Longitudinal Tracking of Left Ventricular Mass Over the Adult Life Course

Clinical Correlates of Short- and Long-Term Change in the Framingham Offspring Study

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Background—Information is limited on the longitudinal tracking of left ventricular (LV) mass over the adult life course and the determinants of such change.

Methods and Results—We used multilevel modeling to evaluate the correlates of LV mass prospectively over a 16-year period in 4217 Framingham study participants (mean age 45 years, 53% women) using up to 4 serial routine echocardiographic observations on each individual (11 762 observations). Age, sex, body mass index, systolic blood pressure, antihypertensive treatment, smoking, and diabetes mellitus were related to longitudinal measures of LV mass. Women and participants with diabetes mellitus experienced a steeper increase in LV mass with advancing age (compared with men and those without diabetes mellitus; P for interactions <0.0001 and 0.0003, respectively). Women also displayed greater increments in LV mass with increasing body mass index (compared with men, $P=0.04$ for interaction). Participants with optimal values of these risk factors experienced lesser increases in LV mass over time. Analyses evaluating short-term (4-year) changes in LV mass (2605 unique individuals providing 4494 observations) identified the same key determinants that influenced its long-term trajectory (ie, body mass index, sex, systolic blood pressure, antihypertensive treatment, and smoking).

Conclusions—Our longitudinal observations on a large community-based sample identified higher blood pressure, excess adiposity, smoking, and diabetes mellitus as fundamental determinants of LV mass tracking over the adult life course. These observations are consistent with the notion that maintenance of optimal levels of these risk factors in midlife will reduce the burden of LV hypertrophy, and possibly heart failure, in older age. **(*Circulation*. 2009;119:3085-3092.)**

Key Words: longitudinal studies ■ hypertrophy ■ epidemiology ■ echocardiography

Clinically overt heart failure is the end point of a long disease continuum characterized by progressive structural and functional changes of the heart, a dynamic process referred to as cardiac remodeling.[1] Given the current burden of heart failure and the projected increase over the next 5 decades,[2] it is important to understand factors that influence cardiac remodeling over the adult life course. Left ventricular (LV) mass is an important cardiac remodeling trait that is an intermediate phenotype for heart failure[3] and is also associated with increased risk for various cardiovascular disease (CVD) outcomes.[4] Epidemiological studies have identified age, sex, blood pressure (BP), and adiposity as the key correlates of LV mass cross-sectionally.[5] Yet data on the clinical determinants of tracking of LV mass over the adult life course and correlates of short-term change in LV mass are sparse and limited to observations in selected patient groups (eg, patients with hypertension[6]) or in adolescents and young adults.[7–9] An investigation of the tracking of LV mass through mid-adulthood would be fundamental to elucidate the evolution of subclinical LV remodeling and stage B heart failure[10] in the community, which antedate overt heart disease by years to decades.

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We hypothesized that key cardiovascular risk factors (ie, age, sex, BP, antihypertensive treatment, smoking, adiposity, and diabetes mellitus), which are correlates of LV mass in cross-sectional studies, are also the critical determinants of

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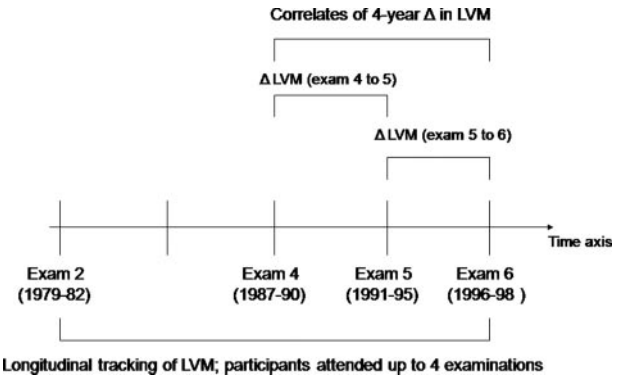

Figure 1. Overview of study design. Δ indicates change; LVM, left ventricular mass.

longitudinal changes in LV mass during short- and long-term follow-up. Further, we postulated that the maintenance of optimal levels of these risk factors in midlife would be associated with a favorable trajectory of LV mass over the adult life course. To test these hypotheses, we investigated a large sample from the community. First, we evaluated the clinical correlates of LV mass longitudinally over a period of 16 years using multilevel modeling. Second, we analyzed correlates of short-term (4 years) change in LV mass (Figure 1).

Methods

Study Sample

The Framingham Offspring Study started in 1971 enrolling 5124 children of the original Framingham cohort and the spouses of these children.[11] Participants are examined at each Heart Study clinic visit, which take place approximately every 4 to 8 years.[11] The Heart Study examination includes a medical history focusing on new onset cardiovascular events since the previous examination, a targeted physical examination including anthropometry, and laboratory assessment of cardiovascular risk factors. The study protocols were approved by the Boston University Medical Center Institutional Review Board. All participants provided written informed consent.

Echocardiographic Measurements

Routine transthoracic echocardiography was performed on Offspring cohort attendees at examination cycles 2 (1979–1982), 4 (1987–1990), 5 (1991–1995), and 6 (1996–1998). The echocardiographic equipment used differed across the examinations: Hoffrel 201 ultrasound receiver (+Aerotech transducer) at examination cycle 2; Hewlett Packard (model 77020AC) ultrasound machine at examination cycles 4 and 5; Sonos 1000 Hewlett-Packard machine at examination cycle 6. All echocardiograms were evaluated by an experienced technician or cardiologist using a standardized reading protocol. End-diastolic LV septal and posterior wall thickness and LV internal dimensions at the end of diastole and systole were obtained using a leading-edge technique.[12] LV mass was calculated as $0.8[1.04(\text{LV internal dimensions}+\text{septal wall thickness}+\text{posterior wall thickness})^3-(\text{LV internal dimensions})^3]+0.6$.[13] The reproducibility of echocardiographic measurements was good.[14]

Of 4337 unique attendees (12 351 observations) at exams 2, 4, 5, or 6 (where echocardiograms were performed), 103 individuals (375 person-exams) were excluded for prevalent or incident myocardial infarction or heart failure; both conditions affect LV mass measurements based on M-mode echocardiography. We also excluded observations if people were <25 or ≥ 75 years of age at the time of that specific observation, leading to the exclusion of 214 observations and 17 individuals (who had none of their echocardiograms performed within the age range of interest). Thus 4217 unique individuals providing 11 762 observations were included in the analyses on longitudinal tracking of LV mass (Figure 1).

Short-term change in LV mass was evaluated in 2605 unique participants who attended at least 2 consecutive examinations at which echocardiography was performed. To maximize the number of observations, data on the change in LV mass from examination cycles 4 to 5 and from cycles 5 to 6 were pooled (n =4494 participants-observations; Figure 1).

Statistical Analyses

Modeling of Individual Growth Curves for Log-LV Mass (Multilevel Modeling)

Multilevel statistical modeling allows the analysis of data that vary at multiple levels. It is applicable to longitudinal data for which repeated measurements are obtained on different occasions (level 1) within the same individual (level 2). Compared with traditional regression models, this analytical approach has the advantage of accommodating participants with missing data at some of the serial examinations and facilitates analyses using the maximum number of observations in a longitudinal investigation.

LV mass was natural-logarithmically transformed to normalize its distribution and stabilize its variance in men and women, permitting pooled sex analysis. We estimated growth curves for LV mass using multilevel statistical modeling (SAS PROC MIXED; using a compound symmetry matrix) and elucidated the associations of LV mass with the following clinical covariates, using a direct entry procedure: age, sex, body mass index (BMI), systolic BP, antihypertensive treatment, smoking status, and diabetes mellitus. These variables were chosen on the basis of their cross-sectional association with LV mass in the published reports.[5]

The examination cycle was included to adjust for variation in LV mass across examinations due to variation in the instrumentation used. Random intercepts were fitted for all models to reflect a different starting value of LV mass for each participant.

We examined age as a random effect and also nonlinear effects of age. Neither the quadratic nor the random effects of age were statistically significant. We fit a series of clinically prespecified models, with direct entry of candidate variables. Statistical interactions between age, sex, and other clinical risk factors were also investigated. Regression coefficients, their respective standard errors and the corresponding P values for all significant predictor variables and interaction terms are provided in the online-only Data Supplement. To facilitate interpretation of the data, percent changes in LV mass per clinically useful increments of the predictor variables are provided for the correlates of longitudinal LV mass measures as well as its short-term change. Growth curves were generated for men and women to display the tracking of LV mass over time.

Finally, for illustrative purposes, we describe the influence of an individual's risk factor burden on long-term LV mass tracking by modeling growth curves for LV mass for the following 4 subgroups (assuming the same risk factor profile at different ages and using regression coefficients shown in the online-only Data Supplement): women with a low CVD risk factor burden (nonsmoker, nonhypertensive [systolic BP of 130 mm Hg and not receiving antihypertensive treatment], free of diabetes mellitus, BMI of 25 kg/m^2); women with a high CVD risk factor burden (smoker, hypertensive [systolic BP of 150 mm Hg and receiving antihypertensive treatment], with diabetes mellitus, BMI of 30 kg/m^2); men with a low CVD risk factor burden (nonsmoker, nonhypertensive [systolic BP of 130 mm Hg and not receiving antihypertensive treatment], free of diabetes mellitus, BMI of 27.5 kg/m^2); and men with a high CVD risk factor

Table 1. Clinical and Echocardiographic Characteristics of the Study Samples Used to Characterize Clinical Correlates of Short-Term (Mean Follow-Up 4 Years) Change in and Long-Term (Maximum 16-Year Period) Tracking of LV Mass

	Sample for Correlates of Long-Term LV Mass Tracking		Sample for Correlates of Short-Term LV Mass Change	
Variable	Men (n=1973)	Women (n=2244)	Men (n=1094)	Women (n=1511)
Clinical features				
Age, y	45±10	45±10	49±10	50±10
Systolic BP, mm Hg	126±16	119±17	127±17	122±19
Diastolic BP, mm Hg	81±9	75±9	81±10	76±10
Antihypertensive treatment, %	11.3	9.6	15.0	11.7
Hypertension, %	29.4	18.9	34.9	25.2
Height, in	69±3	64±2	69±3	64±2
Weight, lbs	182±28	144±29	185±27	147±28
BMI, kg/m	26.8±3.7	24.8±4.9	27.2±3.5	25.3±4.7
Smoking,* %	33.8	35.3	20.4	21.4
Diabetes mellitus, %	4.4	2.3	4.8	2.9
Echocardiographic features				
Baseline LV mass, crude, g	187±41	131±30	188±35	145±29
Follow-up LV mass, crude, g	N/A	N/A	187±37	143±30
Baseline Log-LV mass, g	5.2±0.2	4.8±0.2	5.2±0.2	5.0±0.2
Follow-up Log-LV mass, g	N/A	N/A	5.2±0.2	4.9±0.2

Values are mean±SD or percentages. For the sample evaluating long-term tracking of LV mass, characteristics are from the first eligible examination. N/A indicates not applicable.

*We observed a temporal trend for smoking prevalence in our data set. The prevalences are substantially higher at earlier examination cycles (which have been used to define smoking for the long-term analyses; first exam with echocardiography attended by each participant) than at the later examination cycles, which were used for the short-term analyses (see Figure 1 for overview of the study design).

burden (smoker, hypertensive [systolic BP of 150 mm Hg and receiving antihypertensive treatment], with diabetes mellitus, BMI of 30 kg/m^2).

Analyses of Correlates of Short-Term Changes in LV Mass

Generalized estimating equations, which account for relatedness among participants, were used to determine clinical correlates of change in LV mass during a mean follow-up period of 4 years. As in the above-mentioned analysis, LV mass was logarithmically transformed to harmonize the SD in men and women. Multivariable models incorporated the same set of covariates used for the analyses of longitudinal tracking of LV mass (see above). We also incorporated the interaction terms that were statistically significant in the analyses of long-term LV mass tracking.

All analyses were performed using SAS software. S-PLUS and Microsoft Excel were used to create the graphical displays.

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

Results

The baseline characteristics of the 2 samples that were used to investigate the correlates of longitudinal tracking of LV mass over 16 years and its short-term changes (over 4 years) are displayed in Table 1.

Clinical Correlates of Longitudinal Tracking of LV Mass

Age, sex, BMI, systolic BP, antihypertensive treatment, smoking, and diabetes mellitus were related to tracking of LV mass over the 16-year observation period (Table 2; online-only Data Supplement Table I). We noted a statistically significant interaction between age and sex ($P<0.0001$), with women having a steeper increase in LV mass over time relative to men (Figure 2; Table 2; online-only Data Supplement Table I). We also observed a statistically significant interaction between sex and BMI (online-only Data Supplement Table I, $P=0.04$), indicating that the association of BMI with LV mass over time is of a larger magnitude in women relative to men (Table 2).

The association of diabetes mellitus with LV mass was statistically significant ($\beta=0.03$, $P=0.0016$) in a model that did not incorporate BMI, the BMI×sex or diabetes×age interactions. However, the association of diabetes mellitus was rendered statistically nonsignificant once BMI was added to the multivariable model. These observations suggest that BMI may capture some of the association between diabetes mellitus and LV mass.

The interaction between age and diabetes mellitus was statistically significant (online-only Data Supplement Table I, $P=0.0003$), indicating that the effect of age on LV mass varies according to diabetes status. In men and women free of

Table 2. Clinical Correlates of Longitudinal Tracking of LV Mass Over a 16-Year Period

Predictor Variable	% Change in LVM	95% CI
Men*	31.83	(30.51 to 33.17)
Age (men, without diabetes mellitus, 10-unit increase)	−0.55	(−1.19 to 0.10)
Age (men, with diabetes mellitus, 10-unit increase)	2.87	(0.99 to 4.80)
Age (women, without diabetes mellitus, 10-unit increase)	2.09	(1.46 to 2.74)
Age (women, with diabetes mellitus, 10-unit increase)	5.60	(3.65 to 7.60)
BMI (men, 5-unit increase)	7.51	(6.61 to 8.43)
BMI (women, 5-unit increase)	8.64	(8.01 to 9.29)
Systolic blood pressure (10-unit increase)	1.39	(1.14 to 1.63)
Antihypertensive treatment	2.35	(1.24 to 3.47)
Smoking	1.17	(0.23 to 2.12)
Diabetes mellitus†	−1.61	(−3.80 to 0.62)

The table shows the percentage change in LV mass per increment of the predictor variable as indicated. There was a significant interaction of age and sex, age and diabetes mellitus, and BMI and sex (see online-only Data Supplement Table I for regression coefficients and *P* values). Therefore, the effects of age and BMI are provided in the appropriate subgroups (men and women, and with and without diabetes mellitus). LVM indicates left ventricular mass.

*The effect of men (as compared to women) is for participants with an age of 50 years (mean age of all participants at all exams) and a BMI of 25 kg/m^2.

†The effect of diabetes mellitus is for participants at age 50 years.

diabetes mellitus, there was only a slight increase in LV mass in women and a slight decrease in men over time (Table 2). However, in participants with diabetes mellitus, we observed a much steeper increase in women and men, adjusting for all other covariates in the model (Table 2).

Impact of Cumulative Risk Factor Burden on LV Mass Progression

Women and men with a higher CVD risk factor burden had higher baseline LV mass and a greater increase over time compared with participants with a lower CVD risk factor burden (Figure 3).

Clinical Correlates of Short-Term Changes in LV Mass

Paralleling the analyses of longitudinal tracking of LV mass over a 16-year period, analyses of short-term (4-year) change in LV mass identified the following correlates: sex, BMI, systolic BP, antihypertensive treatment, smoking, and the age×diabetes interaction term were significantly associated with delta LV mass (Table 3; online-only Data Supplement Table II). However, the strongest correlate of change in LV mass was baseline LV mass, being inversely associated with delta LV mass. In the absence of interaction terms (specifically interactions with age), the main effect of age was statistically significant (β=0.008, P=0.015). However, in the presence of interaction terms, neither age nor the age×sex and sex×BMI interaction terms were significantly associated with short-term change in LV mass (Table 3; online-only Data Supplement Table II).

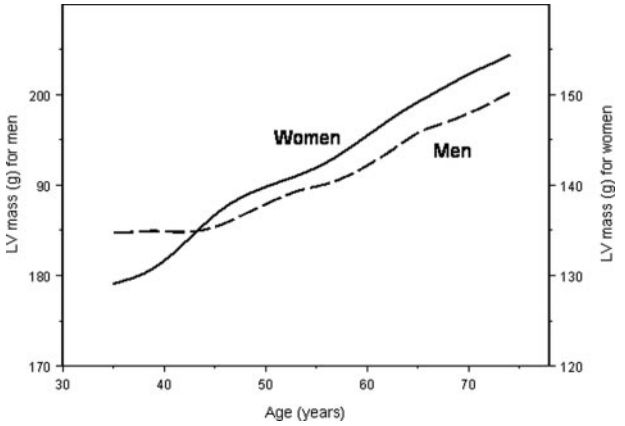

Figure 2. Unadjusted mean LV mass with increasing age for men and women. Left Y-axis, LV mass scale for men; right Y-axis, LV mass scale for women.

Discussion

Given the aging of the US population and the increasing burden of heart failure, it is important to understand determinants of cardiac remodeling over the adult life course. We have previously reported that midlife BP and BMI are powerful determinants of heart failure risk in older age,[15] and we postulated that the effect of these risk factors on LV mass may be a contributory mechanism. In this context, we evaluated clinical correlates of longitudinal tracking of LV mass over a 16-year period using 11 762 observations from 4217 Framingham Heart Study participants. In addition, we analyzed determinants of change in LV mass during a short-term follow-up (4 years) using 4494 participant observations.

Principal Findings

Overall, we observed a remarkable consistency in the correlates of LV mass in analyses conducted using multiple observations over a 16-year period versus evaluation of a 4-year change in LV mass. In addition to sex, age, adiposity (BMI), and BP, LV mass over the adult life course was also related to antihypertensive treatment, smoking, and diabetes mellitus. We observed interesting sex-related differences in the evolution of LV mass with age and increasing adiposity in our long-term analyses, a finding that was not discernible when evaluated over the short term. Women had a greater and steeper increase in LV mass with increasing age and with higher BMI. Participants with diabetes mellitus displayed a steeper longitudinal trajectory of LV mass compared with participants without diabetes mellitus, with the effect being more pronounced in women with diabetes mellitus compared with men with the condition. In addition, baseline LV mass was the strongest predictor of short-term change in LV mass. Finally, cumulative burden of cardiovascular risk factors significantly influenced the LV mass progression over time:

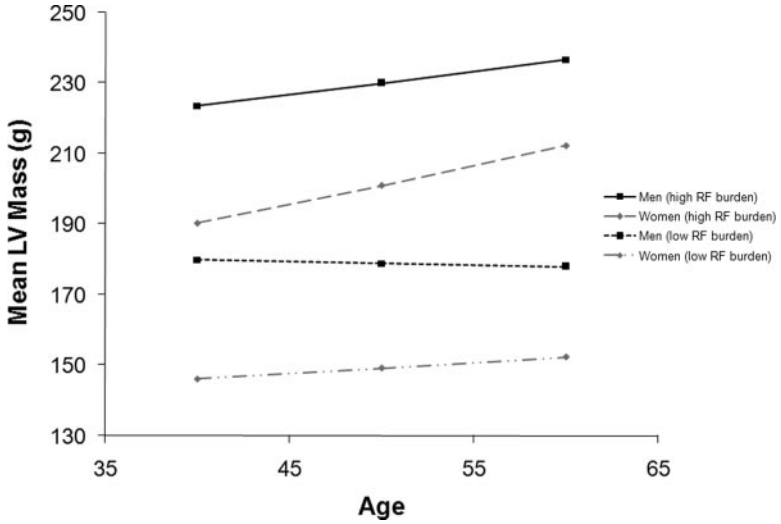

Figure 3. Long-term LV mass tracking in individuals with low and high CVD risk factor (RF) burden. Specifically: in women with a low CVD RF burden (nonsmoker, free of hypertension [systolic blood pressure of 130 mm Hg and not receiving antihypertensive treatment], free of diabetes mellitus, BMI of 25 kg/m^2); in women with a high CVD RF burden (smoker, with hypertension [systolic blood pressure of 150 mm Hg and receiving antihypertensive treatment], with diabetes mellitus, BMI of 30 kg/m^2); in men with a low CVD RF burden (nonsmoker, free of hypertension [systolic blood pressure of 130 mm Hg and not receiving antihypertensive treatment], free of diabetes mellitus, BMI of 27.5 kg/m^2); and in men with a high CVD RF burden (smoker, with hypertension [systolic BP of 150 mm Hg and receiving antihypertensive treatment], with diabetes mellitus, BMI of 30 kg/m^2). Regression coefficients from online-only Data Supplement Table I were used for these estimations.

participants with a greater burden of risk factors displayed higher LV mass values at baseline and experienced a steeper increase over time.

Comparison With the Published Literature

Effect of Age, BP, and Body Composition on Long-Term LV Mass

Age, BP, and excess adiposity are major determinants of LV mass in cross-sectional studies based on single-occasion measurements.[16,17] In the present analyses, we demonstrate that these covariates are also significant correlates of long-term tracking of LV mass over a 16-year period in adulthood and also determine short-term change in LV mass. This is in agreement with prior studies on LV mass progression in children and young adults.[7–9] In addition, LV mass at baseline is an important predictor of future changes in LV mass in our investigation and in previous studies.[7,18] Of note, baseline LV mass was inversely associated with change in LV mass on short-term follow-up. Thus higher values for baseline LV mass are associated with a smaller change in LV mass on short-term follow-up. This is biologically reasonable because of the phenomenon of regression to the mean.[19]

Table 3. Correlates of Short-Term (4 Years) Change in Log-LV Mass in Individuals Who Attended at Least 2 Consecutive Exams Where Echocardiograms Were Performed

Predictor Variable	% Change in LVM	95% CI
Men*	18.28	(16.67 to 19.92)
Age (men, without diabetes mellitus, 10-unit increase)	1.31	(0.35 to 2.27)
Age (men, with diabetes mellitus, 10-unit increase)	4.39	(1.33 to 7.55)
Age (women, without diabetes mellitus, 10-unit increase)	0.30	(−0.48 to 1.09)
Age (women, with diabetes mellitus, 10-unit increase)	3.36	(0.36 to 6.44)
BMI (men, 5-unit increase)	4.08	(2.88 to 5.30)
BMI (women, 5-unit increase)	4.60	(3.79 to 5.43)
Systolic blood pressure (10-unit increase)	1.01	(0.61 to 1.40)
Antihypertensive treatment	2.43	(0.76 to 4.13)
Smoking	1.41	(0.05 to 2.79)
Diabetes mellitus†	−2.08	(−5.29 to 1.24)

The table shows the percentage change in LV mass per increment of the predictor variable as indicated. (See online-only Data Supplement Table II for regression coefficients and *P* values). LVM indicates left ventricular mass.

*The effect for men (as compared with women) is for participants with an age of 50 years (mean age of all participants at all exams) and a BMI of 25 kg/m^2.

†The effect of diabetes mellitus is for participants at age 50 years.

Sexual Dimorphism in LV Mass Tracking

In a previous cross-sectional analysis of Framingham Heart Study data, a greater increase in LV mass with age was observed in women (compared with men).[20] Similar findings were noted when a binary LV mass trait (LV hypertrophy) was used; a 10-year increment was associated with a 15% increased risk for LV hypertrophy in men but with a 67% increased risk in women.[16] Similar findings were reported from the Mayo Clinic and in an autopsy study.[21,22] Consistent with these results, we observed a steeper increase in LV mass in women (relative to men) over a 16-year time interval.

The reasons for the greater increase in LV mass in women are not entirely clear. In a report that focused on healthy individuals free of hypertension, overweight, and prior cardiovascular disease, Dannenberg et al[23] observed only a minor increase in LV mass cross-sectionally in women between the ages of 20 and 90 years and noted a minor decrease in LV mass in men within the corresponding age range. This is consistent with the notion that the increase in LV mass over time may be mainly driven by a higher prevalence of risk factors with increasing age.[23] However, we observed effect modification by sex of the age-LV mass relation in multivariable-adjusted analyses. It is conceivable, therefore, that additional factors may mediate the observed interaction (see below).

Sex hormones might also partly account for the observed sex differences in trajectories of LV mass.[24] Estrogen affects

cardiac remodeling in many ways and probably has an inverse net-association with LV mass.[25] In a small series of hypertensive women, premenopausal participants had lower LV mass than men with the same level of blood pressure, whereas these sex differences were no longer observed in postmenopausal women.[26] Experimental data also suggest a beneficial role of estrogens on LV remodeling,[25] and genetic variants in genes encoding the estrogen receptor α have been associated with age-related changes in LV mass.[27] A decline in estrogen levels with age may, therefore, account for the steeper increase in LV mass with age in women. Another mechanism that may explain the age-associated increase in LV mass in women may be the greater pulsatile vascular load in women compared with men.[28]

We also observed a steeper increase in LV mass in women with increasing BMI. These longitudinal observations confirm cross-sectional findings of a greater sensitivity of cardiac mass in women to the effects of excess adiposity.[29]

Effect of Smoking on LV Mass Progression

Positive associations between smoking and LV mass and LV wall thickness were observed in cross-sectional analyses in different community-based samples.[30–32] Recently, Payne and colleagues[33] reported an association of smoking with exercise-induced LV growth in young army recruits undergoing an intense 12-week training program. In the present analyses, we observed that smoking was positively related to changes in LV mass during short-term follow-up and to tracking of LV mass over a 16-year time interval.

It is well established that smoking modulates vascular remodeling,[34] and increasing evidence indicates that it also affects cardiac remodeling.[35,36] For example, chronic carbon monoxide exposure increased myocardial endothelin-1 expression and induced cardiac hypertrophy in a rat model.[36]

Effect of Diabetes Mellitus on LV Mass Progression

Previous cross-sectional analyses of population-based cohorts have reported positive associations of type 2 diabetes mellitus with higher LV mass and wall thickness and worse systolic function.[32,37,38] In our analyses, we observed that diabetes mellitus modified the association of age with long-term LV mass tracking and with short-term changes in LV mass. Participants with diabetes mellitus had a steeper increase in LV mass over time compared with those without the condition. The steeper trajectory of LV mass in women as compared with men might explain the greater incidence of heart failure in women with diabetes mellitus (as compared with men with the condition) in a postmyocardial infarction sample[39] and in community-based investigations.[40]

Strengths and Limitations

The strengths of the present study include the large sample size, the community-based longitudinal design, the use of multilevel modeling that facilitates evaluation of serial echocardiograms, and the evaluation of both long-term tracking and short-term changes in LV mass. However, some limitations should be acknowledged. The change in instrumentation across examinations raises issues of comparability of measurements across examinations. For this reason, we adjusted for the examination cycle as a covariate in our analyses. Furthermore, the Framingham laboratory has had a limited number of readers over the years and adheres to a rigorous quality-control image acquisition and measurement protocol. Any differences in determination of LV mass across the examination cycles are likely to result in random misclassification, and such measurement errors would bias us toward the null hypothesis of no association between the covariates evaluated and LV mass.

Of all participants who had echocardiographic data available at baseline, a total of 280 participants died during the follow-up period of 16 years. Those who died had a worse CVD risk profile, including higher unadjusted LV mass, as compared with participants who did not die during the follow-up period. However, after adjustment for age and sex, the difference in LV mass was rendered statistically nonsignificant, indicating that our results have not been substantively altered because of informative missingness related to greater mortality of those with higher LV mass.

We focused our analyses on covariates that were identified as key correlates of LV mass in previous cross-sectional analyses and that were available at all 4 examinations when echocardiograms were obtained. We, therefore, did not analyze other variables including physical activity and additional measures of body composition that could yield additional insights into the longitudinal correlates of LV mass.

Although our statistical analysis takes into account longitudinal measures of exposure variables and covariates (all variables were measured at each examination), it does not specifically account for the possibility that some time-dependent covariates also act as mediators (eg, diabetes mellitus), which could result in an underestimation of the true effects of some covariates. Additional studies are warranted to appropriately analyze the effect of time-dependent covariates that are also mediators, such as marginal structural models[41] and G-estimation methods.[42]

Lastly, our participants are middle-aged to elderly and almost exclusively white and of European ancestry. Thus the generalizability of our results to other age groups or ethnicities is unknown.

Conclusions

Given the increasing burden of heart failure in the United States, it is important to understand the determinants of cardiac remodeling over the adult life course. In the present investigation, we identified higher BP, excess adiposity, smoking, and diabetes mellitus as fundamental determinants of LV mass over both the short and long term. These findings are consistent with the notion that maintenance of optimal levels of these risk factors in midlife will reduce the burden of subclinical LV hypertrophy, and presumably heart failure, in older age.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Clinically overt heart failure is the end point of a long disease continuum characterized by progressive structural and functional changes of the heart, a dynamic process referred to as cardiac remodeling. Considering the current burden of heart failure and the projected increase over the next 50 years, it is critical to understand factors that influence cardiac remodeling over the adult life course. Using longitudinal data from the Framingham Offspring cohort (up to 4 serial routine echocardiographic observations on each individual, with 11 762 observations in total) and multilevel statistical modeling, we identified age, sex, body mass index, systolic blood pressure, antihypertensive treatment, smoking, and diabetes mellitus as key correlates of longitudinal tracking of left ventricular mass, an important cardiac remodeling phenotype. Women and participants with diabetes mellitus experienced a steeper increase in left ventricular mass with advancing age (compared with men and those without diabetes mellitus). Women also displayed a greater increase in left ventricular mass with increasing body mass index (compared with men). Participants with optimal values of these cardiovascular risk factors experienced lesser increases in left ventricular mass over time. Analyses evaluating short-term (4-year) changes in left ventricular mass (2605 unique individuals providing 4494 observations) identified the same key determinants that influenced its long-term trajectory (ie, body mass index, sex, systolic blood pressure, antihypertensive treatment, and smoking). These observations are consistent with the notion that maintenance of optimal levels of these risk factors in young to midlife will reduce the burden of left ventricular hypertrophy, and possibly heart failure, in older age.