

Published in final edited form as:

Circulation. 2015 January 20; 131(3): 263–268. doi:10.1161/CIRCULATIONAHA.114.012594.

Familial Clustering of Mitral Valve Prolapse in the Community

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Abstract

Background—Knowledge of mitral valve prolapse (MVP) inheritance is based on pedigree observation and M-mode echocardiography. The extent of familial clustering of MVP among unselected individuals in the community based on current, more specific echocardiographic criteria is unknown. In addition, the importance of non-diagnostic MVP morphologies (NDM; first described in large pedigrees) has not been investigated in the general population. We hypothesized that parental MVP and NDM increase the risk of offspring MVP.

Methods and Results—Study participants were 3679 Generation 3 individuals with available parental data in the Offspring or the New Offspring Spouse cohorts. MVP and NDM were distinguished by leaflet displacement > 2 mm versus ≤ 2 mm beyond the mitral annulus, respectively. We compared MVP prevalence in Generation 3 participants with at least one parent with MVP (n=186) with that in individuals without parental MVP (n=3493). Among 3679 participants (53% women; mean age 40±9 years), 49 (1%) had MVP. Parental MVP was associated with a higher prevalence of MVP in Generation 3 participants (10/186 [5.4%]) compared to no parental MVP (39/3493 [1.1%]) - adjusted odds ratio [OR], 4.51, 95% confidence

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Disclosures: None.

interval [CI], 2.13–9.54; $p < 0.0001$). When parental NDM was examined alone, prevalence of Generation 3 MVP remained higher (12/484 [2.5%]) compared to those without parental MVP or NDM (27/3009 [0.9%] - adjusted OR 2.52, 95% CI, 1.25–5.10; $p = 0.01$).

Conclusions—Parental MVP and NDM are associated with increased prevalence of offspring MVP, highlighting the genetic substrate of MVP and the potential clinical significance of NDM in the community.

Keywords

mitral valve prolapse; echocardiography; epidemiology; genetics

INTRODUCTION

Mitral valve prolapse (MVP) is a common disorder affecting 2–5% of the general population.^{1–3} It is the most important cause of primary mitral regurgitation (MR) requiring surgery.⁴ MVP is characterized by fibromyxomatous changes leading to displacement of one or both leaflets into the left atrium (Figures 1A-B).^{5–8} It can lead to endocarditis, heart failure, and even sudden death.^{9–17, 18–20}

Our knowledge of MVP inheritance is based on observations of pedigrees with familial forms of the condition, case reports in selected individuals with late systolic clicks^{21,22} or reports that used older M-mode echocardiographic diagnostic criteria.²³ Based on these studies, MVP appears to be an autosomal dominant disorder with variable expression. The familial nature of MVP has been proposed for many years since Hancock and Cohn in 1966 observed systolic clicks and murmurs in members of different generations in various families.^{24, 25} Subsequently, about half of first-degree relatives were reported to manifest MVP in both echocardiographic²⁶ and echocardiographic-auscultatory studies.²⁴ Further evidence for autosomal dominant inheritance derives from other reports,²⁶ including twin studies.^{21,27} More recently, our understanding of the 3D shape of the MV has improved the specificity of MVP diagnosis, and turn the yield of genetic studies.^{7,28–31} Although a genetic basis of MVP in selected patients has been described, the extent of familial clustering of MVP among unselected individuals in the community using current, more specific echocardiographic criteria is *unknown*.

In addition, previously non-diagnostic morphologies of MVP (NDM) have been described in the familial context.³⁰ NDM share features of excessive leaflet motion with fully affected individuals, as demonstrated by superior motion towards the left atrium, bulging of the posterior leaflet relative to the anterior (albeit not diagnostic by quantitative assessment), and coaptation asymmetry. In addition, in some NDM, leaflet excess can also manifest itself by anterior motion and a shift of the coaptation point towards the septum and the aortic root (Figure 2). In genetic studies, NDM shared either the complete or a major portion of the haplotype with fully diagnostic MVP.³⁰ These non-diagnostic forms may, therefore, represent an early expression of MVP in those genetically predisposed. NDM have also been observed in the community,³² but their clinical significance is unknown.

We hypothesized that parental MVP and NDM are both associated with a greater prevalence of offspring MVP in a community-based cohort.

METHODS

Participants

Beginning in 1948, 5209 men and women were enrolled into the Original cohort.³³ Clustered random sampling was used to select family members aged 30–59 living in the same household. Two-thirds of households were sampled.³³ Their offspring, and the offsprings' spouses were enrolled into the Offspring cohort (n=5124) starting in 1971, with examination cycles performed at approximately 4 to 8 year intervals (Figure 3).³⁴ Children of the Offspring were enlisted in the Generation 3 cohort (n=4095) between 2002 and 2005.³⁵ Selection of the Offspring and Generation 3 cohorts was not random, as it was based on participation of their parents and grandparents in the Heart Study. If the spouse of an Offspring had not enrolled in the FHS and if at least two of his/her biological children participated in Examination 1 of Generation 3, that spouse was invited to participate in the New Offspring Spouse Examination 1.³⁴ While clinical evaluations were performed at each examination cycle for each cohort, echocardiograms were obtained only at select examinations, as illustrated in Figure 3. For the purpose of this study, we selected the most recent cycles for the Offspring cohort (Examinations 6 or 8 between 1996–1998 and 2005–2008, respectively) based on better echocardiographic image quality. Examination 1 (2002–2005) was selected for Generation 3 and the New Offspring Spouse cohort as this is the only cycle with available echocardiographic data for these cohorts.

Participants in our investigation were 3679 Generation 3 individuals (at their first examination cycle) with parents identified in the Offspring cohort (Examinations 6 or 8) or in the New Offspring Spouse cohort (Examination 1). Two groups were identified among our study subjects, one without parental MVP (n=3493) and one with at least one parent with MVP (n=186). We then compared the two groups with regard to their clinical and echocardiographic characteristics. The Boston University Medical Center Institutional Review Board approved the study, and all participants provided written informed consent.

Clinical characteristics

At Generation 3 Examination 1, attendees underwent a routine medical history, targeted physical examination for cardiovascular disease, anthropometry and laboratory assessment of cardiovascular disease risk factors. Clinical variables used in the present investigation included: age, sex, body mass index (BMI), and the presence of a murmur on auscultation (defined as systolic murmur ≥ 3 in any location, and any diastolic murmur). Additional clinical variables such as history of smoking, diabetes, systolic/diastolic blood pressure, and treatment for hypertension were included in the analysis, as these factors may be considered potential “stressors” on the mitral valve acting upon a genetic substrate of MVP. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or treatment for hypertension. We also determined if any of the study participants had a history of congestive heart failure or myocardial infarction, as both these conditions are associated with valvular heart disease (albeit non-primary) and MR.³⁶

Echocardiographic characteristics

All study participants in the Generation 3, Offspring, and New Offspring Spouse cohorts underwent standard two-dimensional echocardiography with a commercially available system (Sonos 1000, Hewlett–Packard Medical Products, Andover, MA) that used a 2.5-MHz transducer. Images included complete parasternal, apical, and subcostal views and color Doppler assessment of valvular regurgitation; they were stored on VHS and digitized for subsequent review. All measurements were performed with an off-line cardiac analysis system (Digiview, Houston, TX).

Using current two-dimensional echocardiographic criteria,^{7,8} Generation 3 MVP was diagnosed as leaflet displacement > 2 mm beyond the mitral annulus in a parasternal or apical long-axis view at end-systole (Figure 1A). Echocardiograms in Generation 3 were examined blinded to parental MVP diagnosis and clinical history. Parental MVP was diagnosed using similar criteria in the Offspring cohort at Examinations 6 or 8 (if 6 not available), and in the Offspring Spouse cohort at Examination 1. Parental NDM was defined as ≥ 2 mm leaflet displacement beyond the annulus in the same echocardiographic views (Figure 2).^{1,30,32} In all three cohorts, participants were first identified by FHS sonographers as having possible systolic displacement. The diagnosis of MVP or NDM was then confirmed by two cardiologists (EJB and FND).^{1,32} Left atrial size was calculated as the maximal antero-posterior left atrial diameter in systole on M-mode images. MR was assessed qualitatively by 2D color Doppler in a long-axis view and graded as trace, mild, moderate or severe.

Left ventricular internal diameters were obtained in diastole and systole by use of a leading-edge technique and averaging of M-mode measurements from at least 3 cardiac cycles. Left ventricular end-diastolic and end-systolic volumes (LVEDV/LVESV) were derived from M-mode measures by the Teichholz method, and left ventricular ejection fraction was defined as $100 \times (\text{LVEDV} - \text{LVESV}) / \text{LVEDV}$.³⁷

Correlation coefficients among observations made by the same reader on different occasions or among different observers reading the same images were derived from a previous FHS publication¹ to estimate inter- and intra-observer variability for mitral leaflet displacement and degree of MR. These correlations have been previously shown to exceed 0.97 in 20 participants of the Offspring cohort.^{1,32}

Statistical methods

Clinical and echocardiographic characteristics were compared between the two groups (Generation 3 participants with and without parental MVP). We used t-tests to compare continuous variables and Chi-squared tests to compare binary variables (Fisher's exact test for binary variables with low frequencies). We performed logistic regression to estimate the associations of parental MVP and NDM with prevalence of MVP in their children in Generation 3. Multivariable models were estimated adjusting for age, sex, BMI, systolic and diastolic blood pressure. We used the GLIMMIX procedure with a G-side variance components structure to accommodate correlated responses among siblings (equal

correlations among all sibling pairs). All analyses were conducted using SAS version V9.3 (Cary, NC). A two-sided p value < 0.05 was the criterion for statistical significance.

RESULTS

Clinical Characteristics

Clinical characteristics of the 3679 Generation 3 participants (53% women; mean age 40 ± 9 years) with available parental data are summarized in Table 1. The groups with ($n=186$) and without ($n=3493$) parental MVP had similar age, sex, BMI, history of smoking, congestive heart failure, myocardial infarction, diabetes, and a similar prevalence of murmur on auscultation ($p > 0.05$ for all comparisons). Generation 3 participants who had parental MVP had a lower proportion of individuals with hypertension and a lower BMI compared to those without parental MVP ($p=0.003$, and <0.0001 , respectively). Sibling distribution of Generation 3 participants is detailed in a supplemental table (see Online Data Supplements).

Echocardiographic Characteristics

Echocardiographic characteristics are compared in Table 2 based on parental MVP status. Among 3679 participants, 49 had MVP (53% women; mean age 40 ± 8 years). Prolapse most commonly involved only the posterior mitral valve leaflet (21/49 [44%]) followed by bileaflet (16/49 [33%]) and anterior MVP (11/49 [23%]). Generation 3 participants with parental MVP had a higher prevalence of MVP (10/186 [5%] versus 39/3493 [1%], $p < 0.0001$) compared to their counterparts without parental MVP, and a greater prevalence of MR (mild or greater MR in 59/186 [32%] versus 661/3493 [19%], $p < 0.0001$). When we evaluated the prevalence of the combination of MR and MVP, Generation 3 participants with parental MVP also had higher prevalence of MVP-related MR (Table 2, $p < 0.0001$). Of the 10 Generation 3 MVP individuals with parental MVP, only four had analogous leaflet involvement in one of their parents (specifically three Generation 3 MVPs with posterior and one with bileaflet MVP). There were no significant differences in left ventricular diameters, volumes, or ejection fraction between the two groups (parental and non-parental MVP) (Table 2).

Contribution of non-diagnostic MVP morphologies

There were 484/3679 Generation 3 participants with at least one parent with NDM (≥ 2 mm leaflet displacement beyond the mitral annulus without diagnostic criteria for MVP). Of these 484, 12 had MVP, a higher prevalence (2.5%) compared with Generation 3 individuals without parental MVP or NDM (27/3009 [0.9%]).

Association of MVP in Generation 3 participants with parental MVP status

As shown in Table 3, compared with absence of parental MVP, the presence of MVP in one or both parents was associated with greater odds of prevalence of MVP in their children in Generation 3 (multivariable-adjusted odds ratio [OR], 4.51; 95% confidence interval [CI], 2.13–9.54; $p < 0.0001$). The association remained statistically significant even when paternal and maternal MVP were considered separately (multivariable-adjusted OR, 4.96; 95% CI, 1.81–13.57; $p=0.001$ and OR, 5.13; 95% CI, 2.07–12.74; $p=0.0004$, respectively). In addition, when parental NDM was examined alone, the prevalence of Generation 3 MVP

was higher compared to those without MVP or NDM in their parents (multivariable-adjusted OR, 2.52; 95% CI, 1.25–5.10; $p=0.01$).

DISCUSSION

Primary findings

In our community-based sample, parental MVP was associated with a higher prevalence of MVP in Generation 3 after adjustment for standard risk factors, including age, sex, body size, and hypertension. Prior studies on MVP inheritance have focused on observations of pedigrees, case reports in selected individuals with late systolic clicks or investigations that used older M-mode echocardiographic diagnostic criteria for the condition. To our knowledge, our study is the first to demonstrate that a familial component exists for MVP among unselected individuals in the community using current and more specific echocardiographic criteria for this valvulopathy. Interestingly, non-diagnostic MVP morphologies previously described among gene carriers in large pedigrees were associated with increased prevalence of Generation 3 MVP in our community-based study. Thus, mild parental MVP expression may potentially represent more than just an echocardiographic subtlety in the community. Familial clustering of MVP motivates additional studies to elucidate the genetic determinants of this condition.

To date, three loci for autosomal dominant, non-syndromic MVP have been described on chromosomes 11, 16 and 13.^{28–30} Whereas filamin A has been identified as causing an X-linked form of MVP,^{31, 38} the genes for the more common form of autosomal dominant MVP are unknown. Nevertheless, discovery of multiple loci suggest that MVP is a heterogeneous disease and represents an important step towards gene discovery.

There was no statistical difference between Generation 3 participants with and without parental MVP with regard to the prevalence of smoking, diabetes (potential metabolic “stressors” to the mitral valve), or other cardiac pathology (myocardial infarction and congestive heart failure) associated with MR, indicating that these factors (which also have a familial basis) did not contribute to the familial clustering of MVP. Of note, Generation 3 participants with parental MVP had a lower BMI and less hypertension. Hence, inheritance of MVP may be associated with the same favorable metabolic and hemodynamic profile previously observed in Offspring parents with MVP.¹ Lastly, the two groups (with and without parental MVP) had similar small numbers of individuals with a murmur on auscultation (diastolic or systolic), highlighting that the prevalence of clinically detectable valvular disease from all causes was low and could not adequately identify people with familial MVP.

On echocardiography, Generation 3 participants with parental MVP had a higher prevalence of MVP and MVP-related MR, suggesting that the familial basis for MVP includes clustering of a clinical component (mitral regurgitation). As previously observed in selected pedigrees,^{30, 39} variation of leaflet involvement and morphological heterogeneity were also observed among related individuals in our community-based study. This spectrum of valvular abnormalities may represent variations in disease expression, stage of progression, or modifying factors within FHS families. Finally, similar left ventricular dimensions in the

two groups (with and without parental MVP) suggest that MVP was likely not a consequence of a small, hyperdynamic left ventricle. Similarly, there was no difference in left atrial size between the two groups; hence, the degree of MR observed was associated with the primary valve disease, and not with dilated cardiac chambers.

Strengths and limitations

The strengths of our investigation include the unique availability of multi-generational clinical and echocardiographic data, a well characterized phenotype using a contemporary definition, and the ability to evaluate NDM systematically. In contrast, a self-report of MVP or a family history of MVP would likely be more susceptible to ascertainment bias. In addition, MVP was diagnosed blinded to parental MVP status, and risk factors potentially contributing to MVP risk (blood pressure, age, sex, BMI etc.) were systematically and routinely ascertained. Finally, our sample was community-based and our participants were unselected, reducing the likelihood that our sample was enriched for rare genetic variants that may contribute to a familial basis for MVP.

Our study has several limitations. First, our analysis was limited to a single sample of European ancestry and the results may not be generalizable to other populations. Second, the parental MVP sample size was small; hence, some of the non-significant comparisons (between the groups with and without parental MVP) may have been statistically underpowered. Third, as data on Generation 3 was available at only a single time point, we could not assess the association of parental MVP with longitudinal progression of MVP in offspring. Fourth, the true prevalence of familial MVP within and across generations in the FHS could not be assessed comprehensively. Specifically, the number of participants with prevalent MVP in Generation 3 and available parental information was low. There was a limited number of siblings with MVP (3 sib pairs, 0 triplets). However, this may be considered a relative strength as our results are not driven by unusual large pedigrees with rare genetic profiles. Fifth, there was a lack of data on grandparental MVP status in the original Framingham Heart Study cohort (parents of Offspring cohort participants). Current diagnostic criteria for MVP were not implemented at the time of acquisition of echocardiographic data for the Original cohort. In addition, two-dimensional echocardiographic studies were obtained for Original cohort attendees at examination cycle 20, at which time most participants were older than 75 years and many had died. Moreover, we did not assess the risk of developing NDM in Generation 3 based on parental MVP (or parental NDM). We focused on MVP as a primary outcome because this phenotype is better characterized from a prognostic perspective. Although our study has increased our knowledge about the potential clinical significance of NDMs by linking them to the risk of developing MVP, the potential of NDMs to progress to fully diagnostic MVP and/or significant mitral regurgitation remains unknown. Lastly, no systematic assessment of Marfan syndrome (another genetic condition associated with MVP) was conducted during the clinical examinations at the Heart Study.

Clinical and Research Implications

Parental MVP is associated with greater odds of MVP in the offspring, an observation consistent with a genetic contribution to MVP. Prior studies of large pedigrees have

suggested that there are rare, penetrant alleles that cause MVP, and given the discovery of multiple loci associated with such familial disease, they also inform us of the locus heterogeneity of this disease. Familial clustering of MVP *in the community* is consistent with the potential contribution of both rare alleles (with strong effect size) and common variants to MVP occurrence in families. Although MVP prognosis is overall benign in the FHS community,¹ there is a minority of individuals that does progress to severe MR. Parental MVP may be an important determinant of MVP progression, and further studies are needed to identify the genetic determinants (either susceptibility or modifier genes) and the environmental factors involved in the progression of MVP to significant clinical sequelae. Familial clustering of MVP also raises the possibility of screening ‘clinically silent’ unaffected family members. This premise warrants more careful examination in future cost-effectiveness studies, perhaps in a referral-type population with a more severe MVP phenotype.

CONCLUSIONS

Parental MVP and non-diagnostic MVP morphologies are both associated with a higher prevalence of MVP in their offspring. Such familial clustering of MVP motivates additional studies to elucidate the genetic determinants of this condition and investigate the potential role of screening of clinically silent family members of affected individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: This work was supported by the Founders Affiliate American Heart Association Clinical Research Program (Francesca N. Delling), and by the National Heart, Lung and Blood Institute Framingham Heart Study Contract No. N01-HC-25195, and research grants R01HL080124, R01HL0107385 (Ramachandran S. Vasan), and K23HL116652 (Francesca N. Delling).

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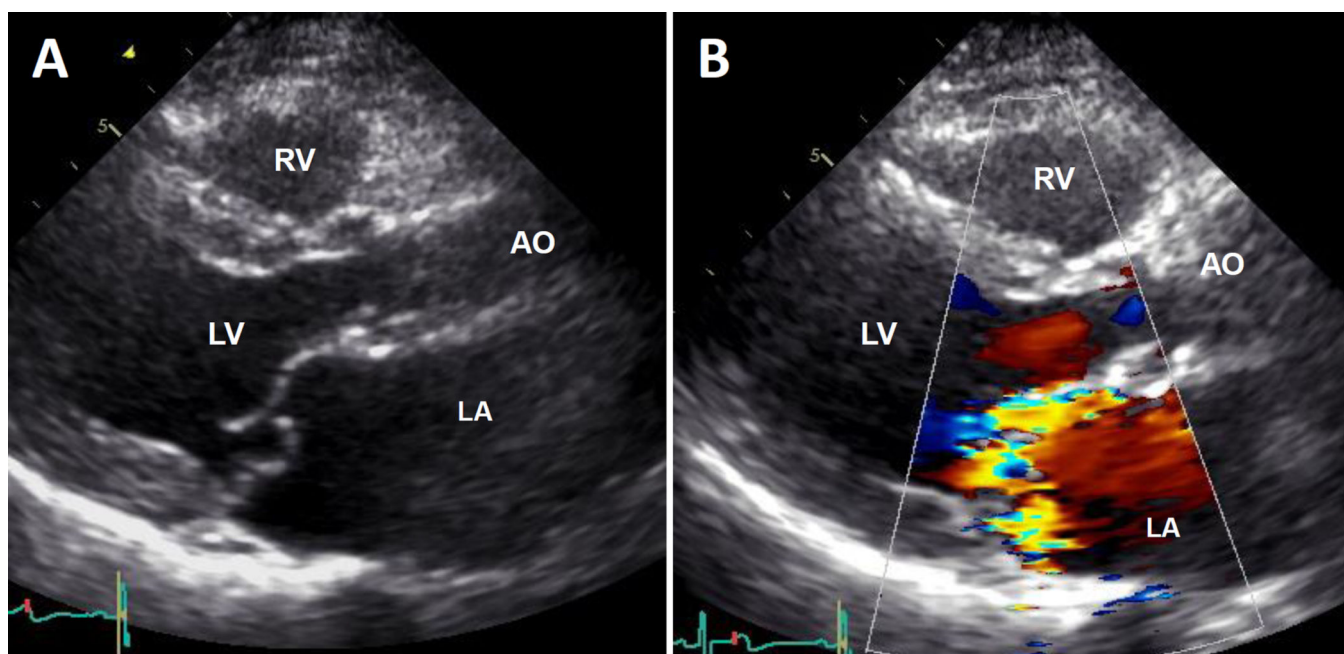


Figure 1.
Example of A) posterior mitral valve prolapse with B) severe mitral regurgitation shown in a long axis view of a 2D transthoracic echocardiogram. 2D, two dimensional. AO, aorta; LV, left ventricle; and RV, right ventricle.

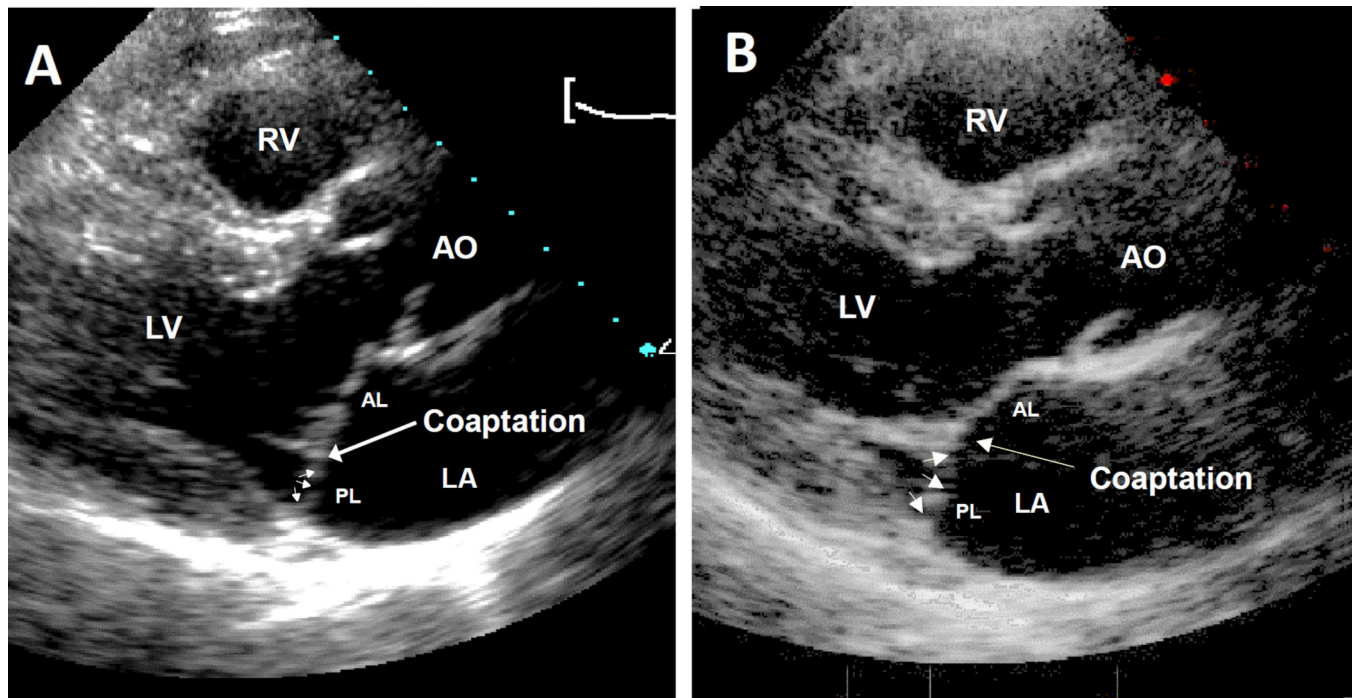


Figure 2.

Two-dimensional parasternal long axis image demonstrating non-diagnostic morphologies: A) minimal systolic displacement with posteriorly coapting leaflets (anterior leaflet [AL]; posterior leaflet [PL]), posterior leaflet asymmetry, but with borderline degree of displacement (≤ 2 mm, involving the posterior leaflet, small arrows); B) 'abnormal anterior coaptation' morphology with increased coaptation height and an elongated posterior leaflet. AO, aorta; LV, left ventricle; and RV, right ventricle.

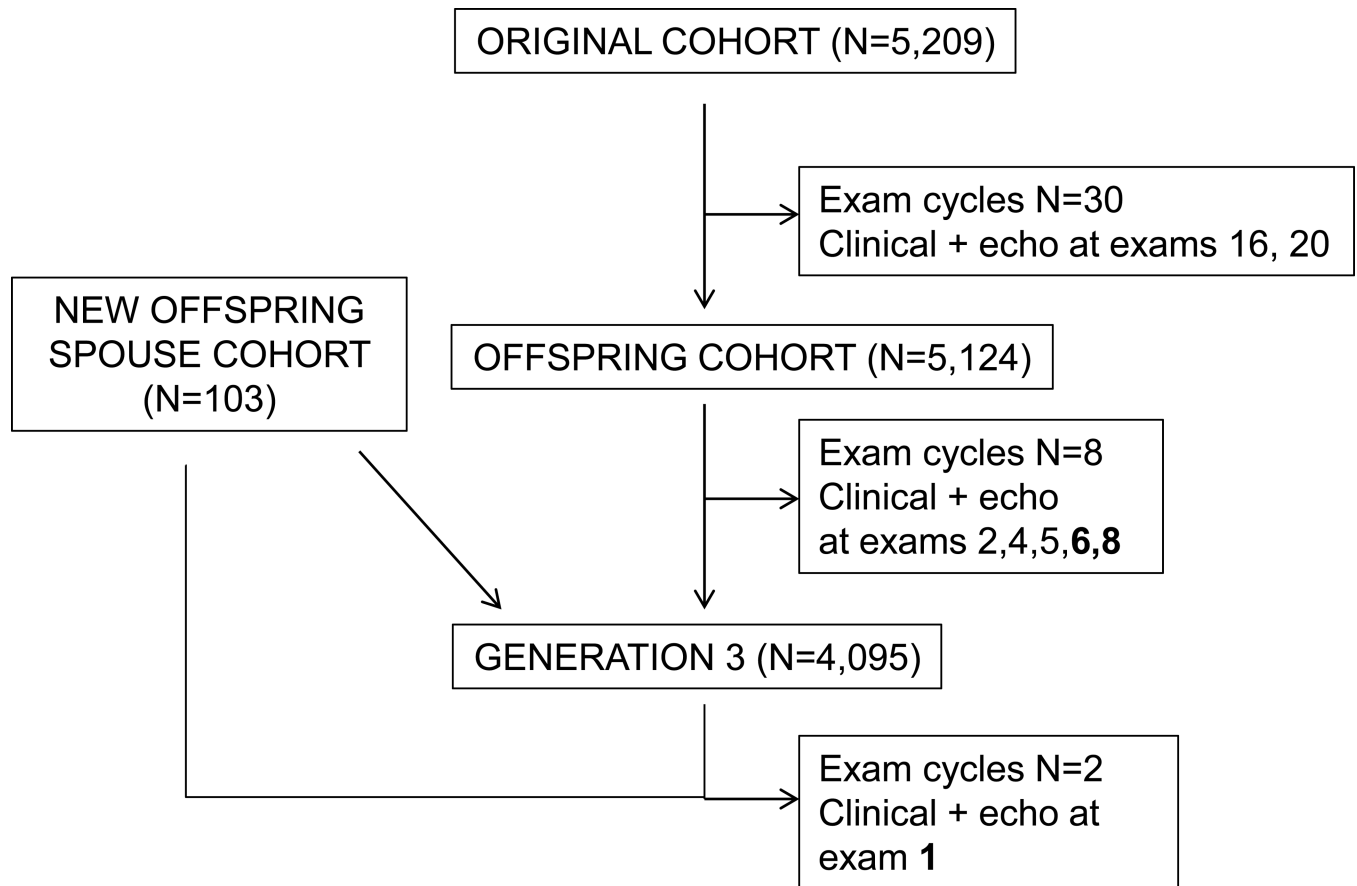


Figure 3.

Patient cohorts in the Framingham Heart Study. Examination cycles are at 2 year intervals for the Original Cohort, at 4–8 years for the Offspring, New Offspring Spouse cohorts and Generation 3. The examinations at which individuals participating in this study underwent both a clinical evaluation and an echocardiogram are shown in bold. The numbers of participants with both clinical and echocardiographic examinations were as follows: N = 3418 and 2888 for Offspring examinations 6 (total N = 3532) and 8 (total N = 3021), respectively; N=103 for New Offspring Spouse examination 1 (total N = 103); N=4080 for Generation 3 examination 1 (total N = 4095).

Table 1

Clinical Characteristics of Generation 3 participants according to parental MVP status

	No Parental MVP N=3493	Parental MVP N = 186	P value
Age, years	39 (8)	40 (8)	0.47
Women, n (%)	1851 (53)	104 (56)	0.43
BMI, kg/m ²	26.9 (5.6)	25.3 (4.5)	<0.0001
Hypertension, n (%)	564 (16)	15 (8)	0.003
Smoking, n (%)	595 (17)	23 (12)	0.09
Diabetes, n (%)	104 (3)	5 (2)	0.81
CHF or myocardial infarction, n (%)	16 (0.5)	0 (0)	0.35
Murmur, n (%)	30 (0.4)	1 (0.5)	0.64

MVP = Mitral valve prolapse; BMI = Body Mass Index; CHF = Congestive Heart Failure. Values in parentheses are percentages for categorical and standard deviations for continuous variables.

Table 2

Echocardiographic Characteristics of Generation 3 participants according to parental MVP status

	No Parental MVP N=3493	Parental MVP N = 186	P value
MVP, n (%)	39 (1)	10 (5)	< 0.0001
mild MR, n (%)	661 (19)	59 (32)	0.006
MVP + mild MR, n (%)	11 (0.3)	7 (4)	<0.0001
LADS, cm	3.7 (0.5)	3.6 (0.4)	0.08
LVEDD, cm	4.9 (0.4)	5.0 (0.4)	0.25
LVESD, cm	3.2 (0.3)	3.2 (0.3)	0.17
LVEDV, ml	116 (22)	117 (20)	0.30
LVESV, ml	40.9 (10.4)	41.8 (9.5)	0.24
LVEF, %	65 (4)	64 (3)	0.38

MVP = mitral valve prolapse; MR = mitral regurgitation; LADS = left atrial dimension in systole; LVEDD = left ventricular (LV) end-diastolic dimension; LVESD = LV end-systolic dimension; LVEDV = LV end-diastolic volume; LV end-systolic volume; LVEF = LV ejection fraction. Values in parentheses are percentages for categorical and standard deviations for continuous variables.

Table 3

Association of prevalence of MVP in Generation 3 according to parental MVP status

	Age-sex adjusted		Multivariable-adjusted*	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Maternal MVP present (vs. absent)	5.57 (2.25–13.73)	0.0002	5.13 (2.07–12.74)	0.0004
Paternal MVP present (vs. absent)	5.19 (1.92–14.06)	0.001	4.96 (1.81–13.57)	0.001
One/both parents with MVP (vs. none)	4.98 (2.36–10.49)	<0.0001	4.51 (2.13–9.54)	<0.0001

MVP = mitral valve prolapse; OR = odds ratio; CI = confidence interval.

* Models adjusted for age, sex, BMI, systolic and diastolic blood pressure.