Published in final edited form as:

J Hypertens. 2016 January ; 34(1): 88–96. doi:10.1097/HJH.0000000000000765.

Genetic Association of Left Ventricular Mass Assessed by M-mode and 2D Echocardiography

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Abstract

Background—Left ventricular (LV) mass offers prognostic information for assessing cardiovascular disease (CVD) risk. M-mode and two-dimensional (2D) echocardiographically-derived LV mass values have shown high accuracy and reproducibility; however, no studies to date have compared LV mass genetic association findings based on both methods. The aim of this study was to compare associations of single nucleotide polymorphisms (SNPs) from genome-wide association study (GWAS) analyses of LV mass using both methods in the same cohort.

Methods and Results—LV mass was determined using 2D and M-mode echocardiography in 711 subjects (390 women); SNP genotype data was obtained using the Genome-wide Human SNP Array 6.0. GWAS analyses were performed to obtain panels of SNPs associated with LV mass and LV mass index. The un-indexed LV mass showed excellent agreement (M-mode: 170±47g vs. 2D: 178±56g, Intraclass Correlation Coefficient 0.929 [95% confidence interval: 0.932, 0.909]). The presence of LVH based on M-mode and 2D-derived LV mass index values showed moderate agreement ($kappa=0.49$). Eleven SNPs showed suggestive association in at least two of four LV mass traits, with one SNP in CDH13 common to all four derived traits.

Conclusions—M-mode and 2D echocardiography LV mass measurements in the same cohort identified suggestive genetic associations, both shared and unshared, suggesting common LV mass biology underlying the two measures of LV mass. The combined use of M-mode and 2D echo is a novel approach that may increase the yield of genetic association with LV mass.

Keywords

Left Ventricular Hypertrophy; Genome Wide Association Studies; GWAS; Echocardiography

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Conflict of Interest

All the authors declare no conflict of interest

Introduction

Left ventricular hypertrophy (LVH), although initially a compensatory response by the heart to increases in cardiac afterload (i.e., hypertension), frequently becomes maladaptive over time, contributing to left ventricular diastolic and systolic dysfunction, symptomatic heart failure, and cardiovascular death. LVH is a strong independent predictor of increased cardiovascular morbidity and mortality; regression of LVH is associated with a favorable prognosis [1, 2].

Echocardiography, the most commonly used imaging modality to assess LV mass, has been shown to reliably characterize LV mass and its use has been extensively validated in clinical care and in research [3, 4]. M-mode and 2D echocardiography are two imaging modalities used to estimate LV mass; adequate methodological standardization exists for both methods [3]. However, the two methods differ in the way images are obtained and in the geometric assumptions used for calculation: while M-mode has better spatial and temporal resolution and reproducibility, it relies on a single dimension. Furthermore, the geometric assumptions used for calculation may not be valid in subjects with significant cardiac pathology (e.g., systolic dysfunction, apical myocardial infarction). The 2D-derived LV mass method has largely supplanted the M-mode derived method in clinical practice due to the need for fewer assumptions related to LV geometry although relatively fewer published normative and prognostic studies are available. Furthermore, the advantages with 2D imaging may come at a cost of lower resolution, which may contribute to missing data and higher measurement variability in subjects with poor acoustic windows [5].

Most epidemiologic studies, and in particular genetic epidemiology studies, have used M-mode for LV mass determination due to its technical feasibility and greater availability, particularly when using data from older longitudinal studies. Although the two imaging modalities are supposed to measure the same anatomic characteristic and have been found to be comparable in some studies [6, 7], others have reported that M-mode overestimates LV mass by approximately 23 g compared to 2D-derived methods [8]. Furthermore, because LV mass is inherently determined by body size, it is common practice to “index” LV mass by some metric representing body size [9]. Adequate indexing is a critical factor in estimating pathologic LVH and acceptable methods of indexing LV mass include division by body surface area, by height^{1.7}, or by height^{2.7} [3]. Despite indexing, normative values differ by sex [10]. To our knowledge there is no published study to date comparing genetic association using both M-mode- and 2D-derived measurements of LV mass.

Heritability estimates of LV mass range from 0.17 to 0.59 depending upon the study design and population [11]. Despite the wide range of estimates, there is robust and consistent support for the underlying genetic influences of this trait. The purpose of this study was to compare associations of SNPs from genome-wide association study (GWAS) analyses of LV mass indices calculated using both M-mode and 2D echocardiography methods. We hypothesized that there would be an overlap of genetic associations shared by both echo-derived measurements of LV mass. This GWAS used both “indexed” and “un-indexed” LV mass values obtained by two echocardiographic methods in the same cohort and, to our knowledge, is the first study to make such a comparison.

Methods

Study population

The Washington University Hypertensive Heart Disease study enrolled non-Hispanic Caucasian subjects (50% with HTN) to study the genetic determinants of hypertensive heart disease. The Washington University Human Research Protection Office approved this study and all subjects provided written informed consent. Hypertensive and normotensive subjects representing a wide-spectrum of health traits were enrolled from 2002 to 2011. Subjects were excluded from enrollment for any of the following reasons: 1) restrictive or hypertrophic cardiomyopathy, pericardial, valvular and/or congenital heart disease, 2) active malignancy, 3) age <21 or >90 years, 4) prisoners or institutionalized individuals, 5) pregnant and/or lactating women, 6) subjects unable or unwilling to provide informed consent.

Echocardiography

Echocardiographic images were acquired and interpreted by a single skilled echocardiographer using a Sequoia C512 ultrasound system (Acuson-Siemens, Mountain View, CA). LV mass was determined by two validated and well-described methods: 1) 2D-guided M-mode-derived truncated ellipsoid method (LVM-MM) which was indexed to height^{2.7} (LVMI-MM); and 2) 2D-derived area-length formula (LVM-2D) which was indexed to body surface area (LVMI-2D) [3]. The decision to index LVM-MM to height^{2.7} was based on prior reports that indexing LVM-MM by body surface area tends to underestimate the prevalence of LVH in overweight and obese subjects [3, 12, 13]. The presence of LVH was defined as greater than two standard deviations above the population mean according to published clinical standards for each imaging modality: LVMI-MM: 51 g/m^{2.7} for men and 49.5 g/m^{2.7} for women [14]; LVMI-2D: 103 g/m² for men and 89 g/m² for women [3]. LV volumes and ejection fraction were determined according to the modified Simpson's Method of Discs [3]. Measurements were reported as the average of three consecutive cardiac cycles, interpreted by an experienced sonographer. The intraclass correlation coefficients (ICC) for echocardiographic indices measured at our laboratory by two independent readers range from 0.75–0.88 for indices of LV mass.

Genotyping

Whole blood collected was in EDTA-treated vacuum containers and DNA extracted using Puregene[®] DNA isolation kit. Genotyping was performed by the Genome Technology Access Center (Department of Genetics, Washington University in St. Louis, MO, USA; <https://gtac.wustl.edu/>) using the Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA, USA). The platform includes more than 906,600 SNPs. Genotypes were assigned using Birdsuite [15] followed by extensive QC as described below.

Statistical Analysis

Data preprocessing and Quality Control—Phenotype quality control (QC) tested for distribution of the variables, check missing rates; appropriate transformations were applied where necessary. LV mass values were standardized separately within sex. Bland-Altman

plots were generated to assess for systematic bias across imaging modalities. Intraclass correlation coefficients (ICC) were obtained using **SAS** (v 9.3, Cary, NC, USA). Correlation coefficients calculated using **R**. Agreement of LVH class assignments by the two modalities was estimated using the *kappa* statistic. After removing Affymetrix internal controls and SNPs without location information, additional extensive QC was applied to the GWAS SNP data using **PLINK** [16] and other standard software as described. Individuals with problematic sex (n=8), high missing rate (>2%, n=5), and extreme heterozygosity rate (n=3), were excluded. SNPs were excluded if A) monomorphic, B) missing rate >1% when the minor allele frequency (MAF) <5%, C) missing rate >5% when MAF >5%; or D) Hardy-Weinberg p-value <10⁻⁵. Individual relatedness and population stratification was examined using the EIGENSTRAT software [17]. The final data set for GWAS analysis included 711 unrelated subjects with 828,493 SNPs.

Association analysis—We examined the distribution of each trait variable and identified outliers >4 standard deviations from the mean and set them ‘missing’ in downstream analyses to ensure that all trait variables had skewness <1.0 and kurtosis <2.0. For GWAS analysis, both LV mass index values, LVMI-MM and LVMI-2D, were adjusted for age, age² and sex; the two (unindexed) LV mass values, LVM-MM and LVM-2D, were adjusted for age, age², sex, as well as BMI (to minimize the effect directly attributable to body size). **Merlin** software [18] was used for performing association analysis. Specifically, the score test option (--fastAssoc) was used for rapidly screening very large numbers of markers. The genomic control method [19] was used to calculate the inflation factor (lambda) to identify undesirable inflation of test statistics that would require adjustment. In addition to specialized software mentioned, the statistical software **R** and packages were for used for routine data analyses and graphics (e.g., quantile-quantile [QQ] and Manhattan plots of GWAS results). Results were reported using two minor allele frequency (MAF) cutoffs (<0.05 and <0.01) and significance thresholds ranging from 10⁻³ to 10⁻⁶. Regional association plots were generated to highlight chromosomal regions with a clustering of SNPs with suggestive association using LocusZoom software, available at <http://csg.sph.umich.edu/locuszoom/>. The linkage disequilibrium (r²) was calculated from the hg19/HapMap Phase II CEU. SNPs (circles) are colored according to their level of linkage disequilibrium of each SNP with the index SNP (purple diamond) selected as the most significant SNP in the region.

Results

After phenotypic and genotypic data QC, the final dataset for association analysis consisted of 711 non-Hispanic Caucasians (321 males and 390 females). Clinical characteristics of the study subjects are provided in Table 1.

Correlation between 2D and M-mode

Measure of LVM and LVMI and other relevant indices determined by 2D and M-mode are shown in Table 2. The un-indexed LV mass measured by M-mode and 2D showed excellent agreement (170±47g vs. 178±56g, ICC=0.929 [95% confidence interval: 0.932, 0.909]). Indexed LV mass indices values are inherently different due to the different indexing

methods: for LVMI-2D: $85 \pm 19 \text{ g/m}^2$ vs. LVMI-MM: $42 \pm 12 \text{ g/m}^2$. LV mass index values showed sufficient correlation (correlation coefficient 0.7) even though the two LV masses were indexed in different manner (LVM-2D indexed to body surface area, LVM-MM indexed to height^{2.7}). For LV mass <200 g, M-mode-derived measures tend to be slightly higher than 2D; the difference becomes greater at higher LV mass values. The trend is reflected by the Bland-Altman plot as shown in Supplemental Digital Content Figure S1. The presence of LVH based on M-mode and 2D-derived LV mass index values (n=149 vs. n=167, respectively) showed moderate agreement ($\kappa=0.49$, Supplemental Digital Content Table S1).

SNP association results

SNP association analyses for LV mass indices derived using 2D and M-mode were performed on the residuals of the trait values after covariate adjustment for age, age², and sex. Using genomic controls, the inflation factors (lambdas) estimated for both phenotypes were 1.001, indicating no substantive inflation of test statistics (see quantile-quantile [QQ] plots in Supplemental Digital Content Figure S2). The Manhattan plots of GWAS results ($-\log_{10}[p]$) are shown for LVMI-MM and LVMI-2D in Supplemental Digital Content Figure S3. A cluster of suggestive associations is clearly seen on chromosome 5 for both indices in the Manhattan plots. While no SNP for either trait reached the genome-wide significance threshold of $<5 \cdot 10^{-8}$, LVMI-MM yielded a greater number of suggestive SNPs compared to those obtained by LVMI-2D. For example, using a p-value threshold 10^{-4} and MAF 0.05, analyses of LVMI-MM yielded 68 SNPs (including 25 SNPs annotated to 19 genes); whereas LVMI-2D found 63 SNPs (including 43 SNPs annotated to 9 genes) (Tables 3 and Supplemental Digital Content Table S2).

Genes with suggestive associations across measured traits and imaging modalities

Using the significance threshold p-value 10^{-4} for suggestive associations, there were 15 associated SNPs clustered in a span of 73,616 bp on chromosome 5q23.1 that were common both LVMI-MM and LVMI-2D. These SNPs are located in an intergenic region ~250 kb downstream of *LINC00992* (long intergenic non-protein coding RNA 992). This region includes a DNase I hypersensitivity site (chr5: 117785640–117785790) (<http://dnase.genome.duke.edu/index.php>) in skeletal muscle and aortic smooth muscle cells [20], which suggests this intragenic region is transcriptionally active. Besides the cluster on Chromosome 5, two other suggestive SNPs were identified in *CDH13* and one in *PTPRN2* that were shared by both LVMI-MM and LVMI-2D (Supplemental Digital Content Table S2).

Since the recommended indexing method is different for each imaging modality, GWAS was also performed using the un-indexed LV mass (adjusted for age, age², sex, and BMI) to test whether differences in indexing methods may play a role in determining the strength of the genetic association. To minimize the effect directly attributable to body size, BMI was included for covariate adjustment prior to association analyses. Manhattan plots for LVM-MM and LVM-2D are shown (Supplemental Digital Content Figure S4).

Fewer SNPs had suggestive associations with un-indexed LVM traits than with indexed LVMI traits (Table 3) (LVM-MM 7 SNPs vs. LVMI-MM 15 SNPs; LVM-2D 6 SNPs vs. LVMI-2D 9 SNPs). Genes identified as having suggestive associations with LV mass were typically unique to one imaging modality (i.e., M-mode or 2D). Furthermore, those few genes with suggestive associations shared by both LVM-MM and LVM-2D were largely distinct from those common to both LVMI-MM and LVMI-2D (Supplemental Digital Content Tables S2 and S3). The exception is one intronic SNP in *CDH13* (rs9646331) that showed suggestive associations across all four tested traits (both indexed and un-indexed LV mass for both M-mode and 2D methods). Figure 1A shows that as the number of rs9646331 rare G alleles increases, there is a trend towards increased LV mass index and LV mass as derived by both imaging modalities. Supplemental Digital Content Figures S5A and S5B show the p-values plotted across the entire *CDH13* gene (1100 SNPs, including 5000 base pairs 5' and 3' of the transcript start and stop sites) for LVMI-MM and LVMI-2D. In addition to *CDH13*, we also found significant SNPs in or adjacent to 9 other genes on chromosomes 2, 3, 4, 5, 6, 16, 17, 20 and 22 shared by both LVM-MM and LVM-2D (Supplemental Digital Content Table S3).

Genes with suggestive associations within measured traits and/or imaging modalities

Associations specific to each one of the LV mass methods were also observed (Supplemental Digital Content Table S4). For example, an intronic SNP within *MYOM1* showed strong association with both LVMI-2D and LVM-2D; mean LVMI-2D and LVM-2D are decreased with one or two copies of the minor allele (Figure 1B). Likewise, an intronic SNP in cardiac transcription factor *MYOCD* showed a decrease in mean LVMI-MM with increasing copies of the minor allele (Figure 1C). Loci with association across multiple LV mass indices may warrant prioritization for further investigation into genes that may contribute to LVH.

Discussion

The purpose of this study was to compare genetic associations of SNPs from GWAS analyses of LV mass calculated by both M-mode and 2D echocardiography. This strategy is similar to that of other investigators testing for genetic association across panels of different, yet correlated, traits (e.g., multiple blood pressure traits [21, 22], indices of obesity [23], endophenotypes for neuropsychiatric disorders [24]). As previously shown by others, LV mass measured by both methods was comparable and there was modest overlap between the two methods in terms of the number of subjects identified as having LVH. Although no genetic associations reaching genome-wide significance were identified, each LV mass method identified sets of SNPs with suggestive association in genes with potential biologic importance.

LVH is one of the most important risk factors for cardiovascular and metabolic diseases and a strong predictor of morbidity and mortality [25, 26]. M-mode and 2D echocardiography is safe, non-invasive, and widely used both clinically and in research studies for the assessment of LV structure and function. However, as technical advances have improved image quality, modern echocardiography has favored 2D methods. The reproducibility of LV mass by 2D images (using the truncated ellipsoid method) has been found to be superior to that of LVM-

MM; while intraobserver variability for LVM-2D was reported as “excellent” (similar data was not provided for LVM-MM[7]).

The data from the present study show that LV mass calculated by 2D and M-mode yielded comparable values which is in agreement with observations by our group and others [8, 27]. Pacezk, et al. showed an adequate correlation for LV mass calculated using M-mode, although with a few technical caveats: 1) Pacezk determined LVM-2D using the truncated ellipsoid formula, which differs slightly from the area-length method used in the present study; and 2) the 2D imaging technology available in our study (“harmonic imaging”) provides improved endocardial definition, which should result in higher accuracy of LV mass assessment compared to “fundamental” imaging as in Pacezk’s study [28]. Thus, the discrepancy between M-mode and 2D-derived LV mass values were more subtle in our study, particularly when LV mass was less than 200 g.

A novel aspect of our study is the comparison of the genetic association between the two imaging modalities in the same population. Our findings demonstrate a modest genetic overlap of 19 SNPs shared between the two methods, which included some genes with potential biologic relevance. Since the two indexing methods are different, we also explored the overlap of genetic variants associated with LVM-MM and LVM-2D and found a comparable number with shared suggestive associations (11 SNPs). Similar results were obtained when we considered overlap at the level of the gene rather than individual SNPs. Contrary to our hypothesis, it was surprising to find that even though the two imaging modalities (M-mode and 2D) are measuring LV mass in the same population, the genetic overlap between them was only modest. Since these measurements are based on different geometric assumptions, it is reasonable to speculate that the identified genetic variants modulate LV mass through their effects on cardiac geometry rather than LV mass *per se*, which may introduce different variance to these measurements.

A SNP in T cadherin (*CDH13*, rs9646331) was the only variant with suggestive associations common across all four measured LV mass traits. T-cadherin is widely expressed in the vasculature [29], implicating this gene in heart and vascular remodeling and angiogenesis. Genetic variants in this gene have been associated with hypertension, a key determinant of LV mass [30], as well as with adiponectin levels [31], hyperlipidemia [32], and other cardiometabolic traits [33]. A previous study found genetic association of this region with LV wall thickness [34].

When LV mass associations were compared across imaging modalities, we also found suggestive associations with 9 genes on chromosomes 2, 3, 4, 5, 6, 16, 17, 20 and 22 in addition to *CDH13*. We note that several of these genes (*INSIG2*, *HS3ST4*, *GAS7*, *TOPI1*, *GALNT15*, *PABPC4L*) were found associated with body size and lipids traits, albeit with different SNPs [35, 36]. A cluster of 11 SNPs downstream of *LINC00992* are of potential interest given their location in region predicted to be transcriptional active in tissue relevant to cardiovascular structure.

Suggestive associations were identified in genes known for their relationship with LV mass and LV hypertrophy. SNPs in *MYOM1* (myomesin 1), whose product contributes to

structural sarcomeric M-bands, have shown suggestive association with blood pressure [37]. Missense mutations in *MYOM1* have been identified in patients with familial hypertrophic cardiomyopathy, a disease histologically characterized by disorganized sarcomeres [38]. *MYOCD* (myocardin) is a smooth and cardiac muscle-specific transcriptional coactivator key for initiating and maintaining muscle differentiation and proliferation. In murine models, *MYOCD* has been shown to mimic other hypertrophic signals and induce cardiac hypertrophy and the fetal cardiac gene program [39]. It is interesting to note that the suggestive association of *MYOM1* was with 2D-derived LV mass indices, whereas that with *MYOCD* was with M-mode-derived LV mass indices. Given that both genes have strong biologic plausibility for involvement in modulating cardiac hypertrophy, one may conclude that using both methods to measure LV mass may increase enhance discovery, and thus this may represent a novel strategy to identify genetic association with LV mass.

Additional suggestive genetic associations with LVM-MM and LVMI-MM included 3 SNPs upstream of *GBE1*. The association with *GBE1* is notable because defects in its product (1,4-alpha-glucan branching enzyme), results in glycogen storage disease that is associated with dilated and hypertrophic cardiomyopathies [40]. Another potentially important suggestive association includes a SNP in *PTPRN2* (protein tyrosine phosphatase, receptor type, N polypeptide 2), an autoantigen associated with insulin-dependent diabetes mellitus [41]. SNPs near *INSIG2* (insulin induced gene 2) have been associated with extreme degrees of obesity [32]. Finally, although there is scant information in the literature on *PABPC4L* (polyA binding protein, cytoplasmic 4-like, chromosome 4), its paralog *PABPC4* (chromosome 1) has been identified in GWAS as associated with the inflammatory biomarker, C-reactive protein [42], and with high-density lipoprotein cholesterol [43]. Given the association between cardiometabolic traits (including inflammation) and left ventricular mass [44], these suggestive findings of association are of interest.

LV mass can be assessed without echocardiography. Electrocardiographically determined LVH has been long associated with cardiovascular events [45] and early hypertension trials have shown regression of electrocardiographic LVH with treatment [46]. To our knowledge, only one genome-wide study identified associations with electrocardiographic indices of LVH in discovery and replications cohorts including 22,033 subjects [47]. However, since electrocardiographically determined LVH is insensitive to identify individuals with LVH, echocardiography has supplanted electrocardiography for the characterization of LV mass in clinical care and in research. Cardiac magnetic resonance image represents the “gold standard” for measuring LV mass. Yet genome-wide association studies of complex traits such as LV mass typically require large cohort sizes that would make the cost and logistic complexities of CMR imaging prohibitive.

Limitations

In the absence of cardiovascular outcomes or anatomic data to support the superiority of one imaging modality over the other, this study cannot support the preferential use of M-mode or 2D-derived measurements of LV mass for use in genetic association studies. Furthermore, the inclusion of only Caucasian-American subjects and the relatively small sample size limit the generalizability of the findings. The limited sample size precluded exploration of

alternative statistical models, such as stratification by sex, which could reveal additional associations not captured by covariate adjustment. These limitations should not negate the novelty of the present study which could potentially increase the yield of genetic association studies by combining M-mode and 2D echo methods in the assessment of LV mass.

Conclusions

Measurements of LV mass obtained by M-mode and 2D echocardiography in the same cohort identified suggested genetic associations shared by both and also unshared ones, suggesting common LV mass biology captured by both methods. Identifying SNPs associated with multiple measures of LV mass may represent a strategy for enhanced discovery in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Alan D. Waggoner for his contributions to this study. This work was supported by National Institutes of Health (NIH) Grants R01HL091028 (CCG and RB), R01HL071782 (VGD and CCG), T32HL083822 (RB), R21HL094668 (LdlF), UL1RR024992 and KL2RR024994 (Washington University), and an American Heart Association grant #0855626G (CCG). Additional support provided by NIH grant S10RR024532, a grant from the Barnes-Jewish Hospital Foundation, and a Lucille P. Markey Fellowship.

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Figure 1. Mean LV mass and LV mass index for genes showing suggestive association

1a. Mean LV mass and LV mass index for *CDH13* SNP rs9646331 by genotype. CC; homozygous CC subjects (n=557); CG; heterozygous subjects (n=144); GG; homozygous GG subjects (n=10). Numbers in brackets indicate number of subjects with genotype.

1b. Mean LV mass and LV mass index for *MYOM1* SNP rs9548298 by genotype. TT; homozygous TT subjects (n=464); TG; heterozygous subjects (n=223); GG; homozygous GG subjects (n=24). Numbers in brackets indicate number of subjects with genotype.

1c. Mean LV mass and LV mass index for *MYOCD* SNP rs12946954 by genotype. TT ; homozygous TT subjects (n=243); TA; heterozygous subjects (n=319); AA; homozygous AA subjects (n=149). Numbers in brackets indicate number of subjects with genotype.

Table 1

Clinical characteristics of study population.

	Males (n=321)	Females (n=390)	All (n=711)
Age (years)	51.8 ± 13.1	51.3 ± 12.8	51.5 ± 13.0
Height (cm)	179 ± 6	165 ± 7	171 ± 10
BMI (kg/m ²)	29.8 ± 5.4	29.8 ± 7.1	29.8 ± 6.4
Heart rate (beats/min)	64 ± 10	67 ± 11	65 ± 11
SBP (mm Hg)	126 ± 15	123 ± 18	125 ± 17
DBP (mm Hg)	81 ± 8	77 ± 9	79 ± 9
MAP (mm Hg)	96 ± 9	93 ± 11	94 ± 10
BSA (m ²)	2.1 ± 0.2	1.9 ± 0.2	2.0 ± 0.3
HTN (n,%)	160 (50%)	187 (48%)	347 (49%)
Diabetics (n,%)	53 (16.5%)	61 (15.6%)	114 (16%)
LDL (mmol/L)	2.79 ± 0.85	2.87 ± 0.82	2.84 ± 0.85
HDL (mmol/L)	1.2 ± 0.36	1.55 ± 0.41	1.39 ± 0.41
TC (mmol/L)	4.76 ± 0.93	5.07 ± 0.98	4.9 ± 0.95
Triglycerides (mmol/L)	1.59 ± 1.1	1.42 ± 0.9	1.5 ± 1.0
Insulin (pmol/L)	74.3 ± 71.5	68.8 ± 61.8	71.5 ± 66.0
Glucose (mmol/L)	5.3 ± 1.31	5.16 ± 1.78	5.2 ± 1.59
Creatinine (mmol/L)	0.09 ± 0.9	0.06 ± 0.01	0.08 ± 0.07

Data are expressed as mean ± standard deviation or n (%). BMI; body mass index; DBP, diastolic blood pressure; HDL high density lipoprotein; LDL; low density lipoprotein; MAP; mean arterial pressure; SBP systolic blood pressure; TC, total cholesterol. To convert LDL, HDL and TC to mg/dL, multiply mmol/L by 38.67. To convert triglycerides to mg/dL, multiply mmol/L by 88.57.

Table 2

Echocardiography derived 2D and M-mode measurements.

	Males (n=321)	Females (n=390)	All (n=711)
2D			
LVM-2D (g)	195 (163,218)	150 (123,171)	170 (138,193)
LVMI-2D (g/m ²)	91 (78,100)	80 (67,88)	85 (73,93)
LV volume, end-diastole (mL)	109 (91,122)	82 (69,94)	94 (76,107)
LV volume, end-systole (mL)	43 (32,48)	30 (23,34)	36 (26,41)
Ejection Fraction (%)	61 (57,66)	64 (61,69)	63 (59,68)
M-mode			
LVM-MM (g)	206 (165,234)	155 (127,179)	178 (140,207)
LVMI-MM (g/m ^{2.7})	43 (35,47)	40 (32,46)	42 (34,47)
LV internal diameter, diastole (cm)	5.2 (4.9, 5.5)	4.8 (4.5,5.1)	5.0 (4.6,5.3)
Ventricular Septal Thickness, Diastole (cm)	1.0 (0.9,1.1)	0.9 (0.8,1.0)	0.9 (0.9,1.1)
Posterior Wall Thickness, Diastole (cm)	1.0 (0.9,1.1)	0.9 (0.8,1.0)	0.9 (0.9,1.1)

Data are expressed as mean (interquartile range).

LVM-2D, left ventricular mass determined by two-dimensional echocardiography; LVM-MM, left ventricular mass determined by M-mode echocardiography; LVMI-2D, left ventricular mass index determined by two-dimensional echocardiography; LVMI-MM, left ventricular mass index determined by M-mode echocardiography; LV volume, Left Ventricular volume.

Table 3
Single SNP analysis results for LVMI and LVM determined by 2D and M-mode and the overlap between traits.

Trait	MAF	# SNPs at P-value threshold				
		10 ⁻³	10 ⁻⁴	10 ⁻⁵	10 ⁻⁶	
Individual traits						
LVMI-MM	0.05	647	68	15	4	
	0.01	742	85	15	4	
LVMI-2D	0.05	591	63	9	0	
	0.01	689	75	9	0	
LVM-MM	0.05	678	80	7	0	
	0.01	785	108	13	0	
LVM-2D	0.05	581	69	6	0	
	0.01	694	90	6	0	
Overlap between traits						
LVMI-MM/LMVL-2D	0.05	85	19	6	4	
	0.01	96	20	6	4	
LVMI-MM/LVM-MM	0.05	97	15	2	0	
	0.01	106	16	2	0	
LVM-MM/LVM-2D	0.05	142	11	0	0	
	0.01	184	18	0	0	
LVMI-2D/LVM-2D	0.05	178	10	0	0	
	0.01	223	14	0	0	

LVM-2D, left ventricular mass determined by two-dimensional echocardiography; LVM-MM, left ventricular mass determined by M-mode echocardiography; LVMI-2D, left ventricular mass index determined by two-dimensional echocardiography; LVMI-MM, left ventricular mass index determined by M-mode echocardiography; MAF minor allele frequency; SNPs, single nucleotide polymorphisms; Trait, outcome variable used for analysis.