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The Association of Obesity and Cardiometabolic Traits With Incident HFpEF and HFrEF

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ABSTRACT

OBJECTIVES This study evaluated the associations of obesity and cardiometabolic traits with incident heart failure with preserved versus reduced ejection fraction (HFpEF vs. HFrEF). Given known sex differences in HF subtype, we examined men and women separately.

BACKGROUND Recent studies suggest that obesity confers greater risk of HFpEF versus HFrEF. Contributions of associated metabolic traits to HFpEF are less clear.

METHODS We studied 22,681 participants from 4 community-based cohorts followed for incident HFpEF versus HFrEF (ejection fraction ≥50% vs. <50%). We evaluated the association of body mass index (BMI) and cardiometabolic traits with incident HF subtype using Cox models.

RESULTS The mean age was 60 ± 13 years, and 53% were women. Over a median follow-up of 12 years, 628 developed incident HFpEF and 835 HFrEF. Greater BMI portended higher risk of HFpEF compared with HFrEF (hazard ratio [HR]: 1.34 per 1-SD increase in BMI; 95% confidence interval [CI]: 1.24 to 1.45 vs. HR: 1.18; 95% CI: 1.10 to 1.27). Similarly, insulin resistance (homeostatic model assessment of insulin resistance) was associated with HFpEF (HR: 1.20 per 1-SD; 95% CI: 1.05 to 1.37), but not HFrEF (HR: 0.99; 95% CI: 0.88 to 1.11; $p < 0.05$ for difference HFpEF vs. HFrEF). We found that the differential association of BMI with HFpEF versus HFrEF was more pronounced among women (p for difference HFpEF vs. HFrEF = 0.01) when compared with men (p = 0.34).

CONCLUSIONS Obesity and related cardiometabolic traits including insulin resistance are more strongly associated with risk of future HFpEF versus HFrEF. The differential risk of HFpEF with obesity seems particularly pronounced among women and may underlie sex differences in HF subtypes. (J Am Coll Cardiol HF 2018;6:701–9)

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CI = confidence interval

HDL = high-density lipoprotein

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HOMA-IR = homeostatic model assessment of insulin resistance

HR = hazard ratio

Heart failure (HF) is a growing public health concern, with increasing incidence and prevalence, that accounts for >1 million admissions per year, affecting nearly 6 million Americans (1). Of individuals with incident HF, approximately one-half have preserved rather than reduced ejection fraction (HFpEF vs. HFrEF), and the prevalence of HFpEF is projected to exceed that of HFrEF in the near future (1–3). Obesity is a known risk factor for the future development of overall HF (4) and is associated with subclinical alterations in systolic and diastolic function cross-sectionally (5).

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Underlying drivers of cardiac remodeling in HFpEF and HFrEF seem at least partially distinct, with obesity postulated as a significant contributor to systemic inflammation leading to myocardial remodeling and resultant HFpEF, specifically (6). An initial study among women supports a greater population-attributable risk of obesity to HFpEF than HFrEF (7). Motivated by these findings, we sought to examine obesity and associated cardiometabolic traits with future HFpEF versus HFrEF by leveraging a unique international collaboration of 4 longitudinal community-based cohorts including both men and women. Specifically, we examined associated traits including abdominal adiposity, insulin resistance, dysglycemia, and dyslipidemia.

Notably, sex differences have been described in the prevalence of obesity, body fat distribution, and energy homeostasis, with a higher prevalence of obesity among women (8). Furthermore, cardiometabolic disease seems to harbor a greater risk of coronary artery disease and hypertension among women than men (9). Although the prevalence of HFpEF is higher among women (8), the role of underlying sex differences in obesity and cardiometabolic dysfunction are unknown. Accordingly, we sought to conduct sex-specific analyses to better understand these differences.

METHODS

STUDY SAMPLE. Participants from 4 community-based cohorts with adjudicated incident HF outcomes were included: 1) the Cardiovascular Health Study (CHS) baseline examination (1989 to 1990; 1992 to 1993 for supplemental African-American cohort); 2) the Framingham Heart Study (FHS) offspring examination 6 (1995 to 1998); 3) the MESA (Multi-Ethnic Study of Atherosclerosis) baseline examination

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(2000 to 2002); and 4) the Prevention of Renal and Vascular Endstage Disease (PREVEND) baseline examination (1997 to 1998) (10–14). Individuals with prevalent HF (n = 321), age <30 years at baseline examination (n = 134), and those with missing covariates (n = 1,640) or missing follow-up (n = 27) were excluded, leaving 22,681 individuals for analysis. Cohort-specific details have been published previously (15).

CLINICAL ASSESSMENT. All participant-level data were harmonized across the 4 cohorts and pooled together. Medical history, physical examination, fasting laboratory assessment, electrocardiography, and waist circumference were collected at the baseline examination. Blood pressure was calculated as the average of 2 seated measurements. Body mass index (BMI) was calculated as weight divided by height squared and expressed as kg/m^2. Diabetes mellitus was defined using 3 criteria: 1) fasting glucose ≥126 mg/dl; 2) random glucose ≥200 mg/dl; or 3) the use of hypoglycemic medications. Modest alcohol use was defined as ≥1 drink per day in both men and women. Electrocardiographic left ventricular hypertrophy was defined based on accepted voltage and ST-segment criteria. Waist circumference was measured in centimeters. Homeostatic model assessment of insulin resistance (HOMA-IR) and triglycerides were log transformed. Metabolic syndrome was defined according to the National Cholesterol Education Program, which includes 3 or more of the 5 following criteria: 1) waist circumference ≥101.6 cm (40 inches, men) or ≥88.9 cm (35 inches, women); 2) triglycerides ≥150 mg/dl or receiving pharmacologic treatment; 3) high-density lipoprotein (HDL) cholesterol ≤40 mg/dl (men) or ≤50 mg/dl (women) or receiving pharmacological treatment; 4) blood pressure ≥130 mm Hg systolic or 85 mm Hg diastolic or receiving pharmacological treatment; and 5) fasting glucose ≥100 mg/dl or receiving pharmacological treatment.

DEFINITION OF INCIDENT HF SUBTYPES. Individuals were prospectively followed for the first occurrence of incident HF or death within 15 years of the baseline examination. Outcomes were adjudicated using established protocols by study investigators after reviewing all hospital and outpatient medical records. HF was defined using a combination of signs and symptoms as previously reported (15). Medical records were reviewed for assessment of left ventricular function at or around the time of the first HF. Each incident HF event was categorized as HFpEF (left ventricular ejection fraction ≥50%), HFrEF (left ventricular ejection fraction <50%), or unclassified (no left ventricular function assessment available). Classification was based on echocardiography in more than 85% of classified HF cases.

STATISTICAL ANALYSIS. Baseline clinical and laboratory covariates were summarized by cohort and in aggregate. In primary sex-pooled analyses, we examined the association of 7 clinical predictors with HF subtype. Cause-specific Cox models were fitted separately for HFpEF and HFrEF, accounting for competing risks of death, other HF subtype, and unclassified HF. Clinical predictors included waist circumference, BMI, waist-to-hip ratio, HOMA-IR, triglyceride-to-HDL ratio, fasting glucose, and systolic blood pressure. For HOMA-IR analyses, we excluded participants with diabetes mellitus. Covariates known to be associated with HF were entered in the multivariable model, including age, systolic blood pressure (except systolic blood pressure analyses), hypertension treatment, diabetes mellitus status, smoking status, prevalent myocardial infarction, total cholesterol, HDL (except HDL analyses), left bundle branch block, and left ventricular hypertrophy. Secondary analyses further adjusted for C-reactive protein and interim myocardial infarction. Hazard ratios (HRs) were reported per pooled SD increase in continuous predictor, and a strata statement was included to specify study cohorts within the analysis. Primary analyses were considered significant using a Bonferroni corrected p value ($p = 0.05/7$ traits tested $= 0.007$).

In secondary analyses, sex-specific Cox models were used to examine the association of clinical predictors with HF subtype and sex*covariate interaction terms tested in sex-pooled analyses. For each clinical predictor, HF subtype-specific coefficients were also compared using the Lunn-McNeil method (16). Cohort-specific analyses were performed, and a random-effects meta-analysis performed to test for potential heterogeneity in the association of BMI with HF subtypes. In exploratory analyses, we examined whether HOMA-IR may act as a mediator in the association of BMI and HFpEF. Furthermore, we examined each of the 5 metabolic syndrome criteria with incident HF subtype using cause-specific Cox models. All statistical analyses were conducted with SAS version 9.4 for Windows (Cary, North Carolina).

RESULTS

Our sample included a total of 22,681 participants from 4 community-based cohorts (23% from CHS, 15% from FHS, 29% from MESA, and 32% from PREVEND). The mean age was 60 ± 13 years, and 53% were women. The mean BMI was 27.1 ± 4.9 kg/m^2, with

TABLE 1 Baseline Clinical and Laboratory Covariates by Cohort

	CHS (n = 5,263)	FHS (n = 3,381)	MESA (n = 6,677)	PREVEND (n = 7,360)	Total (N = 22,681)
Demographics					
Age, yrs	73 ± 6	59 ± 10	62 ± 10	49 ± 12	60 ± 13
Women	3,031 (58)	1,788 (53)	3,521 (53)	3,696 (50)	12,036 (53)
Race					
White	4,456 (85)	3,381 (100)	2,560 (38)	6,992 (95)	17,389 (77)
Black	778 (15)	–	1,838 (28)	65 (1)	2,681 (12)
Other	29 (1)	–	2,279 (34)	248 (3)	2,556 (11)
Clinical covariates					
Systolic blood pressure, mm Hg	136 ± 21	128 ± 19	127 ± 22	129 ± 20	130 ± 21
Heart rate, beats/min	68 ± 11	64 ± 10	63 ± 10	69 ± 10	66 ± 11
Body mass index, kg/m^2	26.7 ± 4.7	27.9 ± 5.1	28.3 ± 5.5	26.1 ± 4.2	27.1 ± 4.9
Waist circumference, cm	94 ± 13	98 ± 14	98 ± 14	88 ± 13	94 ± 14
Hip circumference, cm	102 ± 10	104 ± 10	106 ± 11	100 ± 8	103 ± 10
Hypertension treatment	2,389 (45)	943 (28)	2,478 (37)	999 (14)	6,809 (30)
Diabetes mellitus	816 (16)	326 (10)	841 (13)	271 (4)	2,254 (10)
Current smoker	622 (12)	519 (15)	872 (13)	2,515 (34)	4,528 (20)
Prior myocardial infarction	416 (8)	110 (3)	0 (0)	404 (5)	930 (4)
Laboratory covariates					
Total cholesterol, mg/dl	212 ± 39	206 ± 40	194 ± 36	218 ± 44	208 ± 41
HDL cholesterol, mg/dl	54 ± 16	51 ± 16	51 ± 15	51 ± 15	52 ± 15
Triglycerides, mg/dl	139 ± 76	140 ± 128	132 ± 89	125 ± 88	133 ± 93
Fasting serum glucose, mg/dl	110 ± 36	101 ± 28	97 ± 30	87 ± 20	99 ± 31
HOMA-IR, mg·IU/dl·ml	5 ± 13	3 ± 6	3 ± 6	2 ± 2	3 ± 8

Values are mean ± SD or n (%).
HDL = high-density lipoprotein; HOMA-IR = homeostatic model assessment of insulin resistance.

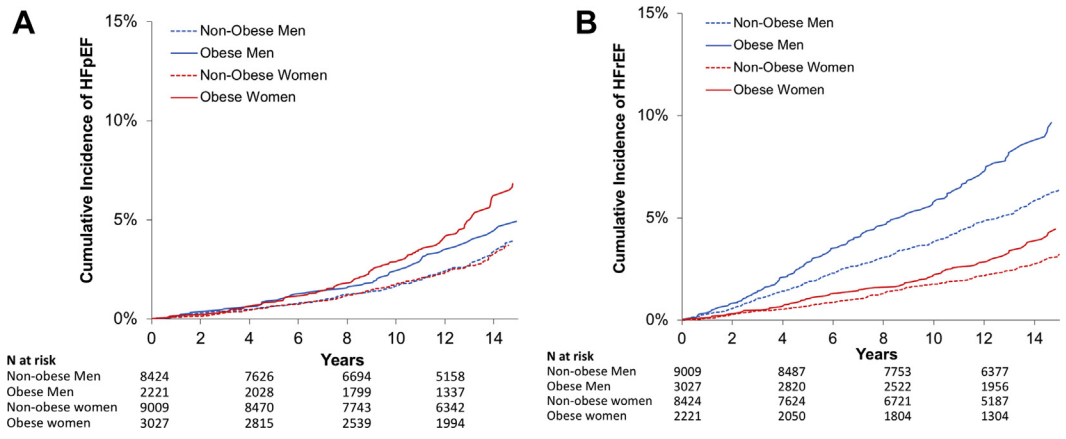
mean waist circumference of 94 ± 14 cm. A total of 23% of participants had obesity (21% of men, 25% of women), and 37% of participants met criteria for metabolic syndrome (37% among both men and women). Baseline characteristics by cohort are detailed in Table 1. Over a mean follow-up of 12 ± 3 years, we observed a total of 2,081 incident HF events, of which 1,463 (70%) were classified into HF subtypes. There were 628 incident HFpEF (358 among women and 270 among men) and 835 incident HFrEF events (295 among women and 540 among men). As shown in Figure 1, nonobese men and women had similar risk of incident HFpEF. Obese women had the highest cumulative incidence of HFpEF, whereas obese men had intermediate incidence.

OBESITY AND RELATED TRAITS ARE ASSOCIATED WITH HF SUBTYPES. In sex-pooled multivariable-adjusted analyses, BMI, waist circumference, waist-to-hip ratio, and fasting glucose independently predicted both HFpEF and HFrEF, albeit with larger effect sizes for HFpEF (Table 2). Specifically, a 1-SD increase in BMI was associated with a 1.34-fold increased hazard of future HFpEF (95% confidence interval [CI]: 1.24 to 1.45; $p < 0.0001$), and a 1.18-fold increased hazard of future HFrEF (95% CI: 1.10 to 1.27; $p < 0.0001$). By contrast, systolic blood pressure predicted HFpEF and HFrEF with similar effect sizes. Conversely, HOMA-IR was significantly associated with HFpEF (HR: 1.20 per 1-SD increase; 95% CI: 1.05 to 1.37; $p = 0.006$) but not HFrEF (HR: 0.99; 95% CI: 0.88 to 1.11; $p = 0.81$). We directly tested whether a given cardiometabolic trait had a differential effect on the risk of HFpEF versus HFrEF and found that both BMI and HOMA-IR portended greater risk of HFpEF versus HFrEF ($p < 0.05$ for difference in HR using Lunn-McNeil method).

In secondary analyses, we further adjusted for C-reactive protein and interim myocardial infarction, neither of which substantively altered effect estimates (Online Tables 1 and 2). In cohort-specific analyses, the effect size of BMI was numerically greater for HFpEF than for HFrEF across all 4 cohorts, although effect sizes were variable between cohorts, with evidence of heterogeneity between cohorts (Online Table 3).

DIFFERENTIAL EFFECTS OF OBESITY-RELATED TRAITS ON HF SUBTYPES AMONG MEN AND WOMEN. We examined the association of obesity-related traits with incident HFpEF and HFrEF in sex-stratified models to better understand sex

FIGURE 1 Cumulative Incidence of HF Subtypes Among Obese and Nonobese Men and Women



Cumulative incidence of **(A)** HFpEF and **(B)** HFrEF in men and women with and without obesity. HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

differences in incident HF subtypes (Table 3). Among men, higher BMI was independently associated with both HF subtypes (HR: 1.34 per 1-SD; 95% CI: 1.18 to 1.52; $p < 0.0001$ for HFpEF; and HR: 1.24; 95% CI: 1.14 to 1.35; $p < 0.0001$ for HFrEF). By contrast, among women, BMI was associated with incident HFpEF but not HFrEF (HR: 1.38 per 1 SD; 95% CI: 1.24 to 1.54; $p < 0.0001$ for HFpEF vs. HR: 1.09; 95% CI: 0.96 to 1.24; $p = 0.18$ for HFrEF, p for difference 0.01). We found that sex modified the association of BMI with HFrEF ($p = 0.03$). Additionally, risk of incident HFpEF increased significantly across quartiles of BMI in both men and women, yet the risk of HFrEF increased only among men ($p < 0.001$) but not women ($p = 0.49$) (Figure 2). Similarly, higher waist circumference was associated with both HF subtypes among men, but only with HFpEF and not HFrEF among women (HR for HFpEF: 1.35 per 1-SD increase; 95% CI: 1.20 to 1.51 vs. HR for HFrEF: 1.11; 95% CI: 0.96 to 1.27; p for difference 0.04). We did not find sex differences in the association of HOMA-IR with HF subtypes.

TABLE 2 Association of Obesity-Related Traits With Heart Failure Subtypes in Sex-Pooled Analyses

		Multivariable-Adjusted	
Predictor	**Outcome**	**HR (95% CI)**	**p Value**
BMI	Incident HFpEF	1.34* (1.24–1.45)	<0.0001
	Incident HFrEF	1.18 (1.10–1.27)	<0.0001
WC	Incident HFpEF	1.32 (1.22–1.44)	<0.0001
	Incident HFrEF	1.19 (1.10–1.29)	<0.0001
WHR	Incident HFpEF	1.19 (1.10–1.29)	<0.0001
	Incident HFrEF	1.14 (1.06–1.22)	0.001
HOMA-IR	Incident HFpEF	1.20* (1.05–1.37)	0.006
	Incident HFrEF	0.99 (0.88–1.11)	0.81
TG/HDL ratio	Incident HFpEF	1.06 (0.96–1.17)	0.27
	Incident HFrEF	1.13 (1.04–1.23)	0.003
Fasting glucose	Incident HFpEF	1.15 (1.08–1.23)	<0.0001
	Incident HFrEF	1.07 (0.99–1.16)	0.08
SBP	Incident HFpEF	1.20 (1.11–1.20)	<0.0001
	Incident HFrEF	1.19 (1.11–1.27)	<0.0001

*p value for difference <0.05 using Lunn-McNeil method to compare HR for HFpEF vs. HFrEF. HR per 1-SD increase in continuous predictor. HOMA-IR, triglycerides, and TG/HDL ratio were log-transformed. The multivariable model was adjusted for age, sex, SBP (except SBP analyses), hypertension treatment, diabetes, smoking, prevalent myocardial infarction, total cholesterol, HDL (except TG/HDL analyses), left bundle branch block, or left ventricular hypertrophy. HOMA-IR analyses excluded participants with diabetes.

BMI = body mass index; CI = confidence interval; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HOMA-IR = homeostatic model assessment of insulin resistance; HR = hazard ratio; SBP = systolic blood pressure; TG/HDL ratio = triglyceride-to-high-density-lipoprotein ratio; WC = waist circumference; WHR = waist-to-hip ratio.

The remainder of cardiometabolic traits are summarized in Table 3. We found that higher fasting glucose and waist-to-hip ratio both predicted incident HFpEF but not HFrEF among women, whereas among men, waist-to-hip ratio was significantly associated with both HFpEF and HFrEF, while fasting glucose was not significantly associated with either. Systolic blood pressure was associated with both HF subtypes among men and women. There was an association of lower HDL cholesterol with incident HFrEF among men ($p = 0.01$). We found no association of triglyceride concentrations with incident HF.

INSULIN RESISTANCE IN PART MEDIATES THE ASSOCIATION OF BMI WITH INCIDENT HFpEF. In exploratory analyses, we examined whether insulin resistance may in part mediate the association of BMI

TABLE 3 Association of Obesity-Related Traits and Incident Heart Failure Subtypes Among Men and Women

		Men		Women		$p_{interaction}$
		Multivariable-Adjusted		Multivariable-Adjusted		
Predictor	Outcome	HR (95% CI)	p Value	HR (95% CI)	p Value	Sex*Covariate
BMI	Incident HFpEF	1.34 (1.18–1.52)	<0.0001	1.38* (1.24–1.54)	<0.0001	0.37
	Incident HFrEF	1.24 (1.14–1.35)	<0.0001	1.09 (0.96–1.24)	0.18	0.03
WC	Incident HFpEF	1.31 (1.16–1.49)	<0.0001	1.35* (1.20–1.51)	<0.0001	0.42
	Incident HFrEF	1.23 (1.13–1.33)	<0.0001	1.11 (0.96–1.27)	0.15	0.09
WHR	Incident HFpEF	1.17 (1.11–1.24)	<0.0001	1.17 (1.06–1.30)	0.003	0.42
	Incident HFrEF	1.13 (1.06–1.20)	0.0003	1.07 (0.94–1.21)	0.32	0.40
HOMA-IR	Incident HFpEF	1.24* (1.02–1.51)	0.03	1.17 (0.98–1.39)	0.08	0.65
	Incident HFrEF	1.02 (0.89–1.17)	0.78	0.88 (0.71–1.11)	0.29	0.44
Log-TG	Incident HFpEF	0.88 (0.75–1.04)	0.14	1.08 (0.94–1.26)	0.29	0.23
	Incident HFrEF	0.98 (0.87–1.09)	0.68	1.08 (0.92–1.26)	0.34	0.18
HDL	Incident HFpEF	0.93 (0.83–1.05)	0.26	0.93 (0.84–1.04)	0.21	0.83
	Incident HFrEF	0.88 (0.81–0.97)	0.01	0.87 (0.76–1.00)	0.05	0.91
Fasting glucose	Incident HFpEF	1.10 (0.97–1.20)	0.12	1.17 (1.08–1.26)	<0.0001	0.14
	Incident HFrEF	1.07 (0.98–1.17)	0.12	1.08 (0.92–1.26)	0.36	0.15
SBP	Incident HFpEF	1.18 (1.06–1.32)	0.003	1.21 (1.09–1.35)	0.001	0.49
	Incident HFrEF	1.13 (1.04–1.23)	0.006	1.28 (1.14–1.44)	<0.0001	0.048

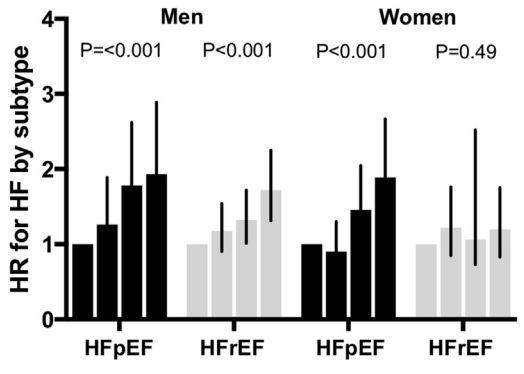
*p value for difference <0.05 using Lunn-McNeil method to compare HR for HFpEF vs. HFrEF. HRs are reported as 1-SD increase in continuous predictor. HOMA-IR, triglycerides, and TG/HDL ratio were log-transformed. The multivariable model was adjusted for age, SBP (except SBP analyses), hypertension treatment, diabetes, smoking, prevalent myocardial infarction, total cholesterol, HDL (except TG/HDL analyses), left bundle branch block, or left ventricular hypertrophy. HOMA-IR analyses excluded participants with diabetes.

Abbreviations as in Tables 1 and 2.

with incident HFpEF. Among men, we estimate that HOMA-IR accounts for 26% of the total effect, whereas in women, we estimate that HOMA-IR accounts for 29% of the effect on HFpEF risk.

THE ASSOCIATION OF METABOLIC SYNDROME WITH HFpEF AND HFrEF. In secondary analyses, we examined the association of each of the metabolic syndrome criteria with HF subtypes. Although each of the criteria with the exception of high triglycerides were independently associated with incident HF, effect sizes for elevated waist circumference, hypertension, and fasting glucose were larger for HFpEF than for HFrEF (Online Table 4). By contrast, low HDL cholesterol was associated with incident HFrEF but not HFpEF.

FIGURE 2 Heart Failure Subtype by Quartile of BMI



Risk of HFpEF or HFrEF in women and men across quartiles of BMI. The p values represent p for trend. BMI = body mass index; HF = heart failure; HR = hazard ratio; other abbreviations as in Figure 1.

DISCUSSION

Our main study findings are 2-fold: first, we demonstrate that obesity and related cardiometabolic traits including insulin resistance are more strongly associated with risk of future HFpEF than HFrEF. Second, we show notable sex differences, wherein obesity in women in particular harbors greater risk of HFpEF versus HFrEF. These findings lend greater granularity to prior studies that have shown an association of obesity and risk of overall HF. We now demonstrate that obesity and cardiometabolic risk predispose to HFpEF, with important sex differences that may underlie the higher prevalence of HFpEF among women.

Obesity has long been described as a major risk factor for the development of overall HF (4), although the differences in HF subtypes have been less clear. More recently, obesity has been proposed as a major driver of systemic inflammation and subsequent myocardial remodeling in HFpEF specifically (6). This

is substantiated by prior community-based studies, demonstrating an association of obesity with future HFpEF specifically in participants of the FHS (17) and PREVEND (18), and African-American participants of the ARIC (Atherosclerosis Risk In Communities) study (19), although direct comparisons with HFrEF were not performed or limited by sample size. Prior studies and new contributions of the current analysis are summarized in **Table 4**. Obesity has also been associated with subclinical phenotypes that precede HFpEF, including systolic and diastolic dysfunction and left ventricular hypertrophy (5,20). We now show that obesity is specifically associated with a higher risk of future HFpEF than HFrEF in a collaboration of 4 large community-based cohorts, leveraging data from more than 22,000 individuals followed for incident HF events.

The mechanisms underlying obesity and HFpEF remain unclear. We specifically investigated obesity-related cardiometabolic traits to shed further light on potential pathways that might lead to HFpEF. We found that obesity (as measured by waist circumference, increased waist-to-hip ratio, and increased BMI), and associated cardiometabolic dysfunction, including insulin resistance, abnormal fasting glucose, and hypertension, were all associated with incident HFpEF. Our findings are in keeping with prior studies demonstrating the importance of hypertension in the development of both HFpEF and HFrEF, and it may be that hypertension mediates obesity-associated HF.

This extends prior cross-sectional studies demonstrating an association of abdominal and visceral adiposity and diastolic dysfunction (21,22). Of note, the association of insulin resistance and overall HF has been described previously (23,24). Specifically, in the ULSAM (Uppsala Longitudinal Study of Adult Men), insulin resistance was an independent predictor of incident HF (23). In ARIC, insulin resistance defined by HOMA-IR levels between 1.0 and 2.0 were associated with incident HF, although values above 2.5 were not (25). Neither study distinguished HFpEF from HFrEF. We now show that HOMA-IR confers a higher risk of future HFpEF, but not HFrEF. Furthermore, our findings suggest that HOMA-IR may in part mediate the association of obesity and HFpEF. Although this finding is novel, it is in concert with existing cross-sectional data, demonstrating an association of HOMA-IR with both lower e′ and higher E/e′ ratios suggestive of worse diastolic dysfunction among a population-based sample (26). Our findings fit with the proposed paradigm that cardiometabolic factors including abdominal adiposity and insulin resistance may produce a systemic inflammatory state (6), including secretion of proinflammatory cytokines (27,28), ultimately predisposing to myocyte remodeling and the development of HFpEF (29).

TABLE 4 Summary of Previous Studies and Novel Aspects of Our Study

First Author (Ref. #)	Findings	New in Current Analysis
Brouwers et al. (18)	Higher BMI was associated with overall HF without differences among HF subtypes among PREVEND participants.	Addition of other cohorts including FHS, CHS, and MESA for a more comprehensive analysis.
Eaton et al. (7)	Higher BMI was associated with incident HFpEF but not HFrEF among post-menopausal women participants of the WHI.	Inclusion of both men and women, and direct comparison of sex-specific effects and differences.
Ho et al. (15)	Higher BMI was associated with incident HFpEF and HFrEF among 28,820 participants from CHS, FHS, and PREVEND, with borderline difference among subtypes (p for equality 0.05).	Addition of MESA cohort for a more comprehensive analysis across 4 cohorts, specific investigation of obesity-related traits previously not analyzed, including waist circumference, insulin resistance, and dyslipidemia.
Ingelsson et al. (23)	Among ULSAM participants, BMI, insulin resistance, and waist circumference independently predicted incident overall HF.	Specific evaluation of insulin resistance and BMI and their associations with HF subtypes (HFpEF vs. HFrEF) with direct comparisons of effect sizes.
Vardeny et al. (25)	Among ARIC participants, insulin resistance and higher BMI were associated with increased risk of overall HF.	Specific evaluation of insulin resistance and BMI and their associations with HF subtypes (HFpEF vs. HFrEF) with direct comparisons of effect sizes.

HF = heart failure; other abbreviations as in **Table 2**.

The second notable finding in our study was focused on sex differences in cardiometabolic risk leading to HFpEF. It has long been observed that the prevalence of HFpEF is greater among women than men (30). Interestingly, among participants of the Women's Health Study (WHS) (7), obesity was associated with a population attributable risk of future HFpEF that was more than 3-fold higher than that of HFrEF. Furthermore, obesity was more common among women than men with existing HFpEF enrolled in the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) trial (31). Motivated by these potential sex differences, we now show that obesity portends a higher risk of HFpEF versus HFrEF among women, whereas this difference is less pronounced in men. The reason

for this sex difference remains unclear but mirrors the differential effect of cardiometabolic risk factors on longitudinal increases in left ventricular mass with aging among women than men (32). Biomarkers, such as natriuretic peptides, predict incident HF subtypes and also seem to have sex-specific effects with lower natriuretic peptide levels in abdominal obesity observed among women versus men (33,34). Whether obesity and associated cardiometabolic risk should raise special attention among women requires further study.

STUDY LIMITATIONS. Obesity and cardiometabolic disease are known to disproportionately affect different race/ethnic groups (35). Although our sample did include ethnic minorities, we did not have enough power to perform race-specific analyses, which will be of high interest in future studies. With respect to the HF endpoint, we were able to classify HFpEF and HFrEF only in individuals who underwent cardiac function assessment at or around the time of their acute HF presentation, which left 30% of cases as unclassified HF. Additionally, once classified by their initial HF presentation, recurrent events and transitions between HFpEF and HFrEF were not captured. The exclusion of individuals missing key covariates may have influenced our results. Furthermore, this was an observational study, limiting potential causal inferences, and further studies are needed to better understand mechanisms underlying obesity and HFpEF. Finally, individual cohorts differed by era of baseline examination and also frequency and timing of follow-up examinations. Thus, secular trends including difference in lifestyle or therapies may have confounded results, and serial measures of BMI and other cardiometabolic traits were not taken into account.

CONCLUSIONS

We found that obesity and associated cardiometabolic traits conferred a higher risk of HFpEF than HFrEF and that obesity among women in particular seemed to predispose to future HFpEF. These findings add to the current understanding of what predisposes certain patients to developing HFpEF. Whether targeting cardiometabolic disease can prevent HFpEF needs further study and is particularly important given the current lack of effective therapies once HFpEF has developed.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Heart failure accounts for a substantial burden of total health care costs worldwide, and about one-half of individuals presenting with heart failure have heart failure with preserved as opposed to reduced ejection fraction. A better understanding of how obesity and related cardiometabolic traits may lead to each heart failure subtype may inform underlying pathways and guide future preventive strategies.

TRANSLATIONAL OUTLOOK: Future studies are needed to examine potential pathways that lead from obesity and metabolic dysfunction to the development of heart failure with preserved ejection fraction.

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APPENDIX For supplemental tables, please see the online version of this paper.