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EDITORIAL COMMENT

Fat, Female, Fatigued

Features of the Obese HFpEF Phenotype*

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The relationship between obesity and heart failure (HF) is complex: beginning with obesity as a known risk factor for HF, currently focused on the discussion whether "obese HF with preserved ejection fraction (HFpEF)" is a specific phenotype (1,2), and extending to the "obesity paradox" in established HF (wherein obese patients with HF are paradoxically protected against adverse outcomes compared to lean or underweight patients with HF). Most prior studies linking obesity to HFpEF, particularly, have studied prevalent cases with cross-sectional comparisons to nonobese HFpEF (1) or HF with reduced EF (HFrEF). Far fewer studies have looked at incident cases, and previous attempts at understanding the risks associated with obesity and future HFpEF have been restricted to: 1) limited studies differentiating the 2 HF subtypes; 2) inadequate understanding of the role of sex differences; and 3) lack of examination of related cardiometabolic traits that may provide insight into underlying mechanisms linking obesity with HFpEF (**Table 1**).

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In this issue of *JACC: Heart Failure*, Savji et al. (3) address these gaps in evidence. Drawing on an international consortium of 4 large community cohorts (CHS [Cardiovascular Health Study], PREVEND [Prevention of Renal and Vascular End-stage Disease], MESA [Multi-Ethnic Study of Atherosclerosis], and FHS [Framingham Heart Study]), the authors assessed 22,681 community-based participants (mean age: 60 ± 13 years of age; 53% women) followed for 12 ± 3 years for incident HFpEF versus HFrEF. In sex-pooled analysis, every 1 SD increase in body mass index (BMI) was associated with 34% and 18% increase in incident HFpEF and HFrEF, respectively ($p < 0.05$ for differences between HF subtypes). Sex-stratified analyses revealed that the differential association between BMI and HFpEF versus HFrEF was more apparent in women (p for difference HFpEF vs. HFrEF = 0.01) than men ($p = 0.34$). Similarly, waist circumference was associated with HFpEF but not HFrEF in women (p for difference between HF subtype = 0.04) and with both HF subtypes in men. The association between obesity and incident HF has been previously described in some of the individual cohorts of the consortia (FHS, PREVEND) but not the differential association with HFpEF versus HFrEF. These findings are also consistent with a recent report from the Women's Health Initiative, showing the larger population attributable risk of obesity for HFpEF versus HFrEF in this exclusively female study population (Online Ref. 1). Thus, taken together with previous reports, Savji et al. (3) provide incremental evidence that obesity is a stronger risk factor for HFpEF than for HFrEF, and that this relationship is more pronounced in women than in men.

The additional study of related cardiometabolic traits provided further insights. Insulin resistance (homeostatic model assessment for assessing insulin resistance [HOMA-IR]) portended a higher risk for future HFpEF but not HFrEF ($p < 0.05$ for difference between HF subtypes); mediating 26% (men) to 29% (women) of the association of BMI with incident

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HFpEF. Furthermore, higher fasting glucose predicted incident HFpEF but not HFrEF among women, whereas there was no association with either HF subtype among men. Although formal testing for interaction by sex was not significant, the totality of the evidence suggested that insulin resistance may be the key factor underlying the association between obesity and HFpEF, especially in women. Indeed, we recently showed that, among 3,950 asymptomatic Asian men and women, insulin resistance was associated with cardiac structural and functional abnormalities (despite preserved EF), along the diabetic continuum extending into the early pre-diabetic and upper normal glucose range and even in the absence of obesity (BMI <23 kg/m^2) (4). These findings are also consistent with prior results from the ULSAM (Uppsala Longitudinal Study of Adult Men) study and ARIC (Atherosclerosis Risk In Communities), showing the association of insulin resistance with overall incident HF.

There are a number of important implications of these findings. By clearly demonstrating the stronger association between obesity and new onset HFpEF compared to HFrEF, these results epidemiologically substantiate the inflammatory paradigm of HFpEF (5), wherein comorbidities such as obesity and diabetes are central drivers of systemic microvascular inflammation, which adversely affects the adjacent cardiomyocyte through decreased nitric oxide bioavailability, reduced cyclic guanosine monophosphate availability, altered phosphorylation of titin, and increased fibrosis. Beyond systemic inflammation, excess adipose tissue can contribute to HFpEF pathophysiology through enhanced pericardial restraint; accelerated coronary atherosclerosis associated with epicardial fat; accelerated renal dysfunction associated with perirenal fat; capillary rarefaction and impaired tissue perfusion from adipose-derived vasoconstrictors; abnormal pulmonary diffusion and ventilation; and impaired skeletal muscle perfusion and mitochondrial function (2). Specifically, these results provide additional motivation to target obesity or insulin resistance in the prevention of HFpEF. Repeated measurements of obesity or cardiometabolic factors would have been helpful to evaluate how changes (e.g., weight loss) over time might have impacted HFpEF risk, although such analyses should carefully distinguish between intentional and unintentional (e.g., cancer cachexia) weight loss. It remains to be determined whether newer antidiabetic therapies which also cause weight loss, such as sodium-glucose cotransporter-2 inhibitors or glucagon-like peptide-1 receptor agonists, may play a role in the treatment or prevention of HFpEF. In fact, it is plausible that a significant proportion of the HF risk reduction in the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial was attributable to HFpEF (although definitive EF data were not available) (6). Therefore, at the very least, future HFpEF trials of such cardiometabolically active agents should be tailored to include obese patients, rather than exclude them based on BMI criteria, as has been the case in prior trials.

Sex-specific findings also reinforce the importance of including women in therapeutic and/or preventive strategies aimed at obesity, a population notoriously under-represented in clinical trials of HF. Furthermore, there is strong impetus to advocate for greater ethnic diversity in such future efforts with emerging evidence from us and others: obese African American women were reported to be at 6-fold higher risk of incident HFpEF than their Caucasian counterparts (Online Ref. 1). We previously reported that among 4,031 asymptomatic Asian adults obesity was associated with unfavorable left ventricular (LV) remodeling and worse global myocardial deformation, indicating subclinical LV contractile dysfunction, worse in women than in men despite preservation of LVEF in both sexes (7). Of note, sex-specific optimal cutoffs of BMI and waist circumference for identifying subclinical LV contractile dysfunction were 23.4 kg/m^2 and 83 cm in Asian women, substantially lower than in Asian men (26.4 kg/m^2 and 87.5 cm, respectively) and much lower than international World Health Organization criteria (7). Furthermore, women showed steeper declines in LV deformation with increasing BMI and waist circumference than men. How the interplay between insulin resistance, obesity, and HF will differ in the metabolically healthy obese African Americans and lean diabetic Asians is very intriguing.

Clearly, much as we have learned to recognize and understand the obese HFpEF phenotype, there are more questions to be answered. The epidemiologic insights from Savji et al. (3) have weighed in heavily to show that “Fat, Female, Fatigued” are key risk features for future HFpEF. Further work should address the optimal anthropometric (BMI, waist measurements, visceral fat imaging) or cardiometabolic (HOMA-IR, fasting glucose) parameter to identify patients at high risk of future HFpEF, whether sex- or ethnicity-specific cutoffs are needed for optimal risk stratification, the relative roles of specific underlying mechanisms (e.g., volume overload/pericardial restraint versus pericardial fat and microvascular inflammation), and whether strategies targeted at improving insulin sensitivity and/or

TABLE 1 Risk of Obesity and Insulin Resistance for Incident HFpEF Vs. HFrEF in Men and Women

First Author, Year, Journal (Ref. #)	Cohort	Participants (Mean Age, % Women)	Ethnicity	Mean Follow-Up yrs	Incident HF Events	BMI, Adjusted HR (95% CI)	
						Stratified by HF Subtype	Stratified by Sex
Kenchaiah, 2002, NEJM (Online Ref. 2)	FHS	5,881 (55 yrs, 54%)	White (100%)	14	Men (238) Women (258)	Not available	Per 1 kg/m^2 increase in BMI, men: 1.05 (1.02–1.09) women: 1.07 (1.04–1.10) >30kg/m^2 vs. 18-24.9 (Ref.) men: 1.90 (1.30–2.79) women: 2.12 (1.51–2.97) $p_{interaction}$ with sex >0.1
Ingelsson, 2005, JAMA (Online Ref. 6)	ULSAM	1,184 elderly men (≥70 yrs, 0%)	Not specified	8.9, 0.01-11.4 (median, range)	Congestive HF (104)	Per 1-SD in men, 1.35 (1.11-1.65)	Not applicable, Only men
Vardeny, 2013, JACC HF (Online Ref. 7)	ARIC	12,606 (range 45-64, 56%)	White (76%) African American (24%)	20.6 (median)	HF (1,455)	Not available	Not available
Ho, 2013, Circ Heart Failure (Online Ref. 3)	FHS	6,340 (60 yrs, 54%)	White (100%)	7.7 ± 1.7	HFpEF (196) HFrEF (261)	Per 4.7 kg/m^2 increase in BMI, HFpEF: 1.44 (1.26-1.64) HFrEF: 1.26 (1.11-1.43) p for difference = 0.06	Not available
Browers, 2013, Eur Heart J (Online Ref. 4)	PREVEND	8,592 (49 yrs, 53%)	White (95%) Black (1%) Others (2%)	11.8 (range 10.8-11.9)	HFpEF (125) HFrEF (241)	For BMI >30 kg/m^2, Mutual 1.62 (1.10-2.37) P_{cr} for HFpEF vs HFrEF 0.75	Not available
Ho, 2016, Circ Heart Failure (Online Ref. 5)	FHS PREVEND CHS	28,820 (60 yrs, 53%)	White (95%) Black (4%)	13.2 ± 3.6	HFpEF (982) HFrEF (909)	Per 4 kg/m^2 HFpEF: 1.28 (1.22-1.36) HFrEF: 1.18 (1.11-1.25) p for equality = 0.05	Exploratory subgroup analysis: $p_{interaction}$ sex >0.1
Eaton, 2017, Circ Heart Failure (Online Ref. 1)	WHS	42,170 post-menopausal women (50-79 yrs, 100%)	White (51.2%) African Americans (33.6%) Hispanic (15.2%)	13.2	HFpEF (902) HFrEF (508)	For BMI >30-35 kg/m^2 vs. BMI <25 (Ref.), HFpEF: 1.35 (1.06, 1.72) HFrEF: 1.00 (0.74, 1.36)	Not applicable, Only post-menopausal women
Savji, 2018, JACC HF (3)	FHS PREVEND CHS MESA	22,681 (60 yrs, 53%)	White (77%) Black (24%) Others (11%)	12.0 ± 3.0	Among men, HFpEF (270) HFrEF (540) Among women, HFpEF (358) HFrEF (295)	Per 1-SD, pooled-sex analysis: HFpEF: 1.34 (1.24-1.45) HFrEF: 1.18 (1.10-1.27) p for difference <0.05	Per 1-SD in men, HFpEF: 1.34 (1.18-1.52) HFrEF: 1.24 (1.14-1.35) p for difference >0.05 Per 1-SD in women, HFpEF: 1.38 (1.24-1.54) HFrEF: 1.09 (0.96-1.24) p for difference = 0.01

TABLE 1 Continued

First Author, Year, Journal (Ref. #)	Waist Circumference, Adjusted HR (95% CI)		Insulin Resistance (HOMA-IR), Adjusted HR (95% CI)	
	Stratified by HF Subtype	Stratified by Sex	Stratified by HF Subtype	Stratified by Sex
Kenchaiah, 2002, NEJM (Online Ref. 2)	Not available	Not available	Not available	Not available
Ingelsson, 2005, JAMA (Online Ref. 6)	Per 1-SD in men, 1.36 (1.10-1.69)	Not applicable, Only men	Per 1-SD in men, 1.15 (0.90-1.46)	Not applicable, Only men
Vardeny, 2013, JACC HF (Online Ref. 7)	Not available	Not available	HR of incident HF by HOMA-IR levels: 2.50 -1.58 (1.43-1.76) 2.75 -1.55 (1.40-1.72) 3.00 - 1.51 (1.35-1.68)	Not available
Ho, 2013, Circ Heart Failure (Online Ref. 3)	Not available	Not available	Not available	Not available
Browers, 2013, Eur Heart J (Online Ref. 4)	Not available	Not available	Not available	Not available
Ho, 2016, Circ Heart Failure (Online Ref. 5)	Not available	Not available	Not available	Not available
Eaton, 2017, Circ Heart Failure (Online Ref. 1)	Not available	Not applicable, Only post-menopausal women	Not available	Not applicable, Only post-menopausal women
Savji, 2018, JACC HF (3)	Per 1-SD, pooled-sex analysis: HFpEF: 1.32 (1.22-1.44) HFrEF: 1.19 (1.10-1.29) p for difference >0.05	Per 1-SD in men, HFpEF: 1.31 (1.16-1.49) HFrEF: 1.23 (1.13-1.33) p for difference >0.05 Per 1-SD in women, HFpEF: 1.35 (1.20-1.51) HFrEF: 1.11 (0.96-1.27) p for difference <0.05	Per 1-SD, pooled-sex analysis: HFpEF: 1.20 (1.05-1.37) HFrEF: 0.99 (0.88-1.11) p for difference <0.05	Per 1-SD in men, HFpEF: 1.24 (1.02-1.51) HFrEF: 1.02 (0.89-1.17) p for difference <0.05 Per 1-SD in women, HFpEF: 1.17 (0.98-1.39) HFrEF: 0.88 (0.71-1.11) p for difference >0.05

BMI = body mass index; CHS = Cardiovascular Health Study; FHS = Framingham Heart Study; HF = heart failure; HFpEF = HF with preserved ejection fraction; HFrEF = HF with reduced ejection fraction; HOMA-IR = homeostatic model assessment for assessing insulin resistance; MESA = Multi-Ethnic Study of Atherosclerosis; PREVEND = Prevention of Renal and Vascular End-stage Disease.

weight loss may be effective in preventing HFpEF. Such preventive strategies are all the more urgently needed, given that to date, we still have no proven therapies to treat established HFpEF.

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