ORIGINAL ARTICLE

Secular trends in echocardiographic left ventricular mass in the community: the Framingham Heart Study

Bernhard M Kaess,[1,2,3] Philimon Gona,[1,4] Martin G Larson,[1,5] Susan Cheng,[6] Jayashree Aragam,[7,8] Satish Kenchaiah,[9] Emelia J Benjamin,[1,9,10] Ramachandran S Vasan[1,8]

▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2013-304600).

For numbered affiliations see end of article.

Correspondence to
Dr Ramachandran S Vasan, Framingham Heart Study, 73 Mt Wayte Ave, Suite 2, Framingham, MA 01702–5803, USA; vasan@bu.edu

Received 14 July 2013
Revised 25 August 2013
Accepted 27 August 2013
Published Online First 16 September 2013

ABSTRACT

Objective To investigate secular trends in echocardiographically determined left ventricular mass (LVM).

Design, setting and participants Longitudinal community-based cohort study in Framingham, Massachussetts. LVM was calculated from routine echocardiography in 4320 participants (52% women) of the Framingham offspring cohort at examination cycles 4 (1987–1991), 5 (1991–1995), 6 (1995–1998) and 8 (2005–2008), totalling 13 971 person-observations.

Main outcome measures Sex-specific trends in mean LVM (and its components, LV diastolic diameter (LVDD) and LV wall thickness (LVWT)), and LVM indexed to body surface area (BSA).

Results In men, age-adjusted LVM modestly increased from examination 4 to 8 (192 g to 198 g, p-trend=0.0005), whereas, in women it decreased from 147 g at examination 4 to 140 g at examination 8 (p-trend<0.0001). The trend for increasing LVM in men tracked with an increasing LVDD (p-trend=0.0002), whereas the decline in LVM in women was accompanied by a decrease in LVWT (p-trend<0.0001). Indexing LVM to BSA abolished the increasing trend in men (p-trend=0.49), whereas, the decreasing trend in women was maintained.

Conclusions In our longitudinal analysis of a large community-based sample spanning two decades, we observed sex-related differences in trends in LVM, with a modest increase of LVM in men (likely attributable to increasing body size), but a decrease in women. Additional studies are warranted to elucidate the basis for these sex-related differences.

Left ventricular hypertrophy (LVH) is a major risk factor for systolic and diastolic heart failure, coronary artery disease, stroke and mortality.[1–4] Apart from age, elevated blood pressure, diabetes and obesity have been identified as critical determinants of increased LV mass (LVM).[5 6] Over the last decades, there have been considerable efforts to control these risk factors, but epidemiological data indicate contrasting patterns in prevalence of these risk factors. For instance, hypertension prevalence has increased, but at the same time hypertension control has improved in recent decades in the USA.[7] Obesity prevalence has increased over the same time period, accompanied by a rising prevalence of diabetes.[8–10] It is unclear if and how these opposing population trends for key determinants of cardiac mass have influenced mean LVM and the prevalence of echocardiographic LVH in the community. Data from the Framingham Heart Study from an earlier time period (1950–1989) indicate that the prevalence of ECG LVH has decreased markedly over that time period, paralleled by and likely related to better control of hypertension.[11] However, these data did not evaluate trends over the more recent decades (1990–2000s) and were based on electrocardiographic criteria for LVH; echocardiography is a more sensitive tool for assessing LVM and for ascertaining the prevalence of LVH.[12] Accordingly, we investigated temporal trends in mean values of LVM mass in a large community-based cohort that underwent serial routine echocardiography over the last two decades and is under continuous surveillance for development of cardiovascular disease events. Given that men and women differ in LV size and morphology, and that known determinants of LV mass exhibit differential effects in men versus women,[6] we specifically assessed sex-related differences in the temporal trends in LVM in our sample.

METHODS

Study sample

The sample comprised participants of the Framingham Offspring Study.[13] Beginning in 1971, investigators enrolled 5124 individuals into the offspring cohort who were the children or the children's spouses of the participants from the original cohort of the Framingham Heart Study. Participants in the Framingham offspring cohort are evaluated approximately every 4–8 years. They undergo a routine examination at the Heart Study that includes an extensive cardiovascular history, a physical examination, blood pressure determination, anthropometry, a 12-lead ECG, and phlebotomy for assessment of cardiovascular disease risk factors. Body Mass Index (BMI) was defined as body weight (kg) divided by square of height (m). Hypertension was defined as blood pressure ≥140/90 or use of antihypertensive medications.[14] Diabetes was defined as fasting glucose ≥126 mg/dL or the use of antidiabetic medications.[15]

All participants provided written informed consent at each heart study examination, and the

To cite: Kaess BM, Gona P, Larson MG, *et al*. *Heart* 2013;**99**:1693–1698.

study protocols for these examinations were approved by the institutional review board at the Boston University Medical Center.

Echocardiography

The current investigation focused on the last two decades when two-dimensional echocardiography was routinely performed, that is, examination cycles 4 (1987–1991), 5 (1991–1995), 6 (1996–1998) and 8 (2005–2008). The echocardiographic equipment varied with examinations: Hewlett Packard (model 77020AC) ultrasound machine at examination cycles 4 and 5; Sonos 1000 Hewlett Packard machine at examination cycle 6 and Sonos 5500 at examination cycle 8. At each of these examinations, two-dimensionally guided M-Mode tracings were recorded with a minimum of three frames for measuring and averaging LVM. All echocardiograms were evaluated by an experienced sonographer or cardiologist using a standardised reading protocol, with routine implementation of a rigorous quality control protocol at examination cycles 5 through 8 (see online supplementary text and table S1 for details). Briefly, we assessed reproducibility of measurements made by the sonographers and cardiologist readers over time (between examinations 5 through 8) using a calibration set of echocardiograms (to assess shifts and drifts in reading), combined with joint reading sessions and substitition of two-dimensional LV measurements when M-Mode LV images were inadequate. Readers were not blinded to sex at any given examination cycle. The end-diastolic thicknesses of the LV septum and posterior wall thickness, and LV internal dimensions at the end-diastole LV diastolic diameter (LVDD) and end-systole were measured using a leading edge to leading edge technique as recommended by the American Society of Echocardiography (ASE).[16] LVM was calculated according to ASE guidelines, using the method of Devereux *et al.*[16] as $0.8(1.04((\text{LV internal dimensions}+\text{septal wall thickness}+\text{posterior wall thickness})^3-(\text{LV internal dimensions})^3))+0.6$. The sum of the diastolic thicknesses of the septum and posterior wall was used as an estimate of LV wall thickness (LVWT). The reproducibility of echocardiographic measurements was very good, as reported previously[17] (see also online supplementary text and table S1). To account for height and body weight, we indexed LVM to body surface area (BSA). BSA was calculated using the DuBois formula as $\text{BSA(m)}=\text{weight (kg)}^{0.425} \times \text{Height(cm)}^{0.725}\times 0.007184$.[18] The presence of echocardiographic LVH was defined as height-indexed LV mass >126 g/m in men and >99 g/m in women, respectively, according to ASE criteria.[19]

Statistical analyses

In primary analyses, we included all available echocardiographic measurements performed in participants aged 30–79 years at each of the examinations, which yielded 6569 observations in men (2058 unique individuals) and 7402 in women (2262 unique individuals). However, since myocardial infarction and heart failure may distort LV geometry (violating assumptions used for calculating LV mass), we also performed sensitivity analyses excluding all observations that were obtained from participants with a history of myocardial infarction or congestive heart failure at the time of the individual echocardiographic assessment. After exclusion of 561 observations, these analyses were performed using 6130 echocardiographic measurements in men (derived from 1925 unique male participants) and 7280 in women (2239 unique female participants).

Adjusted mean values for LVM, LVDD and LVWT were calculated for each examination using sex-specific linear regression models with examination cycle as a predictor variable and LVM as the dependent variable. We assessed two sex-specific models: (1) adjusting only for age; and (2) adjusting for age and major clinical determinants of LVM (excluding height and weight), namely systolic blood pressure, antihypertensive treatment, diabetes mellitus and smoking. These models included covariate measurements from each examination cycle. Repeated measurements of the same individual were accommodated using mixed-effects modelling (SAS PROC GLIMMIX) with a compound symmetry covariance matrix. Adjusted means for LVM, LVDD and LVWT were compared to the values at examination 4 (referent examination) using Dunnett's tests, which account for multiple testing within the assessed group of comparisons. Additionally, we assessed linear trends across examinations. Sex-interaction for LVM trends over time was assessed using a 'three degrees of freedom' test with examination as a class variable in an age-adjusted model pooling both sexes. Use of a 'one degree of freedom' sex interaction test on the linear trends in LVM yielded a similar result ($p<0.0001$).

Age-adjusted ORs for LVH were derived from a logistic mixed-effects model with a compound symmetry covariance matrix. In all models, a two-tailed p value of <0.05 was considered statistically significant. All statistical analyses were performed with SAS V.9.2 for Windows.

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

Clinical, biochemical and echocardiographic characteristics of the study sample across examination cycles by sex are listed in table 1. The (unadjusted) prevalence of echocardiographic LVH increased across examinations in men but declined in women. Age-adjusted characteristics are displayed in online supplementary table S2. In both sexes, age-adjusted systolic and diastolic blood pressure decreased across examinations and were paralleled by rising rates of antihypertensive medication use and declining smoking prevalence. Mean BMI rose across examinations, as did prevalence of diabetes.

Sex-specific secular trends in mean LV mass and presence of LV hypertrophy

Age-adjusted mean LVM in men and women at each examination is shown in table 2. In men, LVM showed a moderate, but significant trend of increasing values over time ($p=0.0005$ for trend), although mean LVM at examination cycle 5 was slightly lower compared with that at examination cycle 4 ($p<0.0001$), which served as the referent. The age-adjusted OR for echocardiographic LVH at examination 8 (compared with examination 4) was estimated at 1.41 (95% CI 1.09 to 1.83, $p=0.008$; figure 1). After indexing LVM to body surface, we no longer observed a consistent trend over time in men ($p=0.49$ for trend; table 2).

In women, mean age-adjusted LVM decreased modestly across the examinations with a highly significant linear trend ($p<0.0001$ for trend), and findings for LVM indexed to BSA were very similar ($p<0.0001$ for trend). The age-adjusted OR for echocardiographic LVH at examination 8 (compared with examination 4) was estimated at 0.46 (95% CI 0.37 to 0.57, $p<0.0001$; figure 1).

The observed sex difference in LVM trends was statistically significant ($p<0.0001$ for interaction test, see Methods for details). In both sexes, results were maintained in multivariable-adjusted analyses that incorporated several known correlates of LVM, and in analyses limited to participants who were free of

Table 1 Clinical and echocardiographic characteristics of the study population

	Men				Women			
	Exam 4 (n=1911)	Exam 5 (n=1784)	Exam 6 (n=1639)	Exam 8 (n=1235)	Exam 4 (n=2066)	Exam 5 (n=1997)	Exam 6 (n=1858)	Exam 8 (n=1481)
Age, years	52±10	55±10	59±10	65±8	52±10	55±10	59±10	65±8
BMI, kg/m²	27.7±3.9	28.2±4.2	28.6±4.4	29.1±4.8	26.1±5.5	26.8±5.5	27.4±5.7	27.9±6.0
SBP, mm Hg	130±18	129±17	130±17	128±16	125±20	124±20	127±20	127±17
DBP, mm Hg	81±10	77±10	77±9	75±10	77±10	73±10	74±9	73±9
Hypertension, %	42	38	45	63	31	31	38	53
Antihypertensive treatment, %	21	21	31	54	16	18	26	44
Diabetes, %	6.8	9.6	12	20	4.0	5.8	8.2	13
Smoking, %	24	19	15	9	25	20	16	10
Myocardial infarction, %	4.9	5.6	6.4	8	0.7	0.9	1.2	2
Heart failure, %	0.5	0.8	1.5	3	0.3	0.6	0.7	1
ECG-LVH (Sokolow-Lyon)*, %	8	10	7	5	2	2	2	2
LVM, g	188±43	183±38	192±43	202±46	144±30	140±30	140±31	143±32
LVMI, g/m²	95±22	91±19	96±20	99±21	84±16	82±16	80±16	81±16
LVWT, cm	1.99±0.23	2.00±0.25	2.02±0.26	2.07±0.26	1.83±0.20	1.82±0.23	1.82±0.22	1.80±0.22
LVDD, cm	5.10±0.45	4.99±0.41	5.10±0.49	5.13±0.47	4.65±0.40	4.58±0.38	4.56±0.41	4.67±0.39
LVH (ASE)†, %	13	12	22	27	29	25	23	26

Continuous variables summarised by mean±SD, binary variables presented as percentage.
*Defined as a combined voltage of S in V1 or V2 plus R in V5 or V6 ≥3.5 mV.
†Defined by height-standardised LVM ≥126 cm³/m in men and ≥99 cm³/m in women, respectively.
ASE, American Society of Echocardiography; BMI, Body Mass Index; DBP, diastolic blood pressure; ECG-LVH, electrocardiographic left ventricular hypertrophy; LVDD, left ventricular diastolic diameter; LVM, left ventricular mass; LVMI, LVM indexed to body surface area; LVWT, left ventricular wall thickness; SBP, systolic blood pressure.

myocardial infarction and heart failure at individual examinations (see online supplementary tables S3 and S4).

Sex-specific secular trends in LVWT and LV diastolic diameter

To further elucidate the changes in LV geometry underlying the observed trends in LV mass, we separately investigated the two major components of LVM: LVWT and LVDD. The results of age-adjusted models are also shown in table 2. In men, mean LVWT did not vary relevantly across examinations. By contrast, LVDD showed a trend of increasing values across exams (p=0.0002 for trend), although mean LVDD at exam 5 was slightly lower than that at referent exam 4 (p<0.0001). In women, LVWT decreased across examinations (p<0.0001), whereas a U-shaped relation was observed for LVDD, with values at examinations 5 and 6 being lower than those at the referent examination cycle 4 and also compared to examination cycle 8. Multivariable analyses and analyses restricted to participants free of myocardial infarction and heart failure yielded results essentially similar to those observed in age-adjusted analyses (see online supplementary tables S3 and S4).

DISCUSSION

We analysed temporal trends in echocardiographic LVM and underlying ventricular geometry in a large, community-based sample that was followed longitudinally over a two-decade period (from the late 1980s to the late 2000s). We observed an intriguing sex-related difference in LVM trends: in men, mean LVM increased slightly, whereas in women, mean LVM decreased over time. The trend for increasing LVM in men was abolished after accounting for BSA, but the decreasing trend in women was not altered by indexing to BSA. The trend for increasing LVM in men tracks with increasing LVDD over time, whereas the trend for decreasing LVM in women appears to be driven by declining LVWT across examinations.

Table 2 Age-adjusted time trends in LVM, LVDD and LVWT, stratified by sex

	Exam 4	p	Exam 5	p (vs exam 4)	Exam 6	p (vs exam 4)	Exam 8	p (vs exam 4)	p for linear trend
Men									
LVM, g	192 (1.3)	referent	186 (1.1)	<0.0001	192 (1.2)	0.99	198 (1.5)	0.005	0.0005
LVMI, g/m²	96 (0.6)	referent	93 (0.5)	<0.0001	95 (0.5)	0.02	96 (0.7)	0.52	0.49
LVDD, cm	5.09 (0.013)	referent	4.99 (0.012)	<0.0001	5.11 (0.014)	0.69	5.15 (0.017)	0.02	0.0002
LVWT, cm	2.01 (0.007)	referent	2.02 (0.007)	0.38	2.01 (0.007)	0.99	2.03 (0.008)	0.046	0.09
Women									
LVM, g	147 (0.8)	referent	143 (0.8)	<0.0001	140 (0.8)	<0.0001	140 (1.0)	<0.0001	<0.0001
LVMI, g/m²	86 (0.4)	referent	83 (0.4)	<0.0001	80 (0.4)	<0.0001	78 (0.5)	<0.0001	<0.0001
LVDD, cm	4.64 (0.010)	referent	4.58 (0.010)	<0.0001	4.57 (0.010)	<0.0001	4.70 (0.013)	0.001	0.0013
LVWT, cm	1.86 (0.005)	referent	1.84 (0.006)	0.053	1.82 (0.005)	<0.0001	1.76 (0.007)	<0.0001	<0.0001

Data are presented as mean (SE). p Values for comparisons between exams were adjusted for multiple testing by Dunnet-Hsu correction.
LVDD, left ventricular diastolic diameter; LVM, left ventricular mass; LVMI, LVM indexed to body surface area; LVWT, left ventricular wall thickness.

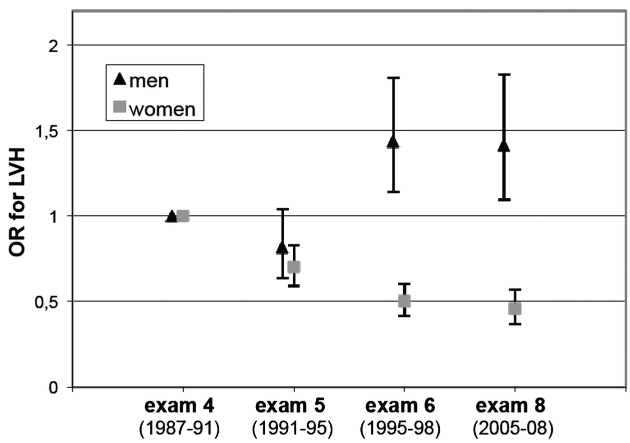

Figure 1 Sex-specific trends in echocardiographic left ventricular hypertrophy. Data are ORs with examination cycle 4 as referent. Error bars represent 95% CIs.

Trends in LV mass: sex-related differences

An earlier investigation from the Framingham Heart Study evaluated electrocardiographic LVH and noted a decreasing prevalence during the time period 1950–1989,[11] a time frame in which use of antihypertensive medication rose sharply. In the present study, we extend these observations into a contemporary time period using a more sensitive tool for assessing cardiac mass, namely echocardiography. Interestingly, we demonstrate disparate trends in both sexes. We can only speculate about the potential factors underlying these sex-related differences in temporal trends in LVM. The slightly increasing trend in LVM in men was abolished after indexing LVM to BSA, indicating that the trend was driven by increasing body size. However, body size in women increased similarly over time, with no concomitant increase in LVM. It seems plausible that the reduction of LVM in women may be secondary to improved treatment of hypertension, a possibility supported by a strong trend for increasing use of antihypertensive medications across the examinations. However, men in the cohort experienced an equally dramatic increase in the use of antihypertensive treatment without an accompanying decrease in LVM. This raises the intriguing possibility that women experienced a greater reduction in LVM with institution of antihypertensive treatment (compared to men). Several studies have investigated the effect of antihypertensive drugs and demonstrated that treatment with inhibitors of the angiotensin-aldosterone system, as well as β blockers and other agents, can reduce LV mass, largely independent of the magnitude of blood pressure lowering.[20–23] The SARA study (eStudio del trAtamiento con candesaRtan en pacientes con hipertension Arterial según criterios electrocardiográfico) noted that women on antihypertensive treatment experienced greater LVH regression assessed using Cornell voltage-based ECG criteria (compared to men).[24] However, the LIFE study (Losartan Intervention for Endpoint Reduction in Hypertension) reported similar reductions in echocardiographic LVM in both sexes.[22] Overall, there is no unequivocal evidence establishing sex-related differences in LVM regression in response to antihypertensive treatment. Nevertheless, limited data suggest that women are more prone than men to developing concentric remodelling in response to hypertension,[25] and animal models have confirmed sex-related differences in cardiac remodelling responses to pressure-overload.[26] Also, histologic studies indicate that women may be less prone than men to develop cardiomyocyte dropout and replacement fibrosis over time, which may potentially render hypertrophic cardiac tissue in women more amenable to regression compared to men.[27]

Another potential explanation of our findings may be that women have a better drug compliance (for antihypertensive treatment) than men. Alternatively, the disparate trends in LVM in women versus men may be driven by a higher prevalence of diabetes in men in our sample. Diabetes strongly enhances age-related LVM growth and reduces beneficial effects of antihypertensive treatment on LVM.[6 28] Lastly, it is also possible that other unidentified factors may have contributed to the sex-related differences we observed.

Trends in LV diameter and wall thickness

In our study, the trend for decreasing LVM mass in women appeared to be driven by a decrease in LVWT, whereas the mean LV diameter showed no consistent pattern. In the LIFE trial, a reduction of approximately 2 mm in posterior wall thickness was reported for both the angiotensin receptor blocker and the β blocker arms, after long-term treatment.[22] Hence, our observed reduction in LVWT of about 1 mm in women may appear seemingly trivial, but it is well within the range that can be expected in a partly treated sample. However, the LIFE study also showed an increase in LVDD with antihypertensive therapy[22] which is not consistently reflected in our data. The slight increase in LVM in men (who experienced similar increase in antihypertensive agent use) casts further doubt on this explanation.

LVH: prognostic implications

It is widely accepted that LVH is an adaptive response to increased afterload, neurohumoral and inflammatory stimuli. Increased LVWT can lead to LV diastolic dysfunction and decreased perfusion of the inner myocardium. LVM increases with age.[6] In the regression models for our present analyses, an expected age-related annual increase of 0.55 g in LVM was estimated for women. Hence, our observed age-adjusted decrease in LVM of 7 g in women from exam 4 to 8 corresponds to a reversal of approximately 13 years (7/0.55) of cardiac aging. Similarly, in men, our regression models estimated an expected age-related annual increase of 0.63 g in LVM. The observed age-adjusted increase of 6 g from examination 4 to 8, therefore, translates to almost 10 years (6/0.63) of additional cardiac aging.

Furthermore, in the Framingham Heart Study, presence of echocardiographic LVH was associated with a more than 50% increased risk for incident cardiovascular events after adjusting for standard cardiovascular risk factors.[2] Correspondingly, a recent meta-analysis reported that regression of echocardiographic LVH with hypertension treatment was associated with an adjusted 46% risk reduction for cardiovascular events.[29] Hence, the disparate trends in echocardiographic LVH observed in men and women in the present investigation may be prognostically important, a premise that warrants further evaluation. Of note, LVM is an accepted precursor of heart failure, and Framingham data have reported a trend for decreasing incidence of heart failure in women (consistent with decrease in mean LVM in this group), but not in men.[30]

Strengths and limitations

To our knowledge, the present investigation is the first report of epidemiological trends in echocardiographic LVM in the community. Our study is based on longitudinal observations of a pre-enrolled closed cohort, precluding recruitment artefacts in the observed trends. The design of the Framingham Heart Study with periodic on-site examinations of participants and

 Kaess BM, *et al*. *Heart* 2013;**99**:1693–1698. doi:10.1136/heartjnl-2013-304600

strict quality-control protocols assure the high quality of echocardiographic and clinical data. Nevertheless, some limitations of our study should be acknowledged. Due to technical advances, the ultrasound equipment changed over time, introducing possibly a source of bias. However, any potential systematic bias would be expected to similarly affect measurements in men and women, and hence, is unlikely to explain the disparate trends observed in the two sexes. Any random error introduced by the change in equipment would only bias our results towards the null hypothesis of no change in LVM over time. Another limitation of our study is the fact that LVH itself is a marker of morbidity, and hence, participants with LVH may be more likely to be lost to follow-up. Such a potential bias may lead to a slight underestimation of mean LVM mass and prevalence of LVH at the more recent Framingham examinations, but cannot explain the sex-related differences in LVM trends we observed. Also, the echocardiographic readers were not blinded to sex at the examinations; this is unlikely to have influenced our findings across examinations. Additionally, the longitudinal design of our cohort study implies that pre-enrolled individuals are restricted to a certain age range and are predominantly Caucasian and of European descent, and may not adequately represent the general population. Last, the observational nature of our investigation does not permit any causal inferences to be drawn. In particular, we cannot directly assess the impact of antihypertensive treatment on LVM.

CONCLUSION

In our longitudinal investigation of a large community-based cohort, spanning an observation period of two decades during which routine two-dimensional echocardiography was performed, we observed sex-related differences in trends in LVM, with a modest increasing trend in men (likely attributable to increasing body size), and a modest decreasing trend in women. Additional studies are warranted to replicate our findings in independent samples and to further characterise factors that may contribute to the sex-related differences in trends observed in our sample.

Author affiliations
[1]National Heart, Blood and Lung Institute's and Boston University's Framingham Heart Study, Framingham, Massachusetts, USA
[2]Deutsches Herzzentrum, Technische Universität, Munich, Germany
[3]Klinik und Poliklinik für Innere Medizin II, Universitätsklinikum Regensburg, Regensburg, Germany
[4]Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, Massachusetts, USA
[5]Mathematics and Statistics Department, Boston University, Boston, Massachusetts, USA
[6]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[7]Veterans Administration Hospital, West Roxbury, Massachusetts, USA
[8]Harvard Medical School, Boston, Massachusetts, USA
[9]Sections of Preventive Medicine and Cardiology, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, USA
[10]Department of Epidemiology, Boston University School of Public Health, Framingham, Massachusetts, USA

Contributors BMK was involved in analyses and data interpretation, drafted and revised the manuscript. PG performed statistical analyses and contributed to manuscript revision. MGL planned and supervised statistical analyses and revised the manuscript. SC contributed to study design and manuscript revision. JA and SK contributed to data interpretation and manuscript revision. EJB contributed to study design, data interpretation and manuscript revision. RSV designed the study and contributed to data analysis and interpretation, and manuscript revision. All authors have approved the manuscript for publication.

Funding This work was supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195), R01HL080124 (RSV), and K99-HL-107642 (SC). Dr Cheng was also supported by a grant from the Ellison Foundation.

Competing interests None.

Ethics approval Institutional Review Board at the Boston University Medical Center.

Provenance and peer review Not commissioned; externally peer reviewed.

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Bernhard M Kaess, Philimon Gona, Martin G Larson, Susan Cheng, Jayashree Aragam, Satish Kenchaiah, Emelia J Benjamin and Ramachandran S Vasan

Heart 2013 99: 1693-1698 originally published online September 16, 2013
doi: 10.1136/heartjnl-2013-304600