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Factor Relationships of Metabolic Syndrome and Echocardiographic Phenotypes in the HyperGEN Study

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Abstract

Metabolic Syndrome (MetS) and its risk factors are predictors of cardiovascular events. MetS is also directly associated with echocardiographic (ECHO) phenotypes. The current study is the first to investigate factors associated with both MetS risk factors and echocardiographic phenotypes and to assess their heritability. Multivariate factor analysis (FA) was performed on 15 traits in 1,393 African Americans and 1,133 Caucasians, as well as stratified by type 2 diabetes mellitus (DM) status. FA with Varimax rotation established four to five latent factors across ethnicities and DM stratifications. Among MetS risk factors, BP was most highly correlated with cardiac traits. The factor domains, ordered by the proportion of variance explained, were “LV wall thickness,” “LV geometry,” “BP,” “body mass index-insulin,” and “lipid-insulin.” FA without any rotation identified special (cross domain) MetS-ECHO factors, “BP-LV geometry” and “BP-LV dimension-wall thickness” in Caucasians. Of the total original risk factors variance, 50%–57% of it was explained by the latent factors. Heritabilities were highest for body mass index-insulin (37–53%), lowest for “BP” factors (15–27%) and intermediate for MetS-ECHO factors. These identified latent factors can be utilized as summary phenotypes in epidemiological, linkage and association studies.

Keywords

Metabolic syndrome; echocardiography; heritability; factor analysis

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INTRODUCTION

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

MetS not only predicts CVD, but it also associates with abnormal structural and dimensional cardiovascular traits. For example, it was shown that patients with MetS have higher ventricular wall thickness than their healthy counterparts.[16–19] Left ventricular dimension and mass, which can be clinically assessed by echocardiography, a non-invasive ultrasound technique, are higher in the subjects 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 direct relationships among MetS risk factors and cardiac phenotypes. However, to the best of our knowledge, few data are available on multivariate relationships among MetS risk factors and echocardiographic cardiac measurements (ECHO). Although previous studies have found positive associations between MetS and cardiovascular traits, the strength of specific correlations among individual MetS risk factors and echocardiographic phenotypes is not fully clear. Hence, this study was undertaken to investigate relations among ECHO phenotypes and MetS risk factors. Utilizing factor analysis (FA) 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 NHLBI Family Blood Pressure Program (FBPP), which studies genetic aspects of high blood pressure and related conditions. Two ethnic groups, Caucasians 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 sib pairs. Questionnaires, blood samples, clinical data were and echocardiographic 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 of HyperGEN participants who underwent echocardiography, 1,547 were Caucasians, 1,996 African Americans, and 7 subjects of other ethnicities. We focused on siblings and their offspring. Within these samples, subjects with fasting time less than 8 hours, or any missing values in a full set of 15 traits studied, were excluded from the analysis. As a result, we analyzed phenotypes of 1,133 Caucasians and of 1,393 African Americans.

A participant was classified with type 2 diabetes mellitus (DM) based on 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 ≥ 126 mg/dl, with age of onset of DM ≥ 40 years.[25–26]

Echocardiography

Echocardiograms were performed by a standard protocol as described previously²⁷ using two-dimensionally (2D) guided M-mode, and Doppler measurements. Correct orientation of imaging planes and Doppler recordings was carried out according to the standard protocol. A computerized review station equipped with digitizing tablet and monitor screen overlay was used for calibration and performance of measurements. The measurements were first made by sonographers or physicians centrally trained at the Reading Center in New York and verified by highly experienced investigators, who were blinded to clinical data.[28–29]

Phenotypic Data Preparation

The 15 risk variables under investigation were fasting glucose (**GLUC**), fasting insulin (**INS**), fasting triglycerides (**TG**), 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 (LV) 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 mitral valve early filling phase and atrial filling phase peak velocities were not included in our study, because the sample size would have been significantly reduced.

The SBP and DBP of the subjects with prescribed anti-hypertensive medication were adjusted for anti-hypertensive medication(s) effect by the method described by Wu et al.[30] and applied in the HyperGEN study to obtain the pre-treatment blood pressure levels for various classes of medications.

All variables underwent appropriate distribution transformations, when deemed necessary to achieve standard normal distributions with means of zero and variances of one. The *Transreg* procedure in SAS (version 9.1.3 for Linux) was used to find the best power transformation. Log transformation was applied to INS, HDLC, TG, BMI, RWT, LVMI, PWT, and PP/SV. The inverse of squared transformation for GLUC ($1/\text{GLUC}^2$) and cubic power transformation for MWS (MWS^3) were applied in both Caucasians and African Americans. The remaining variables did not require transformation before covariate adjustments.

All 15 variables were adjusted within race and gender by regressing on age, age², age³ and field centers, and retaining only the significant terms. Stepwise regression using the *REG* procedure of SAS was used for the covariate adjustments. Age and field center effects were removed both from the means and the variances, and standardized residuals were derived. Outliers beyond ± 4 standard deviations and greater than 1 standard deviation away from the next internal data point were eliminated from the final distribution. Skewness and kurtosis less than 2 were checked and required as two important normal distribution indicators. Final standardized residuals (phenotypes), with a mean of 0 and a variance of 1, were utilized in the FA.

Statistical Analysis

FA was performed using the *FACTANAL* function of the S-PLUS v.7 software (Linux OS) with the option of the maximum likelihood estimate (MLE) method. FA was performed separately in Caucasians and African Americans. Within each ethnic group, the effects of DM were investigated by running FAs either including or excluding subjects with DM. Furthermore, the effect of Varimax rotation in FA was also explored by running FA 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 FA model with the most appropriate number of factors, we applied concurrently the following criteria. At least two risk variables in a latent factor were required with loadings of about 0.4 or greater. Because the variables were pre-standardized and normally distributed, the loadings of FA were essentially the correlation coefficients between each original variable and the latent factor. The sum of squared loadings per latent factor had to be greater than- or approximately one. In addition, the MLE model was required to be significant (p -value < 0.05). The MLE significance employed in the FA tested whether the number of latent factors selected was sufficient to explain the model. These stringent criteria of the FA ensured that significant contributions of the original variables to the latent factors were present in each FA model.

RESULTS

Among the studied subjects, in the subsample with no missing values in any of the 15 variables there were 99 Caucasians and 241 African Americans DM subjects. The Caucasians had higher TG levels. In contrast, African Americans tended to have higher BMI, GLUC, INS, blood pressure (BP), HDLC, HR, and LVMI (Table 1). Among Caucasians and African Americans, age, GLUC and TG were only slightly lower in non-diabetic individuals.

Pearson correlations among adjusted variables showed similar patterns regardless of ethnicity or the presence/absence of type 2 diabetes (Table 2). In general, MetS variables and ECHO variables correlated more strongly among themselves than between the two groups. However, several significant correlations between MetS and ECHO variables were observed with p -values < 0.0001 ; including BMI with LVID (C: 0.27; 0.28; AA: 0.35; 0.36), PWT (C: 0.25; 0.25; AA: 0.29; 0.30), and ARD (C: 0.15; 0.16; AA: 0.18; 0.19) in both ethnicities (C: Caucasian (All, -DM), AA: African American (All, -DM)). INS was correlated with PWT (C: 0.20; 0.20) and RWT (C: 0.14; 0.14) in Caucasians, and in African Americans INS (AA: 0.12; 0.15) and GLUC (AA: -0.12; -0.10) were correlated with PWT. SBP was significantly correlated with 4 ECHO variables in Caucasians (C: LVMI, 0.18; 0.20; LVID, 0.13; 0.15; PWT, 0.21; 0.21; PP/SV, 0.30; 0.31), and SBP (AA: 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 (AA: 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 6 ECHO variables in African Americans. High correlations were observed between BMI-INS, SBP-DBP, and among BMI, GLUC, INS, HDLC, and TG. Glucose was negatively correlated due to 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 no more than 0.2. These observed phenotypic correlations served as the foundations of the factor structures derived in FA.

FA with Varimax rotation showed in general similar factor patterns across ethnicities, and with or without DM (Table 3). Of the 15 original MetS and ECHO variables, five latent factors were identified which 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 of the variance explained (about 12%). The “BMI-INS” factor, including high loadings of BMI and INS, explained about 8% of the overall variance, including 12% in non-diabetic African Americans. The “BP” factor, explained about 11% of the original variance across all groups. The “Lipid-INS” factor, which included primarily TG, HDLC 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 (Tables 4) and the latent factors “BP” and “LV geometry” were combined in Caucasians 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 high loading of SBP and LVID, moderate loadings of DBP and RWT, and a lower contribution of PP/SV, together explaining 11% of the original variance. The fourth factor, in both ethnicities “BMI-INS” was composed of obesity (BMI) and INS (GLUC, INS) domains, but with a slight difference. Caucasians had an additional contribution from the lipids domain (HDL-C and TG) while in African Americans LVMI had a negative loading (borderline at 0.4). These factors explained respectively 11% and 10% of the original variance. Similar factors were found in subjects without DM (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 factors “BMI-INS” (37–53%), and lowest for “BP” (15–27%). ECHO factors “LV wall thickness” and “LV geometry” had moderate (30–40%) heritabilities with a trend for lower heritabilities for “LV wall thickness” in African Americans. The combined MetS-ECHO factors present in Caucasians showed heritabilities in 18–38% range. Latent factors explained 50–57% of the 15 original risk factors variance.

DISCUSSION

Our study investigated associations among MetS and cardiac phenotypes simultaneously for the first time in the HyperGEN study through an exploratory FA. 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]

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

Kraja et al.[26] utilized the full samples of the HyperGEN study and showed that the prevalence of the MetS as defined by the ATP-III criteria was 34% in African Americans and 39% in Caucasians. Also, they found that MetS topology had a predominance of obesity, hypertension, and dyslipidemia. The higher prevalence of MetS in this 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, subjects with MetS were older and had higher BMI, GLUC, INS, SBP, DBP, TG levels and lower HDL-C levels. MetS subjects also had 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 Caucasians. These factors were not found under the Varimax rotation FA, 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 subjects.[36–38] It is known that prevalence of MetS and LVH are higher in African Americans. Our study found intertwined relations between MetS phenotypes 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 agree with the results from Gardin et al.[40] and Fox et al. [41].

Inclusion or exclusion of subjects with DM had no important effect on the factor structures. A negligible effect of DM on MetS factor patterns was also reported in previous studies of the same study network and of 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 may be good candidates for linkage and association genetic analyses due to the moderate to high heritabilities. 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 blood pressure measurements (by medication adjustment of SBP and DBP), the same was not performed for diabetes or dyslipidemic individuals. If a participant was treated for diabetes and/or given lipid-lowering medications, then his/her glucose, insulin, HDL, or TG measurements were confounded by medication treatment. It should also be noted that blood pressure-independent effects of drugs on echo parameters and side effects on glucose and lipids may exist.

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

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Table 1
Phenotypic characteristics of participants in this study (including and excluding type 2 diabetic subjects)

No	Variables	Caucasian All	-DM [†]	African American All	-DM
	Number of subjects	1133	1034	1393	1152
	Female subjects (%)	50.13	49.52	65.47	63.98
	Age	49 ± 14 [*]	49 ± 14	46 ± 13	44 ± 13
1	BMI, Body Mass Index (kg/cm ²)	29.3 ± 5.7	29.0 ± 5.6	32.2 ± 7.5	31.8 ± 7.5
2	GLUC, Glucose (mg/dl)	101.4 ± 33.5	96.7 ± 26.4	108.4 ± 46.8	95.0 ± 16.3
3	INS, Insulin (μU/ml)	8.1 ± 7.1	7.7 ± 5.5	10.7 ± 9.2	10.0 ± 8.3
4	SBP, Medication Adjusted Systolic Blood Pressure (mm-Hg)	134.3 ± 26.4	133.1 ± 26.3	145.5 ± 28.4	142.0 ± 26.6
5	DBP, Medication Adjusted Diastolic Blood Pressure (mm-Hg)	77.8 ± 12.8	77.6 ± 12.9	84.5 ± 15.0	83.7 ± 15.1
6	HDLC, High Density Lipoprotein Cholesterol (mg/dl)	46.6 ± 13.5	46.9 ± 13.5	53.3 ± 15.1	53.5 ± 15.1
7	TG, Triglycerides (mg/dl)	166.8 ± 118.0	160.6 ± 108.9	108.2 ± 81.6	100.5 ± 59.3
8	HR, Heart Rate (beats per minute)	68.2 ± 11.0	67.8 ± 10.9	70.8 ± 12.0	69.8 ± 11.6
9	LVMI, Left Ventricle Mass Indexed to Heights ^{2/7} (g/m ^{2/7})	80.0 ± 20.0	79.3 ± 19.1	85.8 ± 22.5	84.4 ± 21.9
10	LVID, Left Ventricle Internal Diastolic Dimension (cm)	5.2 ± 0.5	5.2 ± 0.5	5.2 ± 0.5	5.2 ± 0.5
11	PWT, Diastolic posterior wall thickness (cm)	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
12	RWT, Diastolic Relative Wall Thickness	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
13	ARD, Aortic Root Diameter (cm)	3.4 ± 0.4	3.4 ± 0.4	3.3 ± 0.4	3.3 ± 0.4
14	PP/SV, Arterial Stiffness as Pulse Pressure Over Stroke Volume	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
15	MWS, Left Ventricle Midwall Shortening (%)	18.0 ± 2.3	18.1 ± 2.2	17.3 ± 2.4	17.5 ± 2.4

^{*} Mean ± standard deviation;

[†] -DM, excluding type 2 diabetes mellitus subjects

Table 2
Correlation matrix of the variables included in factor analysis

Caucasians, Upper Triangle, All Data Excluding DM (n=1034)															
	BMI	GLUC	INS	SBP	DBP	HDLC	TG	HR	LVMI	LVID	PWT	RWT	ARD	PP/SV	MWS
BMI															
GLUC	-0.26 [§]		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 [†]
INS	0.55 [§]	-0.31 [§]		-0.15 [§]	-0.09 [†]	0.18 [§]	-0.19 [§]	-0.19 [§]	-0.003	-0.05	-0.05	-0.03	-0.03	-0.03	0.001
SBP	0.24 [§]	-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 [†]
DBP	0.07 [*]	-0.07 [*]	0.10 [†]	0.68 [§]	0.69 [§]	-0.004	0.14 [§]	0.07 [*]	0.20 [§]	0.15 [§]	0.21 [§]	0.09 [†]	0.06 [*]	0.31 [§]	-0.10 [†]
HDLC	-0.24 [§]	0.22 [§]	-0.36 [§]	-0.01	0.03	0.04	0.08 [†]	0.11 [†]	0.11 [†]	0.05 [*]	0.11 [†]	0.08 [*]	0.12 [§]	0.06	-0.03
TG	0.22 [§]	-0.26 [§]	0.37 [§]	0.15 [§]	0.08 [*]	-0.50 [§]	-0.48 [§]	-0.02	-0.03	-0.08 [*]	-0.09 [†]	-0.05	-0.10 [†]	0.01	0.04
HR	0.08 [*]	-0.22 [§]	0.21 [§]	0.07 [*]	0.11 [†]	-0.03	0.10 [†]	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 [†]	0.09 [†]	-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 [§]		0.78 [§]	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 [§]			-0.03	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, Upper Triangle, All Data Excluding DM (n=1152)															
	BMI	GLUC	INS	SBP	DBP	HDLC	TG	HR	LVMI	LVID	PWT	RWT	ARD	PP/SV	MWS
BMI															
GLUC	-0.29 [§]		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 [†]
INS	0.51 [§]	-0.37 [§]		-0.09 [†]	0.01	0.25 [§]	-0.27 [§]	-0.11 [†]	0.01	-0.08 [†]	-0.10 [†]	-0.04	-0.09 [†]	0.04	0.05
SBP	0.17 [§]	-0.13 [§]	0.03	0.06 [*]	-0.06 [*]	-0.39 [§]	0.35 [§]	0.17 [§]	-0.08 [†]	0.09 [†]	0.15 [§]	0.08 [†]	0.10 [†]	-0.08 [†]	-0.05
DBP	-0.04	-0.02	-0.07 [†]	0.75 [§]	0.75 [§]	0.02	0.09 [†]	0.09 [†]	0.32 [§]	0.18 [§]	0.33 [§]	0.18 [§]	0.07 [*]	0.31 [§]	-0.19 [§]
HDLC	-0.24 [§]	0.24 [§]	-0.35 [§]	0.03	0.08 [†]	0.08 [†]	0.04	0.13 [§]	0.25 [§]	0.09 [†]	0.20 [§]	0.13 [§]	0.13 [§]	0.18 [§]	-0.17 [§]
TG	0.17 [§]	-0.29 [§]	0.33 [§]	0.07 [†]	0.03	-0.42 [§]		-0.02	0.04	-0.02	-0.08 [†]	-0.05	-0.004	0.01	0.06 [*]
HR	0.06 [*]	-0.19 [§]	0.18 [§]	0.09 [†]	0.13 [§]	-0.06 [*]	0.16 [§]	-0.13 [§]	-0.05	0.01	0.03	0.02	0.05	0.01	-0.01
LVMI	0.04	-0.02	-0.07 [†]	0.32 [§]	0.23 [§]	0.02	-0.02	-0.11 [§]	-0.12 [§]	0.63 [§]	0.70 [§]	0.22 [§]	0.25 [§]	0.17 [§]	-0.13 [§]
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 [§]

Caucasians, Upper Triangle, All Data Excluding DM (n=1034)													
	BMI	GLUC	INS	SBP	DBP	HDLC	TG	HR	LVMH	LVID	PWT	RWT	ARD
PWT	0.29§	-0.12§	0.12§	0.33§	0.19§	-0.07‡	0.03	0.002	0.70§	0.21§		0.75§	0.20§
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
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	
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§
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‡

* p<0.05

‡ p<0.01

§ p<0.0001

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	TG	HR	LVMI	LVID	PWT	RWT	ARD	PP/SV	MWS	SSL,*	P. Var.**
LV wall thickness	Caucasian									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	Caucasian	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	Caucasian		-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	Caucasian	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	Caucasian	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

* SSL.-Sum of squared loadings;
** 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	TG	HR	LVMI	LVID	PWT	RWT	ARD	PP/SV	MWS	SSL,*	P. Var.*
LV wall thickness	Caucasian	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	Caucasian	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	0.19	0.64	1.00	0.21	−0.47	0.32	−0.17	−0.21	2.05	0.14
BP-LV dimension wall thickness	Caucasian				0.66	0.49		0.11	0.12	−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	Caucasian	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

* SSL.-Sum of squared loadings; P. Var.-Proportion variance of the original variables explained by factor domains

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

DOMAIN	FACTOR	VARIMAX ROTATION				NO ROTATION			
		CAUCASIANS		AFRICAN AMERICANS		CAUCASIANS		AFRICAN AMERICANS	
		ALL	-DM	ALL	-DM	ALL	-DM	ALL	-DM
		Prop. Var., h ²	Prop. Var., h ²	Prop. Var., h ²	Prop. Var., h ²	Prop. Var., h ²	Prop. Var., h ²	Prop. Var., h ²	Prop. Var., h ²
ECHO	LV wall thickness	15; 40 ± 6 *	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
	Lipids-INS	10; 40 ± 6	8; 47 ± 7	10; 35 ± 7					
Mets-ECHO	BP	11; 15 ± 3	11; 26 ± 6	12; 24 ± 5	11; 19 ± 5			13; 27 ± 5	13; 23 ± 5
	BP-LV geometry					13; 18 ± 4	14; 19 ± 5		
	BP-LV dimension					11; 29 ± 5	11; 38 ± 7		
	wall thickness								
	Total Proportion of Variance	56	54	57	52	50	50	51	52

* Proportion of the original variance explained ± standard deviation, by factor domains and the heritabilities are expressed in percent

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