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Impact of Race, Ethnicity, and Multimodality Biomarkers on the Incidence of New Onset Heart Failure with Preserved Ejection Fraction (From the Multi-Ethnic Study of Atherosclerosis [MESA])

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a prevalent condition with no established prevention or treatment strategies. Furthermore, the pathophysiology and predisposing risk factors for HFpEF are incompletely understood. Therefore we sought to characterize the incidence and determinants of HFpEF in the multi-ethnic study of atherosclerosis (MESA). Our study included 6,781 MESA participants (White, Black, Chinese, and Hispanic men and women 45–84 years of age, free of baseline cardiovascular disease). The primary endpoint was time to diagnosis of HFpEF (left ventricular ejection fraction < 45%). Multivariable adjusted hazard ratios (HR) with 95% confidence intervals (CI) were calculated to identify predictors of HFpEF. Over median follow-up of 11.2 years (10.6 – 11.7), 111 individuals developed HFpEF (cumulative incidence 1.7%). Incidence rates were similar across all races/ethnicities. Age (HR 2.3 [1.7–3.0]), hypertension (HR 1.8 [1.1 – 2.9]), diabetes (HR 2.3 [1.5–3.7]), BMI (HR 1.4 [1.1–1.7]), left ventricular hypertrophy by electrocardiography (HR 4.3 [1.7–11.0]), interim MI (HR 4.8 [2.7–8.6]), elevated NT-proBNP (HR 2.4 [1.5–4.0]), detectable troponin T (HR 4.5 [1.9–10.9]), and left ventricular mass index by MRI (1.3 [1.0–1.6]) were significant predictors of incident HFpEF. Worsening renal function, inflammatory markers, and coronary artery calcium were significant univariate, but not multivariate predictors of HFpEF. Gender was neither a univariate nor multivariate predictor of HFpEF. In conclusion, we demonstrate several risk factors and

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biomarkers associated with incident HFpEF that were consistent across different racial/ethnic groups, and may represent potential therapeutic targets for the prevention and treatment of HFpEF.

Keywords

Heart Failure with Preserved Ejection Fraction; Risk Factors

Heart failure with preserved ejection fraction (HFpEF) is an increasingly prevalent condition associated with significant morbidity and mortality (1–3). In contrast to heart failure with reduced ejection fraction (HFrEF), there are currently no evidenced-based therapies approved for the treatment of HFpEF (2,3), and several recent trials (4–8) have all had negative outcomes. Because of the lack of effective therapies for such a prevalent condition, a multidisciplinary group from the Food and Drug Administration, academia, and industry released a document underscoring the need for additional research to better understand the pathophysiology of new onset HFpEF (3). The identification of risk factors has the potential to elucidate mechanisms of disease and to highlight possible targets for disease prevention. Although prior epidemiologic studies have described the prevalence, comorbidities, and outcomes associated with HFpEF, little is known about the risk factors associated with incident HFpEF. Furthermore, the few studies that have described risk factors for HFpEF have been from ethnically homogeneous Caucasian populations (9,10). Thus even less is known about the incidence and risk factors for new onset HFpEF in people from other racial/ethnic backgrounds. Therefore, we sought to characterize the incidence and risk factors associated with new onset HFpEF among individuals from various racial/ethnic groups in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

MESA is a prospective observational cohort of 6,814 men and women aged 45–84 years who were free of known cardiovascular disease at time of enrollment. Individuals from different racial/ethnic backgrounds (White, Black, Hispanic, and Chinese) were enrolled between July 2000 and September 2002 at six different field centers in the USA (Baltimore; Chicago; Forsyth County, North Carolina; Los Angeles; New York City; and St. Paul, Minnesota). Full details of the MESA study design have been published previously (11). The study was approved by the institutional review board of each site, and all participants gave written informed consent. Of the total population, 33 individuals were missing necessary covariates, and were therefore excluded from the overall analysis, resulting in a final study population of 6,781 participants.

At the initial examination, staff at each center collected baseline information on demographics, medical history, and cigarette use. Blood pressure, anthropometric measurements, electrocardiograms (ECGs), and laboratory data were obtained as previously described (11). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, or medical treatment for hypertension. Diabetes was defined as fasting plasma glucose > 126 mg/dL or a history of medical treatment for diabetes. Interim myocardial infarction (MI) was defined as an MI (diagnosed

by combination of symptoms, ECG findings, and levels of cardiac biomarkers) that occurred during follow up prior to the diagnosis of heart failure.

Estimated glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (12). Serum inflammatory markers, high sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6, were measured as part of the baseline examination. HsCRP was measured using the BNII nephelometer (Dade-Behring Inc., Deerfield, IL), and IL-6 was measured by ELISA (Quantikine HS Human IL-6 Immunoassay, R&D Systems, Minneapolis, Minnesota). A subgroup of 5,569 individuals had baseline measurements of NT-proBNP and troponin T measured by Elecsys immunoassay (Roche Diagnostics Corporation, Indianapolis, IN).

All participants underwent coronary artery calcium (CAC) scoring as part of the baseline examination. Details regarding the methods for scanning and interpretation have been reported previously (13). Each of the six centers measured CAC with either a cardiac-gated electron-beam CT scanner (Chicago, Los Angeles, New York), or a multi-detector CT (Baltimore, Forsyth County, St. Paul). Individuals were scanned twice and mean CAC (Agatston) score was used for all analyses (14). Images were interpreted at the MESA CT reading center (Los Angeles Biomedical Research Institute, Torrance, CA).

A subgroup of 4,980 individuals underwent baseline cardiac MRI using 1.5T magnetic resonance scanners for the determination of left ventricular (LV) mass as has been previously described (15). Briefly, the endocardial and epicardial borders were contoured using a semi-automated method. The difference between the epicardial and endocardial 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. The LV mass index was defined as LV mass divided by body surface area.

Individuals were followed for a median of 11.2 years (Interquartile range [IQR]: 10.6 – 11.7 years). An interviewer contacted each participant or family member by telephone at 9–12 month intervals to inquire about interim hospital admissions, outpatient cardiovascular diagnoses, and deaths. MESA obtained medical records for approximately 98% of hospital events and 95% of outpatient diagnoses. Two physicians from the MESA mortality and morbidity review committee independently classified events. In the event of disagreement, the full committee made the final classification.

The primary outcome of this study was time to new diagnosis of heart failure (HF), defined as a first HF event. HF was an adjudicated event in MESA requiring symptoms such as shortness of breath or edema, a physician diagnosis of HF, and documented medical treatment for HF. Individuals with an adjudicated diagnosis of HF were included in this analysis if they had an evaluation of left ventricular ejection fraction (LVEF) by echocardiography at the time of HF diagnosis that could be obtained from review of medical records. Each new HF diagnosis was categorized as either HFpEF (LVEF ≥ 45%) or HFrEF (LVEF < 45%) as has been previously described (7,9).

Baseline characteristics were reported according to three categories: Individuals who developed HFpEF, individuals who developed HFrEF, and those who did not develop HF.

Continuous variables were reported as mean (standard deviation [SD]) for normally distributed data, and as median (Interquartile Range [IQR]) for right-skewed data including hsCRP and IL-6. For the subgroup of individuals who had baseline measures of NT-proBNP, individuals were categorized as being above or below the 75th percentile (112 pg/mL), which has previously been shown within MESA to be a robust cut point for predicting incident HF (15). The subgroup of individuals with baseline measurements of troponin T were categorized as having detectable or undetectable levels (<0.01).

The cumulative incidence of HFpEF was described using Kaplan-Meier estimates. Proportional hazards regression models were used to evaluate the association between baseline characteristics and incident HFpEF. The Fine-Gray model was used to account for competing risk of death or developing HFpEF (16). The association between interim MI and new onset HFpEF was analyzed by including interim MI as a time-varying covariate into the existing model. Variables which reached significance in univariate analysis ($p < 0.05$) were carried forward into multivariable-adjusted models (adjusted for all covariates which reached significance in the univariate analysis plus the following; gender, race/ethnicity, socioeconomic status [based on level of education], and MESA site). Hazard ratios (HR) with 95% confidence intervals (CI) were calculated per increase in SD for continuous variables, and for change in classification of binary variables. To calculate the HR associated with each racial/ethnic group, the risk of HFpEF in White individuals was used as reference. HRs for hsCRP and IL-6 were calculated using log transformation.

Since NT-proBNP and troponin T were not available in the entire population, they were not entered into the main multivariate model. Instead, univariate and multivariate adjusted HRs for NT-proBNP and troponin T were calculated in a separate but similar model (adjusting for age, gender, race/ethnicity, socioeconomic status, MESA site, and all covariates which reached significance in the univariate analysis) for the 5,569 individuals who had these baseline measures.

Similarly, cardiac MRI was not performed in the entire population, and only 4,980 individuals had LV mass index and the necessary covariates for our study. Therefore, LV mass index was not included in the main multivariate model. The association between LV mass index and incident HFpEF was evaluated in a separate univariate and multivariate adjusted model (adjusted for age, gender, race/ethnicity, socioeconomic status, MESA site, and all covariates which reached significance in the univariate analysis) for the subgroup of individuals who underwent baseline MRI.

To further characterize the relationship between race/ethnicity and incident HFpEF, baseline characteristics for individuals who developed HFpEF were presented according to race/ethnicity. To evaluate for potential effect modification by race/ethnicity for each of the significant multivariate predictors, we included a corresponding interaction term for each individual race/ethnicity with the significant multivariate predictors. A p -value < 0.05 was considered statistically significant. All analyses were performed using Stata version 12 (StataCorp LP, College Station, TX, USA).

Results

In total 257 individuals developed incident HF, of whom 39 did not have a recorded LVEF at the time of diagnosis. Individuals with and without documented LVEF at the time of new HF diagnosis had similar baseline characteristics. Of the 218 individuals with known LVEF at the time of new HF diagnosis, 111 had HFpEF and 107 had HFrEF (supplemental figure 1). Median LVEF in the HFpEF group was 57% (52–63), whereas median LVEF in the HFrEF group was 33% (26–37). Figure 1 demonstrates the distribution of LVEF for the overall cohort at the time of HF diagnosis. The distribution of LVEF among individuals with HFpEF is shown in supplemental figure 2. Baseline characteristics according to HFpEF, HFrEF, or no HF are presented in table 1. The median time to diagnosis of HFpEF was 6.6 (3.3–8.8) years with a cumulative incidence of 1.7%. Figure 2 demonstrates the cumulative incidence of new onset HFpEF. When stratified by race/ethnicity, the cumulative incidence of HFpEF was similar across groups (White = 2.0%, Chinese = 1.5%, Black = 1.3%, Hispanic = 1.7%, $p = 0.369$), and there was no difference in time to new onset HFpEF ($p=0.8779$), as shown in the Kaplan-Meier plot (figure 3).

Unadjusted and multi-variable adjusted HRs for demographic, clinical, and biomarker predictors of incident HFpEF are shown in table 2. After multivariable adjustment, the following demographic and clinical characteristics remained significant predictors of HFpEF: Age (HR 2.3 [1.7–3.0]), hypertension (HR 1.8 [1.1 – 2.9]), diabetes (HR 2.3 [1.5–3.7]), BMI (HR 1.4 [1.1–1.7]), and interim MI (HR 4.8 [2.7–8.6]). The following markers were also significant predictors of HFpEF after multivariate adjustment: Left ventricular hypertrophy (LVH) by electrocardiography (ECG) (HR 4.3 [1.7–11.0]), elevated NT-proBNP (HR 2.4 [1.5–4.0]), detectable troponin T (HR 4.5 [1.9–10.9]), and LV mass index by MRI (1.3 [1.0–1.6]). Increased heart rate, worsening renal function (GFR), elevated inflammatory markers (CRP, IL-6), and presence of coronary artery calcification ($CAC > 0$) were all significant univariate predictors that were no longer significant after multivariable adjustment. Female gender was not associated with an increased risk of HFpEF in either univariate or multivariate adjusted models.

In the unadjusted model, Black individuals had a non significant trend toward lower risk of HFpEF compared to white individuals (HR 0.7 [0.4 – 1.1]), which was significant after multivariable adjustment (HR 0.5, [0.3 – 0.8]).

To better characterize the risk of HFpEF by race/ethnicity, we compared baseline characteristics of individuals who developed incident HFpEF according to racial/ethnic group. As shown in table 3, the different ethnic groups had relatively similar baseline characteristics with a few notable exceptions including BMI, $CAC > 0$, detectable troponin T, and diabetes. The proportion of black and Hispanic individuals with diabetes (58% and 50% respectively) was markedly higher than the proportion of White and Chinese individuals with diabetes (12% and 25% respectively). Although a similar trend was seen in the general population with Black and Hispanic subjects having higher rates of diabetes (18% each versus 6% and 13% for white and Chinese subjects respectively), the disparities were far greater among individuals who went on to develop HFpEF. Statistical testing revealed no interaction between race/ethnicity and the effect of diabetes on incident HFpEF.

The small number of individuals with LVH and detectable troponin T limited our ability to perform interaction testing between race/ethnicity and the impact of these two risk factors on incident HFpEF. However, interaction testing between race/ethnicity and the effect of the remaining clinical risk factors on incident HFpEF showed that race/ethnicity did not modify the effect of the other risk factors on incident HFpEF.

Several of the multivariate predictors for new onset HFpEF were also significant predictors for new onset HFrEF (table 4). Age, hypertension, diabetes, interim MI, elevated NT-proBNP, and LV mass index were shared predictors of HFpEF and HFrEF. Whereas BMI, LVH by ECG, and detectable troponin T were uniquely associated with an increased risk of HFpEF, but not HFrEF. After multivariable adjustment, Black race was associated with a lower risk of HFpEF, whereas there was no significant relationship between Black race and HFrEF. Although gender had no effect on incident HFpEF, female gender was associated with a significantly lower risk of HFrEF. Heart rate, tobacco use, and renal function were also uniquely associated with HFrEF, and had no independent effect on HFpEF.

A sensitivity analysis was performed using an LVEF $\geq 50\%$ as the cutoff for defining HFpEF. The number of patients in the HFpEF group decreased from 111 to 96, and the median LVEF increased from 57% (52–63) to 60% (55–64). Overall results were similar; however LV mass index, LVH by ECG, and hypertension were no longer significant predictors (supplemental table 1).

Discussion

In this large multi-ethnic cohort, we have identified that age, hypertension, diabetes, BMI, interim MI, LVH by ECG, elevated NT-proBNP, detectable Troponin T, and elevated LV mass index were all associated with increased risk for HFpEF, whereas female gender was not. Notably, the incidence of HFpEF did not differ according to race/ethnicity, and the effect of the other clinical risk factors on incident HFpEF was not modified by race/ethnicity.

This current analysis validates previously established risk factors (older age, diabetes, increasing BMI, elevated NT-proBNP and high sensitivity troponin T [hs-TNT]), and identifies additional risk factors that have not previously been shown to predict HFpEF (hypertension, interim MI, LVH by ECG, and elevated LV mass index on MRI) (9,10,17). Similar to an analysis from the Framingham Heart Study (9), we have shown that female gender is not associated with an increased risk of HFpEF. Although cross-sectional studies characterizing individuals at the time of HFpEF diagnosis have suggested that individuals with HFpEF were more likely to be women (18,19), it is important to note that these were not longitudinal studies, and the association may reflect that women have a lower risk of developing HFrEF than men (9).

In our analysis, interim MI was a significant predictor of incident HFpEF, which was not seen in prior HFpEF cohorts (9,10). It is worth noting however, that in these cohorts, prior MI was associated with non-significant trends towards increased risk of HFpEF. Furthermore, although post MI HF has historically been thought of as HFrEF, over the last

two decades the proportion of post MI HF patients presenting with preserved EF has increased, suggesting a possible shift in this landscape (20). A recent analysis from Olmsted County demonstrated that nearly 40% of patients with post MI HF have HFpEF (21).

A key strength of our study is the inclusion of multiple racial/ethnic groups in the MESA cohort. We demonstrate that there was no difference in cumulative incidence or time to new onset HFpEF according to race/ethnicity. Although when stratified by race/ethnicity there were minor differences in baseline characteristics among those who developed HFpEF, there was no significant interaction between race/ethnicity and any risk factors. While these data suggest that the risk factors for HFpEF are similar with comparable effects across ethnic groups, the number of events in each racial/ethnic group was relatively small, thus limiting power to detect subtle differences.

Beyond specific risk factors, we also demonstrate that inflammation may play a role in the pathogenesis of HFpEF. Recent work has led to the hypothesis that comorbidities lead to diffuse systemic inflammation and ultimately microvascular endothelial inflammation which plays a central role in the pathogenesis of HFpEF (22). In our analysis, inflammatory markers IL-6 and CRP were significant univariate predictors of HFpEF. IL-6 had a particularly strong association with a greater than 2-fold increased risk of developing HFpEF. Although these markers were no longer significant predictors after multivariate adjustment, this may be due to the fact that these inflammatory markers are part of the causal pathway for other risk factors associated with new onset HFpEF. Adjustment for these pro-inflammatory risk factors (i.e. hypertension and diabetes) may have attenuated the association between inflammation and new onset HFpEF. Further supporting the role of inflammation in HFpEF, a small pilot study used short term anti-inflammatory therapy with IL-1 blockade in patients with HFpEF, which resulted in reduced inflammation and improved exercise capacity (23). Whether interventions aimed at reducing inflammation could be used to prevent HFpEF in select high risk patients remains to be tested.

Given the lack of effective therapies for treating overt HFpEF, coupled with the rising incidence of disease, prevention seems paramount. Our study highlights the relevance of key risk factors in the development of HFpEF; identifying individuals at risk is a significant first step towards prevention. In addition to standard clinical risk factors, the use of biomarkers such as NT-proBNP and troponin T could further highlight the individuals at significant risk, and thus most likely to benefit from aggressive preventive therapy (24). The St. Vincent's screening to prevent heart failure (STOP-HF) study demonstrated that screening patients with BNP, coupled with more aggressive up-titration of specific therapies (such as inhibition of renin-angiotensin-aldosterone), reduced the risk of LV dysfunction and symptomatic heart failure (25). Furthermore, the identification of individuals at increased risk may result in improved adherence to pharmacologic and lifestyle interventions (24, 25).

This study has limitations that warrant acknowledgement. Although the diagnosis of HF was a pre-specified adjudicated event in MESA, the required LVEF $\geq$ 45% (at the time of HF diagnosis) was obtained from chart review. While the echocardiographic images were not evaluated by a centralized core lab, this is the same process employed by prior studies evaluating predictors of incident HFpEF (9,10). Additionally, 15% of individuals who

developed HF did not have a documented LVEF at the time of diagnosis and were thus excluded. Although we cannot exclude bias, these individuals were similar to those with a documented LVEF, and the proportion of individuals without documented LVEF is comparable to that seen in prior cohorts (9,10,17). Finally, the small number of accrued events may limit power, specifically regarding subgroup analyses and interaction testing by race/ethnicity. Given the small number of events, it is difficult to discern whether the results of the sensitivity analysis (using an LVEF cutoff of 50%) truly reflect a difference in pathophysiology versus inadequate power. Similar limitations exist for detecting a difference in risk according to gender. Although the small number of events is an important limitation, it is worthwhile to note that this is the largest multi-ethnic cohort evaluating longitudinal risk factors for incident HFpEF.

In conclusion, we have identified several clinical risk factors and multimodality biomarkers associated with new onset HFpEF. Our results also suggest that the incidence of HFpEF is similar across racial/ethnic groups. The identification of risk factors and biomarkers has important implications for potential prevention strategies in a disease with no effective treatment options. Whether aggressive risk factor modification (through lifestyle intervention and pharmacotherapy), or modifying specifically targeted pathways (such as inflammation) will reduce the risk of developing incident HFpEF remains to be tested in dedicated randomized controlled trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Distribution of LVEF at the time of Heart Failure diagnosis

Figure 1. Distribution of Left Ventricular Ejection Fraction (LVEF) among individuals with new onset Heart Failure

Cumulative incidence of HFpEF

Figure 2.
Cumulative incidence of Heart Failure with Preserved Ejection Fraction (HFpEF)

Cumulative incidence of HFpEF by ethnicity

Figure 3. Cumulative incidence of Heart Failure with Preserved Ejection Fraction (HFpEF) according to race/ethnicity

Table 1

Baseline Characteristics

	HFpEF N = 111	HFrEF N = 107	No HF N = 6524
Demographics			
Age (years)	70 (± 9)	67 (± 9)	62 (± 10)
Female	54 (48.7%)	30 (28%)	3,480 (53.3%)
Race/Ethnicity			
White	51 (46%)	42 (39.3%)	2,507 (38.4%)
Chinese	12 (10.8%)	1 (0.9%)	784 (12%)
Black	24 (21.6%)	44 (41.1%)	1,799 (27.6%)
Hispanic	24 (21.6%)	20 (18.7%)	1,434 (22%)
Clinical Characteristics			
Heart Rate (beats per minute)	65 (± 10)	65 (± 11)	63 (± 10)
Systolic Blood Pressure (mm Hg)	140 (± 24)	136 (± 22)	126 (± 21)
Hypertension	81 (73%)	77 (72%)	2,860 (43.8%)
Antihypertensive medication use	68 (61.3%)	64 (59.8%)	2,370 (36.3%)
Body mass index (kg/m ²)	29.8 (± 5.8)	29.2 (± 5.4)	28.3 (± 5.5)
Diabetes	35 (31.5%)	30 (28%)	772 (11.9%)
Current Smoking	13 (11.7%)	21 (19.6%)	847 (13%)
Total Cholesterol (mg/dL)	186 (± 34)	188 (± 35)	194 (± 36)
HDL Cholesterol (mg/dL)	49 (± 15)	48 (± 13)	51 (± 15)
eGFR (ml/min)	71 (± 18)	70 (± 20)	78 (± 16)
CRP (mg/L)	2.7 (1.1–6.0)	3.2 (1.2–5.9)	1.9 (0.8–4.2)
IL-6 (pg/mL)	1.6 (1.1–2.8)	1.4 (0.9–2.3)	1.2 (0.8–1.9)
LVH by ECG	5 (4.6%)	5 (4.7%)	55 (0.85%)
CAC > 0	77 (69.4%)	79 (73.8%)	3,193 (48.9%)
Interim MI	16 (14.4%)	12 (11.2%)	140 (2.2%)
NT-proBNP > 75 th percentile *	55 (59.8%)	51 (62.2%)	1,269 (23.7%)
Detectable Troponin T *	12 (13%)	9 (11%)	58 (1.1%)
LV mass index (g/m ²) **	111.0 (± 23.2)	129.7 (± 31.3)	103.5 (± 18.0)

* Available in a subset of the population (5,569 individuals);

** Available in a subset of the population (4,980 individuals)

Table 2

Risk factors for incident HFpEF

	Unadjusted HR (95% CI)	p-value	multivariable adjusted HR (95% CI)	p-value
Demographics				
Age (per SD)	2.33 (1.91–2.86)	<0.001	2.27 (1.72–3.01)	<0.001
Female	0.84 (0.58–1.22)	0.369	0.89 (0.54–1.46)	0.638
Race/Ethnicity				
White	Ref (–)	--	Ref (–)	--
Chinese	0.79 (0.42–1.47)	0.454	1.53 (0.64–3.67)	0.337
Black	0.69 (0.42–1.12)	0.132	0.46(0.26–0.82)	0.009
Hispanic	0.87 (0.54–1.41)	0.576	0.66 (0.34–1.30)	0.231
Clinical Characteristics				
Heart Rate (per SD)	1.26 (1.05–1.50)	0.012	1.11 (0.92–1.36)	0.279
Hypertension	3.44 (2.26–5.23)	<0.001	1.81 (1.14–2.90)	0.013
Body mass index (per SD)	1.27 (1.09–1.49)	0.002	1.35 (1.08–1.68)	0.009
Diabetes	3.42 (2.29–5.11)	<0.001	2.33 (1.47–3.71)	<0.001
Current Smoking	0.91 (0.51–1.62)	0.743	--	--
Total Cholesterol (per SD)	0.79 (0.65–0.97)	0.023	0.94 (0.76–1.16)	0.555
HDL Cholesterol (per SD)	0.86 (0.69–1.06)	0.151	--	--
eGFR (per SD)	1.51 (1.25–1.84)	<0.001	0.92 (0.72–1.17)	0.508
CRP (per log SD)	1.27 (1.09–1.49)	0.003	1.17 (0.93–1.46)	0.177
IL-6 (per log SD)	2.15 (1.64–2.80)	<0.001	1.32 (0.91–1.93)	0.147
LVH by ECG	5.00 (2.01–12.44)	0.001	4.33 (1.70–11.04)	0.002
CAC > 0	2.35 (1.57–3.51)	<0.001	0.91 (0.54–1.51)	0.702
Interim MI	6.66 (3.91–11.34)	<0.001	4.80 (2.67–8.62)	<0.001
NT-proBNP > 75 th percentile *	4.65 (3.07–7.03)	<0.001	2.41 (1.45–4.00)	0.001
Detectable Troponin T *	11.55 (6.24–21.39)	<0.001	4.52 (1.88–10.87)	0.001
LV mass index (per SD) **	1.36 (1.13–1.64)	0.001	1.29 (1.04–1.60)	0.018

* Available in a subset of the population (5,569 individuals);

Available in a subset of the population (4,980 individuals)

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Table 3

Baseline characteristics of individuals who developed incident HFpEF according to race/ethnicity

	White n = 51	Chinese n = 12	Black n = 24	Hispanic n = 24	p-value
Demographics					
Age (years)	71 (±7)	71 (±10)	67 (±10)	69 (±9)	0.16
Female	21 (41.2%)	9 (75%)	15 (62.5%)	9 (37.5%)	0.057
Clinical Characteristics					
Systolic Blood Pressure (mm Hg)	136 (±22)	141 (±23)	148 (±25)	140 (±25)	0.223
Hypertension	36 (70.6%)	8 (66.7%)	21 (87.5%)	16 (66.7%)	0.328
Body mass index (kg/m ²)	29.5 (±5.7)	25.4 (±2.8)	30.6 (±4.8)	31.9 (±7.0)	0.011
Diabetes	6 (11.8%)	3 (25%)	14 (58.3%)	12 (50%)	<0.001
Current Smoking	6 (11.8%)	0 (0%)	5 (20.8%)	2 (8.3%)	0.285
Total Cholesterol (mg/dL)	188 (±33)	180 (±31)	183 (±36)	190 (±38)	0.81
HDL Cholesterol (mg/dL)	50 (±16)	49 (±11)	50 (±16)	46 (±12)	0.68
eGFR (ml/min)	71 (±15)	75 (±18)	74 (±20)	67 (±22)	0.469
CRP (mg/L)	2.4 (1.1–4.6)	1.9 (1.0–3.2)	4.8 (1.1–14.1)	4.0 (1.8–7.0)	0.0849
IL-6 (pg/mL)	1.5 (1.1–2.7)	1.5 (0.9–1.8)	2.4 (1.3–3.0)	2.1 (1.1–3.8)	0.1064
LVH by ECG	2 (4.1%)	0 (0%)	2 (8.3%)	1 (4.2%)	0.709
CAC > 0	37 (72.6%)	12 (100%)	12 (50%)	16 (66.7%)	0.02
Interim MI	6 (11.8%)	3 (25%)	3 (8.3%)	5 (20.8%)	0.407
NT-pro-BNP > 75 th percentile [*]	26 (57.8%)	6 (54.6%)	10 (71.4%)	13 (59.1%)	0.802
Detectable Troponin T [*]	3 (6.7%)	0 (0%)	2 (14.3%)	7 (31.8%)	0.018
LV mass index (g/m ²) ^{**}	107.4 (±18.3)	109.9 (±19.5)	115.6 (±31.9)	116.7 (±27.5)	0.5854

^{*} Available in a subset of the population (92 individuals);^{**} Available in a subset of the population (62 individuals)

Table 4

Risk factors for incident HF-rEF

	Unadjusted HR (95% CI)	p-value	multivariable adjusted HR (95% CI)	p-value
Demographics				
Age (per SD)	1.72 (1.44–2.07)	<0.001	1.30 (1.00–1.70)	0.048
Female	0.34 (0.23–0.53)	<0.001	0.34 (0.21–0.56)	<0.001
Race/Ethnicity, %				
White	Ref (–)	--	Ref (–)	--
Chinese	0.08 (0.01–0.58)	0.013	0.14 (0.02–1.00)	0.05
Black	1.54 (1.01–2.35)	0.044	1.56 (0.95–2.56)	0.08
Hispanic	0.88 (0.52–1.49)	0.633	0.89 (0.45–1.76)	0.738
Clinical Characteristics				
Heart Rate (per SD)	1.26 (1.04–1.53)	0.019	1.25 (1.03–1.51)	0.022
Hypertension	3.26 (2.14–4.97)	<0.001	2.04 (1.23–3.36)	0.003
Body mass index (per SD)	1.15 (0.98–1.35)	0.083	--	--
Diabetes	2.87 (1.88–4.38)	<0.001	1.84 (1.13–3.00)	0.014
Current Smoking	1.68 (1.04–2.70)	0.034	2.00 (1.19–3.36)	0.009
Total Cholesterol (per SD)	0.83 (0.68–1.02)	0.083	--	--
HDL Cholesterol (per SD)	0.78 (0.63–0.97)	0.023	1.01 (0.81–1.27)	0.903
eGFR (per SD)	1.60 (1.29–1.99)	<0.001	1.29 (1.04–1.59)	0.019
CRP (per log SD)	1.25 (1.06–1.48)	0.009	1.22 (0.94–1.58)	0.128
IL-6 (per log SD)	1.68 (1.29–2.19)	<0.001	0.94 (0.62–1.43)	0.772
LVH by ECG	5.14 (2.05–12.89)	<0.001	2.84 (0.98–8.19)	0.054
CAC > 0	2.91 (1.89–4.49)	<0.001	1.47 (0.89–2.42)	0.131
Interim MI	4.81 (2.65–8.71)	<0.001	2.56 (1.32–4.97)	0.005
NT-proBNP > 75 th percentile *	5.11 (3.27–7.98)	<0.001	5.00 (2.70–9.25)	<0.001
Detectable Troponin T *	9.09 (4.56–18.11)	<0.001	1.17 (0.45–3.04)	0.742
LV mass index (per SD) **	1.88 (1.59–2.22)	<0.001	1.94 (1.68–2.25)	<0.001

* Available in a subset of the population (5,569 individuals);

Available in a subset of the population (4,980 individuals)
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