HERITABILITY OF LV MASS IN JAPANESE FAMILIES LIVING IN HAWAII: the SAPPHIRe STUDY

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Heritability of LV mass in Japanese families living in Hawaii: the SAPPHIRE Study

Short Title: Heritability of LV Mass in Japanese

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Keywords: 1) hypertrophy, left ventricular 2) genetics 3) heritability 4) variance components
Abstract

Objective: Established determinants of left ventricular (LV) mass explain only a modest fraction of its variability. Family studies to date suggest that a proportion of the unexplained variability can be accounted for by additive polygenic effects. An estimate of this proportion has not been reported previously in an East Asian population. The objective of this study was to estimate the heritability of LV mass in Japanese families living in Hawaii.

Design and Methods: We analyzed data by components of variance in a sample of 169 hypertensive families (n = 476 subjects) and, separately, in a population based sample of 256 families (n = 501 subjects) participating in the Honolulu Heart Program.

Results: In multivariate models, established predictors of LV mass explained about half the total variance of LV mass. Using SOLAR, our estimates of the narrow sense heritability of LV mass ranged from 42.5% (SE 9.8, p < 0.0001) in our sample of hypertensive families to 60.6% (SE 11.7, p < 0.0001) in our population based sample of families. Parametric bootstrap analyses confirmed that the inference for each sample was appropriate.

Conclusions: Assuming the absence of shared familial environmental effects, close to half of the unexplained variance of LV mass in Japanese subjects living in Hawaii is genetic in nature. This estimate was observed in two independent samples. Therefore, the pursuit of novel genetic determinants of LV mass through either whole genome or candidate gene association studies of this population may be worthwhile. Such studies are certainly feasible.
Introduction

Left ventricular (LV) mass predicts cardiovascular morbidity and mortality well, above and beyond predictions based on other variables. In the Framingham Heart study, an increase of 50 grams per meter in LV mass corrected for height was associated with a 50 to 100 percent increase in cardiovascular events, cardiovascular mortality, sudden death, and total mortality[1, 2]. LV mass is also an independent risk factor for cardiovascular events in subjects with uncomplicated essential hypertension[3, 4].

Major determinants of LV mass in subjects with normal systolic function include age, race, blood pressure (BP), gender, body size, and valvular heart disease[5, 6]. However, in most studies, more than 50% of the variance of LV mass by echocardiography remains unexplained in fully adjusted models.

Several family studies suggest that a proportion of the unexplained variation of LV mass is determined genetically. In six non-twin studies of adults[7-12], after taking all major predictors into account, the estimated heritability of LV mass ranged from 17 to 70%. Three of these studies used a population based sample of families[7, 10, 11], while the other three used families ascertained with a hypertensive proband[8, 9] or a proband at high risk of cardiovascular disease[12]. The lowest heritability was found in American Indians (17%)[7], while the highest heritability was found in African Americans (70%)[8]. One study of Hispanics from the Caribbean reported a heritability of 49%[12]. In four separate studies of Caucasians, the heritability ranged from 23 to 32% [8] [9, 10].
To date, the heritability of LV mass in an East Asian population has not been reported. Accordingly, the purpose of this study was to estimate the heritability in Japanese-Americans participating in the Stanford Asian and Pacific Program for Hypertension and Insulin Resistance (SAPPHIRE). SAPPHIRE is one of four networks in the National Heart, Lung, and Blood Institute’s Family Blood Pressure Program (FBPP) with a primary aim of localizing and characterizing genes contributing to the inter-individual variation in blood pressure and risk of hypertension[13].

**Methods**

**Subjects**

**Source Population**

The SAPPHIRE Network consists of three field centers with the Stanford field center encompassing the greater San Francisco Bay Area; the Hawaii field center covering the island of Oahu and outer islands; and the Taiwan field center consisting of a consortium of the three major hospitals located in Taipei and one branch hospital in Taichung. The SAPPHIRE study was approved by the institutional review board of each field center/hospital, and all participants gave written informed consent.

Phase I of recruitment began in 1995 and ended in 1999. During this time, the three field centers enrolled sib pairs that were either highly concordant or highly discordant for BP. This design was because, initially, the goal of SAPPHIRE was to establish linkage by mapping quantitative trait loci of blood pressure (BP)[14]. A total of 2677 Chinese or Japanese subjects from 747 families were examined in Phase I including 697 Japanese
subjects from 203 families through the field center in Hawaii. All families had a hypertensive proband. Families with a history of both parents being treated for hypertension were excluded. Other exclusion criteria included: treated diabetes, BMI > 35, severe kidney disease, liver cirrhosis, severe chronic and/or terminal illness, recent therapy for cancer, or recent pregnancy. Subjects who were diagnosed with diabetes as a result of SAPPHIRE testing were not excluded. More extensive details relating to Phase I recruitment and phenotyping are published elsewhere [15].

Phase II of recruitment began in 2001 and ended in 2004. By this time, the focus of the SAPPHIRE study had changed to identifying genetic determinants of insulin resistance, hypertension, and LV mass by association[16]. Throughout this phase of recruitment, only Japanese subjects through the field center in Hawaii were enrolled. These subjects were enrolled into 3 cohorts. Cohort 1 consisted of Japanese subjects examined in Phase 1 who were willing to return to clinic for a second exam. Cohort 2 consisted of relatives of cohort 1 including sibs not examined in Phase 1, as well as children, uncles, aunts, and cousins of the hypertensive proband. These relatives were invited to participate regardless of their BP, BMI, diabetic status, or renal status. Because the hypertensive status of both parents was used as an exclusion criterion in Phase 1, parents of the hypertensive proband were not invited to participate. Cohort 3 consisted of offspring of a random sample of all Japanese American men living on Oahu who participated in the Honolulu Heart Program[17] and were ≥ 20 years of age. For this cohort, we preferentially recruited families with more than one sibling willing to participate but did not select sibs on the basis of blood pressure, diabetic status, or BMI. Exclusion criteria for cohort 3
included liver cirrhosis, severe chronic and/or terminal illness, recent therapy for cancer, or recent pregnancy.

A total of 1504 subjects were recruited in Phase II including 370 subjects into Cohort 1, 144 subjects into Cohort 2, and 990 subjects into Cohort 3. Echocardiograms were performed on a subset of 356 subjects (96.2%) in Cohort 1, 130 subjects (90.3 %) in Cohort 2, and 563 subjects (56.9%) in Cohort 3.

**Study Sample**

For this study, we combined all 486 subjects with echocardiograms in Cohorts 1 and 2 into one sample of “hypertensive families” and the first 519 subjects in Cohort 3 with echocardiograms into a second independent “population based” sample of families. We subsequently excluded 2 subjects with severe MR (>2+) and 8 subjects with an EF < 50% from our sample of hypertensive families as well as 2 subjects with severe MR (>2+), 4 subjects with severe AR (>2+), 1 subject with > mild AS, and 11 subjects with an EF < 50% from our population based sample. In both samples, there were no subjects with an echocardiographic diagnosis of hypertrophic obstructive cardiomyopathy (HOCM). The final number of subjects in our sample of hypertensive families was 476 while the final number in our population based sample was 501.

**Clinical Measurements**

**Clinic Visit**

The clinic visit for all participants in Phase II included but was not limited to a detailed history of medications used, measures anthropometric and of blood pressure (BP), blood for DNA isolation and chemistries, and an oral glucose tolerance test. Trained
research assistants measured BP three times using a DINAMAP automated BP reading device in the sitting position by following a standardized protocol[18]. The average of the last 2 measurements was used in this analysis. Subjects with an average clinic systolic BP of greater than 140 mmHG systolic or greater than 90 mmHG diastolic were referred back to their primary care providers for treatment. Subjects with an average clinic systolic BP greater than 160 mmHG or an average diastolic BP > 100 mmHG received exit referrals to specialist for the treatment of hypertension but were not excluded from the study.

**Echocardiogram visit**

Subjects were scheduled for an echocardiogram which occurred sometime after the clinical exam for a large majority of subjects. The median delay from the time of the clinical visit to the echo visit was 43 days (range: -10 to 462 days) for our set of hypertensive families and 196 days (range: 29 to 808 days) for our set of population based families.

A single research sonographer performed all echocardiograms using a standardized protocol developed for the SAPPHiRe study by the FBPP core echocardiography laboratory at New York Hospital, Weill Cornell Medical College[13, 19]. All elements of the protocol were recorded on videotape. The sonographer received training, including written material and didactic as well as hands-on training at the Reading Center in New York, NY. Additionally, test tapes were sent to the reading center and feedback on echocardiographic studies was provided to monitor compliance with the protocol. All studies were read centrally at the core lab and all readers were blinded to the participant’s
clinical data. The sonographer was also formally trained on how to measure BP using an automated device.

We measured LV internal dimension (LVIDd), interventricular septal (SWTd), and posterior wall thickness (PWTd) at end-diastole by American Society of Echocardiography recommendations on 1 to 3 cardiac cycles at or just below the tips of mitral leaflets in parasternal long-axis and short-axis views[20, 21]. When optimal orientation of LV M-mode readings could not be obtained, we performed linear measurements on correctly oriented 2-dimensional images using the American Society of Echocardiography leading-edge convention[21].

We used end-diastolic LV dimensions to derive LV mass by a formula that yields values closely related ($r=0.90$) to necropsy LV weight[22]. This formula is based on modeling the LV as a prolate ellipse of revolution:

$$LV \text{ mass (grams)} = 0.8 \times \{1.04[(LVIDd + PWTd + SWTd)^3 - (LVIDd)^3]\} + 0.6$$

LV mass derived by this formula stratifies a subject's future risk of cardiovascular disease[1]. Our core echo laboratory has reported previously a very high reproducibility of LV mass measures[23].

To detect valve regurgitation or stenosis by Doppler, we used parasternal long-axis and apical views. We quantified the severity of valve dysfunction using established methods[24]. We used the Teichholz method to estimate end-diastolic and end-systolic LV volumes[25] and subsequently to derive the ejection fraction.

The sonographer obtained a single BP measure immediately after completion of the echocardiogram in the supine position. For all participants, this reading was generated by the same PROPAQ automated BP reading device stationed in the echo lab.
Statistical Analysis

Covariates of interest were those related to body size (height and BMI), to BP, and to left sided valve function on echocardiogram (mitral regurgitation or stenosis, aortic regurgitation or stenosis). Other covariates of interest included age, sex, use of antihypertensive medications at the time of the clinic visit, and a history of treated diabetes at the time of the clinic visit.

We used PEDSTATS[26] to calculate pair counts and SAS v 9.13 to calculate the number of families of a given size stratified by sample of families. We also used SAS to calculate the number of pairs counts made up of relatives living in the same household by comparing home addresses provided by all participants, the weighted average family size, the median and range of all quantitative covariates, and the count and proportions of qualitative variables stratified by sample of families. We do not report standard deviations of covariates for each sample nor test for differences in covariates between samples given the lack of independence of observations as well as the differences in pedigree structure between samples. Although we have developed a novel methodology to accomplish such a task identical in principle for the two samples, this methodology is not yet in print.

To estimate the heritability of LV mass, we performed a components of variance[27] analysis using SOLAR v. 2.1.2[28]. In order that the scale of measurement conforms as well as possible to SOLAR’s multivariate normal assumptions, we log transformed measures of LV Mass, BP, height, and BMI for this part of the analysis. We report heritability of the logarithm of LV mass in the narrow sense as the ratio of additive
genetic variance divided by the total variance[27]. For hypertensive families, we conditioned the likelihood function on the logarithm of LV mass of the hypertensive proband, an “ascertainment correction”.

We estimated the proportion of the variability of the logarithm of LV mass explained by each covariate of interest stratified by sample of families. We then estimated the heritability of the residual LV mass variance after adjusting for all covariates of interest in a multivariate model. We tested two multivariate models for each sample of families with the only difference between the two models being the covariate used to adjust for BP. In the first model, we used the BP obtained at the time of echocardiography, while in the second we used the BP obtained at the time of the clinical examination.

Next, we used the “bootstrap”[29] in order to avoid SOLAR’s Gaussian assumptions and computations of variability that would be consequences of them and to assess the “goodness of fit” of SOLAR’s model to our data. No matter the group of subjects, the sampling unit for bootstrap sampling – sampling with replacement from the empirical distribution – was always pedigree (meaning sibships when only they were available). For each bootstrap sample we chose a number of pedigrees (nearly always some not at all and some more than once) equal to the total number of pedigrees in the group. Thus, by design, the number of pedigrees equaled the total number in the group. The expected number of individuals chosen was the total number of individuals, and the expected number of subjects per pedigree was as in the group. Using this sampling algorithm, we formed 1000 bootstrap samples from the original population based sample. We then used SOLAR to estimate the heritability of LV mass in each bootstrap sample first using the multivariate model that included the echo BP followed by the multivariate model
that included the clinic BP. We then calculated the mean, standard deviation, skewness, and kurtosis of the 1000 estimates of heritability for each model. We also calculated the difference between each pair of estimates of heritability generated by the two models for a given bootstrap sample and tested whether that difference was significantly different from zero in all bootstrap samples using a one sample t-test. The bootstrap algorithm was then rerun in exactly the same fashion for the sample of hypertensive families.

**Results**

Table 1 summarizes the number of subjects phenotyped per family and the number and type of pairs stratified by family source. A majority (71.3%) of pairs in this analysis are sib pairs. By design, our population based sample is formed exclusively of sib pairs. Only 42 pair counts (5.9%) in the sample of hypertensive families and 10 pair counts (2.7%) in our population based sample are formed by family members living in the same household at the time they were examined. We included “families” in the analyses with only one individual phenotyped for LV mass because these families contribute to the estimation of the effects of covariates.

Table 2 summarizes the distribution of covariates in study subjects stratified by sample of families. The median LV mass, BP, and BMI are all higher in our sample of hypertensive families, while the median age was similar in both samples. The prevalence of treated hypertension, treated diabetes, and mild aortic stenosis are also higher in the sample of hypertensive families while the prevalence of male gender and mild mitral regurgitation are lower.
Table 3 summarizes the proportion of the total variance of the logarithm of LV mass accounted for by each covariate alone stratified by sample of families. In both samples of families, the covariates that explain the highest proportion of the total variance are gender, height, and BMI. In our population based sample, both the systolic and diastolic BP at the clinic visit explain a noticeable larger proportion of the variance than the respective measures at the time of echo. The presence of any type of mild left sided valve abnormality does not predict LV mass, although the number of individuals with either mild aortic or mitral stenosis is low.

Table 4 summarizes the multivariate estimates of heritability of the logarithm of LV mass stratified by the two samples of families. In all models, established predictors of LV mass explain about half of the total variance. The estimates of heritability for the residual variance are all highly significantly different from 0 with a range of 42.5% to 60.6%. The bootstrap sample derived mean and standard error of the estimates of heritability agree fairly well with the heritability and standard error measurements of the original samples. Furthermore, the skewness and kurtosis of these estimates are all close to zero for all models tested. In our population based sample, the bootstrap samples estimate a heritability that is 16.0% higher in the model using the clinic BP compared with the model using the echo BP. In the sample of hypertensive families, this difference is only 2.9%. Both of these differences are significantly different from zero (p < 0.001).

**Discussion**

This study is the first to report estimates of heritability of LV mass in an East Asian population. This study is also the first to report estimates of heritability in both
hypertensive and population based families within an ethnic/racial group living in the same environment. Our estimates of the heritability of LV mass in our two samples of families range from 42.5% to 60.3% (Table 4). All estimates are highly statistically significantly different from zero and fall about half way between the lowest and highest estimates reported to date in other non-twin studies[7-12]. The presence of a higher degree of shared environmental factors with twin[30-32] compared to non-twin sibs may bias estimates of heritability upwards[27]. So that we compare studies as alike in an obvious way, we compare our results only to other non-twin studies.

Our analyses focus on the explicit phenotype of LV mass estimated by echocardiography. We did not attempt to estimate the heritability of LV dimensions or geometry such as the intraventricular septal thickness, the posterior wall thickness, the internal diameter and the relative wall thickness, because none of these measures has been shown convincingly to predict cardiovascular events above and beyond predictions based on LV mass alone in a population of subjects with ejection fractions in the normal range and no evidence of severe valvular dysfunction or HOCM[33-35] [4].

The distribution of our estimates of heritability using the hybrid parametric-nonparametric bootstrap is consistent with the components of variance model used by SOLAR with chosen scales fitting the data well. The fit for our sample of hypertensive families was good despite the fact we only conditioned the likelihood function on the LV mass of the hypertensive proband rather than on several probands (the sib pair and the parents). Bootstrapping also confirms the plausibility of the considerable range of estimates that can be obtained using the SOLAR model and our scaling of variables, despite the
rather large sample sizes. This range of estimates is not out of line with the estimates of heritability published to date\cite{7-12}.

Certain population specific characteristics may influence estimates of heritability obtained by variance component analysis despite an underlying identical biological mechanism across populations\cite{27}. For example, a genetically homogenous population will produce a lower estimate than will a genetically heterogeneous population, while a population with a greater diversity of environmental factors will often produce a lower heritability than will one with a more homogeneous environment. The majority of the Japanese residents in Hawaii are descendants of the residents of a handful of isolated villages in Japan from which plantation workers were brought to Hawaii. Therefore, the genetic heterogeneity of our sample is probably lower than in other studies of heritability that have focused on a single ethnic/racial group. On the other hand, the geographic isolation of our sample may have biased our heritability upwards by decreasing the diversity of environmental factors influencing LV mass.

Several methodological factors specific to our study may have also influenced our estimates of heritability. First, our study sample consists predominantly of sib pairs which is the only pair type that can contribute to dominance genetic variance \cite{nonlinear effects of transmissible alleles at a single locus}\cite{27}. SOLAR's basic components of variance model used in our analyses assumes the absence of dominance genetic variance. If significant dominance genetic variance does exist, then our estimate of heritability in the narrow sense may underestimate the total heritability of LV mass (heritability in the broad sense). This bias would be more extreme in our population based sample of families consisting entirely of sib pairs. Second, SOLAR's basic components of variance model also assumes
the absence of shared familial environmental factors. If such factors are indeed present, our estimates of heritability are biased upwards because the total variance of LV mass is underestimated (by two times the covariance between environmental and genetic predictors of LV mass). However, a vast majority of pairs in both samples are formed by family members who did not live in the same household at the time they were examined. Therefore, we believe the potential for this type of bias is minimal unless exposure to shared familial environmental factors during childhood has effects on LV mass that persist well into adulthood independent of covariates. Third, we used echocardiography to estimate LV mass in this study. This measure explains about 80% of the variance of a subject’s true LV mass[22] and may result in an underestimate of the heritability because the random measurement error of echocardiography contributes to the environmental variance. Fourth, we did not adjust our estimates of heritability for echocardiographic predictors of LV mass that involve measures of LV volumes[36, 37] such as LV end diastolic volume or stroke work because LV volumes were derived using the measure of LV internal diameter used to estimate LV mass (as per protocol) which would bias this adjustment. Furthermore, we wished to compare our estimates of heritability to those in the literature to date which have not adjusted for covariates that involve LV volumes[7-12].

A methodological factor specific to this study that deserves special attention relates to the choice of BP measure used in our adjusted analyses. Blood pressures were appreciably lower at the time of the echo visit compared to the clinic visit in both samples (Table 2) even in the subset of subjects who had no indication for treatment at the clinic visit (details not shown). Three reasons may account for this difference. First, subjects with either suboptimal control or newly discovered hypertension were provided exit
referrals and may have either adjusted or started antihypertensive therapy between clinic and echo visits. Second, the echo BP reading was performed in the supine position while the clinic reading was performed in the sitting position. Third, the echo BP measurement was made after approximately 30 minutes of imaging in a dark room and probably reflects more the study subject’s nocturnal BP rather than their daytime BP[38]. We explored the effect of adjusting for either measure of blood pressure in our multivariate models because it was unclear to us which of the two measures would best regress out the variability of LV mass due to BP. We were surprised to find significantly higher estimates of heritability when clinic BP was used especially in our population based sample. In the supplementary appendix, we present in detail possible explanations of this finding. Briefly, we believe that individuals from our population based sample were far less likely than individuals in our sample of hypertensive families to have been treated for hypertension at the time of the clinic visit. As well, they were more likely to have been treated for hypertension uncovered at the clinic visit by the time of the echo visit. When these population-based individuals were, at last, treated, their respective treatments may have been more effective than were pre-existing treatment regimes for the other sample. These differences led to higher estimates of heritability when clinic BP versus echo BP was used for the population-based group than for the other group. This owes to differences in estimates of co-variability. A limitation of the SAPPHIRe Phase II study design in relation to these observations is the lack of information on antihypertensive use for all subjects at the time of the echo visit.

In summary, our study suggests that genetic factors have a significant influence on LV mass in Japanese subjects living in Hawaii. Genetic determinants appear to account for
about half of the unexplained variance of LV mass. These genetic determinants are in
addition to those related to other predictors of LV mass such as BMI and hypertension.
Therefore, the pursuit of novel genetic determinants of LV mass through either whole
genome or candidate gene association studies appears worthwhile and feasible in our
population.
References


Table 1. Family Size and Pair Types of study samples

<table>
<thead>
<tr>
<th>Family Size</th>
<th>Sample of hypertensive families (n = 476 subjects)</th>
<th>Population Based sample (n = 501 subjects)</th>
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<tr>
<td>1</td>
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</tr>
<tr>
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<td>13</td>
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<tr>
<td>Total</td>
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<td>256</td>
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<td>Cousins</td>
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<tr>
<td>Total</td>
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<td>372</td>
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1total number of family members phenotyped for LV mass
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<th></th>
<th>Sample of Hypertensive families</th>
<th>Population Based sample</th>
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<tr>
<td></td>
<td>(n=476 subjects, 169 families)</td>
<td>(n=501 subjects, 256 families)</td>
</tr>
<tr>
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<td>56 (39-77)</td>
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<tr>
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<td>125.7 (82.3-186)</td>
</tr>
<tr>
<td>Diastolic BP - clinic (mmHg)</td>
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<td>76 (46.3-113.3)</td>
</tr>
<tr>
<td>Systolic BP - echo (mmHg)</td>
<td>116 (80-188)</td>
<td>110 (70-182)</td>
</tr>
<tr>
<td>Diastolic BP - echo (mmHg)</td>
<td>66 (36-106)</td>
<td>64 (36-100)</td>
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<tr>
<td>Body Mass Index (kg/m²)</td>
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<td>25.8 (16.4-45.5)</td>
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<tr>
<td>LV Mass (g)</td>
<td>120.8 (51.4-305.5)</td>
<td>114.7 (51.4-241.4)</td>
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<table>
<thead>
<tr>
<th></th>
<th>Count (%)</th>
<th>Count (%)</th>
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<tbody>
<tr>
<td>Male</td>
<td>211 (44.3)</td>
<td>234 (46.7)</td>
</tr>
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<td>Treated hypertension</td>
<td>296 (62.2)</td>
<td>159 (31.7)</td>
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<td>Treated diabetes</td>
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<td>139 (27.7)</td>
</tr>
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<td>100 (21)</td>
<td>139 (27.7)</td>
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<tr>
<td>3+ to 4+</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mitral Stenosis</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Aortic Regurgitation</td>
<td>39 (8.2)</td>
<td>41 (8.2)</td>
</tr>
<tr>
<td>1+ to 2+</td>
<td>39 (8.2)</td>
<td>41 (8.2)</td>
</tr>
<tr>
<td>3+ to 4+</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Aortic Stenosis</td>
<td>5 (1.1)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Mild</td>
<td>5 (1.1)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Mod</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

1 calculated as 2 x posterior wall thickness in diastole / left ventricular internal diameter in diastole

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Table 3. Proportions of total variance of LV mass explained by covariates of interest using SOLAR

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Sample of Hypertensive families (n=476 subjects, 169 families)</th>
<th>Population Based sample (n=501 subjects, 256 families)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>26.4 &lt;0.0001</td>
<td>30.2 &lt;0.0001</td>
</tr>
<tr>
<td>Height</td>
<td>25.3 &lt;0.0001</td>
<td>25.6 &lt;0.0001</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>16.8 &lt;0.0001</td>
<td>19.1 &lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP - clinic</td>
<td>11.8 &lt;0.0001</td>
<td>12.5 &lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP - clinic</td>
<td>9.3 &lt;0.0001</td>
<td>16.0 &lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP - echo</td>
<td>12.1 &lt;0.0001</td>
<td>7.0 &lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP - echo</td>
<td>5.1 &lt;0.0001</td>
<td>4.4 &lt;0.0001</td>
</tr>
<tr>
<td>Treated Hypertension</td>
<td>4.2 0.0002</td>
<td>5.8 &lt;0.0001</td>
</tr>
<tr>
<td>Treated Diabetes</td>
<td>1.5 0.0417</td>
<td>0.0 0.5385</td>
</tr>
<tr>
<td>Age</td>
<td>1.1 0.1779</td>
<td>0.5 0.049</td>
</tr>
<tr>
<td>Aortic Stenosis</td>
<td>0.1 0.4753</td>
<td>0.1 0.4851</td>
</tr>
<tr>
<td>Aortic Regurgitation</td>
<td>2.0 0.0197</td>
<td>0.0 0.8454</td>
</tr>
<tr>
<td>Mitral Regurgitation</td>
<td>1.3 0.0265</td>
<td>0.0 0.8032</td>
</tr>
<tr>
<td>Mitral Stenosis</td>
<td>0.0 1</td>
<td>0.0 1</td>
</tr>
</tbody>
</table>

1For test of the null hypothesis that the respective "component of variance" is 0
<table>
<thead>
<tr>
<th>Covariates</th>
<th>Original Sample</th>
<th>1000 Bootstrap Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of Total Variance explained by covariates</td>
<td>% heritability (SE of variance not explained by covariates)</td>
</tr>
<tr>
<td><strong>Sample of Hypertensive Families</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Model 1</strong> - age, sex*, height*, BMI*, treated DM, AR, MR*, AS, MS, SBP echo*, DBP echo, treated HTN</td>
<td>48.6</td>
<td>42.5 (9.8)</td>
</tr>
<tr>
<td><strong>Model 2</strong> - age, sex*, height*, BMI*, treated DM, AR*, MR*, AS, MS, SBP clinic*, DBP clinic, treated HTN</td>
<td>49.2</td>
<td>42.6 (9.7)</td>
</tr>
<tr>
<td><strong>Population Based Sample</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Model 1</strong> - age*, sex*, height*, BMI*, treated DM, AR, MR, AS, MS, SBP echo*, DBP echo, treated HTN*</td>
<td>49.4</td>
<td>44.1 (11.4)</td>
</tr>
<tr>
<td><strong>Model 2</strong> - age*, sex*, height*, BMI*, treated DM, AR, MR, AS, MS, SBP clinic*, DBP clinic, treated HTN*</td>
<td>49.7</td>
<td>60.6 (11.7)</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure, DBP = diastolic blood pressure, HTN = hypertension, AR = aortic regurgitation, MR = mitral regurgitation, AS = aortic stenosis, MS = mitral stenosis, BMI = body mass index

*P < 0.1 for covariate in model (retained)
†For test of null hypothesis that the %heritability is equal to 0
Supplementary Discussion

Possible Explanation of the Difference in Percent Heritability for Population-based Sample in Table 4: BP at Clinic Versus BP at Echo

We explored the effect of adjusting for either measure of BP in our models because it was unclear to us which of the two measures would best regress out the variability of LV mass due to BP. Perhaps surprisingly, estimates of heritability were significantly higher when clinic systolic BP was used in our models in lieu of echo systolic BP. We provide here a formal explanation for this observation with a model that is an extension of the basic display (7-8) of Khoury's et al. "Fundamentals in Genetic Epidemiology" [1]. That the covariance terms of the model need not be 0 allows us to extend the important contributions of Almasy and Blangero [2] in the present context.

Write \( y = \mu + E(y \mid C) + G_A + e \), where \( y \) is (the logarithm of) LV mass; \( \mu \) is a fixed overall mean; \( C \) is the set of covariates used in our analyses with SOLAR; \( G_A \) is the random additive genetic contribution to \( y \); and \( e \) is (random) all else. Here \( E(\cdot \mid \cdot) \) denotes "conditional expectation," in what follows, \( \text{Cov}(\cdot, \cdot) \) denotes "covariance," and \( \text{Var} \) "variance." Necessarily,

\[
\text{Var}(y) = \text{Var}(E(y \mid C) + \text{Var}(G_A) + \text{Var}(e) + 2(\text{Cov}(E(y \mid C), G_A) + \\
\text{Cov}(E(y \mid C), e) + \text{Cov}(G_A, e)).
\]

Analyses reported in Table 4 show that at least approximately,

\[
\text{Var}(E(y \mid C)) = (1/2)\text{Var}(y).
\]

Heritability in the narrow sense, \( h^2 \), is \( \text{Var}(G_A)/\text{Var}(y) \). These entail that at least
approximately,

\[ h^2 = (1/2) - \frac{(\text{Var}(e)/\text{Var}(y)) - 2\{\text{Cov}(E(y \mid C), G_A) + \text{Cov}(E(y \mid C), e) + \text{Cov}(G, e)\}}{\text{Var}(y)}. \]

So, \( h^2 > 1/2 \) implies that

\[ \text{Cov}(E(y \mid C), G_A) + \text{Cov}(E(y \mid C), e) + \text{Cov}(G_A, e) < 0. \]

Now, the first term can be written \( \sigma_{E(y \mid C)} \rho_{G_A, G_A} \), where \( \sigma \) denotes standard deviation and \( \rho \) correlation.

Note that for the population-based sample, BP at clinic, especially diastolic, explains far more variability in LV mass than does BP at echo (Table 3). Therefore, plausibly, if the sign of the coefficient of DBP at clinic is more negative for the model with BP at clinic than it is for the measure taken at echo, then \( \rho_{E(y \mid C), G_A} \) could be negative at clinic, while it is roughly 0 at echo. This would be consistent with treatment at clinic being unusual, and reflecting genuine genetic predisposition to elevated BP, and LV mass. However, treatment at echo could be more prevalent -- we lack data to know -- and the cited correlation being nearly 0 is consistent with our intuition. As well, \( \text{Cov}(G_A, e) \) could be of either sign, or 0; necessarily \( e \) includes whatever dominance effect of genes is present, and we do not know what that number is. Likewise \( \text{Cov}(E(y \mid C), e) \) is unknown, as is any difference in the correlation of \( E(y \mid C) \) and \( e \) that might owe to differences in BP measured at clinic and at echo.
References
