Familial Aggregation of Left Ventricular Geometry and Association
with Parental Heart Failure: The Framingham Heart Study

Running title: Lam et al.; Familial Aggregation of Left Ventricular Geometry

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Journal Subject Codes: [109] Clinical genetics, [115] Remodeling, [31] Echocardiography
ABSTRACT

Background - Data regarding the familial aggregation of left ventricular (LV) geometry and its relations to parental heart failure (HF) are limited.

Methods and Results - We evaluated concordance of LV geometry within 1093 nuclear families in 5758 participants of the Original (parents; N=2351) and Offspring (N=3407) cohorts of the Framingham Heart Study undergoing routine echocardiography in mid-to-late adulthood. LV geometry was categorized based on cohort- and sex-specific 80th percentile cutoffs of LV mass and relative wall thickness (RWT) into normal (both <80th percentile), concentric remodeling (LV mass<80th percentile, RWT>80th percentile), concentric hypertrophy (both >80th percentile) and eccentric hypertrophy (LV mass>80th percentile, RWT<80th percentile). Within nuclear families, LV geometry was concordant among related pairs (parent-child, sibling-sibling) (P=0.0015), but not among unrelated spousal pairs (P=0.60), a finding that remained unchanged after adjusting for clinical covariates known to influence LV remodeling (age, systolic blood pressure, body mass index), excluding individuals with prevalent HF and myocardial infarction, and varying the thresholds for defining LV geometry. The prevalence of abnormal LV geometry was higher in family members of affected individuals, with recurrence risks of 1.4 for concentric remodeling (95%CI, 1.2-1.7) and eccentric hypertrophy (95%CI, 1.1-1.8), and 3.9 (95%CI, 3.2-4.6) for concentric hypertrophy. In a subset of 1497 offspring, we observed an association between parental HF (N=458) and eccentric hypertrophy in offspring (P<0.0001).

Conclusions - Our investigation of a two-generational community-based sample demonstrates familial aggregation of LV geometry, with the greatest recurrence risk for concentric LV geometry, and establishes an association of eccentric LV geometry with parental HF.

Key words: echocardiography; remodeling; risk factors
BACKGROUND

Change in left ventricular (LV) geometry, or LV remodeling, is increasingly recognized as a key determinant of heart failure (HF) incidence, and is associated with increased cardiovascular morbidity and mortality. In overt HF, LV remodeling is thought to contribute independently to disease progression beyond neurohormonal mechanisms, thus supporting therapeutic efforts aimed at preventing or reversing LV remodeling in HF.

In acknowledgement of the importance of LV remodeling in the evolution of HF, research efforts have focused on defining the factors that influence remodeling patterns and the resultant LV geometry in individuals. Overt diastolic and systolic HF are thought to represent different ends of a disease spectrum that may vary with regard to their underlying patterns of LV remodeling. According to this paradigm, some individuals are predisposed to develop concentric hypertrophy and diastolic HF, whereas others preferentially develop eccentric hypertrophy and systolic HF. Clinical determinants of LV remodeling, such as age, sex, blood pressure, or body size, are well-defined but only partially explain the inter-individual variability of LV geometry in the population. To investigate if genetic factors also may contribute, studies have been performed in twins and siblings, providing evidence of familial predisposition to LV hypertrophy or increased LV mass. Of note, LV mass is only one of two principal components characterizing LV geometry. The other component is relative wall thickness (RWT), which also varies independently within the population and, together with LV mass, defines the four distinct types of LV geometric patterns: normal, concentric...
remodeling, concentric hypertrophy and eccentric hypertrophy.\textsuperscript{17} Each of these components (LV mass and RWT) was assessed in the MONItoring of trends and determinants in CArdiovascular disease (MONICA) study,\textsuperscript{16} in which “exposure” to an affected sibling with LV hypertrophy was associated with increased wall thickness and LV mass index compared to “unexposed” members of the population. However, “exposure” of concentric remodeling (without LV hypertrophy) was not assessed, parental geometry was not investigated and individual components of LV mass and RWT were analyzed separately without determination of their conjoint effect on overall LV geometry.

Accordingly, the objectives of the present community-based investigation were to evaluate if LV geometric patterns aggregate within nuclear families of the Framingham Heart Study, and to estimate the ‘recurrence risk’ of abnormal LV geometry in family members. To determine the clinical significance of any familial aggregation of LV geometry, we also examined the association of parental HF with presence of abnormal LV geometry in the offspring. We hypothesized that select LV geometric patterns would cluster within families, and that such familial aggregation would be independent of age, sex, body size or blood pressure, thereby providing evidence for a potential genetic contribution to LV remodeling in the community. We further hypothesized that offspring of parents with overt HF would have a higher prevalence of abnormal LV geometric patterns compared to individuals without parental HF.
METHODS

Participants

As detailed previously, the Framingham Heart Study began in 1948 with the enrollment of the Original cohort who undergo biennial examinations. In 1971 the Framingham Offspring Study was initiated with the recruitment of children of the Original cohort, as well as their spouses, who are examined approximately every four to eight years. Participants of both cohorts are under continuous surveillance for the development of cardiovascular disease events, including HF. All HF events are adjudicated by a panel of 3 physicians according to the Framingham HF criteria.

Recognizing the important influence of age on LV geometry, participants attending specific cohort examination cycles (Original cohort examination cycle 16 and Offspring cohort examination cycle 6) were selected to ensure that both parents and offspring were as close in age as possible during mid to late adulthood at their respective examinations. Eligible participants with prevalent cardiovascular disease were included in the primary analyses, as such individuals are expected to be informative with regard to presence of abnormal LV geometry. However, since prevalent myocardial infarction and HF may be associated with distortion of LV geometry as well as different factors affecting remodeling, participants with these conditions at their index examinations were excluded in secondary analyses.

To investigate the association between parental HF and abnormal LV geometry in offspring, a subset of the Offspring cohort (N=1497) was identified at examination cycle
6, in whom both parents were in the Original cohort. This ensured that complete information regarding both parents’ HF status was available from continuous surveillance. We have previously reported an association between parental HF and LV systolic dysfunction in this subset, but the association between parental HF and abnormal LV geometry has not been investigated before.

All participants provided written informed consent and the study protocols were approved by the Boston University Medical Center Institutional Review Board.

**Characterization of LV geometry**

All participants underwent transthoracic echocardiography using standardized techniques. M-mode measurements of LV internal dimensions and LV wall thickness were made by the leading-edge-to-leading-edge method, with excellent reproducibility demonstrated within examination cycles. LV mass was calculated using the formula: \[ \text{LV mass (g)} = 0.8 \times \left[ 1.04 \times (\text{LVEDD} + \text{SWT} + \text{PWT})^3 - (\text{LVEDD})^3 \right] + 0.6, \] where LVEDD is the LV end-diastolic diameter, SWT is diastolic septal wall thickness, and PWT is diastolic posterior wall thickness. RWT was derived as \[ \left( \frac{\text{SWT} + \text{PWT}}{\text{LVEDD}} \right). \]

To define LV geometry, we empirically used the sex-specific 80th percentile cutoffs for LV mass and RWT. These cutoffs were defined for each cohort separately to account for possible measurement differences due to changes in echocardiographic instrumentation from 1979 (Original cohort examination 16) to 1995 (Offspring cohort examination 6), temporal trends in LV mass and RWT, and/or other birth cohort effects. Further
recognizing the known differences between sexes in heart size, sex-specific cutoffs were used as previously detailed. Thus, increased LV mass (i.e. LV hypertrophy) was defined as LV mass ≥ sex- and cohort- specific 80th percentile of LV mass; and increased RWT as RWT ≥ sex- and cohort- specific 80th percentile of RWT; while values below the respective sex- and cohort- specific 80th percentiles were regarded as ‘normal’. LV geometry was then defined as:

1. Normal geometry (normal LV mass, normal RWT)
2. Concentric remodeling (normal LV mass, increased RWT)
3. Concentric hypertrophy (increased LV mass, increased RWT)
4. Eccentric hypertrophy (increased LV mass, normal RWT)

‘Abnormal’ LV geometry referred to any type of geometry other than ‘normal’ geometry, and therefore included concentric remodeling, concentric hypertrophy or eccentric hypertrophy.

Statistical Analyses

Testing for concordance in LV geometric pattern

In primary analyses, concordance of traits was assessed within nuclear families. The binary traits of normal/increased LV mass and normal/increased RWT were first tested individually, followed by the polychotomous trait of LV geometry (normal/ concentric remodeling/ concentric hypertrophy/ eccentric hypertrophy). Concordant pairs, defined as both individuals having the same abnormal type of LV geometric pattern, were counted among parent-child relationships and among sibships. Spousal pair concordance was evaluated in a separate analysis assessing the effects of shared environmental factors.
Based on the null hypothesis of no familial aggregation, testing was performed using the permutation method.\textsuperscript{26} For each permutation, we randomly permuted phenotypes of all individuals regardless of their family membership, and computed the number of concordance pairs within nuclear families. The number of concordant pairs from all permutations then formed the null distribution. We used $10^5$ permutations in each analysis to assess the probability that the observed number of concordant pairs was greater than that expected under the null hypothesis of random assortment of LV geometric pattern across nuclear families. To account for covariates known to influence LV geometry (age, blood pressure, body size), we regressed age, systolic blood pressure and body mass index in each sex and cohort stratum on LV Mass or RWT, and used the sex- and cohort- specific residuals to categorize LV geometry. Sensitivity analyses were performed to evaluate the effect of using different percentile cutoffs ($80^{th}$, $75^{th}$, $50^{th}$ percentiles), as well as recommended cutoffs by the American Society of Echocardiography,\textsuperscript{17} to define each trait in concordance testing.

In secondary analyses, concordance of LV geometric pattern was assessed within sibships alone. The binary traits of increased LV mass and increased RWT were first tested individually, followed by the polychotomous trait of LV geometry. Pairs of siblings that were concordant for LV geometric pattern pairs were counted among sibships and permutation resampling was conducted to test the null hypothesis of no familial aggregation among siblings.

\textit{Recurrence risk estimates}
Recurrence risk ratios for abnormal LV geometry were estimated within nuclear families and sibships, and defined as the risk of having an abnormal LV geometric pattern given an affected family member (with that pattern) compared to the prevalence of that geometric pattern in the general population. For the polychotomous trait LV geometry, recurrence risk ratios were calculated using 2 definitions of the trait: (1) any abnormal LV geometry (concentric remodeling, concentric hypertrophy or eccentric hypertrophy); and (2) each specific type of LV geometric pattern.

Association with parental HF

In subset analysis of 1497 Offspring with known parental HF status, multivariable logistic regression was performed, where the dependent variable was parental HF and independent variables were Offspring LV geometry (modeled as a categorical variable), age, sex and body size.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Baseline characteristics

The study sample included a total of 5758 participants (2351 Original cohort, 3407 Offspring cohort) who attended the index examinations and provided echocardiographic data for the determination of the LV mass and RWT cohort- and sex-specific 80th
percentile cutoffs. Baseline characteristics by cohort are presented in Table 1. Both parents (Original cohort) and adult children (Offspring cohort) were examined in mid to late adulthood. Compared to the Original cohort, Offspring had larger body size and lower systolic blood pressure at index examination, likely reflecting temporal trends in these variables. In both cohorts, women had lower LV mass but similar RWT compared to men.

Concordance of LV geometry

LV geometry was concordant within nuclear families, whether LV geometry was assessed as separate binary traits (normal/increased LV mass and normal/increased RWT) or as a combined polychotomous trait (Table 2). The familial concordance of LV geometry remained significant in analyses adjusting for key covariates, in analyses that excluded those with prevalent myocardial infarction and HF, and when we evaluated sibling pairs alone (Table 3). In contrast, there was no concordance of LV geometry among spousal pairs in both cohorts (P=0.60). Familial concordance of LV geometry was maintained in analyses using different percentile cutoffs, as well as cutoffs recommended by the American Society of Echocardiography, to define abnormal LV mass and RWT (Online Supplemental Data).

Recurrence risk ratios

The prevalence of any abnormal LV geometry (concentric remodeling, concentric hypertrophy, eccentric hypertrophy), as well as each specific type of LV geometric pattern, was higher in related family members of affected individuals than in the study
population (Figure 1A). Accordingly, the recurrence risk within nuclear families was 1.2
(95% CI, 1.1-1.3) for any abnormal LV geometry, and varied from 1.4 (95% CI, 1.1-1.8)
for eccentric hypertrophy, 1.4 (95% CI, 1.2-1.7) for concentric remodeling, to 3.9
(95% CI, 3.2-4.6) for concentric hypertrophy (Figure 1B). Similar results were seen
among sibling pairs alone.

**Association with parental HF**

In the subset of 1497 Offspring (mean age, 57 years; 55% women) with known parental
HF status during continuous surveillance (both parents in the Original cohort), the
distribution of LV geometry was: 990 (66%) with normal geometry, 207 (14%) with
concentric remodeling, 206 (14%) with eccentric hypertrophy and 94 (6%) with
concentric hypertrophy. There was a positive association between the presence of
parental HF (N=458) and any abnormal LV geometry in offspring, even after adjusting
for age, sex and height ($P<0.0006$). Compared to normal geometry, the odds of parental
HF was significantly increased in offspring with eccentric hypertrophy adjusting for age,
sex and height (adjusted odds ratio 1.9; 95% CI, 1.4-2.7; $P<0.0001$) (Figure 2). The
association of parental HF in offspring with concentric hypertrophy (adjusted odds ratio
1.4; 95% CI, 0.9-2.2) or concentric remodeling (adjusted odds ratio 1.1; 95% CI, 0.8-1.5)
did not reach statistical significance. Adjusting for age, sex, body mass index and systolic
blood pressure yielded similar results (adjusted odds ratio for eccentric hypertrophy 1.5;
95% CI, 1.1-2.1; $P=0.011$).
DISCUSSION

Our investigation of a large two-generational community-based sample demonstrated familial aggregation of LV geometry. The presence of a family member with abnormal LV geometry was associated with a 20 percent increased odds of altered LV geometric pattern in the offspring compared to the prevalence in our study population. Specifically, there was a 40 percent increased odds of eccentric hypertrophy or concentric remodeling, and an almost 4-fold increased odds of concentric hypertrophy among family members of individuals with the corresponding abnormal LV geometric pattern. These associations remained significant after accounting for clinical factors known to influence LV geometry, such as age, sex and body size. These data extend previous reports of the heritability of LV mass by establishing familial concordance of LV geometry, thus underscoring a potential contribution of familial predisposition to patterns of LV remodeling. The association between parental HF and prevalence of eccentric LV geometry in their offspring further suggests that familial factors may play a role in adverse LV remodeling and HF progression in the community.

Current guidelines strongly emphasize that HF is a progressive disorder that begins with the acquisition of clinical risk factors (stage A), involves adaptive cardiac structural changes in the absence of symptoms (stage B) and eventually leads to cardiac decompensation and the development of overt symptoms (stage C). The structural changes that occur in the heart, collectively referred to as LV remodeling, have been postulated to contribute to the pathophysiology of HF independent of neurohormonal mechanisms, predict worse outcomes in natural history studies of HF, and have been
identified as a key therapeutic target in HF. The clinical determinants of LV remodeling have been well-defined and include age, sex, blood pressure and body size. However, these factors only partially account for the inter-individual variability of LV geometry in the population.

To investigate if genetic factors may contribute to LV remodeling, previous studies have examined the individual components of LV geometry, namely LV mass and wall thickness. Several studies in twins and in the general population have demonstrated the heritability of LV mass and wall thickness. None, however, have comprehensively examined familial clustering of LV geometric patterns or their associations with parental HF. In the MONICA study, 319 siblings of participants with LV hypertrophy (mean age 55 years) were compared to 636 age- and gender- matched subjects and found to have increased odds of concentric hypertrophy (odds ratio 1.98), but not of eccentric hypertrophy. Consistent with this observation, we found the highest sibling recurrence risk with the concentric hypertrophy group. The larger estimated risk in our study (recurrence risk 3.9) may be related to the inclusion of the full spectrum of LV geometry, older age at the time of study of our participants, differences in sample size, or possible socio-geographic differences between the study samples. Of note, by studying the aggregation of the polychotomous trait LV geometry in families, we were also able to demonstrate familial clustering of eccentric hypertrophy and concentric remodeling in our sample, although the recurrence risks were smaller than that of concentric hypertrophy.
The relation between the presence of abnormal LV geometry in offspring and increased risk of parental HF deserves comment. We have previously shown that parental HF is associated with increased prevalence of LV systolic dysfunction cross-sectionally, and increased risk of HF longitudinally, in offspring. The current evidence of abnormal LV geometry in offspring with parental HF is consistent with the notion that abnormal LV remodeling may mediate the association between parental HF and development of LV systolic dysfunction or future HF in the offspring. Accordingly, the pattern of LV remodeling most strongly associated with parental HF was eccentric hypertrophy. In contrast, the pattern of LV remodeling associated with the highest familial recurrence risk was concentric hypertrophy. Smaller numbers of offspring with concentric hypertrophy (N=94) compared to eccentric hypertrophy (N=206) in the former subset analysis may explain the lack of statistical significance for concentric hypertrophy in these analyses. Differences in the time course of HF progression in concentric versus eccentric remodeling may also explain these observations: concentric remodeling and diastolic HF are recognized as disorders of the elderly, whereas familial dilated cardiomyopathy is known to be associated with early-onset systolic HF. Offspring were examined at a mean age of 57 years, hence it is possible that at an older mean age (>75 years), when more concentric remodeling and hypertrophy may be expected, an association between concentric hypertrophy and parental HF may emerge. Similarly, an examination restricted to women (female offspring and their mothers) may be revealing since women are more prone to concentric hypertrophy and diastolic HF than men; however, our limited sample size did not allow adequately powered sex-specific analyses. Finally, the contribution of concomitant coronary heart disease to HF progression in the face of
asymptomatic eccentric LV remodeling deserves further study. Overall, our data suggest an important contribution of familial factors to LV remodeling and HF progression in the community.

The strengths of our study include the large sample size, well-defined pedigrees within two generations, prospective community-based design, complete ascertainment of risk factors and routine echocardiography. Limitations include the exclusively white racial make-up of our sample that limits the generalizability of findings to other ethnicities. Findings in younger or older adults may also differ from that observed in our predominantly middle-aged sample. The contribution of shared environment to familial aggregation of LV geometry cannot be excluded, although the lack of concordance among unrelated spousal pairs suggests otherwise. Similarly, while we accounted for important factors known to influence LV geometry (age, blood pressure, body size, myocardial infarction and HF), residual confounding by other factors may still be present. It should be recognized that our results were derived in community-based adults rather than hospital- or clinic-based patients with HF or myocardial infarction, in whom factors affecting remodeling may differ.\textsuperscript{21, 22}

In conclusion, familial aggregation of LV geometry was demonstrated in the large two-generational community-based sample of the Framingham Heart Study. These findings provide support for future studies investigating the genetic mechanisms that underlie LV remodeling and HF progression in the community.
Sources of funding: This work was supported by NHLBI Contract N01-HC-25195; grants: 6R01-NS 17950, and RO1HL080124 (RSV).

Conflicts of Interest Disclosures: None.

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Table 1: Baseline characteristics at index examination

<table>
<thead>
<tr>
<th></th>
<th>Parents (Original cohort)</th>
<th>Children (Offspring cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>N</td>
<td>934</td>
<td>1417</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age, years</td>
<td>70±7</td>
<td>71±7</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.9±3.8</td>
<td>26.4±4.8</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>139±19</td>
<td>141±21</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>79±10</td>
<td>76±10</td>
</tr>
<tr>
<td>Antihypertensive medication, %</td>
<td>31.6</td>
<td>42.1</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>10.1</td>
<td>12.7</td>
</tr>
<tr>
<td>Myocardial infarction, %</td>
<td>13.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>1.1</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Echocardiographic characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass, g</td>
<td>202±67</td>
<td>140±46</td>
</tr>
<tr>
<td>RWT</td>
<td>0.42±0.02</td>
<td>0.44±0.10</td>
</tr>
<tr>
<td>LV geometry*, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Normal</td>
<td>630 (67.5)</td>
<td>967 (68.2)</td>
</tr>
<tr>
<td>- Concentric remodeling</td>
<td>115 (12.3)</td>
<td>167 (11.8)</td>
</tr>
<tr>
<td>- Concentric hypertrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Eccentric hypertrophy</td>
<td>74 (7.9)</td>
<td>116 (8.2)</td>
</tr>
<tr>
<td></td>
<td>115 (12.3)</td>
<td>167 (11.8)</td>
</tr>
</tbody>
</table>

Data are mean±SD or percentage where indicated.
LV, left ventricular; RWT, relative wall thickness;
*Using the following cohort- and sex- specific 80th percentile cutoffs:
- In the Original cohort, LV mass cutoffs of 240g (men) and 170g (women); RWT cutoffs of 0.45 (men) and 0.51 (women).
- In the Offspring cohort, LV mass cutoffs of 217g (men) and 175g (women); RWT cutoffs of 0.43 (men) and 0.42 (women).
Table 2: Concordance within nuclear families

<table>
<thead>
<tr>
<th>Trait*</th>
<th>Observed/ expected concordance pairs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted analyses in entire sample</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased LV mass</td>
<td>86/64</td>
<td>0.006</td>
</tr>
<tr>
<td>Increased RWT</td>
<td>101/63</td>
<td>0.00001</td>
</tr>
<tr>
<td>Abnormal LV geometry</td>
<td>90/64</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Adjusted analyses in entire sample†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased LV mass</td>
<td>92/64</td>
<td>0.0008</td>
</tr>
<tr>
<td>Increased RWT</td>
<td>97/65</td>
<td>0.0002</td>
</tr>
<tr>
<td>Abnormal LV geometry</td>
<td>112/75</td>
<td>0.0005</td>
</tr>
<tr>
<td><strong>Analyses excluding prevalent myocardial infarction and heart failure‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased LV mass</td>
<td>77/54</td>
<td>0.003</td>
</tr>
<tr>
<td>Increased RWT</td>
<td>88/58</td>
<td>0.0003</td>
</tr>
<tr>
<td>Abnormal LV geometry</td>
<td>97/65</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

LV, left ventricular; RWT, relative wall thickness;

* Traits defined using cohort- and sex- specific 80th percentile cutoffs
† Adjusting for age, body mass index and systolic blood pressure
‡ Excluding N=96, 43 and 117 for analyses using the traits ‘Increased LV mass’, ‘Increased RWT’ and ‘Abnormal LV geometry’ respectively
Table 3: Concordance within sibling pairs

<table>
<thead>
<tr>
<th>Trait*</th>
<th>Observed/ expected concordance pairs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted analyses in entire sample</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased LV mass</td>
<td>66/44</td>
<td>0.0006</td>
</tr>
<tr>
<td>Increased RWT</td>
<td>81/40</td>
<td>0.00001</td>
</tr>
<tr>
<td>Abnormal LV geometry</td>
<td>73/44</td>
<td>0.00002</td>
</tr>
<tr>
<td><strong>Adjusted analyses in entire sample†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased LV mass</td>
<td>67/48</td>
<td>0.0030</td>
</tr>
<tr>
<td>Increased RWT</td>
<td>72/43</td>
<td>0.00003</td>
</tr>
<tr>
<td>Abnormal LV geometry</td>
<td>82/55</td>
<td>0.0005</td>
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<tr>
<td><strong>Analyses excluding prevalent myocardial infarction and heart failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased LV mass</td>
<td>58/40</td>
<td>0.006</td>
</tr>
<tr>
<td>Increased RWT</td>
<td>66/43</td>
<td>0.0008</td>
</tr>
<tr>
<td>Abnormal LV geometry</td>
<td>72/48</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

LV, left ventricular; RWT, relative wall thickness;

* Traits defined using cohort- and sex- specific 80th percentile cutoffs

† Adjusting for age, body mass index and systolic blood pressure
FIGURE LEGENDS:

Figure 1 - Familial aggregation of left ventricular geometry

A. The prevalence of any abnormal left ventricular geometry (concentric remodeling, CR; concentric hypertrophy, CH; eccentric hypertrophy, EH), as well as each specific type of LV geometric pattern, was higher in related family members (black bars) and siblings (grey bars) of affected individuals than in unrelated members in our community-based sample (white bars). B. Recurrence risk ratios were estimated within nuclear families and sibships, defined as the risk of having an abnormal left ventricular geometric pattern given an affected family member (with that pattern) compared to the occurrence of that geometric pattern among unrelated individuals in the general population. Symbols and bars represent the means and 95% confidence intervals of recurrence risk within nuclear families (black dots and bars) and among sibling pairs (grey squares and bars).

Figure 2 - Association of parental heart failure with left ventricular geometry in offspring

Parental heart failure (HF) was related to left ventricular geometry in offspring. Compared to normal (NL) geometry, the odds of parental HF was significantly increased in offspring with eccentric hypertrophy (EH) adjusting for age, sex and height (*P<0.0001), with intermediate odds of parental HF in offspring with concentric hypertrophy (CH) and concentric remodeling (CR).
- Familial recurrence risk
- Sibling recurrence risk

Recurrence risk (mean, 95% CI)

Any  CR  CH  EH
Odds of parental HF (mean, 95%CI)

Geometry in offspring

NL CR CH EH
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**SUPPLEMENTAL MATERIAL**

Results of sensitivity analyses for concordance among nuclear families in the entire sample

<table>
<thead>
<tr>
<th>Trait</th>
<th>Percentile</th>
<th>Cutoff</th>
<th>Observed/expected concordance pairs</th>
<th>P value*</th>
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<tr>
<td></td>
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<td>Men, Original cohort</td>
<td>Women, Original cohort</td>
<td>Men, Offspring cohort</td>
</tr>
<tr>
<td><strong>Increased LV mass</strong></td>
<td>80&lt;sup&gt;th&lt;/sup&gt;</td>
<td>240g</td>
<td>170g</td>
<td>217g</td>
</tr>
<tr>
<td></td>
<td>75&lt;sup&gt;th&lt;/sup&gt;</td>
<td>226g</td>
<td>148g</td>
<td>195g</td>
</tr>
<tr>
<td></td>
<td>50&lt;sup&gt;th&lt;/sup&gt;</td>
<td>228g</td>
<td>140g</td>
<td>183g</td>
</tr>
<tr>
<td>ASE</td>
<td></td>
<td>115 g/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>95 g/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>115 g/m&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td><strong>Increased RWT</strong></td>
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<td>0.51</td>
<td>0.43</td>
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<td>75&lt;sup&gt;th&lt;/sup&gt;</td>
<td>0.45</td>
<td>0.54</td>
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<tr>
<td></td>
<td>50&lt;sup&gt;th&lt;/sup&gt;</td>
<td>0.42</td>
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<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
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<tr>
<td><strong>Abnormal LV geometry</strong></td>
<td>80&lt;sup&gt;th&lt;/sup&gt;</td>
<td>240g (LV mass)</td>
<td>170g (LV mass)</td>
<td>217g (LV mass)</td>
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</tr>
</tbody>
</table>

LV, left ventricular; RWT, relative wall thickness; ASE, American Society of Echocardiography

*Adjusting for age, body mass index and blood pressure for analyses using the 80<sup>th</sup>, 75<sup>th</sup> and 50<sup>th</sup> percentile cutoffs within the sample