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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 two 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**).

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 standard deviation 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 HFpEF. Furthermore, higher fasting glucose

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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 (Years)	Incident HF Events	BMI, Adjusted HR (95% CI)	
						Stratified by HF Subtype	Stratified by Sex
Kenchaiah, 2002, NEJM (Online Ref. 2)	FHS	5881 (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 (≥70yrs, 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 4.7kg/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 >30kg/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 Heart Failure (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 Heart Failure (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.