution in African Americans (AA) are sparse. Our aim was to report the prevalence, associated factors and heritability estimates of MetS and its components in AA.

Participants and setting: Data of this cross-sectional study comes from large and community based Jackson Heart Study (JHS). We analyzed a total of 5227 participants, of which 1636 from 281 families were part of the family study subset of JHS.

Methods: Participants were classified as having the MetS according to the Adult Treatment Panel III criteria. Multiple logistic regression analysis was performed to isolate independently associated factors of MetS (n=5227). Heritability was estimated from the family study subset using variance component methods (n=1636).

Results: About 27% of men and 40% of women had MetS. For men, associated factors with having MetS were older age, lower physical activity, higher body mass index, higher homocysteine and adiponectin level ($p<0.05$ for all). For women, in addition to all these, lower education, current smoking, and higher stress were also significant ($p<0.05$ for all). After adjusting for covariates, the heritability of MetS was 32% ($p<0.001$). Heritability ranged from 14 to 45% among its individual components. Relatively higher heritability was estimated for waist circumference (45%), high density lipoprotein-cholesterol (43%) and triglycerides (42%). Heritability of systolic blood pressure (BP), diastolic BP, and fasting blood glucose were 16%, 15%, and 14%, respectively.

Conclusion: Stress and low education were associated with having MetS in AA women, but not in men. Higher heritability estimates for lipids and waist circumference supports the hypothesis

of lipid metabolism playing the central role in the development of MetS and encourages additional efforts to identify the underlying susceptibility genes for this syndrome in AA.

Strengths and limitations of this study

- African American community disproportionately suffers from metabolic syndrome, but relatively little is known about the genetic contribution and the environmental influence of this syndrome among African Americans.
- Using the data from large, community-based Jackson Heart study, this study showed a high prevalence of metabolic syndrome, and reported the associated factors and heritability estimates of metabolic syndrome and its components in African Americans.
- We are not aware of any published data that explored these issues among African American from such a big setting. The large sample size also provided a reliable statistical ground to detect heritability estimates than nuclear families, twin pair data or sib-pair data.
- Potential limitations of this study included the cross-sectional observational design, which could only confirm the associations of the factors with metabolic syndrome, but not the causality, and the absence of information on shared environmental factors like childhood environment and neighborhood factors, which might slightly overestimate the heritability results.
- This study encourages additional efforts to identify the underlying susceptibility genes for metabolic syndrome among African Americans.

BACKGROUND

Metabolic syndrome (MetS) is a clustering of different interrelated cardio-metabolic risk factors including obesity, elevated blood pressure (BP), dyslipidemia, and impaired fasting plasma glucose (IFG). These risk factors often occur together and increases cardiovascular disease (CVD) deaths almost by three to four fold.[1, 2] As MetS is the combined effect of more than one risk factor, the etiology of the MetS is complex. Factors like lifestyle, gender, ethnicity, socioeconomic status, psychosocial factors and some inflammatory markers play key roles in the pathogenesis of MetS.[1-3] Findings also suggest that MetS clusters in families[4-8] and has reasonable heritability, which is defined as the proportion of phenotypic variance in a trait that is attributable to the additive effects of genes.[9-17] Thus, the interplay of both environmental and genetic factors makes MetS a multifactorial disorder.

Though the pathogenesis, diagnosis and the treatment of MetS remain complex because of its multifactorial nature, the construct MetS is an important risk-assessment method for early detection and early intervention of CVD. In spite of steady decline in CVD mortality during recent decades, CVD is still the leading cause of death in all Americans, and is highly prevalent in persons of African ancestry.[18] It is important to note that the majority of studies that explored the associated factors and quantified the heritability of MetS almost exclusively involved Caucasians.[10-14, 19] Relatively little is known about these issues among adult African American (AA) population.[15-17] Using the Jackson Heart Study (JHS) data, the objective of this cross-sectional study was to report the prevalence, risk factors and heritability estimates of MetS and its components in AA.

METHODS

Data Source

Data of this analysis comes from large and community based JHS, which comprises 5301 adult AA enrolled between September 2000 and March 2004 residing in Jackson, Mississippi, metropolitan area.[20] About 24% of 5301 participated in the JHS family study component.[21] The family study component of JHS contained 1st degree (parent-offspring and siblings), 2nd degree (grandparent-grandchild, avuncular, half-siblings) and 3rd degree or more distant (great grandparent-grandchild, grand avuncular, half avuncular, first cousins, half first cousins, second cousins) family members. The JHS was approved by the University of Mississippi Medical Center Institutional Review Board, and the participants gave written informed consent. Details of the study design and data collection methods are described elsewhere.[21, 22] The current study data were obtained from the baseline clinic visit during 2000-2004. After excluding 74 participants who didn't have information on their MetS status, the current analysis had a total of 5227 participants, of which 1636 from 281 families contributed to the heritability analyses.

Measures

We collected information on participant's waist circumference (WC), systolic BP (SBP) and diastolic BP (DBP), fasting plasma glucose (FPG), fasting triglyceride, and plasma high-density lipoprotein cholesterol (HDL-C). Two measures of the waist at the level of the umbilicus and in the upright position were averaged to calculate WC. Sitting BP was measured twice at 5-min intervals with a standardized Hawksley random-zero sphygmomanometer, and

the average of two measurements was used. Fasting blood samples were collected according to standardized protocols, and the assessments of FPG and lipids were processed at the Central Laboratory, University of Minnesota.[23] Respondents were asked about their medication usage for hypertension, diabetes mellitus and high lipid levels. Individuals were classified as having MetS if they had at least three of the following five components: (1) large WC or abdominal obesity (> 102 cm for men and > 88 cm for women); (2) hypertriglyceridemia (fasting plasma triglyceride concentration ≥ 150 mg/dL or on drug treatment); (3) low HDL-C levels (< 40 mg/dL for men and < 50 mg/dL in women or on drug treatment); (4) elevated BP (≥ 130 mm Hg SBP or ≥ 85 mm Hg DBP or on drug treatment); or, (5) IFG (≥ 110 mg/dL or on drug treatment).[24, 25]

Data about socio-demographic (age, sex, and education), the psychosocial (stress) and lifestyle (physical activity, smoking status, and alcohol consumption) variables were also collected. Age was classified as: 20-39, 40-59, 60-79 and 80 years and above. Education status was self-reported and was divided into three categories (less than high school, high school/GED/ some college and college/associate degree or higher, where less than high school was the referent). Stress level was obtained from The Global Perceived Stress Scale, an 8-item questionnaire that measures the severity of chronic stress experienced over a prior period of twelve months.[26] The physical activity index composite score was calculated as the sum of four different domains of physical activity: active living, work, home and garden, and sport and exercise indices.[27] Smoking status was classified as never (referent), current, and former. Alcohol consumption status was defined as "yes" if they currently consumed alcoholic beverages and "no" (referent) if they had stopped drinking for more than a year, or if they never consumed alcohol.

Information on clinical factors like body mass index or BMI (weight in kg divided by height in meter square), C-reactive protein or CRP (mg/dL), serum adiponectin (mg/dL), and serum homocysteine (umol/L) were also obtained.[23]

Analysis

Data from the full cohort (n= 5227) were used to explore the risk factors of MetS. Socio-demographic, psychosocial, lifestyle and clinical characteristics of participants were compared by gender and MetS status using the chi-square or independent t-test. The primary outcome measure for this analysis was the presence of MetS, evaluated as a dichotomous variable. Logistic regression analysis was used to examine the association between each independent variable (age, education level, stress level, physical activity score, smoking status, alcohol consumption status, BMI, CRP, fasting total cholesterol, serum concentration of adiponectin, and serum homocysteine) with the outcome of MetS. A multiple logistic regression model was fitted including all variables to isolate the statistically significant predictors of MetS.

Heritability Analysis

After checking the pedigree data for inconsistencies a total of 1636 individuals from 281 families were analyzed to calculate the heritabilities by variance component methods using SOLAR (Sequential Oligogenic Linkage Analysis Routines) software to quantify the proportion of the variance in MetS and in its individual components that was attributable to the additive effects of genes.[28] We estimated the heritability of individual MetS components (treated as continuous variable) including WC, SBP, DBP, FPG, fasting triglyceride, and plasma HDL-C with adjustment for age, education level, physical activity index composite score, smoking

status, alcohol consumption status and respective medication usage. Log transformed values of FPG and triglycerides were used due to deviation from normal distribution. Heritabilities were calculated using a standard quantitative genetic variance-components model implemented in SOLAR.[28] This approach uses the maximum-likelihood estimation to a mixed-effects model that incorporates fixed covariate effects, additive genetic effects and residual error. The heritability of MetS (discrete variable) was analyzed by a threshold model in SOLAR. The method assumed that an individual belonged to a specific affected status if an underlying genetically determined risk exceeded a certain threshold.[29]

RESULTS

Of the 5227 individuals, 1909 (36.52%, mean age 53.93 years and standard deviation or SD=12.93) were men and 3318 (63.48%, mean age 55.30 ±12.76) were women. Education level were similar for men and women (Table 1). About 40% of men and women had college level education or beyond. A clear gender difference however, was found for alcohol use and smoking, with women being far less likely than men to consume alcohol and smoke cigarettes ($p<0.001$). Women reported greater levels of stress, but lower level of physical activity than men ($p<0.001$). Women also had higher BMI, CRP, adiponectin, and lower homocysteine level than men ($p<0.001$ for all). Table 1 also shows the prevalence of MetS and its individual components among the JHS participants. About 27.34% of the men and 38.94% of the women had MetS ($p<0.001$). In terms of individual components, women had higher abdominal obesity (75.70% versus 41.03%, $p<0.001$) and IFG (22.45% versus 19.64%, $p<0.001$), but lower hypertriglyceridemia (13.23% versus 18.39%, $p <0.001$) than men.

Table 1:

Characteristics of Participants of the Jackson Heart Study by Gender (N=5227)

	Men[a] n=1909	Women[a] n=3318	P value[b]
Age in years	53.93 (12.93)	55.30 (12.76)	0.0002
Education level			
Less than high school	18.73	17.88	
High school/GED or some college	42.82	41.83	
College/associate degree or higher	38.45	40.29	0.4094
Smoking Status			
Never	56.68	74.59	
Former	25.33	15.30	
Current	17.99	10.11	<.0001
Alcohol drinking status			
Yes	58.92	38.41	
No	41.08	61.59	<.0001
Total Physical Activity Score[c]	8.64 (2.63)	8.16 (2.58)	<.0001
Global Stress Total Score[d]	4.50 (4.20)	5.52 (4.45)	<.0001
Body mass index (weight in kg/height in squared meter)	29.83±6.14	32.86 (7.59)	<.0001
High Sensitivity C-Reactive Protein in mg/dL	0.35 (0.96)	0.60 (0.85)	<.0001
Homocysteine in umol/L	10.17 (3.56)	9.00 (5.20)	<.0001
Adiponectin level in µg/mL	4.15 (3.41)	6.15 (4.57)	<.0001
Abdominal obesity[e]	41.03	75.70	<.0001
Hypertriglyceridemia	18.39	13.23	<.0001
Low HDL-C[g]	33.01	39.55	<.0001
Elevated blood Pressure[h]	69.62	70.58	0.4616
impaired fasting glucose[i]	19.64	22.45	0.0171
Metabolic syndrome[k]	27.34	38.94	<.0001

[a]Data presented as mean (SD) or percentage of subjects
[b]Independent t-test or Chi-square test;
[c]sum of the four different domains of physical activity;
[d] sum of 8 item questionnaire that measures the severity of chronic stress experienced over a prior period of twelve months;
[e]waist circumference > 102 cm for men and > 88 cm for women
[f]fasting plasma triglyceride concentration ≥ 150 mg/dL or on drug treatment
[g]HDL cholesterol levels <40 mg/dL for men and < 50 mg/dL in women or on drug treatment
[h]Blood pressure ≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or on drug treatment
[i]fasting glucose ≥ 110 mg/dL or on drug treatment
[k] Metabolic Syndrome defined as having at least three of the following five components: (1) abdominal obesity; (2) hypertriglyceridemia; (3) low HDL cholesterol levels; (4) elevated blood; (5) impaired fasting glucose

Table 2 shows the descriptive characteristics of participants by MetS status. Those who had MetS were older, less educated, less likely to smoke, less likely to consume alcohol, and less physically active ($p<0.001$ for all). They also had higher BMI, higher CRP and higher homocysteine level; but lower adiponectin concentration ($p<0.001$ for all). The unadjusted and the adjusted relationships of MetS with these features are displayed in Table 3. After adjustment, older age remained significant for both men and women. Notably, the trend of having MetS with increasing age was clearer for women than for men. Education was only significant for women, and not for men. Women who went to high school had 24% (adjusted odds ratio or AOR: 0.76; 95% confidence interval or CI:0.59-0.97) decreased odds of having MetS compared to those who had the lowest education level. Like education, higher stress level was also a significant factor for women only (AOR: 1.02; 95% CI: 1.01-1.04). Physical activity decreased the odds of having MetS for both sexes, but alcohol consumption was associated with 26% decreased odds (AOR: 0.74; 95% CI: 0.61-0.90) of MetS for women only. Relationship between smoking and MetS was different for men and women. While current smoking only predicted women's MetS (AOR:1.43; 95% CI:1.07-1.91), former smoking had significant association with men's MetS (AOR: 1.54 ; 95% CI:1.14-2.08). Biomedical risk factors such as increased BMI (AOR:1.18; 95% CI:1.15-1.21 for men and AOR:1.08; 95% CI:1.07-1.10 for women), increased serum homocysteine (AOR:1.05; 95% CI:1.02-1.09 for men and AOR:1.06; 95% CI:1.03-1.09 for women) and decreased serum adiponectin (AOR:0.90; 95% CI:0.85-0.95 for men and AOR:0.90; 95% CI:0.87-0.92 for women) were associated with increased odds of having MetS for both sexes.

Table 2: Characteristics of Jackson Heart Study Participants by metabolic syndrome status (N=5227)

	Metabolic Syndrome[a] (n=1814)	No Metabolic Syndrome[a] (n=3413)	P value[b]
Age in years	58.04 (11.43)	53.07 (13.21)	<.0001
Gender of Participant			
Men	28.78	40.46	
Women	71.22	59.36	<.0001
Education level			
Less than high school	23.32	15.46	
High school/GED or some college	41.94	42.33	
College/associate degree or higher	34.74	42.21	<.0001
Smoking Status			
Never	66.17	69.05	
Former	21.59	17.56	
Current	12.24	13.39	0.0017
Alcohol drinking status			
Yes	37.01	50.63	
No	62.99	49.37	<.0001
Total Physical Activity Score[c]	7.74 (2.56)	8.65 (2.57)	<.0001
Global Stress Total Score[d]	5.11 (4.42)	5.17 (4.37)	0.6251
Body mass index (weight in kg/height in squared meter)	34.87 (6.92)	30.10 (6.86)	<.0001
High Sensitivity C-Reactive Protein in mg/dL	0.65 (1.13)	0.44 (0.74)	<.0001
Homocysteine: The concentration of homocysteine in umol/L	9.94 (6.37)	9.15 (3.44)	<.0001
Serum concentration of adiponectin in µg/mL	4.72 (4.02)	5.79 (4.38)	<.0001

[a]Data presented as mean (SD) or percentage of subjects
[b]Independent t-test or Chi-square test;
[c]sum of the four different domains of physical activity;
[d] sum of 8 item questionnaire that measures the severity of chronic stress experienced over a prior period of twelve months;

Table 3: Association between selected factors and prevalence of metabolic Syndrome among Jackson Heart Study Participants (n=5227)

	Metabolic Syndrome Odds Ratio (95% CI)			
	Men (n=1909)		Women (n=3318)	
	Unadjusted[a]	Adjusted[a]	Unadjusted[a]	Adjusted[a]
Age				
20-39	Reference Level		Reference Level	
40-59	1.34(0.96-1.86)	1.55 (1.02-2.35)	2.44(1.84-3.23)	2.79 (2.00 -3.87)
60-79	1.69(1.20-2.38)	2.17 (1.34-3.51)	4.69(3.54-6.22)	5.50 (3.81-7.93)
80 and above	0.88(0.28-2.71)	2.18 (0.60-8.00)	3.43(1.89-6.24)	5.06 (2.34-10.96)
Education				
Less than High school	Reference Level		Reference Level	
High school or some College	0.95(0.72-1.25)	1.20 (0.83-1.74)	0.53(0.44-0.65)	0.76 (0.59- 0.97)
College degree or higher	0.79(0.60-1.05)	1.05 (0.72 1.55)	0.44(0.36-0.53)	0.82 (0.63-1.07)
Smoking Status				
Never	Reference Level		Reference Level	
Former	1.47(1.16-1.85)	1.54 (1.14-2.08)	1.39(1.15-1.69)	1.20 (0.95-1.52)
Current	0.92(0.69-1.22)	1.29 (0.89-1.86)	1.20(0.95-1.51)	1.43 (1.07-1.91)
Alcohol drinking				
No	Reference Level		Reference Level	
Yes	0.72(0.59-0.88)	0.85 (0.66-1.11)	0.57(0.49-0.66)	0.74 (0.61-0.90)
Physical Activity[b]	0.90(0.86-0.94)	0.93 (0.88- 0.98)	0.86(0.84-0.89)	0.94 (0.91-0.98)
Global Stress[c]	1.01(0.98-1.03)	1.02 (0.99-1.06)	0.98(0.97-1.00)	1.02 (1.01- 1.04)
Body mass index	1.18(1.15-1.20)	1.18 (1.15-1.21)	1.08(1.07-1.09)	1.08 (1.07-1.10)
C-Reactive Protein in mg/dL	1.36(1.15-1.60)	1.10 (0.96- 1.26)	1.29(1.18-1.41)	0.99 (0.89-1.09)
Homocysteine in umol/L	1.04(1.01-1.07)	1.05 (1.02 1.09)	1.07(1.05-1.10)	1.06(1.03-1.09)
Adiponectin in µg/mL	0.89(0.85-0.92)	0.90 (0.85-0.95)	0.91(0.90-0.93)	0.90 (0.87-0.92)

Metabolic Syndrome defined as having at least three of the following five components: (1) abdominal obesity or large waist circumference (> 102 cm for men and > 88 cm for women); (2) hypertriglyceridemia (fasting plasma triglyceride concentration ≥ 150 mg/dL or on drug treatment); (3) low HDL cholesterol levels (< 40 mg/dL for men and < 50 mg/dL in women or on drug treatment); (4) elevated blood pressure (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or on drug treatment); or, (5) IFG or impaired fasting glucose (110 mg/dL or or on drug treatment)

[a]Analysis done using simple and multiple logistic regression. The multivariate models are adjusted for for all other variables in the table.

[b]sum of the four different domains of physical activity;

[c]sum of 8 item questionnaire that measures the severity of chronic stress experienced over a prior period of twelve months;

Table 4 illustrates the heritability estimates along with the proportion of variation explained by covariates (σ_e^2) of MetS and its individual component in the family study subset (n=1636). All components of the MetS were significantly correlated with each other except for the pairs of blood pressure and HDL-C and blood pressure and fasting glucose (results not shown in table). After accounting for the covariates (except medication), the heritability of MetS was about 32% ($p<0.0001$, σ_e^2: 10%). The adjusted heritability of individual MetS components ranged from the lowest of 14% ($p<0.01$, σ_e^2: 33%) for FPG to the highest of 45% ($p<0.0001$, σ_e^2: 8%) for WC after adjusting for all the covariates. The adjusted estimates of DBP (15%, $p<0.01$, σ_e^2: 9%) and SBP (16%, $p<0.001$, σ_e^2: 22%) were on the lower end and similar to the estimate of FPG. Conversely, heritability of triglyceride (42%, $p<0.001$, σ_e^2: 10%) and HDL-C (43%, $p<0.001$, σ_e^2: 11%) was relatively high and similar to the heritability of WC.

Table 4: Heritability estimates of Metabolic Syndrome and its individual components of Jackson Heart Study Participants (n=1636)

	Heritability Estimate	Standard error	P value	Proportion of variation explained by covariates
Metabolic Syndrome[a]	0.32	0.08	<0.0001	0.10[e]
Fasting Plasma Glucose[b,c]	0.14	0.06	<0.01	0.33[d]
Waist Circumference[b]	0.45	0.06	<0.0001	0.08[e]
High Density Lipoprotein Cholesterol[b]	0.43	0.07	<0.0001	0.11[d]
Fasting Triglyceride[b,c]	0.42	0.05	<0.0001	0.10[d]
Systolic blood pressure[b]	0.16	0.07	<0.001	0.22[d]
Diastolic blood pressure[b]	0.15	0.05	<0.01	0.09[d]

[a]Treated as discrete trait, and defined as having at least three of the following five components: (1) abdominal obesity or large waist circumference (> 102 cm for men and > 88 cm for women); (2) hypertriglyceridemia (fasting plasma triglyceride concentration ≥ 150 mg/dL or on drug treatment); (3) low HDL cholesterol levels (< 40 mg/dL for men and < 50 mg/dL in women or on drug treatment); (4) elevated blood pressure (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or on drug treatment); or, (5) IFG or impaired fasting glucose (110 mg/dL or on drug treatment)
[b]Treated as continuous trait
[c]Log transformed
[d] Covariates are age, sex, education, smoking status, alcohol intake, physical activity and respective medication
[e] Covariates are age, sex, education, smoking status, alcohol intake, physical activity

DISCUSSION

We provide here the epidemiological and heritability data about MetS and its related traits according ATP III criteria among AA. Overall, in our study sample, the prevalence of MetS was higher among women than men. Factors independently associated with having MetS for men were older age, lower physical activity level, higher BMI, higher level of homocysteine and lower level of adiponectin. For women, in addition to older age, lower physical activity level, higher BMI, higher level of homocysteine and lower level of adiponectin, , low education, higher stress, current smoking and alcohol consumption were also significant. The

heritability of the MetS was 32% and among its individual components, heritability ranged from 14% for FPG to 45% for WC.

The prevalence of MetS that we found (38.94% of women and 27.34% of men) was almost identical to a recent estimate from a National Survey, which reported 38.2% of AA women and 25.5% of AA men had MetS.[1] A higher prevalence of MetS in women than in men has been reported in several other Asian and Eastern European countries, as well as among Hispanic, and Native Americans.[1, 30-32] However, it is opposite for US Caucasians with higher prevalence in men.[1] This, together with our finding suggest the possibility of an increased risk of MetS for women belonging to an economically disadvantaged or a minority population group. The unfavorable condition of women was also evident from our multivatiate analysis, where we found lower education and stress to be significantly related with MetS for women, but not for men. While in the industrialized society social class and education are typically inversely related to different cardio-metabolic risk factors regardless of gender,[33-35] in our study, this was true only for women, indicating an adverse social environment of our women participants.

Literature have indicated active smoking to be associated with development of MetS.[36, 37] We however found, active smoking to be associated with women's MetS only. The lack of association between current smoking and MetS among men in our study can be partly attributed to the much discussed inverse association between active smoking and obesity as the smoking prevalence was higher and abdominal obesity was relatively lower in the men than women in our analysis.[38] Further, researchers have also found smoking cessation to be frequently

followed by weight gain,[39] which explains our observed association between past smoking and men's MetS.

Although lifestyle, physiological and socio-demographic factors play key roles in the pathogenesis of MetS, there is also strong evidence that the syndrome is inherited.[40-43] We evaluated the contributions of genetic factors to the phenotypic variability of MetS and its traits by heritability estimation. According to various studies from different ethnic groups, heritability of MetS ranges from approximately 19 to 38%.[10-13] A Dutch study estimated a heritability of 19.2% of MetS in an isolated group of population.[11] A heritability of 24% in a Caribbean-Hispanic population has been reported by Lin et al.[12] The heritability for the Caucasian population was about 27% according to large population based study.[10] Bayoumi et al. reported a heritability of 38% of MetS in healthy Omani Arab families.[13] Besides the genetic effect itself, which could be different among different studied populations, the discrepancy in heritability might be attributable to other factors such as different sample sizes, different structure of pedigrees or covariates included in the analysis. Compared to different ethnic groups, relatively little information is available on the heritability of MetS in AA population. The heritability of MetS in our study was 32% after taking into account the contributions of covariates, like age, sex, alcohol consumption, smoking and physical activity level, suggesting that more than one-third of the variance in MetS was attributable to the additive effects of genes in the JHS participants. This estimate is on the higher end of the heritability range reported so far, which suggests significant genetic influences on clustering of risk factors among AA.

Reported heritability from different studies for the individual traits ranges from 10% for plasma glucose to 60% for HDL-C.[10-14, 19] Our estimates correspond well with these findings. In the present study, more than 40% of the variance in HDL-C, triglyceride and WC was attributable to genetic effect. Conversely, a moderate but significant heritability were observed for BP and FPG. In different studies as well, HDL-C, obesity and lipid profiles showed the strongest heritability, and BP and FPG had the lowest heritability.[10-14] While for lipid levels and WC genetic influence remains dominant; it seems, for FPG and BP the environmental contribution play a more prominent role, which was apparent by the remarkable covariate effect that was observed for FPG and BP (33% and 22%, respectively) not only in our findings, but also in some other studies.[10, 12] This hypothesis is further supported by some genetic association studies, where investigators have tried to find a unifying pathogenic mechanism for the different MetS components and identify genetic variants contributing to MetS. No such work among AA were found, but a meta-analysis of 4000 Asian and Caucasian participants reviewing 25 genes reported an association between MetS and single nucleotide polymorphisms in the FTO, TCFL72, IL6, APOA5, APOC3 and CETP genes. [44] Another Swedish study found that genetic variants in the PPARG and ADRB1 genes conferred an increased risk of future MetS [45]. All of these genes are mostly involved in lipid metabolism [44, 45]. These evidence indicate that lipid metabolism plays the central role in MetS development; and possibly, genetic impact FPG and BP have a relatively minor role in MetS clusters. Our finding also indirectly supports this view as we found triglyceride, HDL-C and WC to be strongly correlated with one another and a relatively weaker correlation for blood pressure and FPG with other traits. More importantly, we also found higher and similar heritability estimates for triglyceride, HDL-C and WC and relatively lower heritability estimates for BP and FPG,

suggesting a possible similarity in genetic mechanism of developing MetS for AA population with other ethnic groups.

Our findings reconfirm that MetS is a complex disease and lifestyle, SES, and genetic background play important roles in the development of MetS. It was obvious from our study that social and economic context has disparate impact on women's cardiovascular health and subsequent policies and health educational programs should be particularly directed towards women for future CVD risk reduction. As the causes of the MetS are reversible and the individual components are modifiable, lifestyle change such as increasing physical activity may reduce the prevalence of MetS in AA people. We found a significant and independent inverse association between MetS and adiponectin; and a positive association between MetS and homocysteine. In line with our findings, a number of recent studies also have reported similar results.[46-50] These findings suggest, monitoring circulating adiponectin and homocysteine level could provide useful clinical information on risk of developing MetS and provide effective targets for intervention aimed at modifying lifestyle. However, further studies, including economic evaluations and prospective studies should investigate whether these markers would prove useful and cost effective in the early identification of MetS. In the present study we found considerable heritability of MetS among AA. This provides direct support for performing genome-wide association studies in this population. Our finding also supports the hypothesis of lipid metabolism playing the central role in the development of MetS and strongly encourages additional efforts to identify the underlying susceptibility genes for this syndrome in AA.

Our results should be interpreted within the context of few limitations. We acknowledge that given our cross-sectional observational design, our study can only confirm the associations of the facotors with MetS; and cannot prove the causality. We also recognize the considerable disagreement over the definition and diagnostic criteria related to MetS. Of the various available definitions, we used the ATPIII criteria as this is the most widely used definition in the US [1, 24]. It can be, however, argued that some other available definition of MetS could be equally valid and produce somewhat different result. Though we have accounted for important individual covariates, our heritability estimates were influenced by shared environmental factors like childhood environment and neighborhood factors, and thus, our results could be slightly overestimated. One of the major strengths of our study is, our data although cross-sectional, comes from a large, community-based AA population, who are vastly understudied but have high prevalence of metabolic diseases including obesity, diabetes, hypertension and others. We are not aware of any published data that reported the associated factors and quantified the heritability of MetS among AA from such a big setting. Further, assessment of socio-demographic variables in the JHS was performed uniformly and precise techniques were used to measure all physiological and biochemical values, which makes our findings reliable. JHS also has a complex and extended pedigree structure with a large sample, which provided us a reliable statistical ground to detect genetic effects than nuclear families, twin pair data or sib-pair data.

We report the association of important correlates and significant heritability estimates of the MetS and its components among JHS AA families. Our data suggests inclusion of biomarkers like adiponectin and homocysteine to improve early identification of MetS. We have

demonstrated significant heritability estimates for the metabolic syndrome itself, and also for its individual components. The results strongly encourage efforts to identify the underlying susceptibility genes for this syndrome in AA. Further exploration of the genetic and environmental factors of the MetS among AAs will lead to a more comprehensive understanding and better therapeutic options for the syndrome, and ultimately lead to improved cardiovascular health.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
√**Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
√**Introduction**		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
√**Methods**		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
√**Results**		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

√Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
√Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence, Associated Factors and the Heritability of Metabolic Syndrome and its Individual Components in African Americans: The Jackson Heart Study

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Keywords: Metabolic Syndrome, African Americans, Heritability, Associated factors

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Abstract

Objective: Both environmental and genetic factors play important roles in development of metabolic syndrome (MetS). Studies about its associated factors and genetic contribution in African Americans (AA) are sparse. Our aim was to report the prevalence, associated factors and heritability estimates of MetS and its components in AA men and women.

Participants and setting: Data of this cross-sectional study comes from large and community based Jackson Heart Study (JHS). We analyzed a total of 5227 participants, of which 1636 from 281 families were part of the family study subset of JHS.

Methods: Participants were classified as having the MetS according to the Adult Treatment Panel III criteria. Multiple logistic regression analysis was performed to isolate independently associated factors of MetS (n=5227). Heritability was estimated from the family study subset using variance component methods (n=1636).

Results: About 27% of men and 40% of women had MetS. For men, associated factors with having MetS were older age, lower physical activity, higher body mass index, higher homocysteine and adiponectin level ($p<0.05$ for all). For women, in addition to all these, lower education, current smoking, and higher stress were also significant ($p<0.05$ for all). After adjusting for covariates, the heritability of MetS was 32% ($p<0.001$). Heritability ranged from 14 to 45% among its individual components. Relatively higher heritability was estimated for waist circumference (45%), high density lipoprotein-cholesterol (43%) and triglycerides (42%). Heritability of systolic blood pressure (BP), diastolic BP, and fasting blood glucose were 16%, 15%, and 14%, respectively.

Conclusion: Stress and low education were associated with having MetS in AA women, but not in men. Higher heritability estimates for lipids and waist circumference supports the hypothesis

of lipid metabolism playing the central role in the development of MetS and encourages additional efforts to identify the underlying susceptibility genes for this syndrome in AA.

Strengths and limitations of this study

- African American community disproportionately suffers from metabolic syndrome, but relatively little is known about the genetic contribution and the environmental influence of this syndrome among African Americans.
- Using the data from large, community-based Jackson Heart study, this study showed a high prevalence of metabolic syndrome, and reported the associated factors and heritability estimates of metabolic syndrome and its components in African Americans.
- We are not aware of any published data that explored these issues among African American from such a big setting. The large sample size also provided a reliable statistical ground to detect heritability estimates than nuclear families, twin pair data or sib-pair data.
- Potential limitations of this study included the cross-sectional observational design, which could only confirm the associations of the factors with metabolic syndrome, but not the causality, and the absence of information on shared environmental factors like childhood environment and neighborhood factors, which might slightly overestimate the heritability results.
- This study encourages additional efforts to identify the underlying susceptibility genes for metabolic syndrome among African Americans.

BACKGROUND

Metabolic syndrome (MetS) is a clustering of different interrelated cardio-metabolic risk factors including obesity, elevated blood pressure (BP), dyslipidemia, and impaired fasting plasma glucose (IFG). These risk factors often occur together and increases cardiovascular disease (CVD) deaths almost by three to four fold.[1, 2] As MetS is the combined effect of more than one risk factor, the etiology of the MetS is complex. Factors like lifestyle, gender, ethnicity, socioeconomic status, psychosocial factors and some inflammatory markers play key roles in the pathogenesis of MetS.[1-3] Findings also suggest that MetS clusters in families[4-8] and has reasonable heritability, which is defined as the proportion of phenotypic variance in a trait that is attributable to the additive effects of genes.[9-17] Thus, the interplay of both environmental and genetic factors makes MetS a multifactorial disorder.

Though the pathogenesis, diagnosis and the treatment of MetS remain complex because of its multifactorial nature, the construct MetS is an important risk-assessment method for early detection and early intervention of CVD. In spite of steady decline in CVD mortality during recent decades, CVD is still the leading cause of death in all Americans, and is highly prevalent in persons of African ancestry.[18] It is important to note that the majority of studies that explored the associated factors and quantified the heritability of MetS almost exclusively involved Caucasians.[10-14, 19] Relatively little is known about these issues among adult African American (AA) population.[15-17] Using the Jackson Heart Study (JHS) data, the objective of this cross-sectional study was to report the prevalence, risk factors and heritability estimates of MetS and its components in AA men and women.

METHODS

Data Source

Data of this analysis comes from large and community based JHS, which comprises 5301 adult AA enrolled between September 2000 and March 2004 residing in Jackson, Mississippi, metropolitan area.[20] About 24% of 5301 participated in the JHS family study component.[21] The family study component of JHS contained 1st degree (parent-offspring and siblings), 2nd degree (grandparent-grandchild, avuncular, half-siblings) and 3rd degree or more distant (great grandparent-grandchild, grand avuncular, half avuncular, first cousins, half first cousins, second cousins) family members. The JHS was approved by the University of Mississippi Medical Center Institutional Review Board, and the participants gave written informed consent. Details of the study design and data collection methods are described elsewhere.[21, 22] The current study data were obtained from the baseline clinic visit during 2000-2004. After excluding 74 participants who didn't have information on their MetS status, the current analysis had a total of 5227 participants, of which 1636 from 281 families contributed to the heritability analyses.

Measures

We collected information on participant's waist circumference (WC), systolic BP (SBP) and diastolic BP (DBP), fasting plasma glucose (FPG), fasting triglyceride, and plasma high-density lipoprotein cholesterol (HDL-C). Two measures of the waist at the level of the umbilicus and in the upright position were averaged to calculate WC. Sitting BP was measured twice at 5-min intervals with standardized Hawksley random-zero sphygmomanometer, and the

average of two measurements was used. Fasting blood samples were collected according to standardized protocols, and the assessments of FPG and lipids were processed at the Central Laboratory, University of Minnesota.[23] Respondents were asked about their medication usage for hypertension, diabetes mellitus and high lipid levels. Individuals were classified as having MetS if they had at least three of the following five components: (1) large WC or abdominal obesity (> 102 cm for men and > 88 cm for women); (2) hypertriglyceridemia (fasting plasma triglyceride concentration ≥ 150 mg/dL or on drug treatment); (3) low HDL-C levels (< 40 mg/dL for men and < 50 mg/dL in women or on drug treatment); (4) elevated BP (≥ 130 mm Hg SBP or ≥ 85 mm Hg DBP or on drug treatment); or, (5) IFG (≥ 110 mg/dL or on drug treatment).[24, 25]

Data about socio-demographic (age, sex, and education), the psychosocial (stress) and lifestyle (physical activity, smoking status, and alcohol consumption) variables were also collected. Age was classified as: 20-39, 40-59, 60-79 and 80 years and above. Education status was self-reported and was divided into three categories (less than high school, high school/GED/ some college and college/associate degree or higher, where less than high school was the referent). Stress level was obtained from The Global Perceived Stress Scale, an 8-item questionnaire that measures the severity of chronic stress experienced over a prior period of twelve months.[26] The physical activity index composite score was calculated as the sum of four different domains of physical activity: active living, work, home and garden, and sport and exercise indices.[27] Smoking status was classified as never (referent), current, and former. Alcohol consumption status was defined as “yes” if they currently consumed alcoholic beverages and “no” (referent) if they had stopped drinking for more than a year , or if they never consumed alcohol.

Information on clinical factors like body mass index or BMI (weight in kg divided by height in meter square), C-reactive protein or CRP (mg/dL), serum adiponectin (mg/dL), and serum homocysteine (umol/L) were also obtained.[23]

Analysis

Data from the full cohort (n= 5227) were used to explore the risk factors of MetS. Socio-demographic, psychosocial, lifestyle and clinical characteristics of participants were compared by gender and MetS status using the chi-square or independent t-test. The primary outcome measure for this analysis was the presence of MetS, evaluated as a dichotomous variable. Logistic regression analysis was used to examine the association between each independent variable (age, education level, stress level, physical activity score, smoking status, alcohol consumption status, BMI, CRP, fasting total cholesterol, serum concentration of adiponectin, and serum homocysteine) with the outcome of MetS. A multiple logistic regression model was fitted including all variables to isolate the statistically significant predictors of MetS. The regression analysis was conducted using SAS software, Version 9.3.[28]

Heritability Analysis

After checking the pedigree data for inconsistencies a total of 1636 individuals from 281 families were analyzed to calculate the heritability estimates by variance component methods using SOLAR (Sequential Oligogenic Linkage Analysis Routines) software package to quantify the proportion of the variance in MetS and in its individual components that was attributable to the additive effects of genes.[29] We estimated the heritability of individual MetS components (treated as continuous variable) including WC, SBP, DBP, FPG, fasting triglyceride, and

plasma HDL-C with adjustment for age, education level, physical activity index composite score, smoking status, alcohol consumption status and respective medication usage. Log transformed values of FPG and triglycerides were used due to deviation from normal distribution. Heritabilities were calculated using a standard quantitative genetic variance-components model implemented in SOLAR.[29] This approach uses the maximum-likelihood estimation to a mixed-effects model that incorporates fixed covariate effects, additive genetic effects and residual error. The heritability of MetS (discrete variable) was analyzed by a threshold model in SOLAR. The method assumed that an individual belonged to a specific affected status if an underlying genetically determined risk exceeded a certain threshold.[30]

For all the analyses, significance level set at $p<0.05$ were used.

RESULTS

Table 1 presents the characteristics of JHS participants. Of the 5227 individuals, 1909 (36.52%, mean age 53.93 years and standard deviation or SD=12.93) were men and 3318 (63.48%, mean age 55.30 ±12.76) were women. Education levels were similar for men and women. About 40% of men and women had college level education or beyond. A clear gender difference however, was found for alcohol use and smoking, with women being far less likely than men to consume alcohol and smoke cigarettes ($p<0.001$). Women reported greater levels of stress, but lower level of physical activity than men ($p<0.001$). Women also had higher BMI, CRP, adiponectin, and lower homocysteine level than men ($p<0.001$ for all). Table 1 also shows the prevalence of MetS and its individual components among the JHS participants. About 27.34% of the men and 38.94% of the women had MetS ($p<0.001$). In terms of individual components, women had

higher abdominal obesity (75.70% versus 41.03%, p<0.001) and IFG (22.45% versus 19.64%, p<0.001), but lower hypertriglyceridemia (13.23% versus 18.39%, p <0.001) than men.

Table 1: Characteristics of Participants of the Jackson Heart Study by Gender (N=5227)

	Total[a] n=5227	Men[a] n=1909	Women[a] n=3318	P value[b]
Age in years	54.87 (12.84)	53.93 (12.93)	55.30 (12.76)	0.0002
Education level				
Less than high school	18.4.	18.73	17.88	
High school/GED or some college	42.2	42.82	41.83	
College/associate degree or higher	39.4	38.45	40.29	0.4094
Smoking Status				
Never	67.9	56.68	74.59	
Former	18.9	25.33	15.30	
Current	13.2	17.99	10.11	<.0001
Alcohol drinking status				
Yes	47.2	58.92	38.41	
No		41.08	61.59	<.0001
Total Physical Activity Score[c]	8.31 (2.61)	8.64 (2.63)	8.16 (2.58)	<.0001
Global Stress Total Score[d]	5.14 (4.21)	4.50 (4.20)	5.52 (4.45)	<.0001
Body mass index (weight in kg/height in squared meter)	31.75 (7.24)	29.83±6.14	32.86 (7.59)	<.0001
High Sensitivity C-Reactive Protein in mg/dL	0.51 (0.87)	0.35 (0.96)	0.60 (0.85)	<.0001
Homocysteine in umol/L	9.44 (4.68)	10.17 (3.56)	9.00 (5.20)	<.0001
Adiponectin level in µg/mL	5.41 (4.16)	4.15 (3.41)	6.15 (4.57)	<.0001
Abdominal obesity[e]	62.9	41.03	75.70	<.0001
Hypertriglyceridemia	16.5	18.39	13.23	<.0001
Low HDL-C[g]	37.2	33.01	39.55	<.0001
Elevated blood Pressure[h]	70.3	69.62	70.58	0.4616
impaired fasting glucose[i]	22.4	19.64	22.45	0.0171
Metabolic syndrome[k]	34.4	27.34	38.94	<.0001

[a]Data presented as mean (SD) or percentage of subjects
[b]Independent t-test or Chi-square test comparing characteristics of men and women;
[c]sum of the four different domains of physical activity;
[d] sum of 8 item questionnaire that measures the severity of chronic stress experienced over a prior period of twelve months;
[e]waist circumference > 102 cm for men and > 88 cm for women
[f]fasting plasma triglyceride concentration ≥ 150 mg/dL or on drug treatment
[g]HDL cholesterol levels <40 mg/dL for men and < 50 mg/dL in women or on drug treatment
[h]Blood pressure ≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or on drug treatment
[i]fasting glucose ≥ 110 mg/dL or on drug treatment

[k] Metabolic Syndrome defined as having at least three of the following five components: (1) abdominal obesity; (2) hypertriglyceridemia; (3) low HDL cholesterol levels; (4) elevated blood; (5) impaired fasting glucose

Table 2 shows the descriptive characteristics of participants by MetS status. Those who had MetS were older, less educated, less likely to smoke, less likely to consume alcohol, and less physically active ($p<0.001$ for all). They also had higher BMI, higher CRP and higher homocysteine level; but lower adiponectin concentration ($p<0.001$ for all). The unadjusted and the adjusted relationships of MetS with these features are displayed in Table 3. After adjustment, older age remained significant for both men and women. Notably, the trend of having MetS with increasing age was clearer for women than for men. Education was only significant for women, and not for men. Women who went to high school had 24% (adjusted odds ratio or AOR: 0.76; 95% confidence interval or CI:0.59-0.97) decreased odds of having MetS compared to those who had the lowest education level. Like education, higher stress level was also a significant factor for women only (AOR: 1.02; 95% CI: 1.01-1.04). Physical activity decreased the odds of having MetS for both sexes, but alcohol consumption was associated with 26% decreased odds (AOR: 0.74; 95% CI: 0.61-0.90) of MetS for women only. Relationship between smoking and MetS was different for men and women. While current smoking only predicted women's MetS (AOR:1.43; 95% CI:1.07-1.91), former smoking had significant association with men's MetS (AOR: 1.54 ; 95% CI:1.14-2.08). Biomedical risk factors such as increased BMI (AOR:1.18; 95% CI:1.15-1.21 for men and AOR:1.08; 95% CI:1.07-1.10 for women), increased serum homocysteine (AOR:1.05; 95% CI:1.02-1.09 for men and AOR:1.06; 95% CI:1.03-1.09 for women) and decreased serum adiponectin (AOR:0.90; 95% CI:0.85-0.95 for men and AOR:0.90; 95% CI:0.87-0.92 for women) were associated with increased odds of having MetS for both sexes.

Table 2: Characteristics of Jackson Heart Study Participants by metabolic syndrome status (N=5227)

	Metabolic Syndrome[a] (n=1814)	No Metabolic Syndrome[a] (n=3413)	P value[b]
Age in years	58.04 (11.43)	53.07 (13.21)	<.0001
Gender of Participant			
Men	28.78	40.46	
Women	71.22	59.36	<.0001
Education level			
Less than high school	23.32	15.46	
High school/GED or some college	41.94	42.33	
College/associate degree or higher	34.74	42.21	<.0001
Smoking Status			
Never	66.17	69.05	
Former	21.59	17.56	
Current	12.24	13.39	0.0017
Alcohol drinking status			
Yes	37.01	50.63	
No	62.99	49.37	<.0001
Total Physical Activity Score[c]	7.74 (2.56)	8.65 (2.57)	<.0001
Global Stress Total Score[d]	5.11 (4.42)	5.17 (4.37)	0.6251
Body mass index (weight in kg/height in squared meter)	34.87 (6.92)	30.10 (6.86)	<.0001
High Sensitivity C-Reactive Protein in mg/dL	0.65 (1.13)	0.44 (0.74)	<.0001
Homocysteine: The concentration of homocysteine in umol/L	9.94 (6.37)	9.15 (3.44)	<.0001
Serum concentration of adiponectin in µg/mL	4.72 (4.02)	5.79 (4.38)	<.0001

[a]Data presented as mean (SD) or percentage of subjects
[b]Independent t-test or Chi-square test;
[c]sum of the four different domains of physical activity;
[d] sum of 8 item questionnaire that measures the severity of chronic stress experienced over a prior period of twelve months;

Table 3: Association between selected factors and prevalence of metabolic Syndrome among Jackson Heart Study Participants (n=5227)

	Metabolic Syndrome Odds Ratio (95% CI)			
	Men (n=1909)		Women (n=3318)	
	Unadjusted[a]	Adjusted[a]	Unadjusted[a]	Adjusted[a]
Age				
20-39	Reference Level		Reference Level	
40-59	1.34(0.96-1.86)	1.55 (1.02-2.35)	2.44(1.84-3.23)	2.79 (2.00 -3.87)
60-79	1.69(1.20-2.38)	2.17 (1.34-3.51)	4.69(3.54-6.22)	5.50 (3.81-7.93)
80 and above	0.88(0.28-2.71)	2.18 (0.60-8.00)	3.43(1.89-6.24)	5.06 (2.34-10.96)
Education				
Less than High school	Reference Level		Reference Level	
High school or some College	0.95(0.72-1.25)	1.20 (0.83-1.74)	0.53(0.44-0.65)	0.76 (0.59- 0.97)
College degree or higher	0.79(0.60-1.05)	1.05 (0.72 1.55)	0.44(0.36-0.53)	0.82 (0.63-1.07)
Smoking Status				
Never	Reference Level		Reference Level	
Former	1.47(1.16-1.85)	1.54 (1.14-2.08)	1.39(1.15-1.69)	1.20 (0.95-1.52)
Current	0.92(0.69-1.22)	1.29 (0.89-1.86)	1.20(0.95-1.51)	1.43 (1.07-1.91)
Alcohol drinking				
No	Reference Level		Reference Level	
Yes	0.72(0.59-0.88)	0.85 (0.66-1.11)	0.57(0.49-0.66)	0.74 (0.61-0.90)
Physical Activity[b]	0.90(0.86-0.94)	0.93 (0.88- 0.98)	0.86(0.84-0.89)	0.94 (0.91-0.98)
Global Stress[c]	1.01(0.98-1.03)	1.02 (0.99-1.06)	0.98(0.97-1.00)	1.02 (1.01- 1.04)
Body mass index	1.18(1.15-1.20)	1.18 (1.15-1.21)	1.08(1.07-1.09)	1.08 (1.07-1.10)
C-Reactive Protein in mg/dL	1.36(1.15-1.60)	1.10 (0.96- 1.26)	1.29(1.18-1.41)	0.99 (0.89-1.09)
Homocysteine in umol/L	1.04(1.01-1.07)	1.05 (1.02 1.09)	1.07(1.05-1.10)	1.06(1.03-1.09)
Adiponectin in µg/mL	0.89(0.85-0.92)	0.90 (0.85-0.95)	0.91(0.90-0.93)	0.90 (0.87-0.92)

Metabolic Syndrome defined as having at least three of the following five components: (1) abdominal obesity or large waist circumference (> 102 cm for men and > 88 cm for women); (2) hypertriglyceridemia (fasting plasma triglyceride concentration ≥ 150 mg/dL or on drug treatment); (3) low HDL cholesterol levels (< 40 mg/dL for men and < 50 mg/dL in women or on drug treatment); (4) elevated blood pressure (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or on drug treatment); or, (5) IFG or impaired fasting glucose (110 mg/dL or or on drug treatment)

[a]Analysis done using simple and multiple logistic regression. The multivariate models are adjusted for for all other variables in the table.

[b]sum of the four different domains of physical activity;

[c]sum of 8 item questionnaire that measures the severity of chronic stress experienced over a prior period of twelve months;

Table 4 illustrates the heritability estimates along with the proportion of variation explained by covariates (σ_e^2) of MetS and its individual component in the family study subset (n=1636). All components of the MetS were significantly correlated with each other except for the pairs of blood pressure and HDL-C and blood pressure and fasting glucose (results not shown in table). After accounting for the covariates (except medication), the heritability of MetS was about 32% ($p<0.0001$, σ_e^2: 10%). The adjusted heritability of individual MetS components ranged from the lowest of 14% ($p<0.01$, σ_e^2: 33%) for FPG to the highest of 45% ($p<0.0001$, σ_e^2: 8%) for WC after adjusting for all the covariates. The adjusted estimates of DBP (15%, $p<0.01$, σ_e^2: 9%) and SBP (16%, $p<0.001$, σ_e^2: 22%) were on the lower end and similar to the estimate of FPG. Conversely, heritability of triglyceride (42%, $p<0.001$, σ_e^2: 10%) and HDL-C (43%, $p<0.001$, σ_e^2: 11%) was relatively high and similar to the heritability of WC.

Table 4: Heritability estimates of Metabolic Syndrome and its individual components of Jackson Heart Study Participants (n=1636)

	Heritability Estimate	Standard error	P value	Proportion of variation explained by covariates
Metabolic Syndrome[a]	0.32	0.08	<0.0001	0.10[e]
Fasting Plasma Glucose[b,c]	0.14	0.06	<0.01	0.33[d]
Waist Circumference[b]	0.45	0.06	<0.0001	0.08[e]
High Density Lipoprotein Cholesterol[b]	0.43	0.07	<0.0001	0.11[d]
Fasting Triglyceride[b,c]	0.42	0.05	<0.0001	0.10[d]
Systolic blood pressure[b]	0.16	0.07	<0.001	0.22[d]
Diastolic blood pressure[b]	0.15	0.05	<0.01	0.09[d]

[a]Treated as discrete trait, and defined as having at least three of the following five components: (1) abdominal obesity or large waist circumference (> 102 cm for men and > 88 cm for women); (2) hypertriglyceridemia (fasting plasma triglyceride concentration ≥ 150 mg/dL or on drug treatment); (3) low HDL cholesterol levels (< 40 mg/dL for men and < 50 mg/dL in women or on drug treatment); (4) elevated blood pressure (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or on drug treatment); or, (5) IFG or impaired fasting glucose (110 mg/dL or on drug treatment)
[b]Treated as continuous trait
[c]Log transformed
[d] Covariates are age, sex, education, smoking status, alcohol intake, physical activity and respective medication
[e] Covariates are age, sex, education, smoking status, alcohol intake, physical activity

DISCUSSION

We provide here the epidemiological and heritability data about MetS and its related traits according ATP III criteria among AA. Overall, in our study sample, the prevalence of MetS was higher among women than men. Factors independently associated with having MetS for men were older age, lower physical activity level, higher BMI, higher level of homocysteine and lower level of adiponectin. For women, in addition to older age, lower physical activity level, higher BMI, higher level of homocysteine and lower level of adiponectin, , low education, higher stress, current smoking and alcohol consumption were also significant. The

heritability of the MetS was 32% and among its individual components, heritability ranged from 14% for FPG to 45% for WC.

The prevalence of MetS that we found (38.94% of women and 27.34% of men) was almost identical to a recent estimate from a National Survey, which reported 38.2% of AA women and 25.5% of AA men had MetS.[1] A higher prevalence of MetS in women than in men has been reported in several other Asian and Eastern European countries, as well as among Hispanic, and Native Americans.[1, 31-33] However, it is opposite for US Caucasians with higher prevalence in men.[1] This, together with our finding suggest the possibility of an increased risk of MetS for women belonging to an economically disadvantaged or a minority population group. The unfavorable condition of women was also evident from our multivatiate analysis, where we found lower education and stress to be significantly related with MetS for women, but not for men. While in the industrialized society social class and education are typically inversely related to different cardio-metabolic risk factors regardless of gender,[34-36] in our study, this was true only for women, indicating an adverse social environment of our women participants.

Literature have indicated active smoking to be associated with development of MetS.[37, 38] We however found, active smoking to be associated with women's MetS only. The lack of association between current smoking and MetS among men in our study can be partly attributed to the much discussed inverse association between active smoking and obesity as the smoking prevalence was higher and abdominal obesity was relatively lower in the men than women in our analysis.[39] Further, researchers have also found smoking cessation to be frequently

followed by weight gain,[40] which explains our observed association between past smoking and men's MetS.

Although lifestyle, physiological and socio-demographic factors play key roles in the pathogenesis of MetS, there is also strong evidence that the syndrome is inherited.[41-44] We evaluated the contributions of genetic factors to the phenotypic variability of MetS and its traits by heritability estimation. According to various studies from different ethnic groups, heritability of MetS ranges from approximately 19 to 38%.[10-13] A Dutch study estimated a heritability of 19.2% of MetS in an isolated group of population.[11] A heritability of 24% in a Caribbean-Hispanic population has been reported by Lin et al.[12] The heritability for the Caucasian population was about 27% according to large population based study.[10] Bayoumi et al. reported a heritability of 38% of MetS in healthy Omani Arab families.[13] Besides the genetic effect itself, which could be different among different studied populations, the discrepancy in heritability might be attributable to other factors such as different sample sizes, different structure of pedigrees or covariates included in the analysis. Compared to different ethnic groups, relatively little information is available on the heritability of MetS in AA population. The heritability of MetS in our study was 32% after taking into account the contributions of covariates, like age, sex, alcohol consumption, smoking and physical activity level, suggesting that more than one-third of the variance in MetS was attributable to the additive effects of genes in the JHS participants. This estimate is on the higher end of the heritability range reported so far, which suggests significant genetic influences on clustering of risk factors among AA.

Reported heritability from different studies for the individual traits ranges from 10% for plasma glucose to 60% for HDL-C.[10-14, 19] Our estimates correspond well with these findings. In the present study, more than 40% of the variance in HDL-C, triglyceride and WC was attributable to genetic effect. Conversely, a moderate but significant heritability were observed for BP and FPG. In different studies as well, HDL-C, obesity and lipid profiles showed the strongest heritability, and BP and FPG had the lowest heritability.[10-14] While for lipid levels and WC genetic influence remains dominant; it seems, for FPG and BP the environmental contribution play a more prominent role, which was apparent by the remarkable covariate effect that was observed for FPG and BP (33% and 22%, respectively) not only in our findings, but also in some other studies.[10, 12] This hypothesis is further supported by some genetic association studies, where investigators have tried to find a unifying pathogenic mechanism for the different MetS components and identify genetic variants contributing to MetS. No such work among AA were found, but a meta-analysis of 4000 Asian and Caucasian participants reviewing 25 genes reported an association between MetS and single nucleotide polymorphisms in the FTO, TCFL72, IL6, APOA5, APOC3 and CETP genes. [45] Another Swedish study found that genetic variants in the PPARG and ADRB1 genes conferred an increased risk of future MetS [46]. All of these genes are mostly involved in lipid metabolism [45, 46]. These evidence indicate that lipid metabolism plays the central role in MetS development; and possibly, genetic impact FPG and BP have a relatively minor role in MetS clusters. Our finding also indirectly supports this view as we found triglyceride, HDL-C and WC to be strongly correlated with one another and a relatively weaker correlation for blood pressure and FPG with other traits. More importantly, we also found higher and similar heritability estimates for triglyceride, HDL-C and WC and relatively lower heritability estimates for BP and FPG,

suggesting a possible similarity in genetic mechanism of developing MetS for AA population with other ethnic groups.

Our findings reconfirm that MetS is a complex disease and lifestyle, SES, and genetic background play important roles in the development of MetS. It was obvious from our study that social and economic context has disparate impact on women's cardiovascular health and subsequent policies and health educational programs should be particularly directed towards women for future CVD risk reduction. As the causes of the MetS are reversible and the individual components are modifiable, lifestyle change such as increasing physical activity may reduce the prevalence of MetS in AA people. We found a significant and independent inverse association between MetS and adiponectin; and a positive association between MetS and homocysteine. In line with our findings, a number of recent studies also have reported similar results.[47-51] These findings suggest, monitoring circulating adiponectin and homocysteine level could provide useful clinical information on risk of developing MetS and provide effective targets for intervention aimed at modifying lifestyle. However, further studies, including economic evaluations and prospective studies should investigate whether these markers would prove useful and cost effective in the early identification of MetS. I In the present study we found considerable heritability of MetS among AA. This provides direct support for performing genome-wide association studies in this population. Our finding also supports the hypothesis of lipid metabolism playing the central role in the development of MetS and strongly encourages additional efforts to identify the underlying susceptibility genes for this syndrome in AA.

Our results should be interpreted within the context of few limitations. We acknowledge that given our cross-sectional observational design, our study can only confirm the associations of the facotors with MetS; and cannot prove the causality. We also recognize the considerable disagreement over the definition and diagnostic criteria related to MetS. Of the various available definitions, we used the ATPIII criteria as this is the most widely used definition in the US [1, 24]. It can be, however, argued that some other available definition of MetS could be equally valid and produce somewhat different result. Though we have accounted for important individual covariates, our heritability estimates were influenced by shared environmental factors like childhood environment and neighborhood factors, and thus, our results could be slightly overestimated. One of the major strengths of our study is, our data although cross-sectional, comes from a large, community-based AA population, who are vastly understudied but have high prevalence of metabolic diseases including obesity, diabetes, hypertension and others. We are not aware of any published data that reported the associated factors and quantified the heritability of MetS among AA from such a big setting. Further, assessment of socio-demographic variables in the JHS was performed uniformly and precise techniques were used to measure all physiological and biochemical values, which makes our findings reliable. JHS also has a complex and extended pedigree structure with a large sample, which provided us a reliable statistical ground to detect genetic effects than nuclear families, twin pair data or sib-pair data.

We report the association of important correlates and significant heritability estimates of the MetS and its components among JHS AA families. Our data suggests inclusion of biomarkers like adiponectin and homocysteine to improve early identification of MetS. We have demonstrated significant heritability estimates for the metabolic syndrome itself, and also for its individual components. The results strongly encourage efforts to identify the underlying susceptibility genes for this syndrome in AA. Further exploration of the genetic and environmental factors of the MetS among AAs will lead to a more comprehensive understanding and better therapeutic options for the syndrome, and ultimately lead to improved cardiovascular health.

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Contributorship statement: SKD and RJK conceptualized the study. RJK and RX completed the main data analysis. RJK and SKD prepared the manuscript. SYG, PC and MS contributed to the study design, interpretation of data, and the preparation of manuscript. All authors read and approved the final manuscript.

Conflicts of interest: The authors declare no conflicts of interest.

Ethics approval: University of Mississippi Medical Center Institutional Review Board and National Human Genome Research Institute Institutional Review Board

Data sharing statement: No additional data available

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
√**Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
√**Introduction**		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
√**Methods**		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
√**Results**		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

√Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
√Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.