Factor relationships of metabolic syndrome and echocardiographic phenotypes in the HyperGEN study

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Background **Metabolic syndrome and its risk factors are predictors of cardiovascular events. Metabolic syndrome is also directly associated with echocardiographic phenotypes.**

Methods **The current study is the first to investigate the factors associated with both metabolic syndrome risk factors and echocardiographic phenotypes and assess their heritability. Multivariate factor analysis was performed on 15 traits in 1393 African–Americans and 1133 whites, as well as stratified by type 2 diabetes mellitus status.**

Results **Factor analysis with varimax rotation established four to five latent factors across ethnicities and diabetes mellitus stratifications. Among metabolic syndrome risk factors, blood pressure was the most highly correlated with cardiac traits. The factor domains, in the order of the proportion of variance explained, were 'left ventricle wall thickness', 'left ventricle geometry', 'blood pressure', 'BMI–insulin', and 'lipid–insulin'. Factor analysis without any rotation identified special (cross domain) metabolic syndrome–echocardiographic factors, 'blood pressure–left ventricle geometry' and 'blood pressure–left ventricle dimension-wall thickness' in whites. Fifty to 57% of the total original risk factor variance was explained by the latent factors. Heritability was highest for BMI–insulin (37–53%), lowest for 'blood pressure' factors (15–27%), and intermediate for metabolic syndrome–echocardiographic factors.**

Conclusion **These latent factors identified can be utilized as summary phenotypes in epidemiological, linkage, and association studies.** ***J Hypertens*** **26:1360–1366 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Abbreviations: ARD, aortic root diameter; BP, blood pressure; BMI, body mass index; CVD, cardiovascular disease; DM, type 2 diabetes mellitus; DBP, medication-adjusted diastolic blood pressure; ECHO, echocardiographic; FA, multivariate factor analysis; FBPP, Family Blood Pressure Program; GLUC, glucose; HR, heart rate; HDLC, high-density lipoprotein cholesterol; HyperGEN, Hypertension Genetic Epidemiology Network; INS, insulin; LV, left ventricular; LVID, left ventricular internal diastolic dimension; LVM, left ventricular mass indexed to height$^{2.7}$; MetS, metabolic syndrome; MLE, maximum likelihood estimate; MWS, left ventricular midwall shortening; PP/SV, arterial stiffness defined by pulse pressure over stroke volume; PWT, diastolic posterior wall thickness; RWT, diastolic relative wall thickness; SBP, medication-adjusted systolic blood pressure; TG, triglycerides

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Introduction

Metabolic syndrome (MetS), which comprises clustering of obesity, insulin resistance, glucose intolerance, dyslipidemia, and elevated blood pressure (BP), is gaining epidemic proportion in Western countries [1–8]. The prevalence of MetS is between 20–30%, with higher values in African–Americans, Hispanic–Americans, and women [6,9,10]. Studies have shown that compared with healthy individuals, the odds of developing cardiovascular disease (CVD) is higher, ranging from 1.26 to 3.86, in patients with MetS, depending on the study population and the applied MetS definitions [10–15].

MetS not only predicts CVD but also associates with abnormal structural and dimensional cardiovascular traits. For example, it was shown that ventricular wall thickness was higher in patients with MetS than in their healthy counterparts [16–19]. Left ventricular dimension and mass, which can be clinically assessed by echocardiography, a noninvasive ultrasound technique, are higher in patients with MetS [20]. MetS has also been reported to be associated with diastolic dysfunction [16,21,22] and greater arterial stiffness [23]. These findings suggest a direct relationship among MetS risk fa ctors and cardiac phenotypes. However, to the best of our knowledge, few data are available on the multivariate relationship among MetS risk factors and echocardiographic (ECHO) cardiac measurements. Although previous studies have found positive associations between MetS and cardiovascular traits, the strength of specific correlations among individual MetS

risk factors and ECHO phenotypes is not fully clear. Hence, this study was undertaken to investigate the relationship among ECHO phenotypes and MetS risk factors. Utilizing factor analysis, we aimed to identify MetS–ECHO domains in the Hypertension Genetic Epidemiology Network (HyperGEN) and examine their heritability.

Methods

Study population

HyperGEN is one of four networks of the National Heart, Lung, and Blood Institute (NHLBI) Family Blood Pressure Program (FBPP), which studies genetic aspects of high BP and related conditions. Two ethnic groups, whites and African–Americans, were recruited in the HyperGEN study [24]. They represented hypertensive sibships with at least two members diagnosed with hypertension before the age of 60, a random sample of age-matched subjects from the same source population that included normotensive controls, unmedicated adult offspring of hypertensive siblings, and parents of hypertensive sibling pairs. Questionnaires, blood samples, clinical data, and ECHO measurements were collected from participants at four HyperGEN centers (Minneapolis, Minnesota; Salt Lake City, Utah; Forsyth County, North Carolina; and Birmingham, Alabama). Exclusion criteria included hypertension secondary to kidney disease or other primary causes and type I diabetes.

Of the total 3550 HyperGEN participants who underwent echocardiography, 1547 were whites, 1996 African–Americans, and seven of other ethnicities. We focused on siblings and their offspring. Within these samples, participants with a fasting time of less than 8 h or any missing values in a full set of 15 traits studied were excluded from the analysis. As a result, we analyzed the phenotypes of 1133 whites and 1393 African–Americans.

A participant was classified with type 2 diabetes mellitus based on the participant's self report, use of antidiabetic medication or insulin treatment at the time of the clinical visit, or the presence of fasting plasma glucose level of 126 mg/dl or more, with age of 40 years or more at the onset of diabetes mellitus [25,26].

Echocardiography

Echocardiograms were performed by a standard protocol as described previously [27] using two-dimensional (2D) guided M-mode and Doppler measurements. Correct orientation of imaging planes and Doppler recordings were carried out according to the standard protocol. A computerized review station equipped with digitizing tablet and monitor screen overlay was used to calibrate and perform measurements. The measurements were first taken by sonographers or physicians centrally trained at the Reading Center in New York and verified by highly experienced investigators who were blinded to the clinical data [28,29].

Phenotypic data preparation

The 15 risk variables under investigation were fasting glucose (GLUC), fasting insulin (INS), fasting triglycerides, high-density lipoprotein cholesterol (HDLC), body mass index (BMI), medication-adjusted systolic blood pressure (SBP), medication-adjusted diastolic blood pressure (DBP), heart rate (HR), left ventricular internal diastolic dimension (LVID), diastolic posterior wall thickness (PWT), diastolic relative wall thickness (RWT), LV mass indexed to height$^{2.7}$ (LVMI), aortic root diameter (ARD), arterial stiffness defined by pulse pressure over stroke volume (PP/SV), and LV midwall shortening (MWS). The peak velocities of mitral valve early filling phase and atrial filling phase were not included in our study because the sample size would have been significantly reduced.

The SBP and DBP of the participants with prescribed antihypertensive medication were adjusted for antihypertensive medication(s) effect by the method described by Wu *et al.* [30] and applied in the HyperGEN study to obtain the pretreatment BP levels for various classes of medications.

All variables underwent appropriate distribution transformations when deemed necessary to achieve standard normal distributions with mean values of zero and variance of one. The Transreg procedure in SAS (version 9.1.3 for Linux; SAS Institute, Cary, North Carolina, USA) was used to find the best power transformation. Log transformation was applied to INS, HDLC, triglycerides, BMI, RWT, LVMI, PWT, and PP/SV. The inverse of squared transformation for GLUC ($1/GLUC^2$) and cubic power transformation for MWS (MWS^3) were applied in both whites and African–Americans. The remaining variables did not require transformation before covariate adjustments.

All 15 variables were adjusted within race and sex by regressing on age, age^2, age^3, and field centers, and only significant terms were retained. Stepwise regression using the REG procedure of SAS was used for covariate adjustments. Age and field-center effects were removed from both the means and the variances, and standardized residuals were derived. Outliers beyond ± 4 SD and more than 1 SD away from the next internal data point were eliminated from the final distribution. Skewness and kurtosis values of less than two were checked and required as two important normal distribution indicators. Final standardized residuals (phenotypes), with a mean of zero and a variance of one, were utilized in the factor analysis.

Statistical analysis

Factor analysis was performed using the factanal function of the S-PLUS version 7 software (Linux OS) with the option of the maximum likelihood estimate (MLE) method. Factor analysis was performed separately in whites and African–Americans. Within each ethnic group, the effects of diabetes mellitus were investigated by running factor analyses either including or excluding participants with

diabetes mellitus. Furthermore, the effect of varimax rotation in factor analysis was also explored by running the analysis with and without rotation. When varimax rotation is applied, the variance of the squared loadings across a factor is maximized, in turn, maximizing the independence of the factors [26,31].

To determine the factor analysis model with the most appropriate number of factors, we concurrently applied the following criteria. At least two risk variables in a latent factor were required with loadings of about 0.4 or more. Because the variables were prestandardized and normally distributed, the loadings of the analysis were essentially the correlation coefficients between each original variable and the latent factor. The sum of squared loadings per latent factor had to be more than or approximately one. In addition, the MLE model was required to be significant ($P < 0.05$). The MLE significance employed in the analysis tested whether the number of latent factors selected was sufficient to explain the model. These stringent criteria of the analysis ensured that significant contributions of the original variables to the latent factors were present in each factor analysis model.

Results

Among the studied participants in the subsample with no missing values in any of the 15 variables, there were 99 whites and 241 African–Americans with diabetes mellitus. The whites had higher triglyceride levels. In contrast, African–Americans tended to have higher BMI, GLUC, INS, BP, HDLC, HR, and LVMI (Table 1). Among whites and African–Americans, age, GLUC, and triglycerides were only slightly lower in individuals without diabetes.

Table 1 Phenotypic characteristics of participants in this study (including and excluding patients with type 2 diabetes)

	White		African–American	
Variables	All	−DM[a]	All	−DM
Number of participants	1133	1034	1393	1152
Women participants (%)	50.13	49.52	65.47	63.98
Age (years)	49 ± 14[b]	49 ± 14	46 ± 13	44 ± 13
BMI (kg/m^2)	29.3 ± 5.7	29.0 ± 5.6	32.2 ± 7.5	31.8 ± 7.5
GLUC (mg/dl)	101.4 ± 33.5	96.7 ± 26.4	108.4 ± 46.8	95.0 ± 16.3
INS (μU/ml)	8.1 ± 7.1	7.7 ± 5.5	10.7 ± 9.2	10.0 ± 8.3
SBP (mmHg)	134.3 ± 26.4	133.1 ± 26.3	145.5 ± 28.4	142.0 ± 26.6
DBP (mmHg)	77.8 ± 12.8	77.6 ± 12.9	84.5 ± 15.0	83.7 ± 15.1
HDLC (mg/dl)	46.6 ± 13.5	46.9 ± 13.5	53.3 ± 15.1	53.5 ± 15.1
Triglycerides (mg/dl)	166.8 ± 118.0	160.6 ± 108.9	108.2 ± 81.6	100.5 ± 59.3
HR (beats/min)	68.2 ± 11.0	67.8 ± 10.9	70.8 ± 12.0	69.8 ± 11.6
LVMI$^{2.7}$ (g/m$^{2.7}$)	80.0 ± 20.0	79.3 ± 19.1	85.8 ± 22.5	84.4 ± 21.9
LVID (cm)	5.2 ± 0.5	5.2 ± 0.5	5.2 ± 0.5	5.2 ± 0.5
PWT (cm)	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
RWT	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
ARD (cm)	3.4 ± 0.4	3.4 ± 0.4	3.3 ± 0.4	3.3 ± 0.4
PP/SV	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
MWS (%)	18.0 ± 2.3	18.1 ± 2.2	17.3 ± 2.4	17.5 ± 2.4

ARD, aortic root diameter; DBP, medication-adjusted diastolic blood pressure; GLUC, glucose; HDLC, high-density lipoprotein cholesterol; HR, heart rate; INS, insulin; LVID, left ventricle internal diastolic dimension; LVMI, left ventricle mass index; MWS, left ventricle midwall shortening; PP/SV, arterial stiffness as pulse pressure over stroke volume; PWT, diastolic posterior wall thickness; RWT, diastolic relative wall thickness; SBP, medication adjusted systolic blood pressure. [a] −DM, excluding type 2 diabetes mellitus subjects. [b] Mean ± SD.

Pearson's correlation among adjusted variables showed similar patterns regardless of ethnicity or the presence/absence of type 2 diabetes (Table 2). In general, MetS and ECHO variables correlated more strongly among themselves than between the two groups. However, several significant correlations between MetS and ECHO variables in both ethnicities were observed with P values of less than 0.0001: BMI with LVID (whites: all, 0.27; excluding diabetes mellitus, 0.28; African–Americans: all, 0.35; excluding diabetes mellitus, 0.36), PWT (whites: 0.25; 0.25; African–Americans: 0.29; 0.30), and ARD (whites: 0.15; 0.16; African–Americans: 0.18; 0.19). INS was correlated with PWT (0.20; 0.20) and RWT (0.14; 0.14) in whites, and in African–Americans, INS (0.12; 0.15) and GLUC (−0.12; −0.10) were correlated with PWT. SBP was significantly correlated with four ECHO variables in whites (LVMI, 0.18; 0.20; LVID, 0.13; 0.15; PWT, 0.21; 0.21; PP/SV, 0.30; 0.31) and in African-Americans SBP (LVMI, 0.32; 0.32; LVID, 0.18; 0.18; PWT, 0.33; 0.33; RWT, 0.17; 0.18; PP/SV, 0.35; 0.31; MWS, −0.18; −0.19) and DBP (LVMI, 0.29; 0.25; PWT, 0.19; 0.20; RWT, 0.12; 0.13; ARD, 0.13; 0.13; PP/SV, 0.21; 0.18; MWS, −0.15; −0.17) were correlated with six ECHO variables. High correlations were observed between BMI–INS, SBP–DBP, and among BMI, GLUC, INS, HDLC, and triglycerides. Glucose was negatively correlated because of the inverse transformation performed (see Methods). Among the ECHO variables, high correlations were observed between LVMI–LVID, LVMI–PWT, LVID–RWT, and PWT–RWT. HR was weakly correlated with INS in all models but with a correlation coefficient of not more than 0.2. These observed phenotypic correlations served as the foundation of the factor structures derived in the factor analysis.

Factor analysis with varimax rotation, and with or without diabetes mellitus, in general showed similar factor patterns across ethnicities. (Table 3). Of the 15 original MetS and ECHO variables, five latent factors were identified that were labeled 'LV wall thickness', 'LV geometry,' 'BMI–INS', 'lipid–INS', and 'BP'. The 'LV wall thickness' factor was composed of PWT, RWT, LVMI, and negative MWS contributions, and explained about 15% of the original variance. The 'LV geometry' factor, represented by LVMI, LVID, and negative contributions of RWT, had the second highest proportion (about 12%) of the variance explained. The 'BMI–INS' factor, including high loadings of BMI and INS, explained about 8% of the overall variance including 12% in African–Americans without diabetes. The 'BP' factor explained about 11% of the original variance across all groups. The 'lipid–INS' factor, which primarily included triglycerides, HDLC,

Table 2 Correlation matrix of the variables included in factor analysis

	BMI	GLUC	INS	SBP	DBP	HDLC	Triglycerides	HR	LVMI	LVID	PWT	RWT	ARD	PP/SV	MWS
Whites, lower triangle, all data ($n=1133$)	Whites, upper triangle, all data excluding diabetes mellitus ($n=1034$)														
BMI		−0.25§	0.57§	0.23§	0.09†	−0.24§	0.23§	0.08*	0.06	0.28§	0.25§	0.07*	0.16§	0.03	−0.11†
GLUC	−0.26§		−0.31§	−0.15§	−0.09†	0.18§	−0.19§	−0.19§	−0.003	−0.05	−0.05	−0.03	−0.03	−0.03	0.01
INS	0.55§	−0.31§		0.21§	0.12§	−0.36§	0.37§	0.20§	0.02	0.08†	0.20§	0.14§	0.09†	0.11†	−0.10†
SBP	0.24§	−0.16§	0.21§		0.69§	−0.04	0.14§	0.07*	0.20§	0.15§	0.21§	0.09†	0.06*	0.31§	−0.10†
DBP	0.07*	−0.07*	0.10†	0.68§		0.04	0.08†	0.11†	0.11†	0.05*	0.11†	0.08*	0.12§	0.06	−0.03
HDLC	−0.24§	0.22§	−0.36§	−0.01	0.03		−0.48§	−0.02	−0.03	−0.08*	−0.09†	−0.05	−0.10†	0.01	0.04
Triglycerides	0.22§	−0.26§	0.37§	0.15§	0.08*	−0.50§		0.10†	−0.006	0.01	0.08*	0.08*	0.05	0.11†	−0.06*
HR	0.08*	−0.22§	0.21§	0.07*	0.11†	−0.03	0.10†		−0.10†	−0.17§	0.05	0.15§	0.01	0.16§	−0.13§
LVMI	0.05	−0.01	0.01	0.18§	0.10†	−0.03	−0.01	−0.10†		0.61§	0.65§	0.19§	0.17§	−0.02	−0.34§
LVID	0.27§	−0.04	0.08†	0.13§	0.04	−0.07*	0.01	−0.18§	0.61§		0.09†	−0.51§	0.27§	−0.18§	−0.10†
PWT	0.25§	−0.08†	0.20§	0.21§	0.10†	−0.10†	0.08†	0.05	0.64§	0.09†		0.78§	0.15§	0.08†	−0.39§
RWT	0.07*	−0.05	0.14§	0.10†	0.07*	−0.05	0.08*	0.16§	0.17§	−0.52§	0.78§		−0.03	0.17§	−0.28§
ARD	0.15§	−0.02	0.09†	0.05	0.11†	−0.10†	0.05	0.01	0.16§	0.26§	0.14§	−0.03		−0.16§	−0.01
PP/SV	0.03	−0.05	0.10†	0.30§	0.05	−0.01	0.12§	0.17§	−0.01	−0.18§	0.10†	0.20§	−0.16§		−0.18§
MWS	−0.11†	0.04	−0.09†	−0.10†	−0.04	0.04	−0.06*	−0.14§	−0.34§	−0.11†	−0.38§	−0.27§	−0.01	−0.18§	
African–Americans, lower triangle, all data ($n=1393$)	African–Americans, upper triangle, all data excluding ($n=1152$)														
BMI		−0.32§	0.54§	0.18§	−0.03	−0.26§	0.17§	0.05	0.04	0.36§	0.30§	0.03	0.19§	−0.14§	−0.10†
GLUC	−0.29§		−0.44§	−0.09†	0.01	0.25§	−0.27§	−0.11†	0.01	−0.08†	−0.10†	−0.04	−0.09†	0.04	0.05
INS	0.51§	−0.37§		0.06*	−0.06*	−0.39§	0.35§	0.17§	−0.08†	0.09†	0.15§	0.08†	0.10†	−0.08†	−0.05
SBP	0.17§	−0.13§	0.03		0.75§	0.02	0.09†	0.09†	0.32§	0.18§	0.33§	0.18§	0.07*	0.31§	−0.19§
DBP	−0.04	−0.02	−0.07†	0.75§		0.08†	0.04	0.13§	0.25§	0.09†	0.20§	0.13§	0.13§	0.18§	−0.17§
HDLC	−0.24§	0.24§	−0.35§	0.03	0.08†		−0.38§	−0.02	0.04	−0.02	−0.08†	−0.05	−0.04	0.01	0.06*
Triglycerides	0.17§	−0.29§	0.33§	0.07†	0.03	−0.42§		−0.13§	−0.05	0.01	0.03	0.02	0.05	0.01	−0.01
HR	0.06*	−0.19§	0.18§	0.09†	0.13§	−0.06*	0.16§		−0.12§	−0.14§	0.03	0.09†	0.06	0.17§	−0.13§
LVMI	0.04	−0.02	−0.07†	0.32§	0.23§	0.02	−0.02	−0.11§		0.63§	0.70§	0.22§	0.25§	−0.01	−0.48§
LVID	0.35§	−0.09†	−0.10†	0.18§	0.07†	−0.03	0.05	−0.12§	0.64§		0.21§	−0.46§	0.34§	−0.19§	−0.19§
PWT	0.29§	−0.12§	0.12§	0.33§	0.19§	−0.07†	0.03	0.02	0.70§	0.21§		0.75§	0.20§	0.03	−0.50§
RWT	0.03	−0.05	0.05	0.17§	0.12§	−0.04	−0.002	0.08†	0.20§	−0.47§	0.75§		−0.04	0.15§	−0.32§
ARD	0.18§	−0.07†	0.08†	0.07†	0.13§	−0.004	0.05	0.06*	0.23§	0.32§	0.19§	−0.04		−0.17§	−0.11†
PP/SV	−0.12§	−0.03	−0.07†	0.35§	0.21§	0.03	0.01	0.16§	0.01	−0.17§	0.05*	0.16§	−0.18§		−0.15§
MWS	−0.09†	0.07†	−0.06*	−0.18§	−0.15§	0.07†	−0.03	−0.13§	−0.47§	−0.21§	−0.49§	−0.30§	−0.11†	−0.17§	

ARD, aortic root diameter; DBP, medication-adjusted diastolic blood pressure; GLUC, glucose; HDLC, high-density lipoprotein cholesterol; HR, heart rate; INS, insulin; LVID, left ventricle internal diastolic dimension; LVMI, left ventricle mass index; MWS, left ventricle midwall shortening; PP/SV, arterial stiffness as pulse pressure over stroke volume; PWT, diastolic posterior wall thickness; RWT, diastolic relative wall thickness; SBP, medication adjusted systolic blood pressure. *$P<0.05$. †$P<0.01$. §$P<0.0001$.

and INS, explained about 9% of the original variables variance.

In analyses without rotation of factors, 'LV wall thickness' explained about 14–15% of the original variance of the 15 variables (Table 4), and the latent factors 'BP' and 'LV geometry' were combined in whites into a new MetS–ECHO factor. This 'BP–LV geometry' factor, which captured high loadings of SBP and LVID and moderate loadings of DBP and LVMI, explained 13% of the original variance. A third factor was 'BP–LV dimension-wall thickness', which had a high loading of SBP and LVID, moderate loadings of DBP and RWT, and a lower contribution of PP/SV, together explained 11% of the original variance. In both ethnicities, the fourth factor 'BMI–INS' was composed of obesity (BMI) and INS (GLUC, INS) domains but with a slight difference. Whites had an additional contribution from the lipids domain (HDLC and triglycerides), whereas in African–Americans, LVMI had a negative loading

Table 3 Loadings, sums of squared loadings, and proportion variability explained by factor domains (all subjects, varimax rotation)

Factor domains	Samples	BMI	GLUC	INS	SBP	DBP	HDLC	Triglycerides	HR	LVMI	LVID	PWT	RWT	ARD	PP/SV	MWS	SS L.[a]	P. Var.[b]
LV wall thickness	White									0.64		0.97	0.82	0.10		−0.38	2.21	0.15
	African–American				0.12					0.51	−0.15	0.92	0.91			−0.43	2.17	0.14
LV geometry	White	0.14							−0.20	0.63	0.99		−0.55	0.24	−0.20	−0.10	1.85	0.12
	African–American	0.23			0.18				−0.12	0.76	0.98	0.33	−0.36	0.32	−0.14	−0.29	2.08	0.14
BP	White		−0.10		0.98	0.68									0.32		1.58	0.11
	African–American				0.96	0.76				0.17		0.13	0.12		0.40		1.76	0.12
Lipid–INS	White	0.25	−0.35	0.49			−0.67	0.73	0.16								1.45	0.10
	African–American	0.31	−0.47	0.57			−0.58	0.64	0.28							−0.10	1.50	0.10
BMI–INS	White	0.87	−0.19	0.48	0.15					−0.12	0.13	0.15		0.12			1.13	0.08
	African–American	0.81	−0.16	0.38	0.17					−0.17	0.16	0.18		0.14	−0.12		0.99	0.07

ARD, aortic root diameter; DBP, medication-adjusted diastolic blood pressure; GLUC, glucose; HDLC, high-density lipoprotein cholesterol; HR, heart rate; INS, insulin; LVID, left ventricle internal diastolic dimension; LVMI, left ventricle mass index; MWS, left ventricle midwall shortening; PP/SV, arterial stiffness as pulse pressure over stroke volume; PWT, diastolic posterior wall thickness; RWT, diastolic relative wall thickness; SBP, medication adjusted systolic blood pressure. [a] SS L., sum of squared loadings. [b] P. Var., proportion of the original variables variance explained from a factor.

Table 4 Loadings, sums of squared loadings, and proportion variability explained by factor domains (all subjects, no rotation)

Factor Domains	Samples	BMI	GLUC	INS	SBP	DBP	HDLC	Triglycerides	HR	LVMI	LVID	PWT	RWT	ARD	PP/SV	MWS	SSL.[a]	P. Var.[a]
LV wall thickness	White	0.20		0.17			−0.10			0.59		0.96	0.82	0.12		−0.38	2.19	0.15
	African–American	0.20		0.10						0.54		0.93	0.82	0.13		−0.43	2.09	0.14
BP–LV geometry	White	0.33	−0.14	0.19	0.75	0.47		0.11		0.53	0.75	0.20	−0.28	0.20		−0.14	2.01	0.13
LV geometry	African–American	0.35		0.10	0.18				−0.12	0.64	1.00	0.21	−0.47	0.32	−0.17	−0.21	2.05	0.14
BP–LV dimension wall thickness	White				0.66	0.49		0.11	0.19	−0.33	−0.66		0.47	−0.16	0.37		1.67	0.11
BP	African–American	0.11	−0.12		0.98	0.75			0.12	0.22		0.31	0.28		0.39	−0.15	1.97	0.13
BMI–INS	White	0.63	−0.38	0.70			−0.46	0.45	0.22	−0.26							1.59	0.11
	African–American	0.77	−0.35	0.61		−0.16	−0.33	0.28	0.16	−0.38					−0.12	0.11	1.49	0.10

ARD, aortic root diameter; DBP, medication-adjusted diastolic blood pressure; GLUC, glucose; HDLC, high-density lipoprotein cholesterol; HR, heart rate; INS, insulin; LVID, left ventricle internal diastolic dimension; LVMI, left ventricle mass index; MWS, left ventricle midwall shortening; PP/SV, arterial stiffness as pulse pressure over stroke volume; PWT, diastolic posterior wall thickness; RWT, diastolic relative wall thickness; SBP, medication adjusted systolic blood pressure. [a] SS L., sum of squared loadings; P. Var., proportion variance of the original variables explained by factor domains.

(borderline at 0.4). These factors explained, respectively, 11 and 10% of the original variance. Similar factors were found in participants without diabetes mellitus (results not shown).

Finally, Table 5 summarizes the proportion of the original variance explained by each factor and each factor's additive genetic heritability. The heritability coefficients were highest for factor 'BMI–INS' (37–53%) and lowest for 'BP' (15–27%). ECHO factors 'LV wall thickness' and 'LV geometry' had moderate (30–40%) heritability, with a trend for lower heritability for 'LV wall thickness' in African–Americans. The combined MetS–ECHO factors present in whites showed heritability in the range of 18–38%. Latent factors explained 50–57% of the 15 original risk factors variance.

Discussion

Our study investigated the associations among MetS and cardiac phenotypes simultaneously for the first time in the HyperGEN study through an exploratory factor analysis. We identified several latent patterns that reduce the complexity of a large number of phenotypes. Of the latent factors found, three of them ('BMI–INS', 'BP' and 'lipid–INS') were similar to those reported previously in different study populations [26,32–35].

Factor analysis with varimax rotation explained 54–56% of the original variance in whites and 51–57% in African–Americans (Table 5). Similarly, in the analysis without rotation, variance explained was only slightly reduced to 50% and 51–52% of the original variances in whites and African–Americans, respectively.

Kraja *et al.* [26] utilized the full samples of the HyperGEN study and showed that the prevalence of MetS as defined by the ATP-III criteria was 34% in African–Americans and 39% in whites. Also, they found that MetS topology had a predominance of obesity, hypertension, and dyslipidemia. The higher prevalence of MetS in this

Table 5 Proportion of the original variance explained by factor domains and their heritability estimates

		Varimax rotation				No rotation			
		Whites		African–Americans		Whites		African–Americans	
Domain	Factor	All Prop. Var.; h^2	−Diabetes mellitus Prop. Var.; h^2	All Prop. Var.; h^2	−Diabetes mellitus Prop. Var.; h^2	All Prop. Var.; h^2	−Diabetes mellitus Prop. Var.; h^2	All Prop. Var.; h^2	−Diabetes mellitus Prop. Var.; h^2
ECHO	LV wall thickness	15; 40 ± 6[a]	15; 40 ± 7	14; 5 ± 3	15; 18 ± 5	15; 39 ± 7	15; 39 ± 7	14; 0	14; 14 ± 4
	LV geometry	12; 34 ± 6	12; 33 ± 6	14; 37 ± 6	13; 34 ± 7			14; 38 ± 6	14; 34 ± 7
MetS	BMI–INS	8; 47 ± 7	8; 37 ± 7	7; 46 ± 7	12; 47 ± 9	11; 37 ± 6	11; 35 ± 6	10; 53 ± 8	11; 45 ± 9
	Lipid–INS	10; 40 ± 6	8; 47 ± 7	10; 35 ± 7					
	BP	11; 15 ± 3	11; 26 ± 6	12; 24 ± 5	11; 19 ± 5			13; 27 ± 5	13; 23 ± 5
MetS–ECHO	BP–LV geometry					13; 18 ± 4	14; 19 ± 5		
	BP–LV dimension wall thickness					11; 29 ± 5	11; 38 ± 7		
	Total proportion of Variance	56	54	57	52	50	50	51	52

BP, blood pressure; ECHO, echocardiography; INS, insulin; LV, left ventricle; MetS, metabolic syndrome. [a] Proportion of the original variance explained ± SD, by factor domains and the heritabilities are expressed in percentage.

study population than in the general US population can be explained by the ascertainment of the original HyperGEN network for hypertension [9]. Regardless of ethnicity, in our study samples, participants with MetS were older and had higher BMI, GLUC, INS, SBP, DBP, and triglycerides levels and lower HDLC levels. MetS participants also had a larger LVMI, LV dimension, thicker walls, and stiffer vessels, in agreement with previous findings [16,17,20].

The current study identified two cardiac factor domains, 'LV wall thickness' and 'LV geometry', which had the highest proportion of variances explained. These findings suggest that of all 15 risk factors, those contributing to LV wall thickness and LV geometry, were important in the latent factors created.

Of special interest in the current study was the discovery of MetS–ECHO factor domains, 'BP–LV geometry', and 'BP–LV dimension-wall thickness' in whites. These factors were not found under the varimax rotation factor analysis because applying such an orthogonal rotation made the derived factors more independent. The variables that loaded most strongly into these two factors were SBP and LVID, followed by either DBP and LVMI or DBP and RWT, respectively for 'BP–LV geometry' or 'BP–LV dimension-wall thickness'. LVMI, LVID, and RWT are useful measurements in assessing LV hypertrophy (LVH), a manifestation of preclinical cardiovascular disease with 18–78% prevalence in hypertensive patients [36–38]. It is known that the prevalence of MetS and LVH is higher in African–Americans. Our study found intertwined relations between MetS and ECHO phenotypes in the African–American sample. The fact that BP was correlated significantly with cardiac traits in our study is consistent with results in the Strong Heart Study. Chinali *et al.* [39] reported BP to be the only MetS risk factor that was associated with LV geometric alterations. Our finding on the association between BP and LVMI agrees with the results from Gardin *et al.* [40] and Fox *et al.* [41].

Inclusion or exclusion of subjects with diabetes mellitus had no important effect on the factor structures. A negligible effect of diabetes mellitus on MetS factor patterns was also reported in previous studies on the same study network and on Pima Indians [26,32].

Our findings of four to five factor models offer further insight for understanding the relationship among MetS and ECHO variables. In addition, the heritability coefficients of the factors showed that several of the identified latent variables might be good candidates for genetic linkage and association analyses due to the moderate to high heritability. Although these results are interesting, our study has a limitation in the recruitment of the original study population. The HyperGEN network was originally ascertained for hypertensive probands and their families. Such a background for these participants may limit the generality of this study's results to the entire adult population. In addition, although we addressed the confounding effect of medications on BP measurements (by medication adjustment of SBP and DBP), the same was not performed for patients with diabetes and dyslipidemia. If participants were treated for diabetes and/or given lipid-lowering medications, then their GLUC, INS, HDL, or triglyceride measurements were confounded by medication. It should also be noted that BP-independent effects of drugs on ECHO parameters and side effects on glucose and lipids might exist.

The results of the current study provide empirical insight into the relationship among MetS and cardiovascular traits. In addition to its specific results, our study also presents a methodological paper showing a way to derive factor scores in a multifactorial analysis. Future studies will need to determine whether these factor analysis structures replicate in different (e.g. healthy) populations. Further, as the derived factors capture intercorrelation among variables, they provide greater power that can be utilized in linkage and association analyses to discover the potential genetic foundation of these traits.

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