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# Comorbidities and Cardiometabolic Disease

## Relationship With Longitudinal Changes in Diastolic Function

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**ABSTRACT**

**OBJECTIVES** This study sought to evaluate the course, correlates, and prognosis of longitudinal changes in left ventricular (LV) diastolic dysfunction (DD) in the community-based Framingham Heart Study.

**BACKGROUND** Relationships of clinical risk factors to longitudinal progression of DD are incompletely understood.

**METHODS** Diastolic function was assessed by echocardiography performed at consecutive examinations (visits 1 and 2, mean interval 5.6 years) in 1,740 participants (64 ± 8 years of age at visit 1, 59% women) with normal LV systolic function and no atrial fibrillation.

**RESULTS** Of 1,615 individuals with normal-to-mild DD at visit 1, 198 (12%) progressed to ≥ moderate DD at visit 2. Progression was more likely in women and with advancing age ($p < 0.0001$). Of 125 individuals with ≥ moderate DD at visit 1, 25 (20%) regressed to normal-to-mild DD by visit 2. Regression of DD was associated with younger age ($p < 0.03$). In stepwise regression models, age, female sex, baseline and changes in systolic blood pressure, diastolic blood pressure, body mass index, serum triglycerides, and diabetes were positively associated with worsening diastolic function (all $p < 0.05$). Noncardiac comorbidity tracked with progressive DD. Cardiovascular disease (CVD) or death events occurred in 44 of 1,509 participants free of CVD at visit 2, during 2.7 ± 0.6 years of post-visit 2 follow-up. Presence of ≥ moderate DD was associated with higher risk (age- and sex-adjusted hazard ratio for CVD or death: 2.14; 95% confidence interval: 1.06 to 4.32; $p = 0.03$).

**CONCLUSIONS** In a community-based cohort of middle-aged to older adults, cardiometabolic risk factors and noncardiac comorbidities were associated with DD progression. Moderate or worse DD was associated with higher risk of CVD or death. (J Am Coll Cardiol HF 2018;6:317–25) © 2018 by the American College of Cardiology Foundation.

Left ventricular (LV) diastolic dysfunction (DD) may represent an intermediate stage in the development of cardiovascular disease (CVD) in older individuals and is associated with a number of conditions including heart failure (HF) (1-4), atrial fibrillation (5,6), and cardiovascular mortality (7,8). The pathophysiological link between LV DD and HF with preserved ejection fraction (HFpEF) is

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**ABBREVIATIONS AND ACRONYMS**

**BMI** = body mass index

**CRP** = C-reactive protein

**CVD** = cardiovascular disease

**DD** = diastolic dysfunction

**eGFR** = estimated glomerular filtration rate

**$FEV_1$** = forced expiratory volume in 1 s

**FVC** = forced vital capacity

**HF** = heart failure

**HFpEF** = heart failure with preserved ejection fraction

**HFrEF** = heart failure with reduced ejection fraction

**LV** = left ventricular

particularly strong as progression of subclinical DD is thought to contribute to the pathogenesis of the syndrome (9). HFpEF currently accounts for approximately one-half of new HF diagnoses, and its prevalence relative to HF with reduced ejection fraction (HFrEF) continues to rise (10). As treatment options for HFpEF remain limited (11), despite its considerable morbidity and mortality (12), prevention of HFpEF is vital to individual and population health. Hence, it is critical to understand factors that contribute to the development and progression of LV DD.

Several previous reports have demonstrated the associations of LV DD with modifiable cardiometabolic risk factors such as blood pressure and body mass index (BMI) (13,14). However, strong relationships between age and LV DD and risk factor burden may partially obscure cross-sectional associations between LV DD and risk factors (15–18). Examining relationships of cardiometabolic traits with longitudinal changes in diastolic function measurements may, thus, provide further insight into key contributors to the progression of DD. In addition to conventional cardiovascular risk factors, noncardiac comorbidity—such as chronic kidney disease, chronic lung disease, musculoskeletal weakness, generalized systemic inflammation, and frailty—also predates HF and appears closely related to the development and the prognosis of HFpEF. (2,19,20). The association of noncardiac comorbidity with the longitudinal progression of LV DD has not been well elucidated.

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Accordingly, we sought to evaluate the course, predictors (both cardiac and noncardiac), and prognostic significance of longitudinal changes in LV diastolic function over a 6-year period in a moderately sized community-based cohort consisting of individuals mostly 60 to 70 years of age, when CVD incidence accelerates. We hypothesized that prevalent and worsening cardiometabolic risk factors and comorbidity burden are positively associated with adverse changes in common echocardiographic measurements of LV diastolic function and that worsening LV DD over time was associated with a higher risk of future CVD.

## METHODS

**STUDY SAMPLE.** The design and enrollment of the Framingham Offspring and Omni Generation 1 cohorts have been detailed previously (21,22). We included Framingham Offspring participants who attended both the 8th (2005 to 2008, visit 1) and the 9th (2011 to 2014, visit 2) examination cycles and Omni Generation 1 participants who attended their 3rd (2007 to 2008, visit 1) and 4th (2011 to 2014, visit 2) examinations. From 2,478 participants attending both examinations, we excluded individuals missing LV diastolic function indices (n = 290), baseline LV wall motion abnormalities (n = 78), interim myocardial infarction between examinations (n = 43), LV systolic dysfunction (defined as fractional shortening ≤0.29 or 2-dimensional [2D] evidence of ≥ mild LV systolic dysfunction [n = 21]), ≥ moderate valvular disease (n = 105), paced rhythm (n = 18), atrial fibrillation at the time of echocardiography (n = 2), or missing covariates (n = 181). The final sample of 1,740 was used to evaluate predictors of longitudinal changes in LV diastolic function. To evaluate associations of noncardiac comorbidities with DD progression, we excluded an additional 339 individuals whose data were missing comorbidity measurements. For prospective analyses relating longitudinal changes in diastolic function with incident CVD, we excluded participants with prevalent CVD at visit 2 (n = 231) (Online Figure 1). All participants provided informed consent, and the Boston University Medical Center Institutional Review Board approved all study protocols.

**ECHOCARDIOGRAPHY.** Two-dimensional echocardiography with Doppler color flow imaging was performed at both examination visits (details in Online Appendix). We characterized LV diastolic function as normal, mild DD, moderate DD, or severe DD by using modified Olmsted criteria (excluding mitral inflow velocities during the Valsalva maneuver and pulmonary venous flow patterns, which were not available for the present investigation) (7,23). The following criteria were used: *normal* LV diastolic function: E/A >0.75 and E/E′ <10; *mild DD*, E/A ≤0.75 and E/E′ <10; *moderate DD*, E/A ≤1.5 and E/E′ ≥10; and *severe DD*, E/A >1.5 and E/E′ ≥10.

**COVARIATES.** A comprehensive medical history, a clinical examination focused on cardiovascular health, anthropometry, and phlebotomy were performed at each Framingham Heart Study examination. Details of the assessment of clinical covariates are provided in Online Appendix.

**COMORBIDITY ASSESSMENT AND SCORE.** Select measurements representing kidney (estimated glomerular filtration rate [eGFR]) and lung (forced expiratory volume in 1 s [$FEV_1$]-to-forced vital capacity [FVC] ratio) functions, musculoskeletal weakness (handgrip), frailty (gait speed), and general

inflammation (C-reactive protein [CRP]) were combined to calculate a "comorbidity score" for each participant, using measurements available at both examination cycles (details in the Online Appendix). We then calculated a composite "comorbidity score" by assigning a value of 0 to referent values and 1 to abnormal values ("comorbidity score" range 0 to 5) for each component of the score.

**ASCERTAINING CLINICAL OUTCOME.** Framingham study participants were under longitudinal surveillance for the development of cardiovascular outcomes, which were adjudicated by a committee of 3 investigators after review of pertinent medical records. Our outcome was a composite of first CVD event or death. CVD events were defined as follows: fatal and nonfatal myocardial infarction, acute coronary syndromes without myocardial necrosis, angina, stroke or transient ischemic attack, intermittent claudication, or HF determined using standardized Framingham criteria (24).

**STATISTICAL ANALYSIS.** We displayed characteristics separately for the first and second visits. For categorical analyses, we defined DD as ≥moderate LV DD due to the small number of individuals with severe DD in our sample, and we identified 4 categories to characterize longitudinal changes in DD (**Table 1**). "Progressors" had normal-to-mild LV DD at baseline and moderate-to-severe LV DD at follow-up; "regressors" had moderate-to-severe LV DD at baseline and normal-to-mild LV DD at follow-up; "normal" subjects had normal-to-mild LV DD at both examination cycles, and "stable DD" subjects had moderate-to-severe LV DD at both examination cycles. In secondary analyses, we tested 2 alternate categorization schemes: 1) normal versus ≥mild DD; and 2) use of 3 different categories (i.e., normal, mild DD, and moderate-to-severe DD) (Online Table 1).

Using stepwise multivariate-adjusted regression models, we evaluated the relationship of clinical predictors (including both baseline and longitudinal changes in these variables) with longitudinal changes in quantitative echocardiographic measures of LV DD or with categories of longitudinal changes in DD. Baseline predictor variables, the baseline value of the echocardiographic variable being analyzed and the interval between attendance at the 2 examinations, were forced into the models. For each continuous predictor variable, a "change variable" (Δ) was calculated as the difference between visits, that is [visit 2 − visit 1]. For binary variables (e.g., smoking), the "change variable" was defined as a different value at the 2 examination cycles (e.g., starting smoking or stopping smoking) and was modeled as a 3-level categorical variable. All continuous variables were standardized to a mean = 0 and SD = 1. We tested effect modification by age and sex on the associations of changes in clinical predictors and changes in continuous echocardiographic measures of LV diastolic function by using multiplicative interaction terms.

**TABLE 1 Diastolic Dysfunction "Change Categories"**

| Diastolic Function Category | Visit 2 | |
|---|---|---|
| Visit 1 | Normal-to-mild DD | Moderate-to-severe DD |
| Normal-to-mild DD | Normal | Progressors |
| Moderate-to-severe DD | Regressors | Stable DD |

DD = diastolic dysfunction

In prospective analyses, we used Cox proportional hazards regression models to relate the 4 DD change categories with incident CVD or mortality. Multivariate models were adjusted for age and sex (model 1) and then additionally adjusted for clinical CVD risk factors including systolic blood pressure, hypertension treatment status, BMI, diabetes, smoking, heart rate, ln(triglycerides), and total/HDL cholesterol ratio at visit 2. We tested the proportionality of hazards assumption by assessing the interaction of DD categories with log(survival time).

We also tested the association of the comorbidity score with the presence of moderate-to-severe LV DD at the later examination (i.e., "progressors" and "stable DD" subjects) by using logistic regression models adjusted for age and sex.

We used a 2-sided p value $<0.05$ to determine statistical significance, and we performed all analyses with SAS version 9.4 software (Cary, North Carolina).

## RESULTS

Characteristics for the 1,740 study participants (1,027 women [59%]) are displayed in **Table 2**. The mean age was 64 years old at visit 1 and 70 years of age at visit 2. During an average of 5.6 ± 0.5 years (range: 3.6 to 7.5 years) between visits 1 and 2, changes in the mean values for clinical risk factors were modest. Notably, the proportion of participants on hypertension or lipid-lowering treatment increased. Sex differences in baseline characteristics (Online Table 2) were most pronounced for measurements of LV diastolic function, which were less optimal in women. The prevalence of ≥moderate LV DD was higher in women during both examinations.

**NATURAL HISTORY OF DD.** LV DD ≥ moderate in severity increased in prevalence between visits. Of the 1,615 individuals with normal-to-mild DD at the baseline examination cycle, 198 (12%) developed

**TABLE 2 Characteristics of the Study Sample**

| | Visit 1 (n = 1,740) | Visit 2 (n = 1,740) |
|---|---|---|
| Age, yrs | 64 ± 8 | 70 ± 8 |
| Females | 1,027 (59) | - |
| Nonwhite race | 201 (12) | - |
| Systolic blood pressure, mm Hg | 138 ± 19 | 137 ± 18 |
| Diastolic blood pressure, mm Hg | 70 ± 8 | 65 ± 9 |
| Body mass index, kg/m$^2$ | 28.1 ± 5.3 | 28.3 ± 5.3 |
| Total/HDL cholesterol | 3.5 ± 1.0 | 3.1 ± 0.9 |
| Triglycerides, mg/dl | 115 ± 65 | 112 ± 53 |
| Fasting glucose, mg/dl | 104 ± 20 | 102 ± 20 |
| Heart rate, beats/min | 61 ± 10 | 62 ± 9 |
| Hypertension treatment | 782 (45) | 919 (53) |
| Current smokers | 125 (7) | 116 (7) |
| Lipid-lowering treatment | 660 (38) | 870 (50) |
| Diabetes | 175 (10) | 243 (14) |
| E-wave velocity, cm/s | 64.1 ± 12.7 | 67.6 ± 13.7 |
| A-wave velocity, cm/s | 69.1 ± 14.5 | 71.3 ± 16.6 |
| E/A ratio | 1.0 ± 0.2 | 1.0 ± 0.3 |
| Lateral E′ velocity, cm/s | 9.8 ± 2.1 | 8.9 ± 1.9 |
| E/E′ ratio | 6.8 ± 2.0 | 8.0 ± 2.4 |
| LV diastolic dysfunction ≥ moderate | 125 (7) | 288 (17) |
| **Comorbidity Traits** | **(n = 1,401)** | **(n = 1,401)** |
| Kidney dysfunction, eGFR <60 | 105 (8) | 281 (20) |
| $FEV_1$/FVC <20th percentile | 276 (20) | 291 (21) |
| CRP, >80th percentile | 269 (19) | 292 (21) |
| Handgrip, <20th percentile | 219 (16) | 328 (23) |
| Gait, >80th percentile | 227 (16) | 336 (24) |
| Comorbidity score | 0.8 ± 0.9 | 1.1 ± 1.1 |

Values are mean ± SD or n (%), unless otherwise specified. Percentiles for comorbidity traits were calculated from pooled samples by combining observations from the 2 examination cycles.

CRP = C-reactive protein; E/A ratio = the ratio of the E wave and A wave velocities; E/E′ ratio = the ratio of the lateral E′ and E wave velocities; eGFR = estimated glomerular filtration rate; $FEV_1$ = forced expiratory volume in 1 s; FVC = forced vital capacity; HDL = high-density lipoprotein; LV = left ventricle.

moderate-to-severe DD between visits (**Figure 1,** Online Table 3). Women were more likely than men to progress between visits. The rate of progression increased with age (**Figure 1**). Conversely, of the 125 individuals with moderate-to-severe DD at visit 1, 25 (20%) were categorized as having normal-to-mild DD at visit 2 (**Figure 1,** Online Tables 3 and 4). Younger age was associated with higher odds of regression of LV DD.

**LONGITUDINAL CHANGES IN RISK FACTORS RELATED TO PROGRESSION OF DD.** We observed a negative relationship between changes in the E/A ratio and age, diastolic blood pressure (baseline and change), triglycerides (baseline and change), and heart rate (baseline and change: all p values were <0.05) (**Table 3**). Changes in the component measurements of E and A velocities were, in turn, related to a number of clinical variables (Online Table 5). Decrements in the E′ velocity also were associated with higher age, female sex, systolic blood pressure (baseline and change), diastolic blood pressure (baseline and change), change in BMI, heart rate (baseline and change), and baseline diabetes (p for all <0.03). Rising E/E′ ratio between the examination cycles was directly associated with age, female sex, change in systolic blood pressure, and baseline diabetes ($p < 0.01$).

When DD was analyzed as a categorical variable, we observed similar associations between modifiable risk factors and the presence or progression of DD (**Table 4**). Specifically, age, female sex, systolic blood pressure (baseline and change), baseline BMI, baseline diabetes, and development of diabetes during follow-up were positively associated with stable or progressive DD, and baseline heart rate was inversely associated ($p \leq 0.03$). Similar associations were observed when DD was defined as ≥ mild or as a 3 level variable (Online Tables 6 and 7).

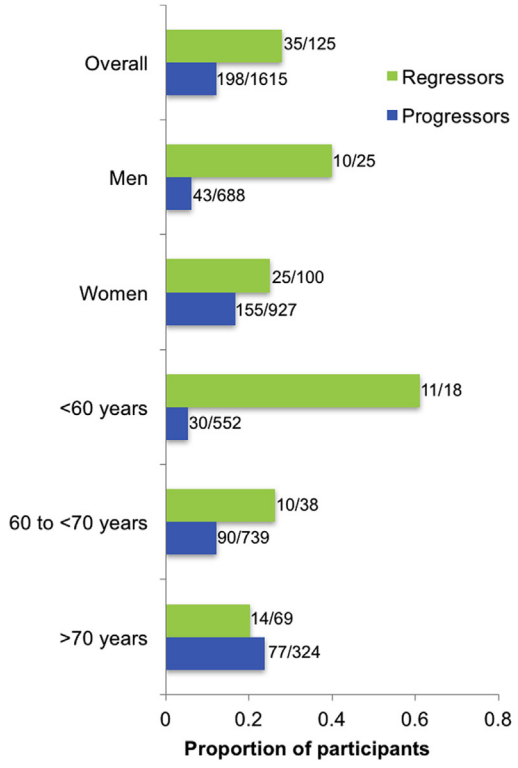
In secondary analyses, we included ln(CRP), ln(insulin), and eGFR (and their change variables) as potential predictor variables (Online Tables 8 and 9). After adjusting for all other clinical variables, we did not observe statistically significant associations between eGFR or CRP with diastolic function measurements. We did observe an association for an increase in insulin concentration over time with a reduction in E/A ratio, but it was not associated with stable or progressive DD.

We evaluated for effect modification by age and sex on the cross-sectional associations of clinical predictors with diastolic function traits and observed several nominally significant interactions (Online Table 10).

**BURDEN OF NONCARDIAC COMORBIDITY RELATES TO DD PROGRESSION.** We examined the relationship between a "comorbidity score" and the progression of DD. The mean "comorbidity score" increased between the 2 visits (**Table 2**) and was higher in individuals with more advanced DD (**Table 5**). Each 1 unit higher comorbidity score at visit 1 was associated with 27% higher odds of having moderate-to-severe DD at visit 2 ("progressors" or "stable DD" subjects) in age- and sex-adjusted analyses (95% confidence interval [CI]: 1.06 to 1.53; $p = 0.01$).

**ASSOCIATION OF DD CATEGORY WITH INCIDENT CVD.** During follow-up after the second examination cycle (2.7 ± 0.6 years), we observed events in 44 participants (17 deaths, 27 incident CVD, of which 5 were HF, 6 were myocardial infarction, 7 were angina-coronary insufficiency, and 9 were stroke or transient ischemic attack). Compared with individuals with normal or improved DD, those with moderate-to-severe DD at visit 2 ("progressors" or "stable DD"

**FIGURE 1** Longitudinal Course of Progression or Regression of DD by Sex and Age




| Characteristic | OR for progressing (95% CI) | OR for regressing (95% CI) |
|---|---|---|
| *By sex* | | |
| Men | Referent | Referent |
| Women | 3.23 (2.25-4.63) P <0.0001 | 0.48 (0.18-1.31) P=0.15 |
| *By age group* | | |
| <60 yrs | Referent | Referent |
| 60-<70 yrs | 2.52 (1.64-3.88) P <0.0001 | 0.26 (0.08-0.86) P=0.028 |
| ≥70 yrs | 5.86 (3.71-9.24) P <0.0001 | 0.16 (0.05-0.49) P=0.001 |

Progressors were defined by normal-to-mild diastolic dysfunction at visit 1 and moderate-to-severe DD at visit 2. Regressors were defined as moderate-to-severe DD at visit 1 and normal-to-mild diastolic dysfunction at visit 2. The proportion of progressors, therefore, consisted of the ratio of individuals with ≥moderate DD at visit 2 and normal diastolic function at visit 1 and the proportion of regressors consisted of the ratio of individuals with normal-to-mild DD at visit 2 to those with ≥moderate DD at visit 1. ORs for progressing represent the relative odds of progressing to moderate-to-severe DD at visit 2 given normal-to-mild DD at visit 1 compared to the referent group. ORs for regressing represent the relative odds of regressing from moderate-to-severe diastolic dysfunction at visit 1 to normal-to-mild diastolic dysfunction at visit 2 cycle compared to the referent group. ORs for the "by sex" analysis were adjusted for age group, and the "by age group" analyses were adjusted for sex. DD = diastolic dysfunction; OR = odds ratio.

subjects) had a >2-fold higher risk of CVD in age- and sex-adjusted models that was partially attenuated upon adjustment for clinical risk factors (**Table 6,** Online Table 11). Compared with individuals with normal diastolic function at both visits, individuals with stable DD had the highest CVD risk, with a >2.5-fold higher relative hazard (Online Tables 12 and 13).

## DISCUSSION

We evaluated the course, correlates, and prognostic significance of longitudinal changes in LV DD in a predominantly middle-aged or older community-based sample. There are several key findings: 1) LV diastolic function generally worsened over time in older people, especially in women and at older ages; 2) some individuals with LV DD could improve or regress to the mean, which is more common at younger ages; 3) modifiable cardiometabolic risk factors (both baseline values and changes over time) were related to worsening diastolic function and progression of LV DD; 4) progression of general (noncardiac) comorbidity tracked in parallel with worsening DD in this age group; and 5) the presence of moderate-to-severe LV DD at visit 2 was associated with the composite outcome of incident CVD or death. Taken together, these findings demonstrate that worsening clinical risk profiles in the seventh to eighth decades of life are associated with progressive LV DD and that progressive LV DD is associated with adverse cardiovascular outcomes.

**LONGITUDINAL CHANGES IN RISK FACTORS PREDICT WORSENING LV DIASTOLIC FUNCTION.** Cardiometabolic risk factors (blood pressure and BMI in particular) have been linked with LV DD in previous

**TABLE 3 Multivariate-Adjusted Associations of Clinical Predictors With Longitudinal Changes in LV Diastolic Function Traits**

| | Change in E/A | | Change in E′ (cm/s) | | Change in E/E′ | |
|---|---|---|---|---|---|---|
| | Estimated β ± SE | p Value | Estimated β ± SE | p Value | Estimated β ± SE | p Value |
| Age, yrs | −0.02 ± 0.01 | 0.005 | −0.30 ± 0.04 | <0.0001 | 0.35 ± 0.05 | <0.0001 |
| Females | −0.01 ± 0.01 | 0.36 | −0.51 ± 0.07 | <0.0001 | 0.70 ± 0.09 | <0.0001 |
| Systolic blood pressure, mm Hg | −0.01 ± 0.01 | 0.18 | −0.11 ± 0.05 | 0.02 | 0.11 ± 0.06 | 0.06 |
| Δ Systolic blood pressure, mm Hg | – | – | −0.12 ± 0.04 | 0.006 | 0.22 ± 0.05 | <0.0001 |
| Diastolic blood pressure, mm Hg | −0.02 ± 0.01 | 0.05 | −0.10 ± 0.05 | 0.03 | 0.05 ± 0.05 | 0.28 |
| Δ Diastolic blood pressure, mm Hg | −0.02 ± 0.01 | 0.004 | −0.13 ± 0.05 | 0.005 | – | – |
| BMI, kg/m$^2$ | 0.00 ± 0.01 | 0.94 | −0.07 ± 0.04 | 0.06 | 0.05 ± 0.05 | 0.26 |
| Δ BMI, kg/m$^2$ | – | – | −0.13 ± 0.03 | 0.0002 | – | – |
| Total/HDL cholesterol | 0.01 ± 0.01 | 0.51 | −0.02 ± 0.05 | 0.63 | −0.05 ± 0.06 | 0.39 |
| Δ Total/HDL cholesterol | – | – | – | – | – | – |
| ln (Triglycerides) | −0.02 ± 0.01 | 0.02 | −0.01 ± 0.05 | 0.88 | 0.06 ± 0.06 | 0.32 |
| Δ ln (Triglycerides) | −0.03 ± 0.01 | <0.0001 | – | – | – | – |
| Heart rate, beats/min | −0.04 ± 0.01 | <0.0001 | −0.12 ± 0.04 | 0.004 | −0.03 ± 0.04 | 0.50 |
| Δ Heart rate, beats/min | −0.05 ± 0.01 | <0.0001 | −0.17 ± 0.04 | <0.0001 | – | – |
| Hypertension treatment status | −0.00 ± 0.01 | 0.97 | 0.02 ± 0.08 | 0.75 | −0.11 ± 0.09 | 0.22 |
| Smoking | −0.03 ± 0.02 | 0.13 | 0.03 ± 0.13 | 0.79 | −0.21 ± 0.16 | 0.21 |
| Diabetes | 0.00 ± 0.02 | 0.86 | −0.35 ± 0.12 | 0.003 | 0.36 ± 0.15 | 0.01 |

Estimated β coefficients represent the estimated change in echocardiographic trait for each 1 SD higher value of the predictor variable. Δ = continuous "change variables," defined as the follow-up value minus the baseline value. Each 1 SD = 7.9 years for age, 18.7 mm Hg for systolic blood pressure, 16.4 mm Hg for change in systolic blood pressure, 8.5 mm Hg for diastolic blood pressure, 8.4 mm Hg for change in diastolic blood pressure, 5.3 kg/m$^2$ for BMI, 2.1 kg/m$^2$ for change in BMI, 1.0 for total/HDL cholesterol, 0.8 for change in total/HDL cholesterol, 0.5 for ln(triglycerides), 0.4 for change in ln(triglycerides), 9.5 beats/min for heart rate, and 8.5 beats/min for change in heart rate. The multivariate models are additionally adjusted for the interval between the 2 examination cycles and the baseline value of the echocardiographic trait. Fasting glucose, change in fasting glucose, change in hypertension treatment status, change in smoking, and change in diabetes were included as potential predictor variables but did not meet criteria for model inclusion.

BMI = body mass index; other abbreviations are as in Table 2.

reports (13,14), but predictors of longitudinal changes in diastolic function are incompletely understood. From the Olmsted County Heart Function Study, Kane et al. (3) demonstrated that DD worsened over time and that progressive DD was associated with incident HF in a sample of individuals with mean age of 61 years old. In a cohort younger than ours, with a mean age of 50 years, Kuznetsova et al. (25) examined the correlates of progressive LV DD and observed that advanced age, higher baseline insulin level, baseline and change in heart rate, baseline blood pressure, change in systolic blood pressure, and initiation of antihypertensive therapy were directly associated with progressive LV DD. Our findings, therefore, complement and extend those of previous reports to a sample approximately 10 to 15 years older (on average) and underscore the contributions of numerous cardiometabolic risk factors to decrements in LV diastolic function. Indeed, longitudinal increases in systolic and diastolic blood pressure, BMI, serum triglycerides, and diabetes were all found to predict worsening diastolic function in our sample. Although these longitudinal findings were observational, they support the hypothesis that adverse changes in cardiometabolic risk profiles may promote DD progression in this age group.

**FACTORS ASSOCIATED WITH REGRESSION OF LV DIASTOLIC DYSFUNCTION.** In our study, some individuals with moderate-to-severe LV DD at baseline were observed to have regression of their DD at the follow-up examination. Transition to more favorable LV diastolic function was more common in younger individuals, and a trend favoring higher odds of LV DD regression in men was observed. To the best of our knowledge, no previous studies have evaluated factors related to amelioration of DD in community-based individuals free of manifested HF. One potential explanation for these findings is "regression to the mean" over time, which may be expected to occur more frequently in younger individuals. However, data from prior studies do support the potential for improved LV DD in response to risk factor modification in select patients with HF (26,27). Our findings, therefore, are consistent with this limited previous evidence, and we speculate that targeting interventions to improve cardiometabolic profiles in individuals most likely to benefit (i.e., individuals at younger age and, potentially, men) may have a substantial impact on the burden of LV DD.

**GENERAL NONCARDIAC COMORBIDITY AND LV DIASTOLIC DYSFUNCTION.** Noncardiac organ dysfunction is known to be highly prevalent in patients with HFpEF (28–31) and to be associated with risk for HFpEF development (19). However, previous reports of relationships of noncardiac predictors to the development of LV DD are scant. Comorbidities are theorized to partially contribute to HFpEF through the actions of associated inflammatory pathways on endothelial and myocyte function (32). These pathophysiological mechanisms may partially explain the association we observed between advanced comorbidity and progressive LV DD by positing the possibility that shared mechanisms (such as systemic inflammation and simultaneous aging of interrelated organ systems) drive both. Other explanations for this observation include potential direct effects of comorbid conditions on LV diastolic function. Our findings are observational and exploratory, and therefore, additional studies are warranted to evaluate the underlying mechanisms explaining the parallelism between progressive DD and advancing noncardiac comorbidity.

**STUDY LIMITATIONS.** Several echocardiographic features previously demonstrated to relate to LV diastolic function, such as the septal E′ velocity, left atrial size, regurgitant velocity through the tricuspid valve, pulmonary vein inflow, LV longitudinal strain, and mitral inflow during the Valsalva maneuver were not obtained due to time constraints during the Framingham Study examination cycle. As a result, we were unable to grade LV DD using the more recent, 2016, guidelines (33). Future studies are warranted to extend our findings to the more contemporary guidelines. Visit 2 was recently performed (2011 to 2014), and the number of CVD events that have been observed since that cycle is, therefore, relatively low, which limits our ability to evaluate the association of longitudinal changes in LV DD with specific CVD outcomes, such as HF. Our study design required participants to attend 2 consecutive examination cycles. Individuals with DD at visit 1 who did not attend visit 2 were, hence, not available for analysis. The extent to which survival bias might have affected our findings is unknown. Our analyses were not adjusted for multiple comparisons; further studies are warranted to confirm our findings. Finally, the generalizability of our results is limited to samples with similar characteristics. Although our sample did include a smaller, nonwhite cohort, most of the study sample consisted of white individuals of European descent; we lacked sufficient numbers of non-European ancestry individuals to analyze differences among ethnic subgroups.

**TABLE 4 Multivariate-Adjusted Associations of Clinical Predictors With LV Diastolic Dysfunction**

| | Stable or Progressive LV DD | | Progressive LV DD | |
|---|---|---|---|---|
| | Odds Ratio (95% CI) | p Value | Odds Ratio (95% CI) | p Value |
| Age, yrs | 1.87 (1.56–2.25) | <0.0001 | 1.68 (1.39–2.02) | <0.0001 |
| Females | 3.70 (2.57–5.32) | <0.0001 | 3.20 (2.19–4.68) | <0.0001 |
| Systolic blood pressure, mm Hg | 1.27 (1.03–1.55) | 0.02 | 1.19 (0.96–1.47) | 0.11 |
| Δ Systolic blood pressure, mm Hg | 1.33 (1.12–1.57) | 0.0011 | 1.30 (1.10–1.55) | 0.003 |
| Diastolic blood pressure, mm Hg | 0.99 (0.82–1.18) | 0.88 | 0.98 (0.81–1.18) | 0.79 |
| Δ Diastolic blood pressure, mm Hg | – | – | – | – |
| Baseline BMI, kg/m$^2$ | 1.27 (1.08–1.48) | 0.003 | 1.26 (1.07–1.48) | 0.005 |
| Δ BMI, kg/m$^2$ | – | – | – | – |
| Total/HDL cholesterol | 0.97 (0.79–1.20) | 0.80 | 0.98 (0.79–1.22) | 0.88 |
| Δ Total/HDL cholesterol | – | – | – | – |
| ln (Triglycerides) | 1.15 (0.93–1.43) | 0.19 | 1.21 (0.97–1.51) | 0.10 |
| Δ ln (Triglycerides) | – | – | – | – |
| Heart rate, beats/min | 0.84 (0.72–0.99) | 0.03 | 0.83 (0.71–0.98) | 0.03 |
| Δ Heart rate, beats/min | – | – | – | – |
| Hypertension treatment status | 0.92 (0.66–1.29) | 0.64 | 0.84 (0.59–1.19) | 0.32 |
| Smoking | 0.85 (0.44–1.61) | 0.61 | 0.82 (0.41–1.65) | 0.58 |
| Diabetes | 1.94 (1.18–3.17) | 0.009 | 1.60 (0.98–2.62) | 0.06 |
| Change in diabetes status | | | | |
| 1. No at visit 1, yes at visit 2 | 2.43 (1.30–4.54) | 0.005 | – | – |
| 2. Yes at visit 1, no at visit 2 | 0.26 (0.03–2.31) | 0.22 | – | – |

Odds ratios represent the odds of having the outcome for each 1 SD higher value of the predictor variable. Δ = continuous "change variables," defined as the follow-up value minus the baseline value. 1 SD = 7.9 years for age, 18.7 mm Hg for systolic blood pressure, 16.4 mm Hg for change in systolic blood pressure, 8.5 mm Hg for diastolic blood pressure, 8.4 mm Hg for change in diastolic blood pressure, 5.3 kg/m$^2$ for BMI, 2.1 kg/m$^2$ for change in BMI, 1.0 for total/HDL cholesterol, 0.8 for change in total/HDL cholesterol, 0.5 for ln(triglycerides), 0.4 for change in ln(triglycerides), 9.5 beats/min for heart rate, and 8.5 beats/min for change in heart rate. The multivariate models are additionally adjusted for the interval between the 2 examination cycles and the baseline value of the echocardiographic trait. Fasting glucose, change in fasting glucose, change in hypertension treatment status, and change in smoking status were included as potential variables but did not meet criteria for model inclusion.

CI = confidence interval; other abbreviations as in Tables 2 and 3.

These limitations notwithstanding, our study has several important strengths. It was conducted in a moderately sized community-based cohort with standardized assessments of echocardiograms, clinical variables (both cardiac and noncardiac), and outcomes; the ability to analyze longitudinal

**TABLE 5 Average Comorbidity Score Across Visits by DD Change Category**

| DD Change Category | Mean Score |
|---|---|
| Normal or regressors (n = 1,187) | 0.87 ± 0.82 |
| Stable DD or progressors (n = 214) | 1.33 ± 1.09 |
| **DD Change Category** | **Mean Score** |
| Normal (n = 1,159) | 0.86 ± 0.81 |
| Regressors (n = 28) | 1.05 ± 0.88 |
| Progressors (n = 152) | 1.19 ± 1.04 |
| Stable DD (n = 62) | 1.66 ± 1.15 |

Abbreviation as in Table 1.

**TABLE 6 Incidence of CVD or Death After Visit 2**

| DD Change Category | Number of Events/Number at Risk | Age- and Sex-Adjusted HR (95% CI) | p Value | Multivariate-Adjusted* HR (95% CI) | p Value |
|---|---|---|---|---|---|
| Normal or regressors | 29/1,275 | Referent | | Referent | |
| Stable DD or progressors | 15/234 | 2.14 (1.06–4.32) | 0.03 | 1.81 (0.87–3.79) | 0.11 |

*Multivariate model was adjusted for age, sex, systolic blood pressure, body mass index, diabetes, hypertension treatment status, smoking, heart rate, ln (triglycerides), and total/HDL cholesterol.

CVD = cardiovascular disease; HR = hazard ratio; other abbreviations as in Tables 1 and 3.

measurements of LV diastolic function in a cohort of this size is rare. Furthermore, our study sample consisted of individuals with a mean ~65 to 70 years of age, which is when the incidence of HF risk climbs. As a result, our findings may be especially informative to HF prevention efforts.

## CONCLUSIONS

In a large community-based sample, we observed that adverse changes in modifiable cardiometabolic risk factors, most notably rising blood pressure, gain in BMI, new onset of diabetes, and increases in concentrations of blood triglyceride relate to longitudinal deterioration in measures of LV diastolic function. Progression of LV DD was also related to increasing levels of noncardiac comorbidity and to incidence of adverse CVD outcomes. Future studies are warranted to investigate if improving cardiometabolic risk profiles results in reductions in (or prevention of) left ventricular diastolic dysfunction and, potentially, heart failure. Additional studies are needed to further explore this premise.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Left ventricular diastolic dysfunction is associated with incident cardiovascular disease. Modifiable cardiovascular risk factors and noncardiac comorbidity are associated with the progression of diastolic dysfunction.

**TRANSLATIONAL OUTLOOK:** Future studies are warranted to investigate whether improving cardiometabolic risk profiles results in reductions in (or prevention of) left ventricular diastolic dysfunction and, potentially, heart failure.

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**KEY WORDS** cardiometabolic risk factors, diastolic function, prevention

**APPENDIX** For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.