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ORIGINAL RESEARCH

Epidemiology of Left Ventricular Systolic Dysfunction and Heart Failure in the Framingham Study

An Echocardiographic Study Over 3 Decades

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CME/MOC Objective for This Article: After reading this article the reader should be able to: 1) recognize the changing profile of heart failure in the community, especially with reference to the preponderance of HFpEF over HFrEF in recent decades; 2) differentiate between the prognosis (5-year mortality and changes over time in mortality rates) of HFrEF vs. HFpEF vs. HFmrEF, thereby better communicate risk to patients with HF; 3) compare the relative contributions of cardiovascular versus non-cardiovascular causes to mortality in HF according to EF category to differentiate treatment strategies to prevent mortality in HF patients; 4) advocate for trials that focus on improving outcomes in HFpEF and HFmrEF; and 5) manage patients with asymptomatic left ventricular systolic dysfunction appropriately by implementing standards of care set by established guidelines.

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ABSTRACT

OBJECTIVES The purpose of this study was to describe the temporal trends in prevalence of left ventricular systolic dysfunction (LVSD) in individuals without and with heart failure (HF) in the community over a 3-decade period of observation.

BACKGROUND Temporal trends in the prevalence and management of major risk factors may affect the epidemiology of HF.

METHODS We compared the frequency, correlates, and prognosis of LVSD (left ventricular ejection fraction [LVEF] <50%) among Framingham Study participants without and with clinical HF in 3 decades (1985 to 1994, 1995 to 2004, and 2005 to 2014).

RESULTS Among participants without HF (12,857 person-observations, mean age 53 years, 56% women), the prevalence of LVSD on echocardiography decreased (3.38% in 1985 to 1994 vs. 2.2% in 2005 to 2014; $p < 0.0001$), whereas mean LVEF increased (65% vs. 68%; $p < 0.001$). The elevated risk associated with LVSD (~2- to 4-fold risk of HF or death) remained unchanged over time. Among participants with new-onset HF ($n = 894$, mean age 75 years, 52% women), the frequency of heart failure with preserved ejection fraction (HFpEF) increased (preserved LVEF ≥50%: 41.0% in 1985 to 1994 vs. 56.17% in 2005 to 2014; $p < 0.001$) and heart failure with reduced ejection fraction (HFrEF) decreased (reduced LVEF <40%: 44.10% vs. 31.06%; $p = 0.002$), whereas heart failure with midrange LVEF remained unchanged (LVEF 40% to <50%: 14.90% vs. 12.77%; $p = 0.66$). Cardiovascular mortality associated with HFrEF declined across decades (hazard ratio: 0.61; 95% confidence interval: 0.39 to 0.97), but remained unchanged for heart failure with midrange LVEF and HFpEF. Approximately 47% of the observed increase in LVEF among those without HF and 75% of the rising proportion of HFpEF across decades was attributable to trends in risk factors, especially a decline in the prevalence of coronary heart disease among those with HF.

CONCLUSIONS The profile of HF in the community has changed in recent decades, with a lower prevalence of LVSD and an increased frequency of HFpEF, presumably due to concomitant risk factor trends. (J Am Coll Cardiol Img 2018;11:1–11) © 2018 by the American College of Cardiology Foundation.

Advances in the management of coronary heart disease (CHD) and its risk factors have favorably affected the epidemiology of CHD (1–4). The incidence of post-myocardial infarction (MI) heart failure (HF) has also declined (5–8), although not all reports are consistent (9). Paralleling these observations, investigators have described a rise in the proportion of heart failure with preserved left ventricular ejection fraction (HFpEF) relative to heart failure with reduced left ventricular ejection

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fraction (HFrEF) in recent decades, presumably due to a decline in the incidence of HFrEF (9–11). More recently, reports have described a third entity, labeled heart failure with midrange left ventricular ejection fraction (HFmrEF) (12–15). Evaluating the relative prevalence of these HF types is challenged by varying data sources, changes in coding practices, differing diagnostic criteria, and a shift toward greater outpatient diagnosis of HF (9,16). Additionally, there are no data regarding trends in the prevalence of asymptomatic left ventricular systolic dysfunction (LVSD) (defined as LVEF <50%), an antecedent of HFrEF.

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We investigated if the profile of LVSD and HF in the community has changed over time due to favorable trends in management of CHD/MI and divergent trends in HF risk factors (i.e., with better rates of control of hypertension and dyslipidemia being offset by increasing rates of obesity and diabetes) (1). We tested the hypothesis that the prevalence of LVSD in the community is decreasing and the occurrence of HFpEF is rising in recent decades using data from the Framingham Heart Study (FHS).

METHODS

STUDY SAMPLES. The selection criteria and study design of the 3 FHS cohorts have been described (17–19). Participants who attended routine FHS examinations between 1985 and 2015, and who were under continuous surveillance for the development of HF events, were eligible for the present investigation. The study protocols were approved by the Boston University Medical Center Institutional Review Board, and all participants provided written informed consent. The measurement and definitions of key covariates are described in the Online Appendix, Section A.

Two different samples were used (Online Figure 1).

Sample 1. For studying temporal trends in the epidemiology of LVSD, we used echocardiographic examinations among participants who were free of overt HF in 3 successive decades: 1985 to 1994, 1995 to 2004, and 2005 to 2014. Accordingly, the original cohort examination 20 and offspring cohort examination 4 (n = 3,901) contributed to the first decade (1985 to 1994); offspring cohort examination 6 and third generation examination 1 (n = 6,459) contributed to the middle decade (1995 to 2004); and offspring examination 8 (n = 2,497) contributed to the most recent decade (2005 to 2014). All covariate data were obtained at the same FHS examination at which echocardiography was performed.

Sample 2. For studying temporal trends in the profile of HF, we evaluated all individuals with a first episode of HF in the 3 decades (n = 894) (Online Figure 1). We evaluated LVEF data closest to and within 6 months after HF onset (based on data from hospitalization records, physician office visits, or FHS) to categorize HF type as HFrEF: LVEF <40%; HFmrEF: LVEF 40% to <50%; and HFpEF: LVEF ≥50%. Covariate data were obtained from the closest FHS examination antedating the HF episode.

ABBREVIATIONS AND ACRONYMS

EF = ejection fraction

HF = heart failure

HFmrEF = heart failure with midrange left ventricular ejection fraction

HFpEF = heart failure with preserved left ventricular ejection fraction

HFrEF = heart failure with reduced left ventricular ejection fraction

LVSD = left ventricular systolic dysfunction

ECHOCARDIOGRAPHIC MEASURES. At the FHS examinations (Sample 1), attendees underwent 2-dimensional echocardiography with Doppler color flow imaging (Online Appendix, Sections B and C), and M-mode measurements were made according to the American Society of Echocardiography guidelines (20). LVEF was calculated using the method of de Simone (21) complemented by the visual assessment of LV systolic function; 2-dimensional quantitation of chamber volume was not routinely performed in the first decade. LVEF was categorized as: normal (LVEF ≥50%), mildly reduced (LVEF 40% to <50%), and moderate or greater impairment (LVEF <40%).

FOLLOW-UP AND OUTCOME EVENTS. Information about events during follow-up was obtained from medical history and physical examination at the FHS, and a review of medical records. All suspected new CVD events were adjudicated by a panel of 3 experienced investigators who evaluated pertinent medical records using previously published criteria (22).

Over the 3 decades, the diagnosis of HF was made using the same FHS criteria (23): the presence of 2 major criteria, or of 1 major criterion and 2 minor criteria (Online Appendix, Section D). The sensitivity and specificity of these criteria compare well with other epidemiological criteria for HF (24).

For analyses of prognosis of LVSD, our primary outcome was a composite of new-onset HF or death. For analyses of outcomes in individuals with HF, we assessed all-cause mortality and cause-specific mortality (death due to CVD vs. non-CVD causes) (25,26).

STATISTICAL METHODS. Sample 1—without overt HF. We evaluated the distribution of LVEF in each of the 3 decades in individuals without HF who underwent echocardiography at FHS, comparing the distributions using the Kolmogorov-Smirnov test and rank correlations. We estimated the frequency of LVSD

TABLE 1 Characteristics of Participants Free of Heart Failure Who Underwent Routine Framingham Study Echocardiography (1985–2014)

	1985–1994 (n = 3,901 Person-Observations)				1995–2004 (n = 6,459 Person-Observations)				2005–2014 (n = 2,497 Person-Observations)			
LVEF	<40%	≥40–<50%	≥50%	p Value*	<40%	≥40–<50%	≥50%	p Value*	<40%	≥40–<50%	≥50%	p Value*
Person-observations, n	31	101	3,769		46	49	6364		14	41	2,442	
Age, yrs	64 ± 12	58 ± 15	55 ± 13	<0.0001	64 ± 8	62 ± 9	47 ± 13	<0.0001	74 ± 9	70 ± 8	66 ± 9	<0.0001
Men, %	80.7	75.3	42.6	<0.0001	87.0	81.6	44.5	<0.0001	78.6	90.2	43.8	<0.0001
Body mass index, kg/m^2	26.0 ± 4.0	26.9 ± 4.8	26.4 ± 4.5	0.74	28.6 ± 4.6	27.1 ± 4.0	26.9 ± 5.1	0.045	26.4 ± 4.8	28.6 ± 4.5	28.1 ± 5.2	0.65
Obese, %	9.7	23.8	18.1	0.16	30.4	24.5	22.6	0.42	21.4	31.7	30.2	0.76
Systolic BP, mm Hg	135 ± 17	135 ± 23	129 ± 21	0.002	134 ± 16	129 ± 18	121 ± 17	<0.0001	120 ± 15	134 ± 19	128 ± 17	0.99
Diastolic BP, mm Hg	76 ± 9	79 ± 11	78 ± 10	0.98	76 ± 9	74 ± 10	75 ± 10	0.94	67 ± 13	74 ± 16	74 ± 10	0.04
HTN, %	71.0	54.5	39.7	<0.0001	69.6	59.2	25.5	<0.0001	64.3	68.3	56.0	0.24
DM, %	9.7	12.1	4.7	0.003	32.6	14.3	4.6	<0.0001	28.6	24.4	11.8	0.009
Smoker, %	22.6	24.8	21.0	0.65	13.0	18.4	14.9	0.74	14.3	12.2	9.1	0.40
Total/HDL cholesterol	4.87 ± 1.35	4.77 ± 1.72	4.49 ± 1.61	0.04	4.66 ± 1.27	4.21 ± 1.16	3.97 ± 1.47	0.0009	3.43 ± 1.28	3.53 ± 0.93	3.46 ± 1.05	0.87
MI, %	41.9	15.8	2.1	<0.0001	50.0	24.5	0.74	<0.0001	28.6	31.7	3.2	<0.0001
CHD, %	71.0	27.7	6.3	<0.0001	65.2	44.9	2.3	<0.0001	35.7	43.9	8.4	<0.0001
AF, %	9.7	6.9	1.5	<0.0001	28.3	14.3	0.93	<0.0001	28.6	31.7	4.8	<0.0001
LVEF, %	34.3 ± 3.2	46.7 ± 2.2	65.6 ± 7.1	<0.0001	33.2 ± 4.2	45.7 ± 1.8	66.4 ± 4.3	<0.0001	33.9 ± 4.0	45.4 ± 2.5	68.1 ± 5.2	<0.0001

Values are mean ± SD unless otherwise indicated. *p value for trend across LVEF categories in a given decade of interest.

AF = atrial fibrillation; BP = blood pressure; CHD = coronary heart disease; DM = diabetes mellitus; FS = fractional shortening; HDL = high-density lipoprotein cholesterol; HTN = hypertension; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NA = serum creatinine not available at index examination.

(ejection fraction [EF] <40%, and EF midrange 40% to <50%) and clinical characteristics of the 3 LVEF groups in each time period. Trends in prevalence of LVSD over time were assessed using logistic regression models adjusting for age and sex. We examined absolute rates of the composite outcome (HF or death) over a follow-up period of 5 years. Using Cox regression (27) models that adjusted for age, sex, and cohort type, we estimated the relative risk of the composite outcome in those with LVSD compared with those with a normal LVEF. We confirmed that the assumption of proportionality of hazards was met. We repeated the Cox regression analyses individually for each LVEF category to compare trends over time in the risk of adverse outcomes for participants in that category. *Given the modest number of individuals with LVSD and LVEF <40%, we repeated analyses defining LVSD as LVEF <50%.*

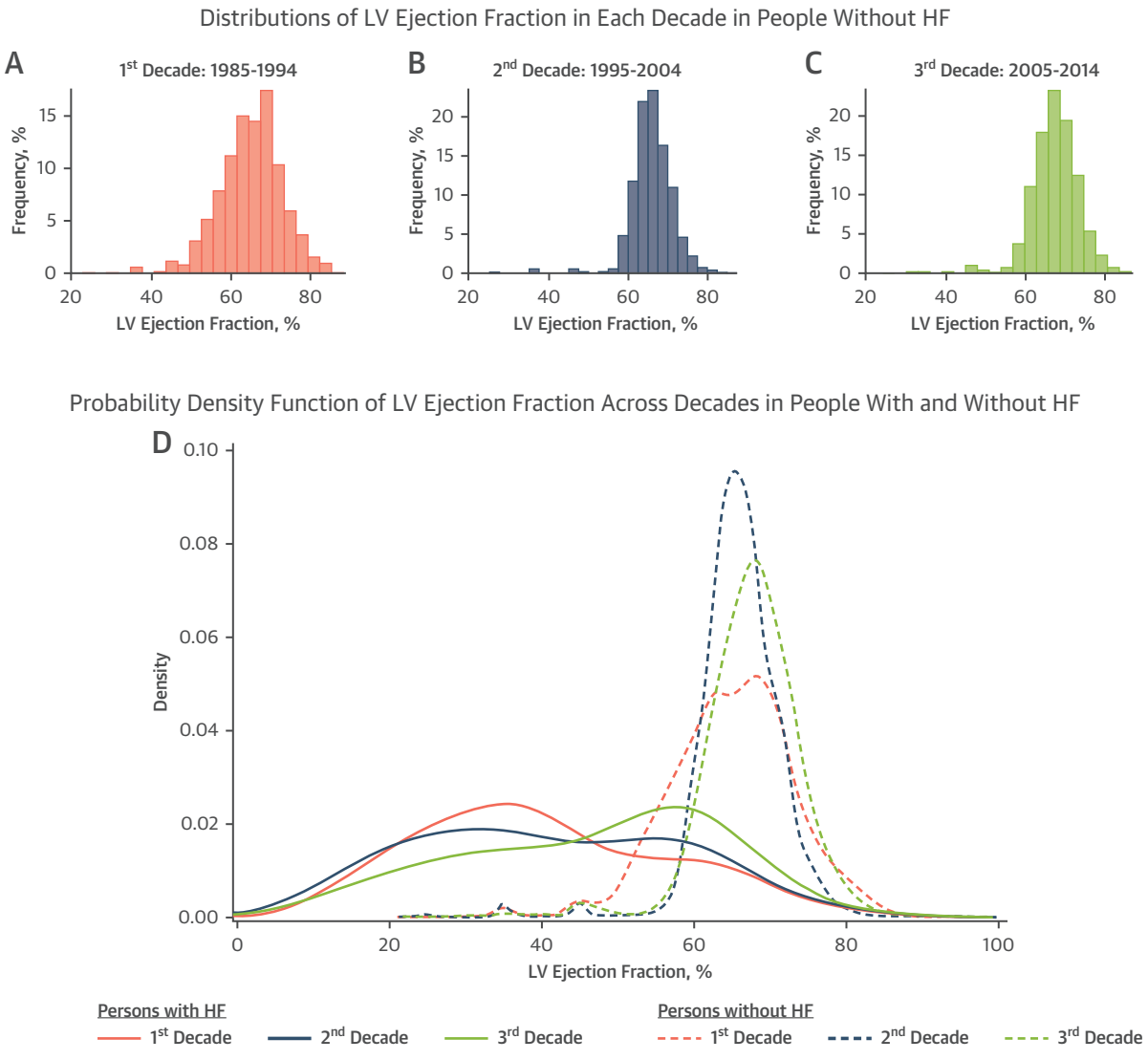
Sample 2—with HF. Among participants with new-onset HF, we assessed the proportions of HFrEF versus HFmrEF versus HFpEF within each decade. We compared clinical characteristics associated with each HF type within each decade. Trends in prevalence of reduced LVEF among participants with HF over time were assessed using logistic regression models adjusting for age and sex. We determined the risk of death (all-cause mortality, and death due to CVD and non-CVD causes) for each HF subtype in each decade over a follow-up period of 5 years. We estimated multivariable Cox regression models adjusting for age and sex, comparing the risk of death in participants with HFrEF and HFmrEF with that of HFpEF (referent). For each HF type, we repeated Cox regression models to compare trends in risk of all-cause mortality and cardiovascular and non-cardiovascular mortality across the 3 decades. *Given the modest number of individuals with HFmrEF, we repeated analyses defining HFrEF as an LVEF <50%.*

In additional analyses, we assessed the contributions of trends in correlates of LVEF (linear models) and HFpEF (logistic models) to the trends in LVEF distribution in participants without and with HF, respectively (Online Appendix, Sections E and F). A 2-sided p value <0.05 was considered statistically significant.

RESULTS

INDIVIDUALS WITHOUT DIAGNOSED HF. Baseline characteristics of individuals without clinical HF are displayed in Table 1 by decade and according to the 3 LVEF categories. Participants with moderate or greater LVSD were older than those with normal LVEF; were predominantly male; and had a higher burden of hypertension, diabetes, CHD, and atrial fibrillation compared with those without LVSD. Participants with LVEF in the midrange had prevalence of diabetes, smoking, and mean values of lipids that were intermediate between the other 2 LVEF

FIGURE 1 **Distribution LVEF by Decade in Participants With and Without HF**



(A to C) Distribution in patients free of heart failure. **(D)** Smoothed probability density function (y-axis) for values of left ventricular ejection fraction (LVEF) (x-axis) by decade in participants free of heart failure (HF) **(dotted lines)** juxtaposed with those with HF **(solid lines)** for comparison. Data for decade 1985 to 1994 are indicated in **pink**, those for decade 1995 to 2004 in **blue**, and for decade 2005 to 2014 in **green**. SAS proc sgplot (SAS Institute Inc., Cary, North Carolina) was used to generate the kernel density plots for the EF distribution by time period for the HF and non-HF samples.

categories. Across the 3 decades, the prevalence of CHD and MI rose (by 58% to 100%) among those with LVEF in midrange, but diminished (by 31% to 50%) in those with LVEF <40%. Prevalence of atrial fibrillation rose 3- to 5-fold across decades in each LVEF category.

Figures 1A to 1C display the distributions of LVEF in the 3 time periods. The entire LVEF distribution shifted to the right (i.e., higher LVEF) over time, with the median value increasing from 65% in the first decade to 68% in the last decade (Online Figure 2) ($p < 0.0001$ for both Kolmogorov-Smirnov test and rank correlations). **Table 2** shows that the prevalence of LVSD decreased from 3.38% in the first decade to 2.2% in the last decade, with a marked decline in the odds of LVSD (**Table 2**). Online Figure 3 demonstrates the Kaplan-Meier curves for survival free of the composite outcome in individuals without baseline clinical HF by LVEF category in each time period and pooled across the 3 time periods. Individuals with

TABLE 2 Prevalence Over Time of Reduced Left Ventricular Ejection Fraction in Participants Without and With Overt Heart Failure

Decade	Proportion With LVEF (%)			Age- and Sex-Adjusted Odds Ratio (95% CI) for LV Systolic Dysfunction, LVEF <50%	p Value
	<40%	40-<50%	≥50%		
Participants Free of HF					
1985–1994	0.79	2.59	96.62	1.00 (Referent)	–
1995–2004	0.71	0.76	98.53	0.64 (0.49–0.85)	0.002
2005–2014	0.56	1.64	97.80	0.36 (0.26–0.50)	<0.0001
Chi-square p value*		<0.0001			
Participants With HF					
1985–1994	44.10	14.93	40.97	1.00 (Referent)	–
1995–2004	43.94	12.67	43.40	0.93 (0.67–1.28)	0.64
2005–2014	31.06	12.77	56.17	0.54 (0.38–0.77)	0.0007
p value for trend across decades†	0.002	0.66	0.001	0.74 (0.62–0.89)	0.001‡

*The chi-square test was used due to small number of individuals in cells. †Comparisons within LVEF category. ‡p for trend across decades.
HF = heart failure; LVEF = left ventricular ejection fraction.

LVEF in the midrange had a prognosis intermediate between those with LVEF <40% and those with normal LVEF. Online Table 1 (Part A) provides the absolute rates of the composite outcome for the 3 LVEF categories in each decade. Unadjusted rates were considerably higher for the 2 lower LVEF categories in each decade relative to those with normal LVEF; event rates were lower in the middle decade in which participants were also younger (due to inclusion of FHS third generation participants). Unadjusted absolute events rates for the groups with midrange LVEF almost doubled in the most recent decade compared with 1985 to 1994. In Cox regression analyses adjusting for age, sex, and cohort type, LVSD conferred a 2- to 4-fold risk of developing the composite outcome (Online Table 2, Part A, data pooled over the decades). Within each LVEF category, the adjusted risk of developing the composite outcome remained unchanged across the decades (Online Table 2, Part B). *Results were unchanged when a single cut point (LVEF <50%) was used to define LVSD* (Online Table 2, parts C and D).

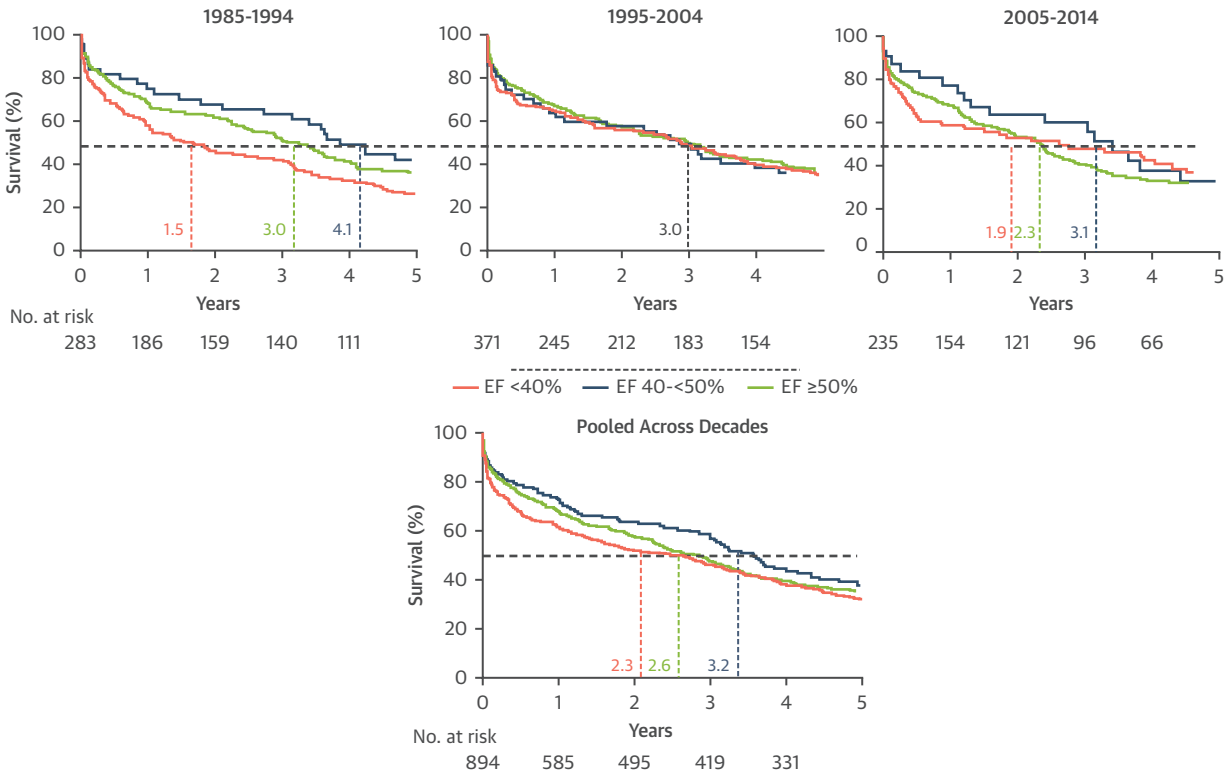
INDIVIDUALS WITH DIAGNOSED HF. Table 3 demonstrates the characteristics of patients with HFrEF, HFmrEF, and HFpEF within each decade. The average age of onset of HFpEF and HFmrEF increased in the most recent decade. Within each time period, clinical characteristics of patients with HFmrEF were intermediate between those with HFrEF and HFpEF. Across time, and in each HF type, there was a rising prevalence of obesity, hypertension, and atrial fibrillation, whereas the prevalence of dyslipidemia, CHD, MI, and smoking declined. Mean levels of blood pressure and the ratio of total to high-density lipoprotein cholesterol concentrations decreased across decades, concomitant with rising treatment rates for hypertension and dyslipidemia in each HF subtype. Although the prevalence of CHD declined across

TABLE 3 Characteristics of Participants With Clinically Diagnosed New-Onset Heart Failure in the Framingham Study (1985–2014)

	1985-1994 (n = 288)				1995-2004 (n = 371)				2005-2014 (n = 235)			
	HFrEF (<40%)	HFmrEF (≥40-<50%)	HFpEF (≥50%)	p Value*	HFrEF (<40%)	HFmrEF (≥40-<50%)	HFpEF (≥50%)	p Value*	HFrEF (<40%)	HFmrEF (≥40-<50%)	HFpEF (≥50%)	p Value*
n	127	43	118		163	47	161		73	30	132	
Age, yrs	73 ± 12	75 ± 9	74 ± 15	0.71	73 ± 13	71 ± 17	77 ± 12	0.02	72 ± 13	76 ± 11	78 ± 12	0.002
Men, %	56.7	46.5	41.5	0.06	62.0	46.8	31.1	<0.0001	64.4	53.3	40.2	0.004
BMI, kg/m^2	27 ± 5	29 ± 6	28 ± 5	0.47	28 ± 5	29 ± 5	29 ± 6	0.12	29 ± 6	28 ± 5	29 ± 7	0.78
Obese, %	23	38	25	0.17	26	32	34	0.35	38	41	42	0.91
Systolic BP, mm Hg	147 ± 26	152 ± 23	146 ± 25	0.69	140 ± 21	151 ± 21	141 ± 23	0.54	135 ± 19	138 ± 21	140 ± 22	0.09
Diastolic BP, mm Hg	76 ± 12	76 ± 12	76 ± 11	0.66	72 ± 13	79 ± 13	71 ± 12	0.57	71 ± 12	69 ± 13	70 ± 11	0.43
HTN, %	78.9	81.0	79.3	0.96	76.7	85.1	75.6	0.39	74.0	76.7	86.8	0.06
DM, %	21.4	30.8	22.2	0.47	34.7	39.4	26.3	0.25	36.8	24.0	21.2	0.07
Smoker, %	22.4	21.4	18.6	0.76	16.8	22.2	11.2	0.13	15.1	6.9	3.0	0.006
Tc/HDL	5.5 ± 2.0	5.7 ± 2.0	5.2 ± 1.7	0.42	4.8 ± 1.9	5.1 ± 1.9	4.4 ± 1.6	0.10	4.1 ± 1.5	3.7 ± 1.9	3.5 ± 1.1	0.02
MI, %	58	63	35	0.0002	52	60	24	<0.0001	38	33	20	0.01
CHD, %	69	74	50	0.0022	65	70	40	<0.0001	49	57	36	0.05
AF, %	28	28	41	0.07	39	32	55	0.003	37	53	52	0.11
LVEF (at time of HF), %	35 ± 5	42 ± 2	58 ± 5	<0.0001	32 ± 7	42 ± 2	59 ± 9	<0.0001	28 ± 8	43 ± 3	60 ± 7	<0.0001

Values are mean ± SD unless otherwise indicated. *p value for trend across heart failure categories in a given decade of interest.
HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; other abbreviations as in Table 1.

FIGURE 2 **Kaplan-Meier Curves for Survival of Participants With HFrEF, HFmrEF, and HFpEF in the 3 Decades and Pooled Across Decades**



The **horizontal line** indicates median survival, and the **vertical lines** show median survival time for participants with new-onset heart failure (HF) for each subtype of HF. EF = ejection fraction; HFpEF = heart failure with preserved left ventricular ejection fraction; HFmrEF = heart failure with midrange left ventricular ejection fraction; HFrEF = heart failure with reduced left ventricular ejection fraction.

decades for all 3 HF subtypes, it was highest in participants with HFmrEF in the last decade.

Figure 1D shows a rightward shift in the LVEF distribution of participants with new-onset HF across the 3 decades. **Table 2** confirms the rising proportion with HFpEF (15% absolute increase) in the most recent decade, paralleled by a decrease in HFrEF prevalence (13% absolute decrease); the frequency of HFmrEF held steady at 13% to 15%. The odds ratio of developing HF with an EF <50% in the most recent decade declined to 0.54.

Figure 2 shows the Kaplan-Meier curves for survival following HF onset by LVEF category in each time period and pooled across decades. Median survival time improved for HFrEF but remained the same or increased in the other 2 categories. Online Table 1 (Part B) demonstrates absolute rates of death for the 3 HF categories in each decade. Participants with HFmrEF demonstrated the best survival in the initial decade relative to the other 2 HF categories, a pattern that changed with convergence of survival among the groups over the next 2 decades. There was no significant difference in the risk of death between the 3 HF subtypes in any of the 3 decades (Online Table 3). *The use of a single cut point (LVEF <50%) to define HFrEF yielded essentially similar results* (Online Table 3, bottom).

Analyses of cause-specific mortality within HF type demonstrated a decline in cardiovascular mortality for HFrEF over time, and an increase in noncardiovascular mortality for HFmrEF (**Table 4**). Cardiovascular and noncardiovascular mortality remained unchanged over the decades for HFpEF. *Nearly identical results were obtained when cause-specific mortality was evaluated defining HFrEF as an LVEF <50%* (Online Table 4).

ADDITIONAL ANALYSES: RISK FACTORS. The results of additional analyses relating temporal trends in CVD risk factors to shifts in the mean values of LVEF (in those without HF) and to change in the proportion of HFpEF (among new-onset HF cases) are shown in Online Tables 5 and 6. Increasing rates of treatment for

TABLE 4 Temporal Trends in Cause of Death Among Participants With Overt Heart Failure: Results of Age- and Sex-Adjusted Cox Regression

	All-Cause Mortality			CVD Mortality			Non-CVD Mortality		
	No. Event/ No. at Risk	Hazard Ratio (95% CI)	p Value*	No. Event/ No. at Risk	Hazard Ratio (95% CI)	p Value*	No. Event/ No. at Risk	Hazard Ratio (95% CI)	p Value*
All participants with heart failure									
1985–1994	194/288	1.00 (Referent)		123/288	1.00 (Referent)		71/288	1.00 (Referent)	
1995–2004	236/371	0.88 (0.73–1.06)	0.18	127/371	0.77 (0.60–0.98)	**0.04**	109/371	1.10 (0.81–1.48)	0.54
2005–2014	149/235	0.93 (0.75–1.15)	0.51	64/235	0.62 (0.46–0.84)	**0.0018**	85/235	1.44 (1.05–1.98)	**0.02**
Participants with HFrEF									
1985–1994	94/127	1.00 (Referent)		71/127	1.00 (Referent)		23/127	1.00 (Referent)	
1995–2004	106/163	0.78 (0.59–1.03)	0.08	70/163	0.70 (0.51–0.98)	**0.04**	36/163	1.00 (0.59–1.69)	0.99
2005–2014	43/73	0.79 (0.55–1.14)	0.21	25/73	0.61 (0.39–0.97)	**0.04**	18/73	1.33 (0.71–2.48)	0.37
Participants with HFmrEF									
1985–1994	25/43	1.00 (Referent)		18/43	1.00 (Referent)		7/43	1.00 (Referent)	
1995–2004	30/47	1.36 (0.80–2.32)	0.26	15/47	0.92 (0.46–1.84)	0.82	15/47	2.49 (1.01–6.11)	**0.047**
2005–2014	18/30	1.11 (0.60–2.04)	0.74	6/30	0.51 (0.20–1.29)	0.16	12/30	2.66 (1.04–6.81)	**0.04**
Participants with HFpEF									
1985–1994	75/118	1.00 (Referent)		34/118	1.00 (Referent)		41/118	1.00 (Referent)	
1995–2004	100/161	0.88 (0.65–1.20)	0.42	42/161	0.81 (0.51–1.27)	0.36	58/161	0.95 (0.64–1.42)	0.81
2005–2014	88/132	1.00 (0.73–1.36)	0.99	33/132	0.79 (0.49–1.28)	0.34	55/132	1.18 (0.78–1.79)	0.42

*p value for comparison of decades. p values <0.05 are shown in **bold**.
CVD = cardiovascular disease (coronary disease, stroke, peripheral vascular disease, or heart failure); other abbreviations as in Table 3.

hypertension and decreasing prevalence of CHD/MI were key correlates of declining LVSD prevalence and rising HFpEF frequency, respectively. Approximately 47% of the change in mean LVEF values and 75% of the change in prevalence in HFpEF were attributable to changes in key risk factors for LVSD and HF (Online Appendix, Sections E and F).

DISCUSSION

PRINCIPAL FINDINGS. We have characterized concomitant changes in the epidemiology of LVSD and HF subtypes in a large, community-based cohort over 3 decades by analyzing approximately 13,000 echocardiograms and nearly 900 well-phenotyped HF cases over a 30-year time period. We observed a decrease in the prevalence of asymptomatic LVSD, accompanied by a shift in HF phenotype toward a preponderance of HFpEF over HFrEF, with the proportion of HFmrEF remaining unaltered. Participants presenting with a midrange EF (both without and with HF) were intermediate in terms of their risk factor profile relative to their counterparts with lower or higher EF, confirming other reports (13,27). We demonstrated that the prognosis of asymptomatic LVSD remained essentially unchanged over time, Among HF patients, the prognosis of those with HFrEF improved, whereas that of HFmrEF and HFpEF remained unchanged. *Use of an LVEF cut point of 50% to define LVSD (in those without HF) or HFrEF (in those with HF) yielded essentially similar results.*

CHANGING EPIDEMIOLOGY OF ASYMPTOMATIC LVSD. The rightward shift in the entire LVEF distribution suggests that the decline in prevalence of LVSD was not limited to the lower extreme (LVEF <40%) of the distribution. Temporal trends in risk factors accounted for about 45% of the shift in LVEF distribution. This observation likely reflects the net balance between positive (rising burden of hypertension and obesity, and declining rates of smoking and total to high-density lipoprotein cholesterol ratio) and negative correlates of LVEF (increase in prevalence of diabetes [1] and MI). Improved management of MI and decline in the occurrence of ST-segment elevation MI (28) may have also contributed. It is important to note that more than one-half of the change in mean LVEF remained unexplained, suggesting the need for additional study. We did not observe any change in prognosis of LSVD over time, with a 2- to 4-fold increased risk of the composite outcome, despite availability of evidence-based treatment recommendations for those with LVEF <40% (29).

CHANGING EPIDEMIOLOGY OF OVERT HF. Using the same standardized criteria for HF consistently over a 30-year period, we confirm and extend prior

observations made in Olmsted County from 2000 to 2010 (10) (using validated International Classification of Diseases, Ninth Revision codes) documenting the increasing predominance of HFpEF over HFrEF. Temporal trends in risk factors for HFrEF versus HFpEF (a lower prevalence of CHD and rising hypertension rates among those with HF) (1) explained about 75% of the observed shift toward a greater prevalence of HFpEF. An increased awareness of HFpEF in recent decades may have also contributed to this trend.

Among HF patients in our investigation, the prognosis of those with HFrEF improved over the last 2 decades, as evidenced by a 30% to 40% decline in cardiovascular mortality. All-cause and cardiovascular mortality for the HFmrEF and HFpEF groups remained unchanged. The absolute mortality rates in individuals with HFrEF were higher than in the other 2 groups with HF in the initial decade (1985 to 1994). In the most recent decade (2005 to 2014), the mortality rates for all 3 HF subtypes converged.

The overall similar mortality risk for HFpEF versus HFrEF in the last decade of our investigation is consistent with some community-based reports (11,30) and data from 2 registries of HF patients (31,32). In contrast, 2 recent large meta-analyses (26,33) that included data from both observational studies and randomized trials reported a lower mortality risk for HFpEF relative to HFrEF. In the latter meta-analysis (33), the difference in mortality risk for HFpEF versus HFrEF narrowed in patients over age 75 years, a threshold that approximates the average age of HF onset in the FHS sample. Disease spectrum bias may also contribute to the similar mortality rates for HFrEF and HFpEF observed in cohort studies compared with randomized trials that have reported a better prognosis for HFpEF (34).

The decline in cardiovascular mortality for HFrEF over the decades suggests the effectiveness of evidence-based management strategies. In comparison, the prognosis of HFmrEF and HFpEF remained unchanged, underscoring the importance of ongoing trials of HFpEF patients (35). Data from Olmsted County also suggest a trend toward decreasing mortality for HFrEF but not for HFpEF (11). The trend toward increasing non-CVD mortality in participants with HFmrEF in our investigation requires confirmation in larger samples.

STUDY STRENGTHS AND LIMITATIONS. Key strengths of our investigation include the conjoint analysis comparing and linking trends in LVEF in participants without and with HF over a 30-year time period; the large, community-based sample undergoing routine serial echocardiography; the use of the same criteria for diagnosis of HF across these decades; and the parsing of the epidemiology of HFmrEF from that of HFrEF and HFpEF. Nonetheless, several limitations warrant consideration. These include unavoidable biases due to differential missingness of echocardiographic data in those free of HF (Sample 1), and possible misclassification of LVEF due to changes in the echocardiographic equipment over time and potential intrareader temporal drifts (36). Individuals with missing echocardiograms often have a higher risk (37). We implemented several quality control procedures in our echocardiography laboratory (Online Appendix, Section C) to minimize drifts in echocardiographic measurements. Tissue Doppler-based echocardiographic measures provide important information about LV diastolic function, and are a component of criteria for the diagnosis of HFpEF. However, the lack of availability of these measures and of plasma natriuretic peptide levels in the first 2 decades was an unavoidable limitation. The small sample sizes for HFmrEF in each of the 3 decades are an unavoidable limitation, given the overall lower prevalence of the condition (12% to 15% of all HF). Therefore, findings for this condition must be interpreted with caution and should be replicated in larger samples. Additionally, we were unable to evaluate the reasons for the unchanged prognosis of LVSD (without HF) over the decades in our sample. Last, our study sample included middle-aged to elderly white individuals of European ancestry, limiting the generalizability of our findings.

CONCLUSIONS

Our observations over the last 3 decades suggest that secular trends in CVD risk factors may be altering the profile of HF in the community, marked by a decline in the prevalence of asymptomatic LVSD paralleled by a concomitant increase in the prevalence of HFpEF. The cardiovascular mortality of HFrEF has declined over the last 3 decades, reflecting the effect of major clinical trials. The unchanged prognosis of asymptomatic LVSD and of HFmrEF and HFpEF indicate unmet needs of patients with these conditions.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Serial observations in our large, community-based cohort over the last 3 decades suggest that temporal trends in CVD risk factors may be altering the profile of HF in the community, characterized by a decline in the prevalence of asymptomatic LVSD with a concomitant increase in the prevalence of HFpEF. The cardiovascular mortality of HFrEF has declined over the last 3 decades, reflecting the effect of major clinical trials. The unchanged prognosis of asymptomatic LVSD and of HFmrEF and HFpEF indicate unmet needs of patients with these conditions.

TRANSLATIONAL OUTLOOK: It is important that our findings be explored and replicated in multiethnic samples, and future studies are warranted to elucidate the additional factors that may have contributed to the changing profile of LVSD and HF in the general population. The unchanged prognosis of LVSD in the absence of clinical HF, despite the availability of evidence-based treatment, underscores the need for strategies to better implement guidelines-based care for this condition. The prognosis of HFmrEF and HFpEF remain largely unchanged over the 30-year period, identifying major areas for improvement. Evidence-based management of patients with HFmrEF is challenged by the fact that they have not been consistently targeted in clinical trials and by the overall modest prevalence of the condition among HF patients (12% to 15%). Meta-analysis of data from controlled clinical trials of HF that enrolled patients with LVEF in the range 40% to 50% may inform future guidelines for managing these patients, and future clinical trials could consider pre-specifying this subgroup for analyses.

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

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