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ORIGINAL RESEARCH

Association of Pulmonary Function With Late-Life Cardiac Function and Heart Failure Risk: The ARIC Study

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BACKGROUND: Pulmonary and cardiac functions decline with age, but the associations of pulmonary dysfunction with cardiac function and heart failure (HF) risk in late life is not known. We aimed to determine the associations of percent predicted forced vital capacity (ppFVC) and the ratio of forced expired volume in 1 second (FEV_1) to forced vital capacity (FVC; FEV_1/FVC) with cardiac function and incident HF with preserved or reduced ejection fraction in late life.

METHODS AND RESULTS: Among 3854 HF-free participants in the ARIC (Atherosclerosis Risk in Communities) cohort study who underwent echocardiography and spirometry at the fifth study visit (2011–2013), associations of FEV_1/FVC and ppFVC with echocardiographic measures, cardiac biomarkers, and risk of HF, HF with preserved ejection fraction, and HF with reduced ejection fraction were assessed. Multivariable linear and Cox regression models adjusted for demographics, body mass index, coronary disease, atrial fibrillation, hypertension, and diabetes. Mean age was 75±5 years, 40% were men, 19% were Black, and 61% were ever smokers. Mean FEV_1/FVC was 72±8%, and ppFVC was 98±17%. In adjusted analyses, lower FEV_1/FVC and ppFVC were associated with higher NT-proBNP (N-terminal pro-B-type natriuretic peptide; both $P<0.001$) and pulmonary artery pressure ($P<0.004$). Lower ppFVC was also associated with higher left ventricular mass, left ventricular filling pressure, and high-sensitivity C-reactive protein (all $P<0.01$). Lower FEV_1/FVC was associated with a trend toward higher risk of incident HF with preserved ejection fraction (hazard ratio [HR] per 10-point decrease, 1.31; 95% CI, 0.98–1.74; $P=0.07$) and HF with reduced ejection fraction (HR per 10-point decrease, 1.24; 95% CI, 0.91–1.70; $P=0.18$), but these associations did not reach statistical significance. Lower ppFVC was associated with incident HF with preserved ejection fraction (HR per 10-unit decrease, 1.21; 95% CI, 1.04–1.41; $P=0.013$) but not with HF with reduced ejection fraction (HR per 10-unit decrease, 0.90; 95% CI, 0.76–1.07; $P=0.24$).

CONCLUSIONS: Subclinical reductions in FEV_1/FVC and ppFVC differentially associate with cardiac function and HF risk in late life.

Key Words: cardiopulmonary ■ elderly ■ heart dysfunction ■ lung function ■ respiratory disease

Subclinical impairments in pulmonary function detected by spirometry are associated with alterations in cardiac structure and function and cardiovascular events in early adulthood and midlife.[1,2] Among persons in early and midlife, an obstructive spirometric pattern reflected in a reduction in the forced expired volume in 1 second/forced vital capacity ratio (FEV_1/FVC) has been associated with left ventricular (LV) underfilling and lower cardiac output,[3] even in the absence of a clinical diagnosis of chronic obstructive pulmonary disease or asthma. In contrast, reduced vital capacity, as seen in restrictive phenotypes, has

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CLINICAL PERSPECTIVE

What Is New?

- In a community-based cohort free of heart failure (HF) or pulmonary disease, both obstructive and restrictive spirometric patterns associate with higher pulmonary pressure, higher NT-proBNP (N-terminal pro-B-type natriuretic peptide), and higher risk of incident HF.
- A restrictive spirometric pattern is further associated with greater left ventricular mass and filling pressure, and with a higher incidence of HF with preserved ejection fraction beyond traditional risk factors.

What Are the Clinical Implications?

- Subclinical lung dysfunction in late life, assessed using low cost and widely available spirometry, may help to identify older adults at increased risk of HF beyond traditional risk factors.
- Restrictive spirometric pattern in particular is associated with diastolic dysfunction and heighted risk of incident HF with preserved ejection fraction, the most prevalent HF type in late life.
- Prospective studies are necessary to determine whether pulmonary dysfunction represents a modifiable risk factor for HF and whether interventions targeting pulmonary dysfunction decrease risk of HF, and HF with preserved ejection fraction in particular, in older adults.

Nonstandard Acronyms and Abbreviations

ARIC	Atherosclerosis Risk in Communities
CARDIA	Coronary Artery Risk Development in Young Adults
FEV_1/FVC	forced expired volume in 1 second and Forced vital capacity ratio
Health ABC	Health, Aging, and Body Composition
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
JHS	Jackson Heart Study
MESA	Multi-Ethnic Study of Atherosclerosis
PASP	estimated pulmonary arterial systolic pressure
PIROUETTE	Pirfenidone in Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction
ppFVC	percent predicted forced vital capacity

been associated with increased LV mass and higher cardiac output.[2] Reductions in FVC have been independently associated with cardiovascular events[4] and HF hospitalizations in particular,[5] and these associations appear more robust than those with obstructive spirometric patterns.[6] In addition, the rate of subclinical decline in both FEV_1/FVC and FVC is associated with heightened risk of cardiovascular events, such that the risk of incident HF in particular is higher in rapid decliners.[1,5]

The prevalence of HF increases exponentially with age, disproportionately burdening the elderly, among whom HF with preserved ejection fraction (HFpEF) accounts for up to 80% of prevalent HF.[7] Age-related alterations in both cardiac and pulmonary structure and function are well described.[8,9] However, the extent to which subclinical lung-heart interactions previously described in early life and midlife extend into late life is unclear.[10] Furthermore, pulmonary dysfunction—and reduced FEV_1/FVC in particular—has previously been associated with risk of incident HFpEF compared with HF with reduced ejection fraction (HFrEF).[11] However, few data exist as to whether reduced FVC and FEV_1/FVC differentially associate with incident HFpEF in late life.

We hypothesized that worse FEV_1/FVC and FVC differently associate with cardiac structure and function and consequently with incident HF phenotypes in late life. We leveraged the comprehensive phenotyping of elderly participants in the ARIC (Atherosclerosis Risk in Communities) study to (1) define the extent to which FEV_1/FVC and FVC assessed in late life, and their change from midlife to late life, associate with cardiac structure and function in late life; and (2) determine their associations with incident HFpEF and HFrEF in late life.

METHODS

Detailed policies for requesting ARIC study data can be found at https://sites.cscc.unc.edu/aric/pubs-policies-and-forms-pg. ARIC study data can also be obtained from the National Heart, Lung, and Blood Institute BioLINCC repository (https://biolincc.nhlbi.nih.gov/studies/aric/).

Study Population

ARIC is an ongoing cohort that enrolled 15 792 participants from 4 US communities between 1987 and 1989.[12] This analysis included 3854 HF-free participants who underwent echocardiography and spirometry at the fifth study visit (2011–2013; age ≥65 years) (Figure S1). For analyses using FEV_1/FVC as the primary exposure (obstructive ventilatory pattern), we excluded participants with an FVC below the lower

limits of normal from the National Health and Nutrition Examination Survey III equation[13,14] to avoid mixed deficits, resulting in 3476 participants. Conversely, for analyses with percent predicted FVC (ppFVC) as the primary exposure (restrictive pattern), we excluded participants with FEV_1/FVC below the National Health and Nutrition Examination Survey III lower limit of normal on the basis of age, sex, race, and height, leaving 3325 participants in this analysis. The ARIC study was approved by institutional review boards from each site, and all participants provided written informed consent.

Clinical Characteristics

Methods for ascertaining participant characteristics and laboratory measures in ARIC have previously been described[15–22] and are detailed in Data S1. All laboratory measures were performed at visit 5.

Assessment of Lung Function

Lung function was assessed using spirometry at ARIC visits 1 (1987–1989), 2 (1990–1992), and 5 (2011–2013) following standard protocols and American Thoracic Society quality criteria.[13] Employed equipment and methods are detailed in Data S1. Predicted values for all 3 visits derived from National Health and Nutrition Examination Survey III equations.[14] The primary exposures were FEV_1/FVC and ppFVC assessed at visit 5. Secondary analyses further assessed longitudinal changes in these variables by calculating the differences between the visit 5 and the highest of visit 1 and 2 values.

Assessment of Cardiac Structure and Function

Echocardiography at visit 5 has been described in detail.[23] All studies were acquired using uniform imaging equipment and acquisition protocol.[24,25] Images were analyzed in a dedicated echocardiography reading center, blinded to clinical information, in accordance with the American Society of Echocardiography recommendations.[26,27]

Incident HF After Visit 5

Incident HF after visit 5 was based on active surveillance of hospitalizations and by participant self-report. Hospitalizations with International Classification of Diseases (ICD) codes associated with HF undergo chart abstraction and adjudication by centrally trained and certified physicians as previously described.[21,22] LV ejection fraction (LVEF) at the time of hospitalization was abstracted. If LVEF at time of hospitalization was unavailable, then the most recent LVEF available within 6 months of the index hospitalization was used if no intercurrent myocardial infarction was present. Death was ascertained through the National Death Index. Participants were followed up through December 31, 2018.

Statistical Analysis

Participant characteristics at visit 5 were described according to sex-specific quartiles of FEV_1/FVC and ppFVC, with tests for trend adjusted for demographics (age, sex, and race). FEV_1/FVC is expressed as a percentage, in which the ratio was multiplied by 100. For associations with echocardiographic outcomes, additional models further adjusted for body mass index, current or prior smoking, hypertension, diabetes, atrial fibrillation, and log-transformed NT-proBNP (N-terminal pro-B-type natriuretic peptide) and high-sensitivity C-reactive protein. The continuous associations between FEV_1/FVC and ppFVC with echocardiographic measurements were assessed using restricted cubic splines for possible nonlinear associations. Similar analyses were performed using spirometry change as the exposure.

For associations with incident HF, Cox proportional hazards regression models adjusted for demographics, and then additionally for obesity, coronary disease, atrial fibrillation, diabetes, hypertension, and NT-proBNP. We quantified the magnitude to which each covariate attenuated the association of ppFVC with incident HF by comparing the ppFVC model coefficient in models with or without each covariate. All models adjusted for demographics and 95% confidence intervals were derived from 2000-bootstrap samples. Nonlinear associations were investigated using restricted cubic splines with the number of knots selected to minimize the model Akaike information criterion (3 to 7 knots tested). The proportional hazards assumption was tested for all models using Schoenfeld residuals.

Statistical analysis was performed using STATA 14.2 (StataCorp LP, College Station, TX).

RESULTS

Population Characteristics

Among the 3854 participants included, age was 75.0±5.0 years, 60% were women, 19% were Black, and 61% were ever smokers (Table S1). Participants excluded because of missing or poor-quality spirometry or echocardiography or to prevalent HF were older, more frequently Black, with a higher body mass index (BMI), higher prevalence of cardiovascular and metabolic diseases, and higher levels of high-sensitivity C-reactive protein and NT-proBNP (Table S1). Sex and smoking status were similar between those included and excluded.

Table 1. Characteristics of the Study Population According to Sex-Specific Quartiles of FEV_1/FVC ratio (n=3476) and ppFVC (n=3325) at ARIC Baseline Visit 5

	FEV_1/FVC					ppFVC				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Participants, n	870	869	869	868	*P* trend*	832	831	831	831	*P* trend*
Female, range, %	28.21–69.84	69.86–74.69	74.70–78.90	78.91–96.26		34.40–87.26	87.31–97.66	97.68–109.64	109.65–173.90	
Male, range, %	25.19–66.24	66.27–71.84	71.89–76.74	76.75–91.65		43.23–85.23	85.24–95.61	95.67–106.34	106.35–154.83	
Demographics										
Age, y	76.2±5.3	75.6±4.8	74.7±5.0	74.2±4.7	<0.001	74.2±4.6	74.3±4.6	75.0±4.8	76.5±5.4	<0.001
Male	338 (40)	338 (40)	338 (40)	337 (40)	…	325 (39)	325 (39)	325 (39)	325 (39)	…
Black	112 (13)	132 (15)	176 (20)	272 (31)	<0.001	159 (19)	137 (17)	169 (20)	209 (25)	<0.001
Center					<0.001					<0.001
Forsyth	215 (25)	196 (23)	160 (18)	168 (19)		155 (19)	179 (21)	168 (20)	180 (22)	
Jackson	97 (11)	122 (14)	163 (19)	253 (29)		150 (18)	128 (15)	154 (18)	189 (23)	
Minneapolis	297 (34)	297 (34)	268 (31)	228 (26)		256 (31)	258 (31)	278 (33)	249 (30)	
Washington	261 (30)	254 (29)	278 (32)	219 (25)		271 (33)	266 (32)	231 (28)	213 (26)	
Medical history										
Hypertension	682 (78)	691 (79)	691 (79)	697 (80)	0.81	712 (86)	670 (81)	649 (78.1)	642 (77.3)	<0.001
Diabetes	233 (27)	276 (32)	312 (36)	310 (36)	<0.001	363 (44)	289 (35)	259 (31.2)	234 (28.2)	<0.001
Smoking status										
Current	72 (8)	41 (5)	43 (5)	25 (3)	<0.001	54 (7)	43 (5)	36 (4)	24 (3)	0.002
Ever	622 (71)	498 (57)	484 (56)	471 (54)	<0.001	505 (61)	486 (58)	466 (56)	453 (54)	0.02
Atrial fibrillation	52 (6)	44 (5)	32 (4)	22 (3)	0.01	37 (4)	35 (4)	32 (4)	36 (4)	0.34
Chronic kidney disease	242 (28)	208 (24)	204 (24)	191 (22)	0.31	194 (23)	197 (24)	215 (26)	194 (23)	0.05
Coronary artery disease	90 (11)	78 (9)	70 (8)	83 (10)	0.49	81 (10)	80 (10)	80 (10)	71 (9)	0.06
Myocardial infarction	67 (8)	59 (7)	44 (5)	64 (8)	0.91	64 (8)	53 (7)	49 (6)	55 (7)	0.19
Physical examination										
Height, cm	165±9	166±10	165±9	165±9	<0.001	166±9	166±9	166±9	164±9	<0.001
BMI, kg/m^2	26.8±5.0	27.8±4.8	29.0±5.4	29.4±5.2	<0.001	30.6±6.1	29.0±5.2	28.1±4.9	27.2±4.5	<0.001
BMI >30 kg/m^2	196 (23)	258 (30)	310 (36)	334 (39)	<0.001	408 (49)	301 (36)	264 (32)	186 (22)	<0.001
Heart rate, bpm	62±10	61±10	62±10	62±10	0.46	63±10	62±10	61±10	61±10	<0.001
Systolic BP, mm Hg	129±17	130±18	130±17	130±17	0.17	131±18	129±16	130±17	130±17	0.004
Diastolic BP, mm Hg	66±10	66±10	67±10	68±10	0.06	68±10	67±10	67±10	67±10	0.22
Laboratory tests										
Hemoglobin, g/dL	13.4±1.4	13.4±1.3	13.5±1.7	13.3±1.5	0.67	13.3±1.4	13.4±1.4	13.4±1.8	13.3±1.3	0.01
eGFR, mL/min, 1.73 m^2	69.3±16.9	71.0±15.4	71.8±15.9	72.9±16.6	0.16	71.9±17.1	71.8±16.2	70.6±16.6	71.1±16.1	0.16

(*Continued*)

Table 1. Continued

	FEV_1/FVC					ppFVC				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Participants, n	870	869	869	868	*P* trend*	832	831	831	831	*P* trend*
Spirometry										
FEV_1, L	1.9±0.6	2.2±0.6	2.3±0.6	2.4±0.6	<0.001	1.8±0.5	2.2±0.5	2.3±0.6	2.5±0.7	<0.001
FVC, L	3.0±0.8	3.1±0.9	3.1±0.8	2.9±0.8	<0.001	3.0±0.8	3.1±0.9	3.0±0.8	2.9±0.8	<0.001
FEV_1/FVC, %	61.8±7.4	71.1±2.1	75.8±1.8	81.3±2.9	…	74.8±5.2	74.6±4.9	74.6±5.1	73.6±5.3	<0.001
ppFVC, %	101±17	102±15	100±14	99±15	<0.001	77.0±8.1	92.0±3.2	102.3±3.6	119.9±11.2	…

Values are expressed as mean±SD or n(%). Chronic kidney disease was considered if Chronic Kidney Disease Epidemiology Collaboration glomerular filtration rate is <60 mL/min per 1.73 m^2. ARIC indicates Atherosclerosis Risk in Communities; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; FEV_1/FVC indicates forced expired volume in 1 second and forced vital capacity ratio; and ppFVC, percent predicted forced vital capacity ratio.

*P value for trend adjusted for age sex and race.

Obstructive Ventilatory Pattern

Among the 3476 participants without restrictive deficits, the average FEV_1/FVC was 72.5±8.3, FVC was 3.1±0.9 L, and ppFVC was 100±15%. Of participants in quartile 1 of FEV_1/FVC, 75% had FEV_1/FVC >60%. Lower FEV_1/FVC was associated with older age and non-Black race. Accounting for age, sex, and race, lower FEV_1/FVC was also associated with smoking and atrial fibrillation but less diabetes and lower BMI (Table 1). In adjusted models, lower FEV_1/FVC associated with higher NT-proBNP but was not independently associated with high-sensitivity C-reactive protein or measures of cardiac structure or function (Table 2). When modeled continuously, lower FEV_1/FVC was also associated with higher estimated pulmonary arterial systolic pressure (PASP) in fully adjusted models (ß coefficient, −0.04; 95% CI, −0.07 to −0.01; *P*=0.004; Figure 1; Table S2). At a median follow-up of 5.6 (25th–75th percentile 5.1–6.1) years, 335 participants died and 160 developed HF (78 HFpEF, 64 HFrEF, 18 unknown LVEF). Lower FEV_1/FVC was associated with heightened risk for incident HF overall (Table 3 and Figure S2), and all-cause mortality (Table 3; Figure 2). Similar results were observed in sensitivity analysis excluding participants with moderate or greater valvular heart disease (n=64; Table S3).

The mean absolute decline in FEV_1/FVC from visit 1 or 2 to visit 5 was −4.6±5.5. Change in FEV_1/FVC was not associated with late-life cardiac structure or function beyond the visit 5 FEV_1/FVC in the multivariable models (Table S4). Decline in FEV_1/FVC from midlife to late life was not significantly associated with risk of incident HF or all-cause mortality in late life beyond the visit 5 FEV_1/FVC value (Table S5).

Restrictive Ventilatory Pattern

Among the 3325 participants without obstructive deficits, the average FEV_1/FVC was 75.0±4.9, FVC was 3.0±0.9 L, and ppFVC was 98±17% (Table 1). Of participants in quartile 1 of ppFVC, 75% had a ppFVC >73%. Lower ppFVC was associated with younger age and non-Black race. Accounting for age, sex, and race, lower ppFVC was associated with smoking, hypertension, diabetes, and higher BMI (Table 1). In models adjusted for demographics, lower ppFVC was associated with higher high-sensitivity C-reactive protein and NT-proBNP, greater LV wall thickness and mass, lower LV end-diastolic volume index, worse longitudinal strain, lower stroke volume index, larger left atrial volume, and higher E/e′ and PASP (Table 4). After further adjustment for clinical comorbidities and biomarkers, the associations with LV wall thickness and mass, LV end-diastolic volume index, longitudinal strain, E/e′ and PASP persisted (Table 4 and Figure 1). Similar findings were observed when ppFVC was modeled

Table 2. Biomarkers and Echocardiography Variables of the Study Population According to Sex-Specific FEV_1/FVC Ratio Quartiles at ARIC Baseline Visit 5 (n=3476)

FEV_1/FVC	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Model1 *P*-trend	Mode 2 *P*-trend
Biomarkers						
High-sensitivity CRP, mg/L	1.7 (0.9–3.7)	1.7([0.8–3.4)	2.0 (1.0–4.3)	1.9 (0.9–4.0)	0.29*	…
NT-proBNP, pg/mL	150 (77–272)	127 (70–239)	107 (56–200)	88 (49–168)	<0.001*	<0.001*
Structure						
Mean wall thickness, cm	0.96±0.14	0.97±0.14	0.98±0.13	0.97±0.12	0.14	…
Relative wall thickness	0.42±0.07	0.42±0.07	0.43±0.07	0.42±0.07	0.67	…
LV mass index, g/m^2	77±19	79±19	77±18	76±16	0.55	…
LV mass, g	140±42	145±3	145±41	142±36	0.45	…
LVEDV index, mL/m^2	43±10	44±10	43±10	43±10	0.14	…
Systolic function						
LV ejection fraction, %	65.9±5.9	65.9±6.0	66.0±58	66.1±5.7	0.09	…
Longitudinal strain, %	–18.1±2.4	–18.2±2.4	–18.1±2.3	–18.3±2.3	0.15	…
Stroke volume index, mL/m^2	50±15	49±13	47±13	48±16	0.98	…
Diastolic function						
E wave, cm/sec	67±19	66±18	66±17	66±17	0.10	…
A wave, cm/sec	79±19	78±19	80±18	80±18	0.05	…
E/A ratio	0.87±0.28	0.87±0.27	0.84±0.26	0.85±0.27	0.004	0.56
Lateral e′, cm/s	7.2±2.1	7.1±2.0	7.1±2.0	7.2±2.0	0.04	0.47
E/e′ lateral	10.1±3.9	9.9±3.6	9.9±3.7	9.7±3.3	0.84	…
LA volume index, mL/m^2	25.5±9.9	26.1±7.9	25.0±8.0	25.1±7.4	0.38	…
Right ventricle and pulmonary pressure						
Estimated PASP, mm Hg	28.2±5.5	27.5±5.1	27.5±5.0	27.3±5.2	0.09	…
RV fractional area change	0.53±0.08	0.53±0.08	0.52±0.07	0.52±0.07	0.26	…

Values are expressed as mean±SD or median (25th–75th percentile). Model 1: age, sex, race. Model 2: age, sex, race, current or prior smoking, hypertension, diabetes, atrial fibrillation, body mass index, log high-sensitivity CRP, log NT-proBNP. Model 2 analyses were performed only when $P<0.05$ in model 1. ARIC indicates Atherosclerosis Risk in Communities; CRP, C-reactive protein; FEV_1/FVC, forced expired volume in 1 second and forced vital capacity ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LA, left atrial; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; PASP, pulmonary artery systolic pressure; and RV, right ventricular.

*P value for the log-transformed CRP and NT-proBNP trend.

continuously (Table S6). Similar findings were observed in analyses using quartiles of FVC adjusted for sex, age, height, and race, instead of ppFVC (Table S7).

At a median follow-up of 5.6 (25th–75th percentile 5.1–6.1) years, 157(5.1%) participants developed HF and 310 (9.3%) died. Of incident HF cases, 78 were HFpEF, 58 were HFrEF, and 21 occurred with unknown LVEF. Accounting for age, sex, and race, lower ppFVC was associated with heightened risk of HFpEF, and all-cause mortality, but not of incident HFrEF (Table 3, Figure 2). In fully adjusted models, associations with incident HFpEF and all-cause mortality persisted. NT-proBNP and BMI accounted for the greatest attenuation of the association of ppFVC with incident HF (Table S8). Similar findings were observed with absolute FVC as the exposure (Table S9).

The mean absolute ppFVC decline from visit 1 or 2 to visit 5 was –3.1±13.3, ranging from a mean of –18.6±7.1 (quartile 1) to +13.8±9.9 (quartile 4) (Table S10). Accounting for demographics and the visit 5 ppFVC value, greater ppFVC decline from midlife to late life was associated with greater late-life mass, left atrial volume, E/A ratio, and PASP. Associations were also observed with lower LVEF and higher right ventricular fractional area change. In fully adjusted models, associations with LV mass, left atrial volume, E/A ratio, and right ventricular fractional area change persisted, but the mid-to-late-life decline in ppFVC was not significantly associated with incident HF or death beyond the visit 5 value (Table S6).

DISCUSSION

While previous studies have demonstration the association of spirometric deficits with risk of HF in mid- and early-late life, and with clinical outcomes in prevalent HF, their prognostic relevance—and that of reduced FVC in particular—for incident HF and HF phenotype (HFpEF, HFrEF) have not been well established

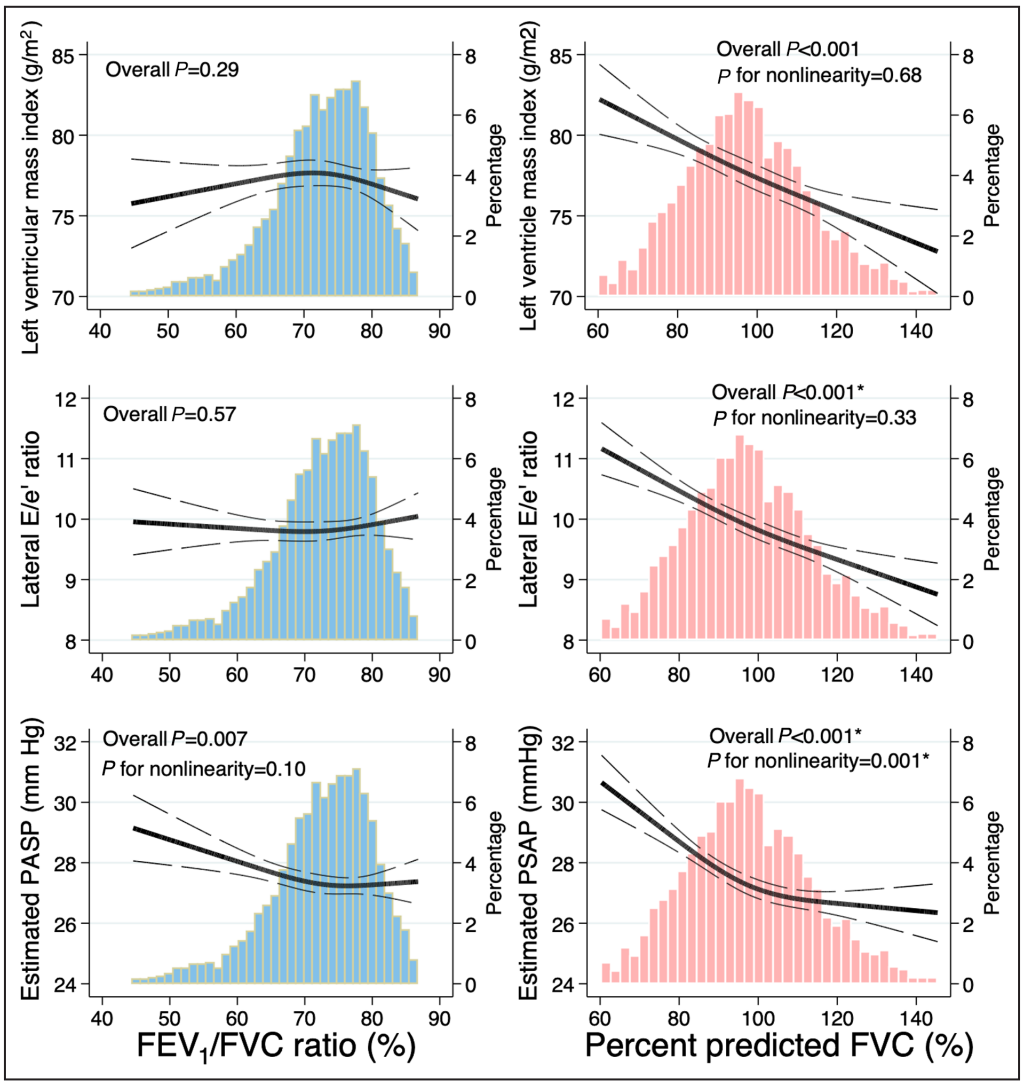

Figure 1. Continuous association of FEV_1/FVC (blue) and percent predicted FVC (light red) with LV mass, E/e′ ratio, and PASP at visit 5 using restricted cubic splines.
Models were adjusted for age, sex, and race and primary exposure variables (FEV_1/FVC and percent predicted FVC) using restricted cubic splines with 3 knots. *P<0.05 in models further adjusted for body mass index, prevalent coronary artery disease, prevalent atrial fibrillation, hypertension, diabetes, log(NT-proBNP) and the other spirometric measure (FEV_1/FVC or ppFVC). FEV_1/FVC indicates forced expired volume in 1 second and forced vital capacity ratio; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, estimated pulmonary arterial systolic pressure; and ppFVC, percent predicted forced vital capacity ratio.

in late life. In this analysis of a large number of well-characterized community-based people in late life, we report the following novel findings: (1) lower ppFVC, and greater decline in ppFVC from midlife to late life, are robustly associated with higher LV mass, higher LV filling pressure, and higher PASP in late life, accounting for common comorbidities; (2) lower ppFVC is associated with heightened risk of incident HFpEF beyond BMI and other cardiovascular comorbidities; and (3) lower FEV_1/FVC is independently associated with higher PASP but not with HF phenotypes (Figure 3). Together, these findings demonstrate that important subclinical associations between pulmonary and cardiovascular dysfunctions persist into late life, and highlight cardiovascular associations with restrictive spirometric patterns that have been relatively understudied.

Prevalent lung disease associates with heightened risk of cardiovascular diseases, particularly among the elderly.[28] Community-based longitudinal cohorts of people in early life and midlife have demonstrated that lung disease of lesser severity, or even subclinical alterations in lung function, associate with subclinical impairments in cardiac structure and function and with prognosis. Among 2816 participants in MESA

Table 3. Association of Spirometric Function at the Fifth ARIC Visit With Incident HFpEF and HFrEF (Median Follow-Up Time, 5.6 y), and Overall Mortality (Median Follow-Up Time, 5.7 y)

Outcome	Events	Model 1*		Model 2*	
		HR (95% CI) per 10-point decrease	*P* value	HR (95% CI) per 10-point decrease	*P* value
FEV_1/FVC (n=3476)					
HFpEF	78	1.24 (0.97–1.60)	0.09	1.31 (0.98–1.74)	0.07
HFrEF	64	1.28 (0.98–1.68)	0.07	1.24 (0.91–1.70)	0.18
Heart failure	160	1.27 (1.07–1.51)	0.006	1.28 (1.06–1.57)	0.012
Mortality	335	1.37 (1.23–1.54)	<0.001	1.29 (1.14–1.46)	<0.001
Percent predicted FVC (n=3325)					
HFpEF	78	1.32 (1.15–1.51)	<0.001	1.21 (1.04–1.41)	0.013
HFrEF	58	1.00 (0.86–1.16)	0.96	0.90 (0.76–1.07)	0.24
Heart failure	157	1.20 (1.09–1.32)	<0.001	1.09 (0.98–1.21)	0.11
Mortality	310	1.14 (1.07–1.22)	<0.001	1.12 (1.04–1.21)	0.002

*Model 1: age, sex, and race. Model 2: age, sex, race, body mass index, prevalent coronary artery disease, ever smoking, hypertension, diabetes, log(NT-proBNP), and stratified by prevalent atrial fibrillation, all at baseline visit 5. ARIC indicates Atherosclerosis Risk in Communities; FEV_1/FVC, forced expired volume in 1 second and forced vital capacity ratio; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

(Multi-Ethnic Study of Atherosclerosis; mean age, 61±10 years), greater airway obstruction based on percentage of emphysema from chest computed tomography or lower FEV_1/FVC was associated with lower LV end-diastolic volume, stroke volume, and cardiac output.[3] Furthermore, in a younger sample of 3000 participants at study year 25 of the CARDIA (Coronary Artery Risk Development in Young Adults) study (mean age, 50±4 years), greater decline in FEV_1/FVC from early adulthood to middle age was associated with smaller left atrial size and lower cardiac output.[2] However, less is known if such relationship persists in late life, when multiple accumulated cardiovascular comorbidities may influence cardiac structure and function. In our analysis of people 75.0±5.0 years of age, worse FEV_1/FVC was associated with higher PASP. Unlike CARDIA, change in FEV_1/FVC from midlife to late life was not independently associated with cardiac structure and function. It is possible that age-related changes and cumulative burden of multiple cardiovascular comorbidities exert more robust effects on cardiac structure and function relative to pulmonary function in elderly compared with younger cohorts.

While established chronic obstructive pulmonary disease is associated with cardiovascular disease and HF, subclinical reductions in FEV_1/FVC also appear predictive of incident HF,[1,28] but the relationship with HF phenotype is less clear. In a cross-sectional analysis of the Gutenberg Health Study (mean age, 55±11 years), lower FEV_1/FVC was associated with higher odds of both HFpEF and HFrEF in adjusted analyses.[29] In contrast, in the Framingham Heart Study (mean age, 76±5 years), lower FEV_1/FVC was predictive of incident HFpEF—but not HFrEF—in adjusted analyses. We observed associations of lower FEV_1/FVC with incident HF and all-cause mortality, but not with HFpEF and HFrEF individually.

Fewer data are available regarding the association of restrictive ventilatory patterns with cardiac structure and function, although existing data suggest associations even in the absence of overt cardiovascular disease. Restrictive physiology may result from alterations in the lung parenchyma, pleura, chest wall, or neuromuscular apparatus,[30] especially in the elderly, among whom kyphoscoliosis and sarcopenia are frequent. In the Jackson Heart Study (median age, 55 years), a restrictive spirometry was associated with higher E/A ratio and PASP, but not LV mass index.[31] Similarly, in the Gutenberg Health study, lower FVC was also associated higher E/A ratio and E/e′.[29] In the CARDIA study, greater longitudinal decline in FVC from early adulthood to midlife was associated with higher LV mass but lower E/A ratio in midlife.[2] Few data exist regarding these associations in late life. In our study, participants were ≈20 to 25 years older than those in the JHS (Jackson Heart Study) and CARDIA. Lower ppFVC was associated with greater LV mass, worse diastolic indices, and higher PASP independent of common cardiovascular comorbidities including BMI. Furthermore, greater longitudinal decline in ppFVC from midlife to late life predicted higher E/A ratio, left atrial volume, and LV mass independent of the late-life ppFVC value. Importantly, greater LV mass, worse diastolic function, and higher PASP all characterize HFpEF, which is particularly prevalent in late life.

Reduced FVC has consistently been associated with mortality,[32] and since the initial observation in the Framingham Heart Study,[33] associations with incident HF are well described.[5,31,34] However, whether

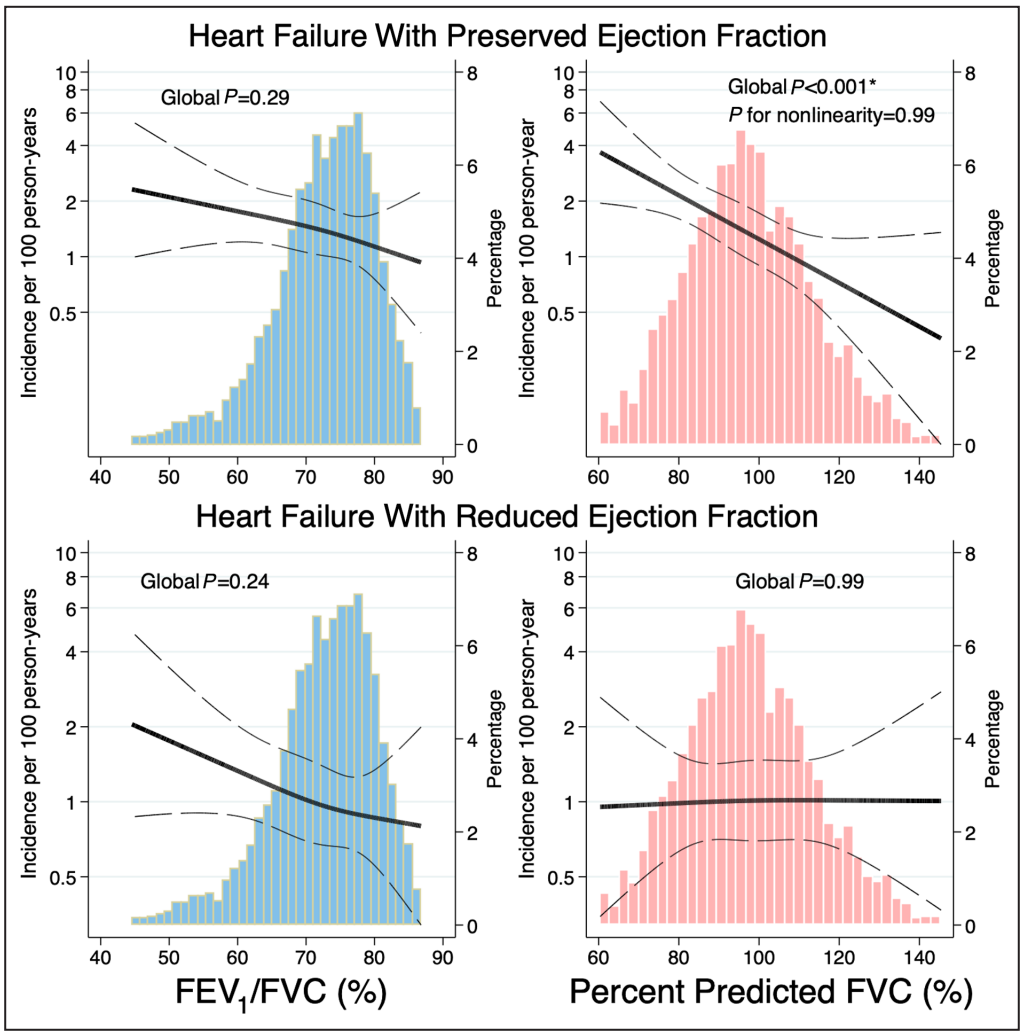

Figure 2. Continuous associations of FEV_1/FVC (blue) and percent predicted FVC (light red) at visit 5 with subsequent incidence of HF overall, HFpEF, and HFrEF.
Models were adjusted for age, sex, race, and primary exposure variables (FEV_1/FVC and percent predicted FVC) using restricted cubic splines with 3 knots. *P<0.05 in models further adjusted for body mass index, prevalent coronary artery disease, prevalent atrial fibrillation, hypertension, diabetes, log(NT-proBNP), and the other spirometric measure (FEV_1/FVC or ppFVC). FEV_1/FVC indicates forced expired volume in 1 second and forced vital capacity ratio); HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and ppFVC, percent predicted Forced vital capacity ratio).

reductions in FVC differentially predict incident HFpEF versus HFrEF is unclear. In our study, lower ppFVC was associated with heightened risk of incident HFpEF, but not HFrEF, independent of BMI, common cardiovascular comorbidities, and NT-proBNP. Our findings are supported by previous observations in 2125 participants from the Health ABC (Health, Aging, and Body Composition) study, among whom each 10% decrease in ppFVC was associated with incident HFpEF (LVEF>40%) independent of BMI.[35] Of note, in that study, lower ppFVC was also associated with incident HFrEF, and associations were not adjusted for NT-proBNP.

The mechanisms underlying the association of a restrictive spirometry pattern with alterations in cardiac structure and function and risk of incident HFpEF are unclear. It is possible that reduced ppFVC may reflect subtle/early interstitial pulmonary edema. The association of lower ppFVC with higher NT-proBNP levels maybe consistent with this. However, if this were the primary mechanism linking lower ppFVC to incident HFpEF, we would expect clinical manifestation of HF to occur relatively soon after pulmonary assessment. We therefore believe that the median time to incident HF of 5.6 years argues against this as a primary mechanism. Obesity is a common cause of restrictive

Table 4. Biomarkers and Echocardiography Variables of the Study Population According to Sex-Specific Percent Predicted FVC Quartiles at ARIC Baseline Visit 5 (n=3325)

ppFVC	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Model1 *P* trend	Mode 2 *P* trend
Biomarkers						
High-sensitivity CRP, mg/L	2.5 (1.2–5.3)	2.0 (1.0–4.1)	1.7 (0.8–3.5)	1.4 (0.7–3.1)	<0.001*	<0.001*,†
NT-proBNP, pg/mL	126 (64–241)	111 (55–218)	113 (59–213)	111 (63–208)	<0.001*	<0.001*
Structure						
Mean wall thickness, cm	1.00±0.14	0.98±0.12	0.97±0.13	0.96±0.12	<0.001	0.005
Relative wall thickness	0.43±0.08	0.42±0.07	0.43±0.07	0.42±0.07	0.01	0.55
LV mass index, g/m^2	80.1±18.8	77.4±18.6	76.9±18.1	76.0±16.7	<0.001	0.31
LV mass, g	155±44	146±42	143±41	137±37	<0.001	0.002
LVEDV index, mL/m^2	42±9	43±10	43±10	44±10	<0.001	<0.001
Systolic function						
LV ejection fraction, %	65.7±6.1	65.8±5.8	66.1±6.1	66.0±5.4	0.06	…
Longitudinal strain, %	–17.9±2.6	–18.2±2.4	–18.4±2.3	–18.2±2.3	<0.001	0.03
Stroke volume index, mL/m^2	48±14	47±13	49±16	49±15	0.013	0.31
Diastolic function						
E wave, cm/sec	69±19	67±17	66±17	64±16	<0.001	<0.001
A wave, cm/sec	81±20	80±18	79±18	78±18	<0.001	0.006
E/A ratio	0.87±0.30	0.86±0.26	0.86±0.26	0.84±0.26	0.53	…
Lateral e′, cm/s	7.1±2.0	7.1±2.0	7.1±2.0	7.2±2.1	0.001	0.04
E/e′ lateral	10.5±3.9	10.0±3.6	9.8±3.4	9.5±3.3	<0.001	<0.001
LA volume index, mL/m^2	25.9±9.1	25.3±8.5	25.2±7.2	25.5±7.8	0.005	0.79
Right ventricle and pulmonary pressure						
Estimated PASP, mm Hg	28.7±6.1	27.7±5.3	27.2±4.8	27.2±4.7	<0.001	0.005
RV fractional area change	0.52±0.08	0.52±0.07	0.52±0.08	0.53±0.07	0.08	…

Values are expressed as mean±SD or median (25th–75th percentile). Model 1: age, sex, and race. Model 2: age, sex, race, current or prior smoking, body mass index, hypertension, diabetes, log Hs-CRP, log NT-proBNP. Model 2 analyses were performed only when $P<0.05$ in model 1. ARIC indicates Atherosclerosis Risk in Communities; CRP, C-reactive protein; FEV_1/FVC, forced expired volume in 1 second and forced vital capacity ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LA, left atrial; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; PASP, pulmonary artery systolic pressure; and RV, right ventricular.

*P-value for the log-transformed CRP and NT-proBNP trend.

†Log NT-proBNP was excluded for model 2.

spirometry and an important contributor to the HFpEF syndrome.[36] However, the associations of lower ppFVC with LV structure, diastolic indices, and PASP, and with incident HFpEF, persisted in models adjusted for BMI and other cardiovascular comorbidities. Notably, in the National Health and Nutrition Examination Survey, the prevalence of ventilatory restriction was higher in participants who were underweight than in participants who were obese, and despite increases in the prevalence of obesity over time, the prevalence of a restrictive spirometry pattern remained relatively stable. These data emphasize that a restrictive spirometry pattern should not be viewed as solely a manifestation or epiphenomenon of obesity.[32]

However, it is likely that close associations of FVC with cardiovascular risk factors contribute to our findings. Lower FVC, but not FEV_1/FVC, is consistently associated with incident hypertension[37] and diabetes.[38] While age-related changes of the lung have classically been characterized by airspace enlargement with alveolar dilatation and reduced static elastic recoil resulting in an "emphysema-type" pattern,[39–41] recent advances in CT-based chest imaging increasingly recognize interstitial fibrosis in asymptomatic community dwelling individuals and patients with even mild chronic obstructive pulmonary disease.[42,43] These fibrotic areas associate with decreased lung compliance and increased resistance in late life in animal models,[44] increase in prevalence and progression with advancing age in humans,[43,45] and predict mortality in general population samples.[43,45] While the underlying drivers of this age-related fibrosis in the lungs are unclear, they may overlap with the factors promoting well-recognized age-related changes in the heart, including increases in LV mass, higher filling pressure, and higher pulmonary pressure.[46–51] Indeed, fibrosis also appears to be important in HFpEF in clinical and preclinical studies, and may represent one common pathophysiological mechanism underlying both lung and heart

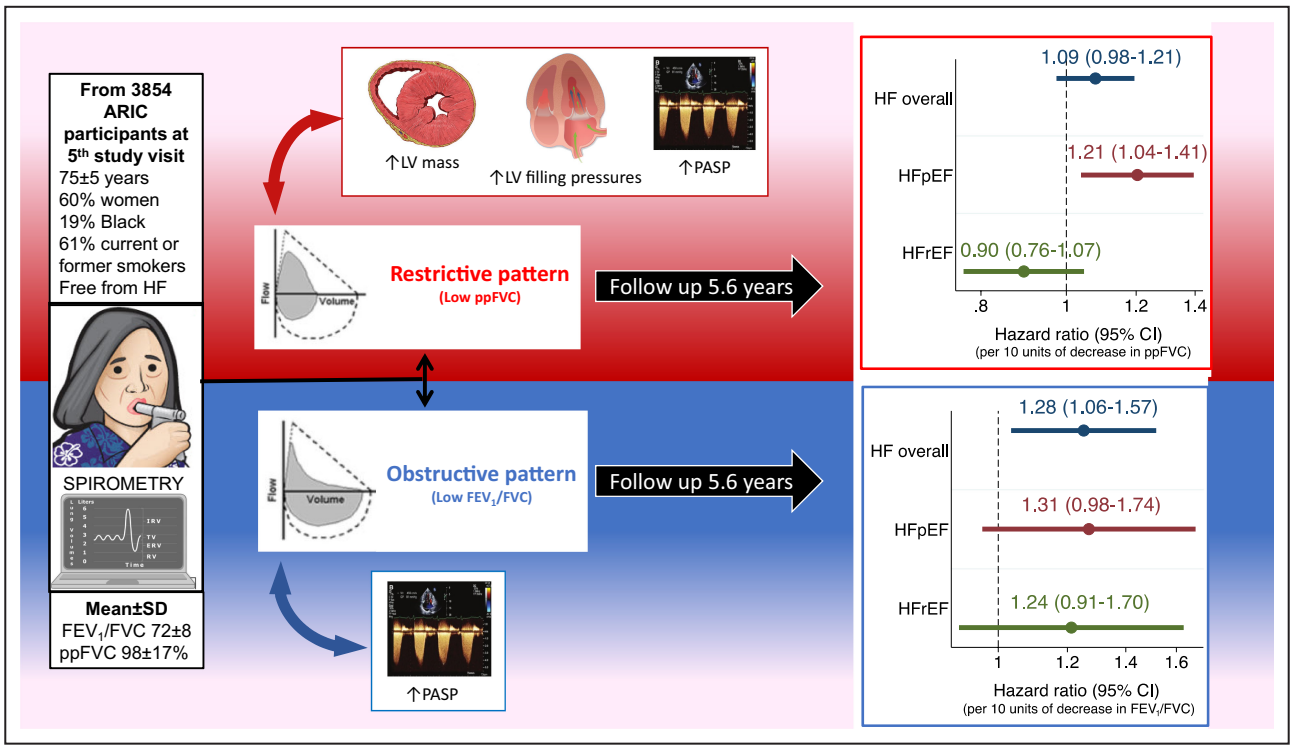

Figure 3. Differential associations of obstructive and restrictive ventilatory patterns cardiovascular structure and function and incident HF in late life.
Lower FEV_1/FVC was associated with higher PASP and with incident overall HF. In contrast, lower ppFVC was associated with higher LV mass, higher LV filling pressure, and higher PASP, and with incident HFpEF. FEV_1/FVC indicates forced expired volume in 1 second and forced vital capacity ratio; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; PASP, estimated pulmonary arterial systolic pressure; and ppFVC, percent predicted forced vital capacity ratio.

dysfunction.[52,53] Recently, data from the PIROUETTE (Pirfenidone in Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction) trial[54] demonstrate that the antifibrotic agent pirfenidone, effective in restrictive lung disease caused by pulmonary fibrosis, reduces myocardial fibrosis compared with placebo in HFpEF, supporting potential shared cardiopulmonary inflammation-fibrosis underlying HFpEF in at least a subset of patients.[55] It is possible that chronic systemic inflammation related to cardiometabolic risk factors and cardiovascular disease acts as a shared underlying driver for pulmonary and cardiac fibrosis and associated dysfunction.[32] Markers of systemic inflammation predict greater decline in FEV_1 and FVC,[56] and associate with both cardiac and extracardiac comorbidities.[36]

Beyond shared risk factors driving inflammation and pulmonary and cardiac fibrosis in parallel, recent data from the UK Biobank using Mendelian randomization suggest a potential causal association between lower FVC and coronary artery disease.[57] It is possible that causal associations also exist with subclinical coronary disease and microvascular dysfunction, leading to the myocardial ischemia, fibrosis, and remodeling that underlie HF development. Future studies with phenotyping of coronary morphology and microvascular function will be necessary to explore this hypothesis.

Several limitations should be noted. First, the observational nature precludes determinations of causality, and residual/unmeasured confounders likely exist for the observed associations. Only a subset of ARIC participants alive at the time of the study visit chose to attend, and only a subset of those attending had the necessary data for analysis, potentially introducing selection bias. Indeed, among visit 5 attendees, participants included in this analysis tended to be healthier (Table S1), which may have resulted in an attenuation of the observed associations. Furthermore, given the time difference between ARIC visits 1 to 2 and 5, survival bias may have limited our ability to detect associations between spirometry changes and study outcomes. Spirometry was performed without bronchodilators, so we were unable to detect reversible obstruction and may have overestimated the prevalence of restrictive patterns. Total lung capacity was unavailable, and restrictive ventilatory pattern was based solely on FVC as reported in other community-based epidemiologic cohorts like ARIC. Diffusion capacity for CO_2 and ventilatory strength measurements were unavailable to further investigate reduced FVCs. An isolated ppFVC value

cannot distinguish nonspecific ventilatory patterns (low FVC but normal total lung capacity), which potentially lowers specificity for true restrictive patterns.[58] Data on conditions such as sarcoidosis, autoimmune diseases, prior chest radiation, and amyloidosis, which may underlie both interstitial lung disease and HF, were not available in ARIC, nor were data on supplemental oxygen use. Chest computed tomography imaging to assess for interstitial lung disease was not available at ARIC visit 5. Longitudinal echocardiographic data from visit 1 or 2 and visit 5 were not available to assess the association of changes in spirometric measures with changes in cardiac function. Our analysis could have been underpowered to detect an association of reduced FEV_1/FVC with the incidence HFpEF or HFrEF.

CONCLUSIONS

In this large community-based cohort of persons in late life, lower ppFVC was independently associated with greater LV mass, filling pressures, and PASP, and with incident HFpEF but not HFrEF. Lower FEV_1/FVC was associated with higher PASP and with HF overall, which did not appear differential by incident HF phenotype. These findings highlight the importance of pulmonary dysfunction with cardiac dysfunction interactions and the differential associations of obstructive and restrictive spirometric deficits with HF risk and particularly HFpEF in late life.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Tables S1–S10
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

ARIC is an ongoing population-based cohort study which enrolled 15,792 participants from four communities in the United States (North Carolina, Mississippi, Minnesota and Maryland) between 1987-1989[12]. This analysis included 3,854 HF-free participants who underwent echocardiography and had acceptable quality spirometry[13] at the 5th study visit (2011-2013; age ≥65 years) (Figure S1). For analyses with obstructive ventilatory pattern based on FEV_1/FVC ratio as the primary exposure, we excluded participants with an FVC below the lower limits of normal for age, sex, race, and height based on the NHANES III equation[14] to exclude those with mixed obstructive and restrictive deficits. This analysis included 3,476 participants. Conversely, for analyses with restrictive ventilatory pattern based on FVC as the primary exposure, we excluded participants with an FEV_1/FVC below the lower limit of normal according to the NHANES III equation, leaving 3,325 participants in this group. The ARIC study was approved by Institutional Review Boards from each site and all participants provided written informed consent.

Clinical Characteristics

Prevalent hypertension and diabetes were defined based on self-report, medication use, or measurements at any study visit (blood pressure above 140/90 mmHg and fasting glucose ≥126 or random glucose≥200mg/dL, respectively) as previously described[4]. Smoking status was ascertained through questionnaires at each study visit[15]. Atrial fibrillation was defined based on ECG from any study visit or ARIC surveillance of relevant ICD codes from hospitalizations as previously described[16]. Chronic kidney disease was defined as estimated glomerular filtration <60 mL/min/1.73m^2 using the CKD-Epi equation[17]. Coronary artery disease (myocardial infarction or coronary intervention) was ascertained through ongoing ARIC surveillance of deaths and hospitalizations and annual phone interviews, with chart abstraction and central physician adjudication as previously described[18, 19]. N-terminal fragment of prohormone for B-type natriuretic peptide (NT-proBNP; Elecsys 2010

Immunoassay analyzer; Roche Diagnostics, Indianapolis, Indiana) and high-sensitivity C-reactive protein (hs-CRP; Immunoturbidimetric Modular P chemistry analyzer; Roche Diagnostics) were measured at Visit 5[20]. Participants with prevalent HF at Visit 5 were excluded from this analysis. Prevalent HF was ascertained from multiple sources: physician committee adjudicated HF hospitalization occurring since 2005 as previously published[21]; International Classification of Disease, 9th Revision and 10th Revision with codes associated to heart failure[22]; HF self-report at Visits 3 through 5 or on annual follow-up phone calls.

Assessment of Lung Function

Lung function was assessed based on the following spirometric variables: FEV_1, FVC and their ratio. FEV1 was obtained as the volume of gas exhaled in the first second of expiration. FVC was obtained as the volume of gas vigorously exhaled after maximal inspiratory effort[13] . At ARIC visits 1 (1987-1989) and 2 (1990-1992), spirometry was conducted using a water-sealed Collins Survey II volume displacement spirometer (Collins Medical, Fairfield, Connecticut) and Pulmo-Screen II software (PDS Healthcare Products, Brookfield, Wisconsin). At Visit 5 (2011-2013) a dry SensorMed 827-Spirometer (Ohio Medical Instruction Company, Cincinnati-OH) was used, connected to a software (Occupational Marketing, Inc., Houston-TX). Spirometry was performed following the American Thoracic Society quality criteria[13]. Three or more acceptable spirograms were obtained from at least 5 forced expirations. The best single spirogram was identified and confirmed by a trained technician. Predicted reference values for all three visits were derived from NHANES III equations, according to age, sex, race, and height[14]. The primary exposures were FEV_1/FVC and percent predicted FVC (ppFVC) assessed at Visit 5. Secondary analyses further assessed longitudinal changes in these spirometric measures by calculating the differences between the Visit 5 value and the highest value at Visits 1 or 2.

Assessment of Cardiac Structure and Function

Echocardiography in ARIC at Visit 5 has been previously described in detail[23-25]. Briefly, all studies were acquired using uniform imaging equipment and acquisition protocol. All quantitative measures were performed in a dedicated Echocardiography Reading Center, blinded to clinical information. Quantitative measurements were performed in accordance with the recommendations of the American Society of Echocardiography,[26,27] including measures of left ventricular (LV) structure, systolic and diastolic function, right ventricular(RV) function and pulmonary hemodynamics[24]. Pulmonary artery systolic pressure (PASP) was estimated from Doppler-echocardiography tricuspid regurgitation jet peak velocity when available[23].

Incident Heart Failure Post-Visit 5

ARIC cohort participants undergo active surveillance for incident cardiovascular events, including HF. Incident HF after Visit 5 was based on ARIC Study committee adjudication of hospitalizations with ICD codes associated with HF as previously described[21]. Centrally trained and certified physicians adjudicated the HF diagnosis as definite or possible acute decompensated HF or chronic stable HF.[21] LV ejection fraction (LVEF) at the time of hospitalization was abstracted if available. Outcomes of interest included all incident HF post-Visit 5, incident HF with LVEF ≥50% at hospitalization (HFpEF), and incident HF with LVEF <50% at hospitalization (HFrEF). If LVEF at time of hospitalization was not available, then the most recent LVEF available within 6 months of the index hospitalization was used if no intercurrent myocardial infarction was present. Death was ascertained through the National Death Index. Participants were followed up through December 31, 2018.

Statistical Analysis

For the cross-sectional analysis, participants were categorized according to sex- specific quartiles of FEV_1/FVC and ppFVC, with the first quartile representing the worst and the fourth quartile the best lung function. For comparability of the orders of magnitude, FEV_1/FVC is expressed using

percentage, in which the ratio was multiplied by 100. Baseline characteristics at Visit 5 were described using mean and standard deviation or median and 25^{th}-75^{th} percentile for continuous variables and absolute numbers and percentages for categorical variables. Linear and logistic regressions and chi-square tests for trend were used to assess associations between characteristics and measures of lung function in both unadjusted and demographically (age, sex, and race) adjusted models. For the association of lung function with echocardiographic outcomes, additional models also adjusted for potential confounders (body mass index, current or prior smoking, hypertension, diabetes, atrial fibrillation, and log-transformed NT-proBNP and hsCRP). The continuous associations between FEV_1/FVC and ppFVC and echocardiographic measurements were assessed using restricted cubic splines to assess for possible nonlinear associations. Similar analyses were performed using lung function change as the exposure.

Cox proportional hazards regression models were used to determine the association of continuous and categorical lung function at baseline (Visit 5) and subsequent incident HF and death. Multivariable models adjusted for demographics, obesity, coronary artery disease, atrial fibrillation, diabetes, hypertension, and NT-proBNP. We quantified the magnitude to which each covariate attenuated the association of ppFVC with incident HF by comparing the model coefficient for ppFVC in models with or without each covariate. All models adjusted for demographics, and 95% confidence intervals were derived from 2000 bootstrap samples. Non-linear association were investigated using restricted cubic spline regression with the number of knots selected to minimize the model AIC (3 to 7 knots tested). The proportional hazards assumption was tested for all models using Schoenfeld residuals.

A two-sided p-value <0.05 was considered significant for all analyses. Statistical analysis was performed using Stata software Version 14.2 (Stata Corp LP, College Station, TX).

Table S1. Baseline characteristics in all participants who attended the 5th visit of ARIC study (n=6538). Values are expressed as mean±SD, n(%) or median[25th-75th percentile].

	Excluded (n=2684)	Included (n=3854)	p
Demographics			
Age, years	76.93 ± 5.50	75.03 ± 4.96	<0.001
Male, n(%)	1141 (42%)	1552 (40%)	0.07
Black, n(%)	797 (30%)	746 (19%)	<0.001
Center, n(%)			<0.001
Forsyth	283 (24%)	496 (22%)	
Jackson	319 (27%)	430 (19%)	
Minneapolis	308 (26%)	699 (31%)	
Washington	257 (22%)	661 (29%)	
Medical history			
Hypertension, n(%)	2413 (90%)	3086 (80%)	<0.001
Diabetes, n(%)	1212 (45%)	1303 (34%)	<0.001
Smoking status, n(%)			
Ever	1680 (63%)	2335 (61%)	0.10
Current	139 (6%)	224 (6%)	0.85
Atrial fibrillation, n(%)	323 (12%)	174 (4%)	<0.001
Chronic Kidney disease, n(%)	927 (36%)	936 (24%)	<0.001
Myocardial infarction, n(%)	524 (21%)	267 (7%)	<0.001
Physical examination			
Height, cm	165.5 ± 9.8	165.7 ± 9.4	0.46
BMI, kg/m^2	29.2 ± 6.4	28.5 ± 5.4	<0.001
Heart rate, bpm	64 ± 11	62 ± 10	<0.001
Systolic BP, mmHg	132 ± 20	130 ± 17	<0.001
Diastolic BP, mmHg	66 ± 12	67 ± 11	0.033
Laboratory tests			
Hemoglobin, g/dL	13.1 ± 1.5	13.4 ± 1.5	<0.001
Hemoglobin A1c, %	6.1 ± 1.9	5.9 ± 0.8	<0.001
eGFR, mL/min/1.73m^2	66.5 ± 18.9	71.3 ± 16.5	<0.001
Hs-CRP, mg/L	2.3 [1.1, 5.2]	1.9 [0.9, 4.0]	<0.001
NT-proBNP, pg/mL	176.1 [85.9, 407.7]	119.2 [62.2, 225.7]	<0.001

BMI: body mass index; FEV1: forced expired volume in 1 second; FVC: forced vital capacity; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; NT-pro-BNP: N-terminal fragment of prohormone for B-type natriuretic peptide.

Table S2. Echocardiographic parameters of the study population according to continuous FEV1/FVC at ARIC baseline visit 5.

	Model 1		Model 2	
	Coefficient (95%CI)	p-value	Coefficient (95%CI)	p-value
Structure				
Mean wall thickness, cm	0.0005 (0.0001; 0.0011)	0.04	0.0005 (-00002; 0.0010)	0.06
Relative wall thickness	0.0001 (-0.0002; 0.0004)	0.43		
LV mass index, g/m^2	0.027 (-0.071; 0.076)	0.94		
LV mass, g	0.154 (-0.013; 0.309)	0.05		
LVEDV index, mL/m^2	-0.011 (-0.050; 0.028)	0.58		
Systolic function				
LV ejection fraction, %	0.022 (-0.020; 0.045)	0.07		
Longitudinal strain, %	-0.012 (-0.022; -0.002)	0.02	-0.007 (-0.017; 0.003)	0.16
Stroke volume index, mL/m^2	0.003 (-0.055; 0.061)	0.91		
Diastolic function				
E wave	-0.042 (-0.115; 0.030)	0.25		
A wave	0.074 (-0.018; 0.151)	0.06		
E/A ratio	-0.0012 (-0.0025; -0.002)	0.02	-0.0003 (-0.014; 0.0009)	0.65
Lateral e', cm/s	-0.010 (-0.018; -0.002)	0.014	-0.006 (-0.014; 0.003)	0.19
E/e' lateral	0.003 (-0.012; 0.017)	0.72		
LA volume index, mL/m^2	0.001 (-0.033; 0.035)	0.96		
Right ventricle and Pulmonary pressure				
Estimated PASP, mmHg	-0.039 (-0.067; -0.011)	0.007	-0.043 (-0.072; -0.014)	0.004
RV fractional area change	-0.0001 (-0.0004; 0.0003)	0.67		

BMI: body mass index; FEV1: forced expired volume in 1 second; FVC: forced vital capacity; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; NT-pro-BNP: N-terminal fragment of prohormone for B-type natriuretic peptide; LV: left ventricle; LVEDV: LV end diastolic volume; LA: left atrium; TAS': tricuspid annular peak systolic myocardial velocity; PASP: pulmonary artery systolic pressure.
Model1: age, sex, race; Model 2: age, sex, race, ever smoking, atrial fibrillation, hypertension, diabetes, body mass index, log Hs-CRP, log NT-proBNP. Model 2 analyses were only performed when $p<0.05$ in Model 1

Table S3. Association of spirometric function at the 5th ARIC visit with incident heart failure with preserved (HFpEF) and with reduced ejection fraction (HFrEF) (median follow up time 5.6years), and overall mortality (median follow up time 5.7years), in participants free from moderate or greater valvular heart disease (64 exclusions).

Outcome	Events	Model 1* HR (95%CI) per 10%-point decrease	p	Model 2* HR (95%CI) per 10%-point decrease	p
FEV_1/FVC (n=3419)					
HFpEF	75	1.29 (0.99-1.66)	0.05	1.33 (1.00-1.77)	0.05
HFrEF	61	1.24 (0.94-1.65)	0.13	1.19 (0.88-1.62)	0.26
Heart Failure	153	1.27 (1.06-1.51)	0.008	1.17 (1.04-1.54)	0.017
Mortality	329	1.38 (1.28-1.54)	<0.001	1.28 (1.13-1.45)	<0.001
Percent predicted FVC (n=3267)					
HFpEF	74	1.29 (1.12-1.48)	<0.001	1.18 (1.02-1.38)	0.03
HFrEF	56	1.00 (0.86-1.17)	0.98	0.90 (0.77-1.06)	0.22
Heart Failure	151	1.19 (1.08-1.31)	<0.001	1.07 (0.97-1.19)	0.17
Mortality	305	1.14 (1.07-1.22)	<0.001	1.13 (1.05-1.21)	0.001

*Model 1: age sex and race. Model 2: age, sex, race, body mass index, prevalent coronary artery disease, ever smoking, hypertension, diabetes, log(NT-proBNP), and stratified by prevalent atrial fibrillation, all at baseline Visit 5. Definitions of moderate or greater valvular disease have been previously published[14].

Table S4. Characteristics of the study population according to sex-specific quartiles of FEV_1/FVC ratio change (Visit 5 - highest of Visits 1 or 2) in ARIC cohort from 1987 to 2013 (n=3476). Values are expressed as mean±SD, n(%) or median[25^{th}-75^{th} percentile].

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Model 1 p-trend	Model 2 p-trend	Model 3 p-trend
Participants, n	870	869	869	868			
Mean FEV_1/FVC change	-11.5 ± 5.0	-5.6 ± 1.2	-2.7 ± 1.1	1.5 ± 2.4			
CLINICAL							
Demographics							
Age at visit 5, years	75.7 ± 5.1	75.3 ± 4.9	74.7 ± 4.9	75.0 ± 5.1	<0.001*		
Age at visit 1, years	51.8 ± 5.0	51.6 ± 4.9	51.2 ± 4.7	51.4 ± 5.0	0.005*		
Male, n(%)	338 (40%)	338 (40%)	338 (40%)	337 (40%)	-		
Black, n(%)	168 (19%)	153 (18%)	167 (19%)	191 (22%)	0.02*		
Center, n(%)					0.11*		
Forsyth	182 (21%)	195 (22%)	171 (20%)	191 (22%)			
Jackson	154 (18%)	145 (17%)	151 (17%)	185 (21%)			
Minneapolis	278 (32%)	277 (32%)	296 (34%)	239 (27%)			
Washington	254 (29%)	252 (29%)	251 (29%)	253 (29%)			
Medical history							
Hypertension, n(%)	676 (78%)	702 (81%)	674 (77%)	709 (82%)	0.15		
Diabetes, n(%)	246 (28%)	293 (34%)	295 (34%)	297 (34%)	0.02		
Smoking status, n(%)							
Current	82 (10%)	42 (5%)	35 (4%)	22 (3%)	<0.001		
Ever	571 (66%)	501 (58%)	511 (59%)	492 (57%)	<0.001		
Atrial fibrillation, n(%)	52 (6%)	37 (4%)	33 (4%)	28 (3%)	0.02		
Chronic kidney disease, n(%)	221 (26%)	214 (25%)	193 (22%)	217 (25%)	0.85		
Coronary artery disease, n(%)	81 (10%)	85 (10%)	81 (9%)	74 (9%)	0.86		
Myocardial infarction, n(%)	69 (8%)	64 (8%)	54 (6%)	47 (6%)	0.04		
Physical examination							
Height, cm	165.1 ± 9.3	166.0 ± 9.6	165.3 ± 9.	165.2 ± 9.3	0.19		
BMI, kg/m^2	26.8 ± 5.1	28.4 ± 5.2	28.8 ± 5.2	29.0 ± 5.1	<0.001		
BMI >30 kg/m^2, n(%)	201 (23%)	285 (33%)	309 (36%)	303 (35%)	<0.001		
Heart rate, bpm	62 ± 10	62 ± 11	61 ± 10	62 ± 10	0.89		
Systolic pressure, mmHg	129 ± 17	130 ± 17	131 ± 18	130 ± 17	0.17		
Diastolic pressure, mmHg	66 ± 10	67 ± 10	67 ± 10	67 ± 10	0.02		
Laboratory tests							

Hemoglobin, g/dL	13.4 ± 1.4	13.4 ± 1.7	13.5 ± 1.3	13.3± 1.4	0.7		
Hemoglobin A1c, %	5.8 ± 0.7	5.9 ± 0.8	5.9 ± 0.8	6.0 ± 0.8	<0.001		
eGFR, mL/min/1.73m^2	71.0 ± 17.0	71.2 ± 15.8	71.5 ± 15.3	71.4 ± 16.9	0.47		
High sensitivity-CRP, mg/L	1.7 [0.8, 3.6]	1.8 [0.9, 3.9]	1.8 [0.8, 4.0]	2.0 [0.9, 4.1]	0.24[#]		
NT-proBNP, pg/mL	134.3 [71.8, 261.5]	122.1 [66.2, 219.2]	105.2 [53.9, 204.1]	101.0 [57.3, 212.9]	<0.001[#]		
Spiromery							
V1 FEV1/FVC	75.0 ± 7.2	76.7 ± 5.6	76.7 ± 5.2	75.9 ± 5.6	0.02		
V5 FEV1/FVC	64.7 ± 9.3	72.1 ± 5.5	74.8 ± 5.2	78.4 ± 5.5	<0.001		
Change in FEV_1, L	-10.7 ± 13.4	-4.0 ± 10.7	-1.3 ± 11.5	1.8 ± 11.3	<0.001		
Change in FVC, L	-0.96 ± 0.39	-0.98 ± 0.33	-1.00 ± 0.35	-1.09 ± 0.37	<0.001		
Change in ppFVC, %	1.5 ± 14.8	-0.84 ± 11.5	-1.8 ± 12.3	-4.7 ± 11.9	<0.001		
ECHOCARDIOGRAPHIC							
Structure							
Mean wall thickness, cm	0.96 ± 0.14	0.98 ± 0.13	0.97 ± 0.13	0.98 ± 0.12	0.004	0.03	0.13
Relative wall thickness	0.42 ± 0.07	0.43 ± 0.07	0.42 ± 0.07	0.43 ± 0.07	0.28	0.45	
LV mass index, g/m^2	77.1 ± 19.2	76.9 ± 17.5	77.7 ± 18.6	77.0 ± 17.1	0.52	0.45	
LV mass	140.0 ± 43.7	143.9 ± 40.3	145.1 ± 41.5	144.0 ±38.1	0.02	0.15	
LVEDV index, mL/m^2	43.4 ± 9.7	42.7 ± 9.7	43.8 ± 10.5	43.2 ± 10.3	0.82	0.49	
Systolic function							
LV ejection fraction, %	65.8 ± 6.0	65.8 ± 5.5	66.0 ± 5.8	66.2 ± 6.0	0.32	0.06	
Longitudinal strain, %	-18.2 ± 2.5	-18.2 ± 2.3	-18.1 ± 2.3	-18.3 ± 2.3	0.64	0.22	
Stroke volume index, mL/m^2	48.7 ± 13.5	47.7 ± 13.2	47.9 ± 12.8	48.2 ± 17.2	0.73	0.73	
Diastolic function							
E wave	67.7 ± 19.0	65.6 ± 17.2	65.4 ± 16.6	66.1 ± 17.1	0.08	0.19	
A wave	78.9- ± 19.2	78.7 ± 18.5	79.2 ± 17.8	80.5 ± 19.8	0.01	0.09	
E/A ratio	0.88 ± 0.28	0.86 ± 0.27	0.85 ± 0.25	0.85 ± 0.29	0.01	0.19	
Lateral e', cm/s	7.24 ± 2.02	7.08 ± 2.02	7.05 ± 1.96	7.17 ± 2.03	0.10	0.83	
E/e' lateral	10.00 ± 3.93	9.87 ± 3.50	9.88 ± 3.49	9.81 ± 3.50	0.71	0.47	
LA volume index, mL/m^2	25.61 ± 8.11	25.32 ± 9.47	25.34 ± 8.24	25.37 ± 7.61	0.95	0.91	
Right ventricle and Pulmonary hemodynamics							
Estimated PASP, mmHg	27.7 ± 5.4	27.7 ± 5.5	27.6 ± 4.9	27.5 ± 5.1	0.63	0.14	
RV fractional area change	0.53 ± 0.08	0.53 ± 0.08	0.52 ± 0.07	0.53 ± 0.07	0.72	0.91	

BMI: body mass index; FEV1: forced expired volume in 1 second; ppFVC: percent predicted forced vital capacity; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; NT-pro-BNP: N-terminal fragment of prohormone for B-type natriuretic peptide; LV: left ventricle; LVEDD:

LV end diastolic diameter; LVESD: LV end systolic diameter; LVEDV: LV end diastolic volume; LVESV: LV end systolic volume; LA: left atrium; PASP: pulmonary artery systolic pressure.
Model 1: age, sex, race; Model 2: Model 1+ FEV_1/FVC at visit 5. Model 3: Model 2 + ever smoking, hypertension, diabetes, body mass index, log Hs-CRP, log NT-proBNP, myocardial infarction and atrial fibrillation. Model 3 analyses were only performed when $p<0.05$ in Model 2.
*unadjusted p-value for trend. # p-value for the log transformed CRP and NT-pro-BNP trend.

Table S5. Association of spirometric function change (5th ARIC visit minus the peak function at 1st or 2nd study visit, with incident heart failure (HF) (median follow up time 5.6years), including HF with preserved (HFpEF) and with reduced ejection fraction (HFrEF), and overall mortality (median follow up time 5.7years).

Outcome	Events	Model 1* HR (95%CI) per 10%point decrease	p	Model 2* HR (95%CI) per 10%point decrease	p
FEV_1/FVC (3476)					
Heart Failure	160	0.89 (0.60-1.33)	0.58	0.95 (0.63-1.42)	0.79
HFpEF	78	0.66 (0.37-1.18)	0.16	0.78 (0.43-1.41)	0.43
HFrEF	64	1.19 (0.64-2.24)	0.57	1.11 (0.59-2.10)	0.74
Mortality	335	1.10 (0.83-1.45)	0.52	1.08 (0.81-1.43)	0.61
Percent predicted FVC (3325)					
Heart Failure	157	1.11 (0.95-1.29)	0.20	1.00 (0.85-1.17)	0.99
HFpEF	78	1.29 (1.02-1.62)	0.03	1.13 (0.88-1.44)	0.34
HFrEF	58	0.91 (0.71-1.16)	0.45	0.88 (0.69-1.12)	0.31
Mortality	310	1.03 (0.92-1.15)	0.60	1.02 (0.91-1.15)	0.70

Model 1: age sex, race and respective pulmonary function at visit 5 (FEV_1/FVC or ppFVC).
Model 2: Model 1 plus visit 1 body mass index (BMI), visit 5 BMI, ever smoking, prevalent coronary artery disease at visit 5, hypertension, diabetes, logNT-proBNP at visit 5 and stratified by prevalent atrial fibrillation at visit 5.

Table S6. Echocardiographic parameters of the study population according to percent predicted FVC at ARIC baseline visit 5.

	Model 1		Model 2	
	Coefficient (95%CI)	p-value	Coefficient (95%CI)	p-value
Structure				
Mean wall thickness, cm	-0.0013 (-00015; -0.0010)	<0.001	-0.0005 (-0.0007; -0.0002)	<0.001
Relative wall thickness	-0.0002 (-0.0004; -0.0001)	0.001	-0.0001 (-0.0002; 0.00001)	0.07
LV mass index, g/m^2	-0.112 (-0.147; -0.076)	<0.001	-0.026 (-0.062; 0.009)	0.15
LV mass, g	-0.425 (-0.501; -0.350)	<0.001	-0.127 (-0.198; -0.056)	<0.001
LVEDV index, mL/m^2	0.037 (0.018; 0.056)	<0.001	0.042 (0.023; 0.062)	<0.001
Systolic function				
LV ejection fraction, %	0.012 (-0.0001; 0.023)	0.05		
Longitudinal strain, %	-0.010 (0.015; -0.006)	<0.001	-0.005 (-0.010; -0.0003)	0.04
Stroke volume index, mL/m^2	-0.010 (-0.019; 0.038)	0.51		
Diastolic function				
E wave	-0.133 (-0.169; -0.098)	<0.001	-0.093 (-0.130; -0.056)	<0.001
A wave	-0.114 (0.151; -0.077)	<0.001	-0.056 (-0.095; -0.018)	0.004
E/A ratio	-0.0002 (-0.0008; 0.0003)	0.37		
Lateral e', cm/s	0.006 (0.002; 0.010)	0.002	0.004 (0.0005; 0.009)	0.03
Septal e', cm/s	0.0025 (-0.0004; 0.0054)	0.10		
E/e' lateral	-0.029 (-0.036; -0.021)	<0.001	-0.020 (-0.027; -0.012)	<0.001
E/e' septal	-0.031 (0.039; -0.023)	<0.001	-0.019 (-0.027; -0.011)	<0.001
LA volume index, mL/m^2	-0.030 (-0.046; -0.014)	<0.001	-0.001 (-0.017; 0.014)	0.84
Right ventricle and Pulmonary pressure				
Estimated PASP, mmHg	-0.050 (-0.063; -0.036)	<0.001	-0.026 (-0.040; -0.012)	<0.001
TAS' (cm/s)	0.006 (0.0005; 0.012)	0.03	0.005 (-0.001; 0.011)	0.14
RV fractional area change	0.0002 (0.000001; 0.0003)	0.05	0.00005 (-0.0001; 0.0002)	0.60

BMI: body mass index; FEV1: forced expired volume in 1 second; ppFVC: percent predicted forced vital capacity; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; NT-pro-BNP: N-terminal fragment of prohormone for B-type natriuretic peptide; LV: left ventricle; LVEDD: LV end diastolic diameter; LVESD: LV end systolic diameter; LVEDV: LV end diastolic volume; LVESV: LV end systolic volume; LA: left atrium; TAS': tricuspid annular peak systolic myocardial velocity; PASP: pulmonary artery systolic pressure.
Model1: age, sex, race; Model 2: age, sex, race, ever smoking, body mass index, hypertension, diabetes, log Hs-CRP, log NT-proBNP.
Model 2 analyses were only performed when p<0.05 in Model 1

Table S7. Biomarkers and Echocardiography variables of the study population according to sex-specific FVC quartiles at ARIC baseline visit 5 (n=3325). Values are expressed as mean±SD or median [25th-75th percentile].

FVC	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Model1 p-trend	Mode 2 p-trend
Participants, n	833	830	831	831		
FVC, L	2.25±0.56	2.78±0.59	3.15±0.65	3.75±0.83		
Demographics						
Age, years	76.5±5.2	75.4±5.1	74.8±4.7	73.4±4.3	<0.001	
Male	326 (39%)	324 (39%)	325 (39)	325 (39%)		
Black	279 (33%)	205 (25%)	129 (15%)	61 (7%)	<0.001	
Height, cm	162±9	165±9	166±9	169±9	<0.001	
BMI, kg/m^2	30.5±6.2	29.2±5.3	28.1±4.8	27.0±4.4	<0.001	
Ever smoker	469 (56%)	491 (59%)	460 (55%)	490 (59%)	0.83	
Biomarkers						
High sensitivity-CRP, mg/L	2.4 [1.1, 5.1]	2.1 [1.0, 4.4]	1.8 [0.8, 3.6]	1.5 [0.7, 3.0]	<0.001*	<0.001*†
NT-proBNP, pg/mL	134 [68, 262]	120 [58, 230]	109 [60, 214]	105 [57, 184]	<0.001*	<0.001*
Structure						
Mean wall thickness, cm	1.00 ± 0.14	0.98 ± 0.13	0.97 ± 0.13	0.96 ± 0.12	<0.001	0.05
Relative wall thickness	0.44 ± 0.08	0.42 ± 0.07	0.42 ± 0.07	0.42 ± 0.07	0.01	0.35
LV mass index, g/m^2	80.0 ± 19.0	78.5 ± 18.6	76.9 ± 18.1	75.1 ± 16.6	<0.001	0.09
LV mass, g	148 ± 43	147 ± 42	143 ± 41	142 ± 39	<0.001	0.07

LVEDV index, mL/m^2	42 ± 10	43 ± 10	43 ± 10	45 ± 10	<0.001	<0.001
Systolic function						
LV ejection fraction, %	65.6± 5.9	65.8 ± 6.4	66.0 ± 5.9	66.1 ± 5.3	0.03	0.28
Longitudinal strain, %	-17.8 ± 2.6	-18.1 ± 2.5	-18.4 ± 2.2	-18.4 ± 2.2	<0.001	0.003
Stroke volume index, mL/m^2	50 ± 16	48 ± 14	48 ± 14	47 ± 13	0.787	-
Diastolic function						
E wave, cm/sec	69 ± 19	67 ± 17	65 ± 17	65 ± 16	<0.001	<0.001
A wave, cm/sec	84 ± 20	80 ± 18	79 ± 18	75 ± 17	<0.001	0.006
E/A ratio	0.84 ± 0.29	0.85 ± 0.27	0.85 ± 0.26	0.89 ± 0.27	0.53	-
Lateral e', cm/s	6.8 ± 2.0	7.1 ± 1.9	7.1 ± 2.0	7.4 ± 2.1	0.01	0.07
E/e' lateral	10.7 ± 3.9	9.9 ± 3.4	9.8 ± 3.5	9.3 ± 3.3	<0.001	<0.001
LA volume index, mL/m^2	26.3 ± 9.3	25.6 ± 8.3	25.0 ± 7.5	24.9 ± 7.3	0.001	0.94
Right ventricle and Pulmonary pressure						
Estimated PASP, mmHg	28.9 ± 6.1	27.6 ± 5.3	27.4 ± 4.9	26.8 ± 4.4	<0.001	0.02
RV fractional area change	0.52 ± 0.08	0.52 ± 0.08	0.53 ± 0.08	0.53 ± 0.07	0.06	-

CRP: C-reactive protein NT-pro-BNP: N-terminal fragment of prohormone for B-type natriuretic peptide; LV: left ventricle; LVEDV: LV end diastolic volume; LA: left atrium; PASP: pulmonary artery systolic pressure.

Model1: age, sex, race, height; Model 2: age, sex, race, height, current or prior smoking, body mass index, hypertension, diabetes, log Hs-CRP, log NT-proBNP. Model 2 analyses were only performed when $p<0.05$ in Model 1. *p-value for the log transformed CRP and NT-pro-BNP trend. †log NT-proBNP was excluded for Model 2.

Table S8. Mediation proportion of covariates in Cox regression models for the association of dichotomic percent predicted FVC and Overall heart failure.

Models	ppFVC and Overall HF		
	HR (95% CI)	**Coef**	**Reduction of Coef. (95% CI)**
Demographics (age, sex, and race)	1.73 (1.24, 2.46)	0.56	REF.
Demographics + Body mass index	1.56 (1.10, 2.21)	0.44	20% (7% to 71%)
Demographics + Coronary disease	1.74 (1.24, 2.45)	0.55	0.3% (-5% to 6%)
Demographics + Atrial fibrillation	1.82 (1.29, 2.57)	0.60	-8% (-31% to 2%)
Demographics + Hypertension	1.67 (1.18, 2.35)	0.51	8% (3% to 26%)
Demographics + Diabetes	1.67 (1.18, 2.35)	0.51	8% (1% to -30%)
Demographics + NTproBNP(log)	1.47 (1.04, 2.09)	0.39	30% (7% to 92%)

The bootstrap derived from 2000 samples indicated that the indirect effect coefficient was significant for NT-proBNP and BMI, which are suggested to be the main contributors for the association of low ppFVC and heart failure in this model, such that HR is mostly attenuated by NT-proBNP followed by BMI.

Table S9. Association of FVC at the 5th ARIC visit with incident HF, HFpEF and HFrEF (median follow up time 5.6years) and overall mortality (median follow up time 5.7years).

Outcome	Events	Model 1* HR (95%CI) per unit of decrease	p	Model 2* HR (95%CI) per unit of decrease	p
FVC (n=3325)					
HFpEF	78	2.61 (1.66-4.10)	<0.001	1.85 (1.13-3.04)	0.015
HFrEF	58	1.13 (0.69-1.86)	0.62	0.76 (0.45-1.31)	0.33
Heart Failure	157	1.98 (1.45-2.71)	<0.001	1.37 (0.98-1.93)	0.07
Mortality	310	1.61 (1.23-2.03)	<0.001	1.61 (1.23-2.07)	<0.001

*Model 1: age, sex, race and height. Model 2: age, sex, race, height body mass index, prevalent coronary artery disease, ever smoking, hypertension, diabetes, log(NT-proBNP), and stratified by prevalent atrial fibrillation, all at baseline Visit 5.

Table S10. Characteristics of the study population according to sex-specific quartiles of percent predicted FVC ratio change (Visit 5 - highest of Visits 1 or 2**)** in ARIC cohort from 1987 to 2013 (n=3321). Values are expressed as mean±SD, n(%) or median[25th-75th percentile].

	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**Model 1 p-trend**	**Model 2 p-trend**	**Model 3 p-trend**
Participants, n	831	830	831	829			
Mean ppFVC change	-18.6 ± 7.1	-7.3 ± 2.2	-0.4 ± 2.3	13.8 ± 9.9			
CLINICAL							
Demographics							
Age at visit 5, years	74.0 ± 4.6	74.4 ± 4.5	74.9 ± 4.9	76.7 ± 5.4	<0.001*		
Age at visit 1, years	50.4 ± 4.4	50.8 ± 4.4	51.3 ± 4.7	53.1 ± 5.4	<0.001*		
Male	325 (39%)	324 (39%)	325 (39%)	324 (39%)			
Black	123 (15%)	112 (14%)	107 (13%)	330 (40%)	<0.001*		
Center					<0.001*		
Forsyth	161 (19%)	166 (20%)	202 (24%)	152 (18%)			
Jackson	120 (14%)	107 (13%)	93 (11%)	299 (36%)			
Minneapolis	318 (378%)	301 (36%)	271 (33%)	151 (18%)			
Washington	232 (28%)	256 (31%)	265 (32%)	227 (27%)			
Medical history							
Hypertension	676 (81%)	665 (80%)	650 (78%)	680 (82%)	0.002		
Diabetes	298 (36%)	288 (35%)	257 (31%)	300 (36%)	0.10		
Smoking status							
Current	51 (6%)	32 (4%)	31 (4%)	42 (5%)	0.57		
Ever	505 (61%)	463 (56%)	467 (56%)	473 (57%)	0.42		
Atrial fibrillation	58 (7%)	26 (3%)	19 (2%)	37 (4%)	0.002		
Chronic kidney disease	188 (23%)	197 (24%)	203 (25%)	211 (26%)	0.21		
Coronary artery disease	92 (11%)	70 (8%)	88 (11%)	62 (8%)	0.08		
Myocardial infarction	70 (9%)	44 (6%)	56 (7%)	51 (6%)	0.19		
Physical examination							
Height, cm	166.2 ± 9.2	166.2 ± 8.9	165.5 ± 9.1	164.0 ± 10.0	<0.001		
Body mass index, kg/m^2	30.8 ± 5.8	28.9 ± 5.1	27.8 ± 4.7	27.3 ± 4.9	<0.001		
Body mass index >30 kg/m^2	412 (50%)	300 (36%)	238 (29%)	207 (25%)	<0.001		
Heart rate, bpm	62 ± 10	61 ± 9	61 ± 10	62 ± 10	0.34		
Systolic pressure, mmHg	130 ± 18	130 ± 17	129 ± 17	131 ± 17	0.003		
Diastolic pressure, mmHg	68 ± 10	67 ± 10	66 ± 10	66 ± 10	<0.001		
Laboratory tests							
Hemoglobin, g/dL	13.4 ± 1.4	13.5 ± 1.4	13.4 ± 13	13.2 ± 1.8	0.48		

HbA1c, %	5.93 ± 0.77	5.88 ± 0.79	5.84 ± 0.70	5.92 ± 0.83	0.001		
eGFR, mL/min,1.73m^2	72.5 ± 16.3	71.3 ± 16.5	70.9 ± 16.5	70.6 ± 16.7	0.98		
High sensitivity-CRP, mg/L	2.5 [1.2, 5.1]	1.9 [1.0, 4.0]	1.7 [0.8, 3.6]	1.6 [0.8, 3.4]	<0.001[#]		
NT-proBNP, pg/mL	133.0 [65.0, 257.2]	106.9 [62.1, 209.2]	113.1 [59.6, 203.5]	111.0 [55.2, 210.9]	<0.001[#]		
Spiromery							
V1 ppFVC	102.4 ± 12.8	101.2 ± 11.7	100.0 ± 12.8	96.5 ± 17.6	<0.001		
V5 ppFVC	84.6 ± 13.7	94.8 ± 11.9	100.4 ± 12.8	111.4 ± 17.9	<0.001		
Change in FEV_1, L	-15.8 ± 9.7	-5.9 ± 6.8	0.01 ± 7.7	7.8 ± 12.2	<0.001		
Change in FVC, L	-1.5 ± 0.4	-1.1 ± 0.2	-0.9 ± 0.2	-0.7 ± 03	<0.001		
Change in FEV_1/FVC	-2.3 ± 4.5	-3.2 ± 4.1	-3.6 ± 3.9	-4.6 ± 4.4	<0.001		
ECHOCARDIOGRAPHIC							
Structure							
Mean wall thickness, cm	1.00 ± 0.14	0.97 ± 0.13	0.97 ± 0.13	0.96 ± 0.12	<0.001	<0.001	0.014
Relative wall thickness	0.43 ± 0.07	0.42 ± 0.07	0.42 ± 0.08	0.43 ± 0.07	0.001	0.05	
LV mass index, g/m^2	80.2 ± 18.8	77.2 ± 17.7	77.3 ± 18.2	75.6 ± 17.4	<0.001	0.002	0.16
LV mass, g	155.5 ± 43.4	145.9 ± 40.8	142.7 ± 40.0	136.4 ± 39.5	<0.001	<0.001	0.01
LVEDV index, mL/m^2	43.1 ± 9.8	42.9 ± 9.8	43.7 ± 10.8	43.2 ± 9.9	0.39	0.15	
Systolic function							
LV ejection fraction, %	65.4 ± 6.1	66.2 ± 5.3	66.0 ± 5.9	66.0 ± 6.1	0.002	0.02	0.18
Longitudinal strain, %	-17.9 ± 2.6	-18.4 ± 2.3	-18.3 ± 2.3	-18.1 ± 2.3	0.004	0.05	
Stroke volume index, mL/mL^2	47.6 ± 13.8	47.8 ± 14.8	48.5 ± 13.6	48.2 ± 15.3	0.84	0.82	
Diastolic function							
E wave	69.7 ± 19.2	66.6 ± 16.8	65.3 ± 16.5	64.2 ± 17.5	<0.001	0.001	0.11
A wave	79.5 ± 20.0	79.2 ± 18.4	79.8 ± 18.3	80.0 ± 17.9	0.04	0.19	
E/A ratio	0.90 ± 0.31	0.86 ± 0.25	0.84 ± 0.24	0.82 ± 0.28	<0.001	<0.001	0.001
Lateral e', cm/s	7.3 ± 2.2	7.1 ± 1.9	7.1 ± 1.9	7.1 ± 2.1	0.88	0.04	0.06
Septal e', cm/s	5.84 ± 1.45	5.79 ± 1.35	5.75 ± 1.47	5.70 ± 1.55	0.67	0.58	
E/e' lateral	10.3 ± 3.9	9.9 ± 3.5	9.8 ± 3.4	9.7 ± 3.5	<0.001	0.35	
E/e' septal	12.5 ± 4.5	12.0 ± 3.7	11.9 ± 3.8	11.8 ± 3.8	<0.001	0.04	0.46
LA volume index, mL/m^2	26.9 ± 9.6	25.0 ± 7.4	25.2 ± 7.9	24.8 ± 7.4	<0.001	<0.001	<0.001
Right ventricle and Pulmonary hemodynamics							
TAS' (cm/s)	11.8 ± 3.0	11.9 ± 2.7	11.8 ± 2.8	11.8 ± 2.8	0.42	0.70	

Estimated PASP, mmHg	28.8 ± 5.9	27.7 ± 5.5	27.2 ± 4.8	27.1 ± 4.9	<0.001	0.002	0.65
RV fractional area change	0.52 ± 0.08	0.53 ± 0.07	0.53 ± 0.08	0.53 ± 0.08	<0.001	<0.001	0.004

BMI: body mass index; FEV1: forced expired volume in 1 second; FVC: forced vital capacity; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; NT-pro-BNP: N-terminal fragment of prohormone for B-type natriuretic peptide; LV: left ventricle; LVEDD: LV end diastolic diameter; LVESD: LV end systolic diameter; LVEDV: LV end diastolic volume; LVESV: LV end systolic volume; LA: left atrium; TAPSE: tricuspid annular peak systolic myocardial velocity; PASP: pulmonary artery systolic pressure.

Model1: age, sex, race; Model 2: Model 1+ ppFVC at Visit 5; Model 3: Model 2 + body mass index from visits 5 and 1, hypertension, atrial fibrillation, log Hs-CRP, log NT-proBNP. Model 3 analyses were only performed when $p<0.05$ in Model 2.

*unadjusted p-value for trend. # p-value for the log transformed CRP and NT-pro-BNP trend.

Figure S1. Flow diagram demonstrating the derivation of the study sample.

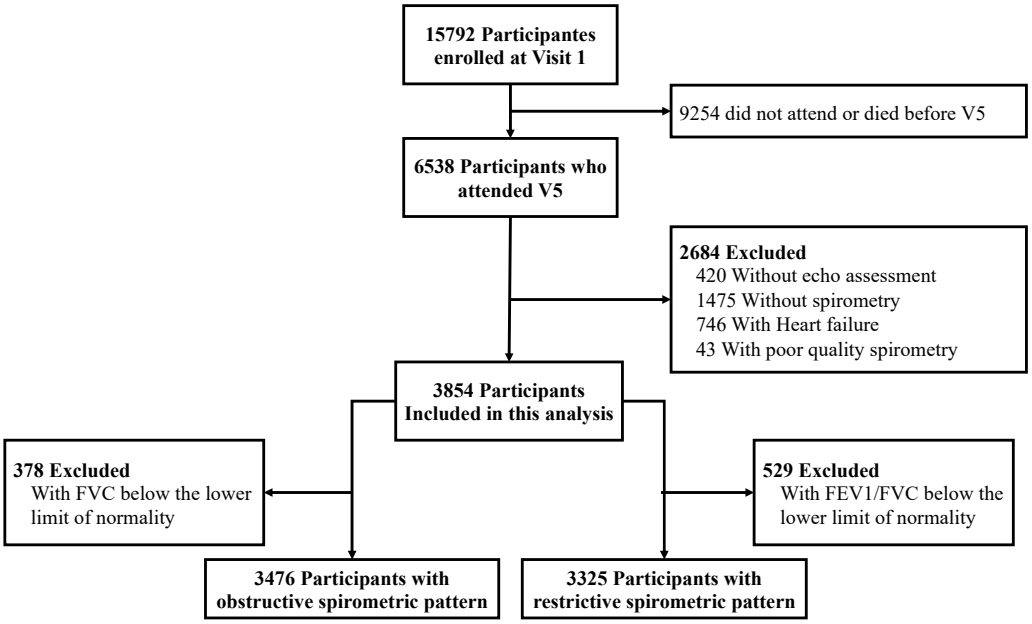
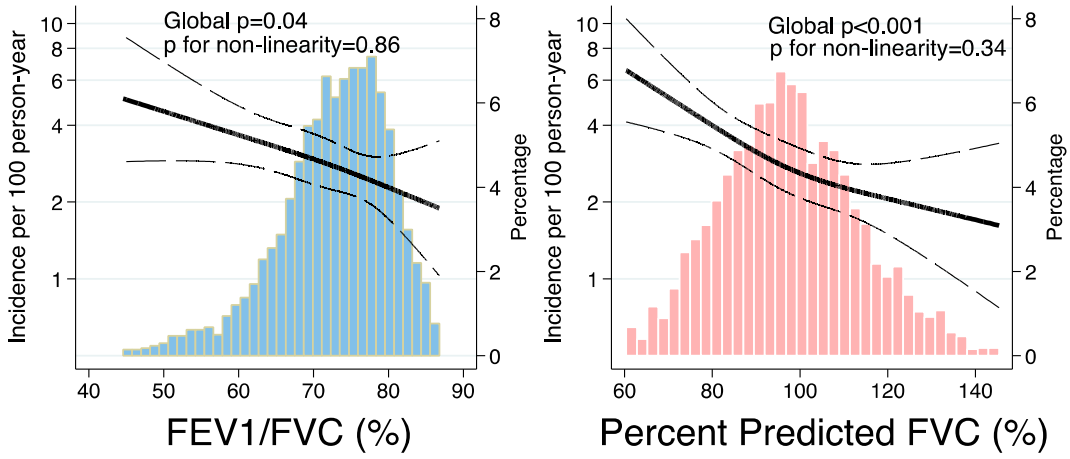


Figure S2. Continuous associations of FEV_1/FVC (blue) and percent predicted FVC (light red) at Visit 5 with subsequent incidence of HF overall.



Models were adjusted for age, sex, race, and primary exposure variables (FEV1/FVC and percent predicted FVC) using restricted cubic splines with 3 knots. *p <0.05 in models further adjusted for body mass index, prevalent coronary artery disease, prevalent atrial fibrillation, hypertension, diabetes, ever smoking, log(NT-proBNP) and the other spirometric measure (FEV_1/FVC or ppFVC).