

Fibroblast Growth Factor-23 and Heart Failure With Reduced Versus Preserved Ejection Fraction: MESA

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Background—Higher fibroblast growth factor-23 (FGF-23) levels are associated with incident heart failure (HF) in MESA (the Multiethnic Study of Atherosclerosis). FGF-23 is also associated with left ventricular hypertrophy. Whether the FGF-23 association with HF is similar for heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) is not well established.

Methods and Results—We studied 6542 participants (mean age 62 ± 10 years, 53% women, mean estimated glomerular filtration rate of 81 ± 18 mL/min per 73 m^2) from MESA who were free of cardiovascular disease at baseline (2000–2002). HF events were ascertained by an adjudication committee for a median follow-up of 12.1 years. We classified HF events as HFrEF (ejection fraction [EF] $<50\%$) or HFpEF (EF $\geq 50\%$) at the time of diagnosis. Cox proportional hazard regression was used to compute hazard ratios and 95% confidence intervals for the association between baseline serum FGF-23 and incident HFrEF and HFpEF. A total of 134 events were classified as HFpEF, 151 HFrEF, and 49 unknown EF. Following imputation, 149 were classified as HFpEF, 176 HFrEF, and 291 participants had HF (34 participants had HFpEF then HFrEF). In the fully adjusted model, higher FGF-23 levels were associated with incident HFpEF but not with HFrEF (hazard ratio 1.29, 95% confidence interval, 1.08–1.54) versus (hazard ratio 1.04, 95% confidence interval, 0.84–1.29) for each 20 pg/mL higher serum FGF-23 concentration.

Conclusions—FGF-23 association with HF is driven by the association with HFpEF but not with HFrEF in a population-based cohort. Further studies are needed to determine the pathological mechanisms mediating this association. (*J Am Heart Assoc.* 2018;7:e008334. DOI: 10.1161/JAHA.117.008334.)

Key Words: ejection fraction • fibroblast growth factor • heart failure • left ventricular hypertrophy

Heat failure (HF) is a major cause of morbidity and mortality and associated high healthcare-related costs.¹

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It is estimated to affect almost 5.7 million Americans and >23 million people worldwide.^{2,3} Half of these people have normal left ventricular ejection fraction (EF) $>50\%$ and are classified as having HF with preserved ejection fraction (HFpEF).⁴ While the morbidity and mortality of HF with reduced ejection fraction (HFrEF) is improving,⁵ outcomes for HFpEF are unchanged.^{6–8}

Although several evidence-based therapies are now available for the treatment of patients with HFrEF,⁹ the same cannot be said about HFpEF.¹⁰ In fact, the exact pathophysiologic processes, which are considered to be multifactorial and heterogeneous, are not completely understood.^{11–13} Additional research is needed to better characterize the phenotype of HFpEF, and identify risk factors and pathophysiologic processes associated with this condition.

Fibroblast growth factor-23 (FGF-23), a hormone involved in phosphorus and vitamin D homeostasis,^{14–16} is linked to the development of HF and left ventricular hypertrophy (LVH).^{17,18} The administration of recombinant FGF-23 promotes cardiomyocyte growth in animal models and higher

Clinical Perspective

What Is New?

- Fibroblast growth factor-23 is a new novel biomarker for heart failure with preserved ejection fraction independent of traditional risk factors.

What Are the Clinical Implications?

- Further studies are needed to determine whether changes in fibroblast growth factor-23 levels will affect heart failure with preserved ejection fraction incidence and management.

circulating FGF-23 concentrations are associated with HF and cardiovascular events in kidney disease and general populations.¹⁸ Among 6542 participants in MESA (Multiethnic Study of Atherosclerosis), higher FGF-23 concentrations were associated with all incident HF events over 7.5 years of follow-up.¹⁹ Such associations could represent HFpEF, given known biological effects of FGF-23 on ventricular hypertrophy. On the other hand, LVH is associated with HFrEF, and FGF-23 is associated with other pathologies that could promote HFrEF, such as arterial stiffness, endothelial dysfunction, and vascular calcifications.²⁰

The primary goal of this study is to delineate and contrast associations of serum FGF-23 concentrations with incident HFpEF and HFrEF events in MESA, a multiethnic community-based cohort that was free of cardiovascular disease at baseline and includes adjudicated HF events during long-term follow-up. In a supplemental analysis among participants with cardiac magnetic resonance (CMR) imaging at baseline, we also tested whether these associations were explained in part by differences in left ventricular (LV) mass.

Methods

The data, analytic methods, and study materials will be/have been made available to other researchers for purposes of reproducing the results or replicating the procedure. The MESA mechanism for public access to data is via the BioLINCC repository.²¹

Study Population

MESA is a prospective cohort study of cardiovascular disease among 6814 community-living individuals free of clinical cardiovascular disease and aged 45 to 84 years of age at enrollment.²¹ Between 2000 and 2002, individuals were recruited from 6 US sites: Baltimore, MD; Chicago, IL; St. Paul, MN; Forsyth County, NC; New York, NY; and Los Angeles, CA.

MESA recruited a final population that was 38% white, 28% black, 22% Hispanic, and 12% Asian, predominantly of Chinese descent. The study excluded people with self-reported history of myocardial infarction, angina, stroke, transient ischemic attack, heart failure, atrial fibrillation, nitroglycerin use, angioplasty, coronary artery bypass grafting, valve replacement, pacemaker or defibrillator, or any surgery on the heart or arteries. All participants gave informed consent, and institutional review board approval was obtained for each site.

We evaluated all participants who had serum FGF-23 measurements at baseline and who were followed for the development of either incident HFrEF or HFpEF through 2012 (N=6542; Figure 1). Three participants were excluded because they had extremely out of range FGF-23 values and were considered by the laboratory to represent laboratory error.

Measurements of Other Variables

Medical and personal histories were ascertained using standardized questionnaires. Information was gathered to ascertain participant's demographic data, tobacco usage, alcohol consumption, medical conditions, and current use of prescription and nonprescription medications and supplements. Blood pressure, ECGs, and laboratory data were obtained as previously described.²¹ Body mass index was calculated as weight in kilograms divided by height in meters squared. MESA investigators defined diabetes mellitus by the use of a diabetes mellitus medication or a fasting blood glucose level ≥ 126 mg/dL. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg or medical treatment for hypertension.

The University of Vermont Laboratory for Clinical Biochemistry measured serum creatinine using a modified Jaffe reaction that was indirectly calibrated to Cleveland Clinic laboratory standards, serum cystatin C and C-reactive protein concentrations using a BNII system nephelometer (Siemens), and urine albumin and creatinine from spot morning collections using nephelometry and the rate Jaffe reaction, respectively. Serum and urine phosphate were measured from frozen samples using timed-rate colorimetry on a Beckman-Coulter DxC chemistry analyzer. Estimated glomerular filtration rate (eGFR) was calculated using serum creatinine and cystatin C concentrations from the 2012 CKD-EPI equation.²²

Study Procedures: CMR Imaging

A subset of MESA participants (n=4980) without contraindications (internal metal fragments, implants, electrical devices, or severe claustrophobia) underwent CMR imaging at the MESA baseline examination by using 1.5-T scanners (Avanto

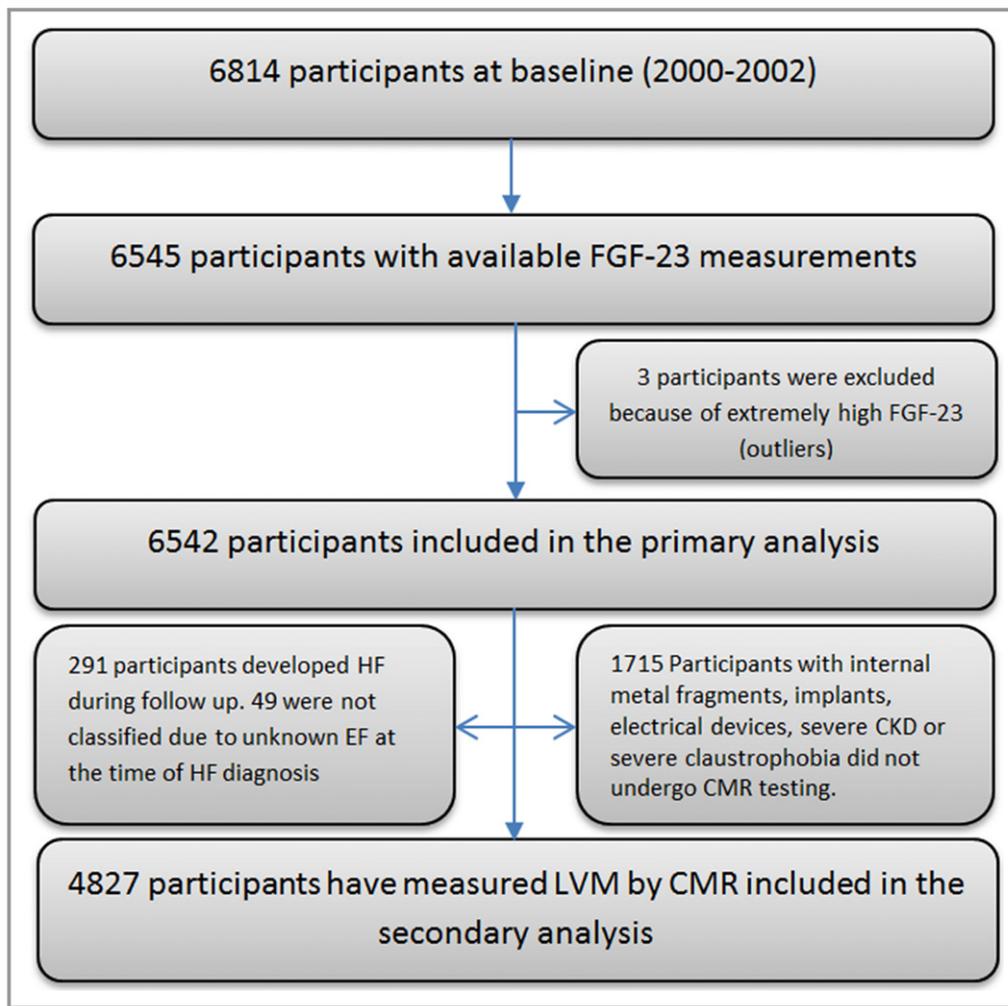


Figure 1. Participant enrollment for the current study. CKD indicates chronic kidney disease; CMR, cardiac magnetic resonance; EF, ejection fraction; FGF-23, fibroblast growth factor-23; HF, heart failure; LVM, left ventricular mass.

and Espree, Siemens Medical Systems, Erlangen, Germany) with a 6-channel anterior phased-array torso coil and corresponding posterior coil elements. LV function, dimensions, and myocardial mass were assessed by a cine steady-state free precession sequence. Twelve short-axis slices, one 4-chamber view, and one 2-chamber view were acquired as previously described.²³ The endocardial and epicardial borders were contoured using a semiautomated method. The difference between the endocardial and epicardial areas for all slices was multiplied by slice thickness and section cap and then multiplied by the specific myocardial density (1.04 g/mL) to determine LV mass.

Measurement of Serum FGF-23 Concentrations

Blood samples stored at the University of Vermont Laboratory for Clinical Biochemistry were shipped on dry ice to the University of Washington, where serum FGF-23 concentrations

were measured using the Kainos Immunoassay,²⁴ which detects the full-length biologically intact FGF-23 molecule via midmolecule and distal epitopes. Standardized high- and low-value FGF-23 controls within each run were used to monitor quality control. The coefficient of variation for singlicate high and low control samples across 81 plates were 6.7% and 12.4%, respectively.

Ascertainment of HF Events

MESA personnel screened participants for incident clinical events through telephone contacts and scheduled follow-up examinations. Personnel abstracted any hospital records suggesting cardiovascular events and recorded symptoms, history, and biomarkers; scanned ECGs, echocardiograms, catheterization reports, outpatient records, and other relevant diagnostic reports; and transmitted these to the Coordinating Center.

Two study physicians blinded to other study data independently reviewed the medical records. Incident HF events were considered as probable or definite. Definite or probable HF required HF symptoms, such as shortness of breath or edema, as asymptomatic disease is not a MESA end point. In addition to symptoms, probable HF required HF diagnosed by a physician and patient receiving medical treatment for HF. Definite HF required 1 or more other criteria, including pulmonary edema/congestion by chest radiograph; dilated ventricle or poor LV function by echocardiography or ventriculography; or evidence of LV diastolic dysfunction. We considered participants with a physician diagnosis of HF but without any other HF criteria as having no HF. The Events Committee classified HF as HFrEF (EF <50%) or HFpEF (EF ≥50%) at the time of HF diagnosis. The EF was obtained from echocardiographic or radionuclide data available at the HF diagnosis (Figure 1).

Before imputation, 134 were classified as HFpEF, 151 as HFrEF, and 49 HF events were not classified. Sixteen participants had 1 type and then had the other type. The imputation was done for each HF type separately and therefore was not mutually exclusive. Following imputation, 149 events were classified as HFpEF and 176 as HFrEF (149+176=325). Thirty-four participants had 1 type of HF and then had the other (eg, HFpEF then HFrEF), therefore they were only included once for HF (325–34=291). Thus, a total of 291 participants had HF during follow-up.

Statistical Analysis

Continuous variables are presented as mean±SD and categorical variables as frequencies and percentages. Baseline characteristics were compared across serum FGF-23 quartiles. We explored the functional relationship of serum FGF-23 concentrations with HF events using restricted cubic spline models; given linear associations for each HF type, we proceeded to analyze FGF-23 as a continuous linear variable, scaled to increments of 20 pg/mL to facilitate interpretation. We further evaluated the association between FGF-23 and each HF type using quartiles of FGF-23 to ensure that a threshold effect does not exist. We evaluated the time to first HFrEF and HFpEF event using separate Cox proportion hazards models for each HF type without censoring on the opposing type to avoid potential bias. Unknown HF types (N=49) were handled through multiple imputation using chained equations that were combined using Rubin's rules to account for variability in the imputation procedure. All covariates from the fully adjusted model were used in the imputation.^{25,26} Models were adjusted as follows; Model 1 was unadjusted. Model 2 was adjusted for age, sex, race/ethnicity, highest education level completed (high school or less, some college but no degree, college degree or more),

study site, height, and weight. Model 3 was further adjusted for systolic blood pressure (continuous), antihypertensive medications (yes; no), diabetes mellitus status (yes; no), high-sensitivity C-reactive protein, smoking (current versus former and never), urine albumin–creatinine ratio, and eGFR_{CKD-Epi}. Model 4 was further adjusted for N-terminal pro B-type natriuretic peptide, 25(OH)vitamin D, parathyroid hormone, and phosphate. We tested for the proportional hazards assumption and found no evidence of departure from this assumption.

In sensitivity analyses, we adjusted for LV mass detected by CMR to estimate the amount of association that may be explained through this characteristic. Furthermore, we used time-updated covariates for additional sensitivity analyses using the following variables as time-dependent covariates: height, weight, diabetes mellitus, smoking, urine albumin–creatinine ratio, and eGFR_{CKD-Epi}. In final sensitivity analysis, we also looked at complete case analysis by HF type. A 2-sided *P* value of <0.05 was considered statistically significant for all analyses including interaction terms. Statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC), and R 3.3.2 (R Core Team; 2016, Vienna, Austria), and SPSS 24.0 (IBM Corp., 2016, Armonk, NY).

Results

There were 6542 participants (4827 of whom had CMR data) included in our analysis (Figure 1). Participants (mean age 62±10 years) included 53% women, 39% white, 12% Chinese, 27% black, and 22% Hispanic. The mean serum FGF-23 concentration was 40±15 pg/mL and mean eGFR was 81±18 mL/min per 1.73 m². Compared with participants in the lowest FGF-23 quartile (<31 pg/mL), those in the highest quartile (>46 pg/mL) were older, had higher body mass index, higher systolic blood pressure and LV mass, lower eGFR, and were more likely to have diabetes mellitus (Table 1).

During a median follow-up of 12.1 (interquartile range: 11.6–12.7) years, 291 participants developed incident HF. Following imputation, 176 were classified as HFrEF and 149 were classified as HFpEF. Qualitatively, higher serum FGF-23 concentrations corresponded with progressively greater risks of HFpEF in a generally linear pattern (Figure 2). However, there was no graphical evidence for a relationship of serum FGF-23 concentrations with HFrEF events. Incidence rates reported as 1000-person-years for both HFrEF and HFpEF by FGF-23 quartiles are shown (Figure 3).

In unadjusted models, higher serum FGF-23 concentrations were associated with a greater hazard of HFpEF events. After full adjustment for demographics, comorbidities, medications, and socioeconomic variables, each 20 pg/mL higher FGF-23

Table 1. Baseline Characteristics by FGF-23 Quartiles: The Multiethnic Study of Atherosclerosis 2000–2002

Characteristic	Overall	FGF-23 Quartiles				P Value
		<31 pg/mL	31–38 pg/mL	38–46 pg/mL	>46 pg/mL	
No. of participants	6542	1636	1635	1636	1635	
Age, y	62±10	61±10	62±10	62±10	64±10	<0.001
Sex						
Men	3058 (47%)	678 (41%)	786 (48%)	783 (48%)	811 (50%)	<0.001
Race/ethnicity						
White, %	2539 (39%)	524 (32%)	621 (38%)	655 (40%)	739 (45%)	<0.001
Chinese, %	795 (12%)	192 (12%)	214 (13%)	194 (12%)	195 (12%)	
Black, %	1777 (27%)	485 (30%)	444 (27%)	432 (26%)	416 (25%)	
Hispanic, %	1431 (22%)	435 (27%)	356 (22%)	355 (22%)	285 (17%)	
Diabetes mellitus	809 (12%)	203 (12%)	201 (12%)	175 (11%)	230 (14%)	0.03
Current smoking	843 (13%)	274 (17%)	218 (13%)	199 (12%)	152 (9%)	<0.001
Education						
High school or less (%)	2314 (36%)	527 (32%)	606 (37%)	576 (35%)	605 (37%)	0.004
Some college (%)	1174 (18%)	333 (21%)	324 (20%)	289 (18%)	228 (14%)	
College degree or more (%)	3032 (46%)	769 (47%)	701 (43%)	764 (47%)	798 (49%)	
Body mass index (kg/m ²)	28±5.5	27.8±5.4	27.9±5.2	28.5±5.4	29±5.6	<0.001
SBP, mm Hg	126±22	125±22	125±21	126±21	129±22	<0.001
HTN medication	2400 (37%)	511 (31%)	534 (33%)	583 (36%)	772 (47%)	<0.001
Estimated GFR, mL/min per 1.73 m ²	81±18	87±17	83±20	81±17	75±18	<0.001
LV mass (g) (n=4827)	120±29	116±28	120±29	121±30	124±31	<0.001

Values are mean±SD. FGF-23 indicates fibroblast growth factor-23; GFR, glomerular filtration rate; HTN, hypertension; SBP, systolic blood pressure; Smoking, current and former vs never; LV mass, left ventricular mass.

concentration was associated with an estimated 29% greater risk of incident HFpEF (hazard ratio [HR] 1.29; 95% confidence interval, 1.08–1.54, *P* value 0.001) (Table 2). In contrast, serum FGF-23 concentrations were not associated with HFrEF events in fully adjusted analyses. In quartiles analyses, the risk of incident HF was significantly higher in the highest quartile compared with the lowest quartile of FGF-23 (HR 1.51; 95% confidence interval, 1.00–2.30) (Table 2). While similar results were observed for HFpEF with higher FGF-23 quartiles (HR 1.85; 95% confidence interval, 1.03–3.33), there was no significant association with HFrEF (HR 1.25; 95% confidence interval, 0.72–2.17). There was a trend toward an association of FGF-23 with unclassified HF events that was attenuated in fully adjusted models (Table S1).

In sensitivity analyses, we evaluated the association between serum FGF-23 and HFpEF for the subset of participants with measured LV mass at baseline (N=4827) after adjustment for Model 4 used in the main analysis, then after additional adjustment for LV mass (Table S2). Greater FGF-23 concentrations (per 20 pg/mL higher) still remained statistically significantly associated with HFpEF risk even after

accounting for LV mass (HR 1.28, 95% confidence interval, 1.02–1.62).

Additionally, we observed similar results using time-updated covariates (Table S3).

In final sensitivity analysis looking at the complete case analysis by HF type, we found similar results (Table S4).

Discussion

In summary, we found higher serum FGF-23 concentrations to be associated with HFpEF events, but not HFrEF events, in a large, multiethnic population that was initially free of clinical cardiovascular disease. Associations were observed for adjudicated HF events and HF type over long-term follow-up and included adjustment for relevant comorbid conditions and other potential confounding characteristics. Associations of FGF-23 and HFpEF remained significant even after accounting for differences in LV mass. These findings suggest that FGF-23 is a novel risk factor for HFpEF in the general population.

FGF-23, a phosphaturic hormone that inhibits 1,25(OH)₂ (activated) vitamin D production, has been associated with a

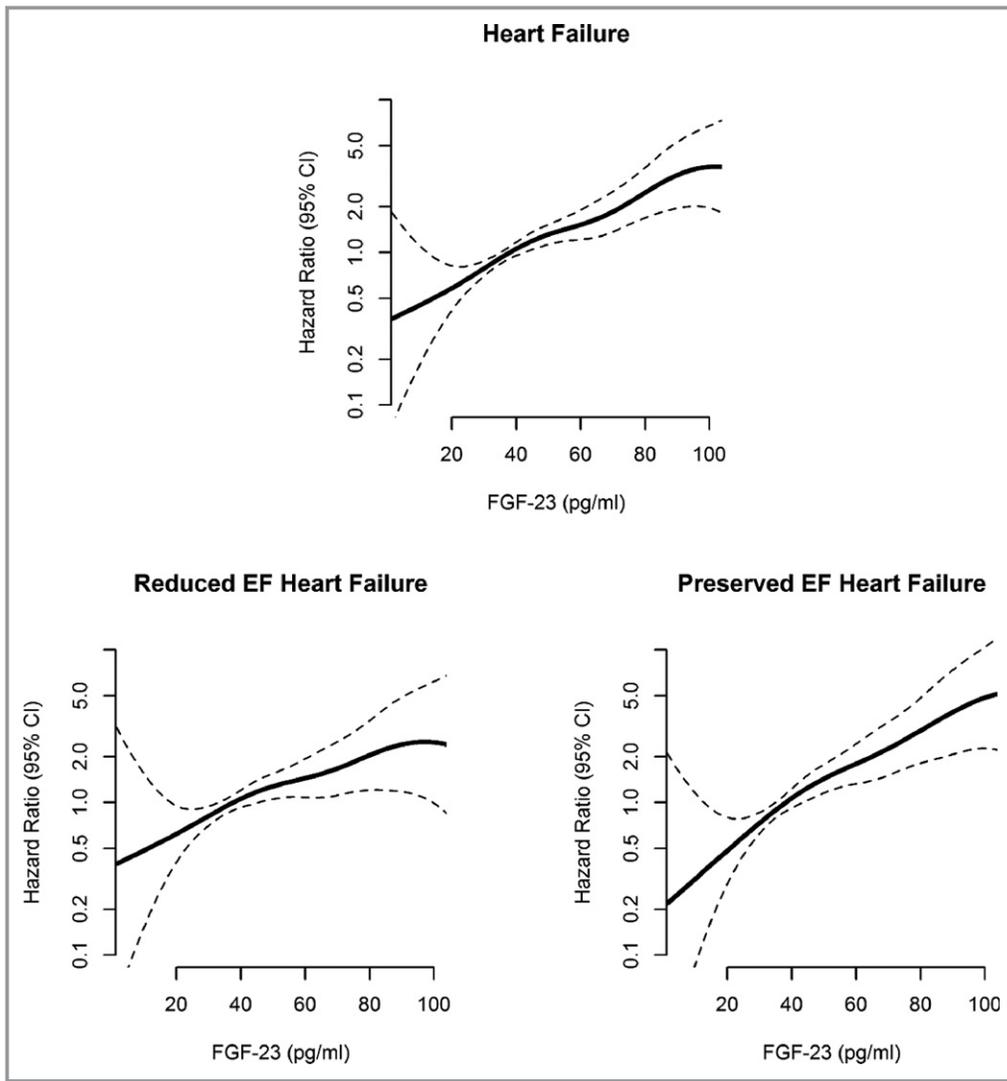


Figure 2. Hazard ratios of FGF-23 for incident HF, HFrEF, and HFpEF using restricted cubic spline Cox model analysis: The Multiethnic Study of Atherosclerosis. CI indicates confidence interval; FGF-23, fibroblast growth factor-23; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

wide range of cardiovascular outcomes, particularly among patients who have chronic kidney disease. Specific associations have been reported for incident hypertension, LVH, incident HF, higher coronary calcium scores, and incident coronary heart disease.^{17,19,27,28} In this study we confirmed previous findings reported by Kestenbaum et al linking serum FGF-23 to incident HF, and further studied the association with subtypes of HFpEF and HFrEF.

Potential mechanisms by which FGF-23 could be linked to incident HFpEF include FGF-23 effects on LVH, cardiac remodeling, neurohormonal changes, sodium retention, and myocardial fibrosis. In experimental models, administration of recombinant FGF-23 to mice affects cardiac myocytes directly and induces LVH.^{18,29} FGF-23 exerts a direct stimulatory

effect on the renin-angiotensin-aldosterone system through suppression of angiotensin-converting enzyme-2,³⁰ which suggests an alternative mechanism of the negative cardiovascular outcomes associated with FGF-23. Other mechanisms by which FGF-23 could lead to adverse cardiovascular consequences include calcitriol deficiency, altered phosphorus homeostasis, systemic inflammation and oxidative stress, and sodium retention.^{31–33} Additionally, FGF-23 may down-regulate soluble α -klotho,³⁴ an enzyme with anti-aging effects that was shown to protect the heart against cardiac hypertrophy and cardiac remodeling.^{35,36} In a study by Reindl et al, FGF-23 was significantly higher in patients who developed LV remodeling post ST-segment-elevation myocardial infarction even after adjustment for biomarkers of

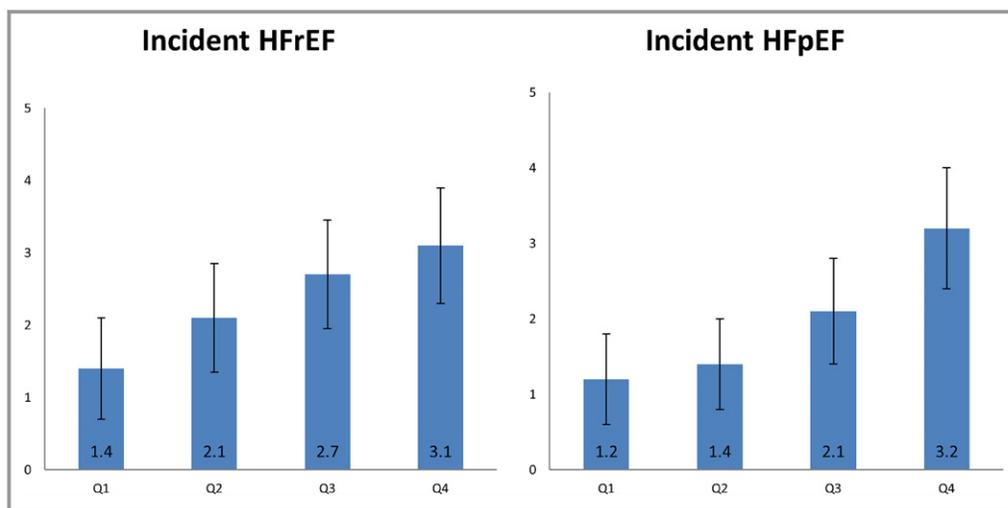


Figure 3. Incidence rates (per 1000 person-years) by FGF-23 quartiles of incident HFrEF and HFpEF: The Multiethnic Study of Atherosclerosis. FGF-23 indicates fibroblast growth factor-23; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

myocardial necrosis, myocardial stress, and inflammation.³⁷ Finally, FGF-23 may promote myocardial fibrosis through upregulation of β -catenin, transforming growth factor- β , procollagen I, and procollagen III, which may exacerbate diastolic dysfunction.³⁸

Several previous reports demonstrated that higher LV mass is associated with greater risk of HF events.^{39–41} In a study by Velagaleti et al, eccentric LVH was associated with higher risk of HFrEF, while concentric LVH was associated with higher risk of HFpEF.³⁹ Furthermore, Seliger et al demonstrated that LVH was associated with higher risk of both types of HF, but especially HFrEF in older adults without prior HF or myocardial infarction in the Cardiovascular Health Study.⁴¹ Our findings of a strong association between higher FGF-23 and higher risk of HFpEF cannot be explained fully by previous observations of the association between FGF-23 and LV mass.^{18,19} In sensitivity analyses we found that the association of FGF-23 and HF remained significant even after adjusting for LV mass, suggesting that other pathological mechanisms could be mediating the association between FGF-23 and the development of HF as mentioned in previous paragraphs. Nonetheless, LV mass measurements were performed on only a single occasion; it remains possible that changes in LV mass could have contributed to the observed association.

In this study, we found no significant association between higher FGF-23 and HFrEF events, while previous studies suggested an association of higher FGF-23 concentrations with lower LVEF.^{42–44} However, these studies showed very modest association with reduced EF. For example, in a study by Agarwal et al, the difference in mean EF between the lowest and highest quartiles of FGF-23 was negligible (62.2% versus 59.7%, respectively) and was still considered as normal

EF.⁴² Furthermore, in a post-kidney transplant cohort, no significant association was found between FGF-23 and LVEF.⁴⁵ Further longitudinal studies are needed to study the significance of these observations.

Several previous studies showed important associations between N-terminal pro B-type natriuretic peptide and incident HF,⁴⁶ atrial fibrillation,⁴⁷ and subclinical cardiovascular disease.⁴⁸ Ndumele et al demonstrated that N-terminal pro B-type natriuretic peptide is a strong predictor of incident HF in individuals with and without obesity.⁴⁶ We demonstrated in this study that FGF-23 is significantly associated with incident HFpEF independent of N-terminal pro B-type natriuretic peptide levels, which suggests that FGF-23 may be a novel predictor of incident HFpEF in the general population.

To our knowledge, this is the first study comparing the associations of FGF-23 with HFrEF and HFpEF. Previous studies examined the association between FGF-23 with EF as a continuous variable. Kestenbaum et al found no significant relationship between FGF-23 and EF.¹⁹ In previous community-based studies, FGF-23 was associated with reduced EF.^{44,49} However, these studies were in participants with chronic kidney disease,⁴⁹ and in a population undergoing elective coronary angiography.⁴⁴ Both of these populations have sicker participants with more cardiovascular risk factors.

Our study has several strengths, including the large, multiethnic, community-based population, which improves the external validity of the study findings. MESA participants were free of clinical cardiovascular disease at baseline, reducing the possibility of confounding by this condition. Participants were followed for more than 10 years for ascertainment of relatively large numbers of incident HF events, which were adjudicated by an expert panel.

Table 2. Associations of FGF-23 and Incident HF, HFrEF, and HFpEF (HRs for Each 20 pg/mL Higher FGF-23 Concentration and Per Quartiles of FGF-23): The Multiethnic Study of Atherosclerosis

	Participants (n)	Events (n)	Model 1	Model 2	Model 3	Model 4
			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Incident HF						
FGF-23						
per 20 pg/L increase	6542	291	1.34 (1.21, 1.48)	1.20 (1.08, 1.35)	1.17 (1.04, 1.32)	1.18 (1.02, 1.37)
Q1	1638	45	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1636	62	1.30 (0.84, 2.01)	1.14 (0.74, 1.77)	1.18 (0.76, 1.83)	1.17 (0.75, 1.80)
Q3	1634	81	1.67 (1.11, 2.52)	1.34 (0.88, 2.03)	1.45 (0.95, 2.21)	1.37 (0.90, 2.08)
Q4	1634	103	2.44 (1.66, 3.61)	1.72 (1.15, 2.56)	1.68 (1.11, 2.54)	1.51 (1.00, 2.30)
Incident HFrEF						
FGF-23						
per 20 pg/L increase	6542	176	1.33 (1.13, 1.56)	1.25 (1.04, 1.51)	1.13 (0.93, 1.37)	1.04 (0.84, 1.29)
Q1	1638	27	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1636	40	1.40 (0.81, 2.42)	1.26 (0.73, 2.18)	1.32 (0.76, 2.30)	1.29 (0.75, 2.24)
Q3	1634	51	1.56 (0.92, 2.66)	1.31 (0.76, 2.24)	1.40 (0.81, 2.42)	1.26 (0.73, 2.17)
Q4	1634	58	2.22 (1.34, 3.67)	1.65 (0.98, 2.77)	1.50 (0.88, 2.57)	1.25 (0.72, 2.17)
Incident HFpEF						
FGF-23						
per 20 pg/L increase	6542	149	1.48 (1.28, 1.70)	1.36 (1.15, 1.61)	1.31 (1.11, 1.55)	1.29 (1.08, 1.54)
Q1	1638	23	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1636	27	1.17 (0.61, 2.24)	1.01 (0.53, 1.94)	1.06 (0.55, 2.04)	1.05 (0.55, 2.02)
Q3	1634	40	1.90 (1.06, 3.41)	1.46 (0.81, 2.64)	1.59 (0.87, 2.89)	1.51 (0.83, 2.75)
Q4	1634	59	3.00 (1.73, 5.21)	1.96 (1.12, 3.44)	1.99 (1.11, 3.57)	1.85 (1.03, 3.33)

Cox proportional models were used to calculate the HRs for the development of incident HF, HFrEF, and HFpEF with each 20 pg/mL higher serum FGF-23 concentration and again with quartiles of FGF-23. Model 1; unadjusted, Model 2; adjusted for age, sex, race/ethnicity, education, study site, height, and weight; Model 3 adjusted for Model 2 and systolic blood pressure, antihypertensive medications, diabetes mellitus, smoking, C-reactive protein, urine albumin–creatinine ratio, and eGFR_{CKD-EPI}. Model 4 is further adjusted for NT-proBNP, 25(OH) vitamin D, PTH, and phosphate. CI indicates confidence interval; eGFR, glomerular filtration rate; FGF-23, fibroblast growth factor-23; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PTH, parathyroid hormone.

Our study has some limitations. FGF-23 is an individual biomarker within complex pathways of bone and phosphate metabolism. These pathways include other factors that are linked with FGF-23 and could also influence HF development. Furthermore, as we mentioned in the Methods section, diagnosis of HFpEF is sometimes difficult and requires physical examination, assessment of LVEF, LV diastolic function, chest radiograph, and other supportive findings, all of which are subject to potential errors. Thus, potential misclassification of these events cannot be excluded. In some instances, the type of HF could not be determined, reducing study power and potentially inducing misclassification. Finally, relatively few MESA participants had overtly low eGFR values, precluding analyses of associations in a CKD population, in which FGF-23 concentrations are substantially higher. Furthermore, no causal relationships between FGF-23 and HFpEF can be established.

In summary, higher serum FGF-23 concentrations are associated with higher risk of incident HFpEF but not with HFrEF in the MESA.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Associations of FGF-23 and incident unclassified HF (Hazard ratios for each 20 pg/ml higher FGF-23 concentration): The Multi-Ethnic Study of Atherosclerosis.

Model	Incident unclassified HF events	Hazard ratio (95% CI)	P value
Model 1	49	1.28 (0.97-1.68)	0.078
Model 2	49	1.08 (0.77-1.53)	0.649
Model 3	48	1.02 (0.72-1.46)	0.907
Model 4	48	0.91 (0.59, 1.42)	0.683

Cox proportional models were used to calculate the hazards ratios for the development of incident HF, HF_rEF and HF_pEF with each 20 pg/ml higher serum FGF-23 concentration. Model 1; unadjusted, Model 2; adjusted for age, sex, race/ethnicity, education, study site, height and weight Model 3 adjusted for model 2 and systolic blood pressure, antihypertensive medications, diabetes mellitus, smoking, C-reactive protein, urine albumin-creatinine ratio and eGFR_{CKD-EPI}.

Table S2. Associations of FGF-23 and incident HFpEF before and after adjustment for LV mass (Hazard ratios for each 20 pg/ml higher FGF-23 concentration): The Multi-Ethnic Study of Atherosclerosis.

Model	Incident HFpEF events	Hazard ratio (95% CI)	P value
Model 4	93	1.31 (1.09, 1.57)	0.033
Model 4 + LV mass	93	1.28 (1.02, 1.62)	0.035

Cox proportional models were used to calculate the hazards ratios for the development of incident HFpEF with each 20 pg/ml higher serum FGF-23 concentration. (Only participants with baseline CMR derived LV mass were included N= 4827). Model 3; adjusted for age, sex, race/ethnicity, education, study site, height, weight, systolic blood pressure, antihypertensive medications, diabetes mellitus, smoking, C-reactive protein, urine albumin-creatinine ratio and eGFR_{CKD-EPI}.

Table S3. Associations of FGF-23 and incident HF, HF_rEF and HF_pEF (Hazard ratios for each 20 pg/ml higher FGF-23 concentration using time-updated covariates): The Multi-Ethnic Study of Atherosclerosis.

		Participants (n)	Events (n)	Model 1	Model 2	Model 3	Model 4
				HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Incident HF							
FGF-23	per 20 pg/L increase	6542	291	1.34 (1.21, 1.48)	1.22 (1.10, 1.35)	1.14 (1.01, 1.29)	1.17 (1.01, 1.35)
Incident HF_rEF							
FGF-23	per 20 pg/L increase	6542	176	1.28 (1.11, 1.48)	1.17 (1.02, 1.35)	1.07 (0.90, 1.26)	1.02 (0.82, 1.26)
Incident HF_pEF							
FGF-23	per 20 pg/L increase	6542	149	1.44 (1.27, 1.62)	1.27 (1.12, 1.45)	1.18 (1.02, 1.39)	1.25 (1.03, 1.50)

Cox proportional models were used to calculate the hazards ratios for the development of incident HF, HF_rEF and HF_pEF with each 20 pg/ml higher serum FGF-23 concentration and again with quartiles of FGF-23. Model 1; unadjusted, Model 2; adjusted for age, sex, race/ethnicity, education, study site, height and weight; Model 3 adjusted for model 2 and systolic blood pressure, antihypertensive medications, diabetes mellitus, smoking, C-reactive protein, urine albumin-creatinine ratio and eGFR_{CKD-EPI}. Model 4 is further adjusted for NT-proBNP, 25(OH)vitd, PTH and Phosphate.

Table S4. Associations of FGF-23 and incident HFrEF and HFpEF (Hazard ratios for each 20 pg/ml higher FGF-23 concentration using complete case analysis): The Multi-Ethnic Study of Atherosclerosis.

		Participants (n)	Events (n)	Model 1	Model 2	Model 3	Model 4
				HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Incident HFrEF							
FGF-23	per 20 pg/L increase	6542	151	1.37 (1.16, 1.61)	1.31 (1.09, 1.59)	1.20 (0.98, 1.47)	1.13 (0.93, 1.41)
	Q1	1638	19	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Q2	1636	36	1.86 (0.99, 3.48)	1.70 (0.90, 3.18)	1.77 (0.94, 3.33)	1.75 (0.93, 3.30)
	Q3	1634	46	2.10 (1.13, 3.87)	1.79 (0.96, 3.32)	1.91 (1.02, 3.57)	1.78 (0.95, 3.35)
	Q4	1634	50	2.71 (1.49, 4.90)	2.08 (1.14, 3.82)	1.92 (1.03, 3.61)	1.75 (0.92, 3.31)
Incident HFpEF							
FGF-23	per 20 pg/L increase	6542	134	1.48 (1.28, 1.71)	1.37 (1.16, 1.63)	1.32 (1.11, 1.57)	1.31 (1.09, 1.57)
	Q1	1638	22	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Q2	1636	24	1.06 (0.54, 2.10)	0.92 (0.46, 1.82)	0.97 (0.49, 1.92)	0.96 (0.48, 1.91)
	Q3	1634	35	1.90 (1.04, 3.47)	1.46 (0.80, 2.69)	1.59 (0.86, 2.94)	1.53 (0.82, 2.83)
	Q4	1634	53	2.81 (1.58, 4.97)	1.86 (1.04, 3.34)	1.89 (1.03, 3.46)	1.77 (0.96, 3.27)

Model 1; unadjusted, Model 2; adjusted for age, sex, race/ethnicity, education, study site, height and weight; Model 3 adjusted for model 2 and systolic blood pressure, antihypertensive medications, diabetes mellitus, smoking, C-reactive protein, urine albumin-creatinine ratio and eGFR_{CKD-EPI}. Model 4 is further adjusted for NT-proBNP, 25(OH)vitd, PTH and Phosphate.