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RESEARCH ARTICLE

# Sex and central obesity in heart failure with preserved ejection fraction

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**Aims** Obesity is a risk factor for heart failure with preserved ejection fraction (HFpEF), particularly in women, but the mechanisms remain unclear. The present study aimed to investigate the impact of central adiposity in patients with HFpEF and explore potential sex differences.

**Methods and results** A total of 124 women and 105 men with HFpEF underwent invasive haemodynamic exercise testing and rest echocardiography. Central obesity was defined as a waist circumference (WC) ≥88 cm for women and ≥102 cm for men. Exercise-normalized pulmonary capillary wedge pressure (PCWP) responses were evaluated by the ratio of PCWP to workload (PCWP/W) and after normalizing to body weight (PCWL). The prevalence of central obesity (77%) exceeded that of general obesity (62%) defined by body mass index ≥30 kg/m$^2$. Compared to patients without central adiposity, patients with HFpEF and central obesity displayed greater prevalence of diabetes and dyslipidaemia, higher right and left heart filling pressures and pulmonary artery pressures during exertion, and more severely reduced aerobic capacity. Associations between WC and fasting glucose, low-density lipoprotein (LDL) cholesterol, peak workload, and pulmonary artery pressures were observed in women but not in men with HFpEF. Although increased WC was associated with elevated PCWP in both sexes, the association with PCWP/W was observed in women but not in men. The strength of correlation between PCWP/W and WC was more robust in women with HFpEF as compared to men (Meng's test $p = 0.0008$), and a significant sex interaction was observed in the relationship between PCWL and WC ($p$ for interaction = 0.02).

**Conclusions** Central obesity is even more common than general obesity in HFpEF, and there appear to be important sexual dimorphisms in its relationships with metabolic abnormalities and haemodynamic perturbations, with greater impact in women.

**Keywords** Waist circumference • Central obesity • Heart failure

## Introduction

The global prevalence of obesity is increasing at an alarming rate, particularly in the United States where it is projected that 1 in 2 adults will be obese by 2030.[1] Obesity and adiposity-related comorbidities such as diabetes, dyslipidaemia, and hypertension interact with aging to confer an increased risk of heart failure (HF) with preserved ejection fraction (HFpEF).[2] This risk appears to be more strongly tied to increases in visceral adipose tissue, a characteristic feature of central obesity that is more strongly linked to cardiometabolic stresses including insulin resistance, hypertension, and diabetes mellitus.[3–5]

General obesity, as defined by body mass index (BMI) ≥30 kg/m$^2$, is a stronger risk factor for development of HFpEF in women than

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men,[6] and central obesity is more strongly tied to development of diabetes in women.[7] Increased waist circumference (WC) provides a non-invasive measure of central obesity that is associated with adverse cardiac function in adults without HF[8] and increased mortality in patients with HFpEF.[9] While clinical, cardiac, and haemodynamic abnormalities in the general obese phenotype of HFpEF defined by BMI are well described,[10] no prior study has yet specifically evaluated the impact of central obesity in HFpEF, or evaluated for potential sex differences in the relationships between central obesity and cardiac function.

The primary objective of the present study was to investigate the prevalence and clinical significance of central obesity as defined by increases in WC in patients with HFpEF, with the secondary objective to explore whether central obesity is more strongly associated with metabolic and haemodynamic abnormalities with exercise haemodynamics in women compared to men with HFpEF.

# Methods

## Study population

In this retrospective study, consecutive patients with HFpEF who underwent invasive haemodynamic exercise testing with supine cardiopulmonary testing for the evaluation of unexplained dyspnoea, with available measurements of waist and hip circumference within 6 months after the date of catheterization at the Mayo Clinic in Rochester, MN, between July 2006 and February 2018, were included. All patients underwent upright cardiopulmonary exercise testing on a separate day within 6 months of the supine exercise test. Waist and hip circumference were directly measured at the time of upright exercise test, and body fat percentage estimated by skin calipers in a subset of patients. HFpEF was defined according to current guidelines: New York Heart Association functional class II–III dyspnoea, ejection fraction ≥50% with an elevated pulmonary capillary wedge pressure (PCWP) ≥15 mmHg at rest and/or ≥25 mmHg with exercise in the absence of clinically significant ischaemic heart disease, valvular heart disease, cardiomyopathy, pericardial disease, or high output HF.[11,12] The study was approved by the Mayo Clinic Institutional Review Board and all participants provided consent for data use through completion of research authorization forms.

## Non-invasive assessments

Two-dimensional, M-mode, Doppler, and tissue Doppler echocardiography assessments were performed by experienced sonographers in accordance with the American Society of Echocardiography guidelines.[13] Left ventricular (LV) mass and left atrial (LA) volume were indexed to height$^{2.7}$.[14,15] Venous blood samples were obtained after overnight fasting in a compensated state. Serum haemoglobin, creatinine, glucose, lipid profiles and N-terminal pro B-type natriuretic peptide were measured using routine automated laboratory procedures. Echocardiogram and blood samples were obtained within 1 month of catheterization. Waist and hip circumferences were measured in accordance with the World Health Organization recommendations within 6 months of catheterization.[16] Briefly, patients were asked to stand relaxed with the arms at the sides, feet positioned close together, and weight evenly distributed across the feet. WC was measured midpoint between the lowest rib and the top of the iliac crest. Hip circumference was measured at the level of the widest portion of the buttocks. General obesity was defined as a BMI ≥30 kg/m$^2$. Central obesity was defined as WC ≥88 cm for women and ≥102 cm for men.[9,17] To evaluate potential sex differences in the relationships with central obesity, patients were stratified according to these sex-specific WC cut-offs and the values above and below the median values. The Mayo Clinic Institutional Review Board approved the study protocol, and all patients provided written informed consent.

## Invasive haemodynamic assessment

Patients from the invasive cohort underwent symptom-limited supine cycle ergometry testing with simultaneous expired gas analysis, in accordance with previously described methods.[18] Right heart catheterization was performed via the right internal jugular vein using a 9-Fr sheath. Right atrial (RA) pressure, pulmonary artery (PA) pressure, and PCWP were measured at end-expiration (mean of ≥3 beats) on distinct respiratory cycles using 2 Fr high-fidelity micromanometer-tipped catheters advanced through the lumen of a 7 Fr fluid-filled catheter. Transducers were zeroed at the mid-thorax, which were measured using laser calipers in each patient. The PCWP position was confirmed based on appearance on fluoroscopy, characteristic pressure waveforms, and oximetry values (saturation ≥94%). Pressure tracings were digitized (240 Hz) and analysed offline in a blinded fashion.

A radial arterial cannula (4–6 Fr) was used to measure arterial blood pressure and to sample arterial blood gases throughout the study. The arterio-venous oxygen difference ($AVO_2$ diff) was directly measured as the difference between systemic arterial and PA oxygen content. Oxygen consumption ($VO_2$), carbon dioxide production ($VCO_2$) and respiratory exchange ratio (RER = $VCO_2/VO_2$) were measured via expired gas analysis (MedGraphics, St. Paul, MN, USA), with values taken as the mean over a 30 s interval preceding arterial and venous blood sampling in each phase. Percent predicted peak $VO_2$ was calculated based on the Wasserman–Hansen equation.[19] Cardiac output (CO) was then calculated using the direct Fick method (CO = $VO_2/AVO_2$ diff). After baseline data were acquired, haemodynamic assessments and expired gas analyses were performed during supine cycle ergometry.

Exercise testing was initiated and maintained at 20 W for 5 min, which was followed by 10–20 W increments in workload (3-min stages) to patient-reported exhaustion. To describe the PCWP response to exercise intensity, the ratio of PCWP at peak exercise to workload (PCWP/W) was calculated, and then normalized body weight (PCWL [mmHg/W/kg]), as previously described.[20]

## Statistical analysis

Data are presented as the mean (standard deviation), median (interquartile range, IQR), or number (%). Between-group differences were compared using unpaired *t*-tests, Wilcoxon rank-sum tests, chi-square tests, or Fisher's exact tests, as appropriate. Within-group differences in the prevalence of general and central obesity was assessed using the McNemar test. Univariable linear regression analyses were used to assess relationships of WC with laboratory and haemodynamic data, and the standardized betas were plotted. Multivariable linear regression models with an interaction term were performed to test the influence of sex differences on the association between central haemodynamics and WC. Differences of correlation coefficients were assessed using a Meng's *Z*-test. No correction was made for multiple hypothesis testing. We also performed sensitivity analysis evaluating the impact of central obesity among non-obese patients with HFpEF (BMI <30 kg/m$^2$). A two-sided *p*-value <0.05

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was considered statistically significant. All data were analysed using JMP14.0 (SAS Institute Inc., Cary, NC, USA).

# Results

## Baseline characteristics

Of the 554 patients with HFpEF evaluated between 2006 and 2018, 229 had necessary anthropometry measurements for inclusion (online supplementary *Figure Appendix S1*). Of these patients, 39 (17%) were also included in a previous study evaluating relationships with visceral fat.[4] Baseline characteristics of patients who underwent WC measurement were similar to patients who did not (online supplementary *Table Appendix S1*). From this group, 142 patients (62%) had a BMI $\geq$30 kg/m$^2$ (general obesity), while 177 patients (77%) had central obesity ($p < 0.0001$ compared with prevalence of general obesity) (*Figure 1*). The concordance between central adiposity and general obesity was 83%, with 16% of patients having a central fat distribution in the absence of general obesity. Body fat percentage (available in 64%) was greater in patients with as compared to without central adiposity (32 $\pm$ 5 vs. 26 $\pm$ 6%, $p < 0.0001$).

There were no differences in age or sex in patients with HFpEF with or without central obesity (*Table 1*). The prevalence of diabetes, dyslipidaemia and chronic obstructive pulmonary disease was greater in patients with central adiposity compared to those without. HFpEF with central obesity displayed higher fasting glucose and worse lipid profile compared to those without. Patients with HFpEF and central obesity displayed greater LV diastolic dimension, higher LV mass index, and lower mitral septal e′ velocity compared to those without central obesity.

The median time between supine and upright exercise was 10 (IQR 2–62) days. There were no differences in RA pressure, PA pressures, PCWP, and cardiac index at rest in HFpEF with central obesity compared to those without (*Table 2*). During exercise, those with HFpEF and central obesity displayed higher RA, PA pressures and PCWP, as well as higher PCWP/W and PCWL compared to those without central obesity. Aerobic capacity scaled to body weight (peak $VO_2$) during both supine exercise during invasive testing (8.9 $\pm$ 2.9 vs. 11.6 $\pm$ 3.4 ml/kg/min, $p < 0.0001$) and upright exercise (15.1 $\pm$ 4.7 vs 17.1 $\pm$ 5.2 ml/kg/min, $p = 0.01$) was lower in HFpEF with central obesity compared to those without (*Table 2*). Conversely, absolute supine peak $VO_2$ (not scaled to body weight) was similar in HFpEF with and without central obesity, while absolute peak $VO_2$ and percent predicted peak $VO_2$ with upright exercise were in fact higher in HFpEF with central obesity than without. Peak exercise RER was lower during supine exercise in patients with central obesity than without.

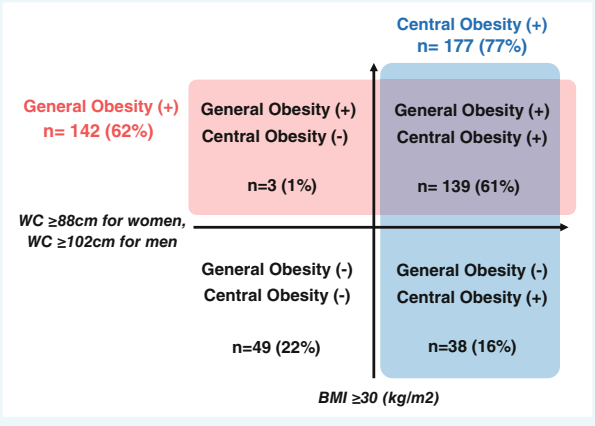


**Figure 1** Distribution of general (body mass index [BMI] $\geq$30 kg/m$^2$) and central obesity (waist circumference [WC] $\geq$88 cm for women and $\geq$102 cm for men) in heart failure with preserved ejection fraction.

## Central adiposity in HFpEF without general obesity

Of 87 patients with HFpEF and a BMI in the non-obese (<30 kg/m$^2$) category, 38 (44%) patients had a central fat distribution (*Figure 1*). Consistent with the broader comparisons, those with HFpEF and central obesity displayed a greater prevalence of diabetes and dyslipidaemia, as well as lower high-density lipoprotein (HDL) cholesterol and higher triglyceride (online supplementary *Table S2*). They also had more impaired LV relaxation exhibited by lower mitral e′ velocities, and worse exercise haemodynamics including higher PA pressure, more impaired PCWP/W and PCWL, and lower peak $VO_2$ scaled to body weight (online supplementary *Table S3*).

## Impact of sex

Age, BMI, and the prevalence of general obesity were similar between women and men (online supplementary *Table S4*). The prevalence of dyslipidaemia and usage of lipid-lowering treatments were less in women than in men. Fasting glucose was lower, while HDL cholesterol was higher in women than in men.

Consistent with sex differences that exist in adults without HF, women with HFpEF displayed decreased LV size and higher LV ejection fraction compared with men with HFpEF, with lower WC, greater hip circumference, and lower waist-to-hip ratio (online supplementary *Table S4* and *Figure S2*). The prevalence of central obesity was similar in women and men with HFpEF (75% vs. 80%, $p = 0.4$), and both exceeded the respective prevalences of general obesity (BMI $\geq$30 kg/m$^2$) for both men and women (61% vs. 63%, $p = 0.8$).

There were no clinically meaningful differences in rest or exercise haemodynamics comparing women and men with HFpEF overall (online supplementary *Table S5*). Peak exercise workload achieved was slightly lower in women, CO tended to be lower, and exercise heart rate was higher as compared to men with HFpEF.

## Impact of increased waist circumference stratified by sex

Among women with HFpEF, the prevalence of diabetes, fasting glucose, and low-density lipoprotein (LDL) cholesterol levels were

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**Table 1 Baseline characteristics**

| | HFpEF without central obesity ($n$ = 52) | HFpEF with central obesity ($n$ = 177) | $p$-value |
|---|---|---|---|
| Age (years) | 67 ± 15 | 67 ± 11 | 0.8 |
| Women, $n$ (%) | 31 (60) | 93 (53) | 0.4 |
| Height (cm) | 167 ± 9 | 169 ± 10 | 0.2 |
| Weight (kg) | 72 ± 11 | 98 ± 19 | <0.0001 |
| Body surface area ($m^2$) | 1.82 ± 0.18 | 2.11 ± 0.24 | <0.0001 |
| BMI ($kg/m^2$) | 25.7 (37.8–27.1) | 32.9 (30.5–36.5) | <0.0001 |
| General obesity (BMI >30 $kg/m^2$), $n$ (%) | 3 (6) | 139 (79) | <0.0001 |
| Waist to hip ratio | 0.83 ± 0.10 | 0.95 ± 0.10 | <0.0001 |
| Body fat (%, available in $n$ = 146) | 26 ± 6 | 32 ± 5 | <0.0001 |
| Comorbidities, $n$ (%) | | | |
| Hypertension | 43 (83) | 160 (90) | 0.1 |
| Diabetes mellitus | 4 (8) | 54 (31) | 0.0003 |
| Atrial fibrillation | 22 (42) | 57 (32) | 0.2 |
| Dyslipidaemia | 33 (63) | 141 (80) | 0.02 |
| COPD | 1 (2) | 30 (17) | 0.001 |
| Medications, $n$ (%) | | | |
| Beta-blocker | 27 (52) | 105 (59) | 0.3 |
| ACEI/ARB | 25 (48) | 98 (55) | 0.4 |
| Diuretics | 31 (60) | 104 (59) | 0.9 |
| Oral hypoglycaemic drug | 4 (8) | 29 (16) | 0.1 |
| Insulin | 3 (6) | 19 (11) | 0.3 |
| Lipid-lowering drug | 24 (46) | 103 (58) | 0.1 |
| Laboratories | | | |
| Haemoglobin (g/dl) | 13.0 ± 1.4 | 13.2 ± 1.5 | 0.4 |
| Creatinine (mg/dl) | 1.0 (0.8–1.2) | 1.0 (0.9–1.3) | 0.08 |
| Fasting glucose (mg/dl) | 96 (87–106) | 104 (94–127) | 0.03 |
| NT-proBNP (pg/ml) | 473 (166–1124) | 346 (104–1049) | 0.4 |
| LDL-C (mg/dl) | 79 (60–98) | 90 (65–120) | 0.03 |
| HDL-C (mg/dl) | 60 (49–75) | 46 (38–58) | <0.0001 |
| Triglyceride (mg/dl) | 84 (61–112) | 138 (93–192) | <0.0001 |
| Echocardiography | | | |
| LV diastolic dimension (mm) | 47.6 ± 5.3 | 49.3 ± 4.9 | 0.04 |
| LV mass (g) | 153 (126–187) | 181 (153–232) | 0.0003 |
| LV mass index ($g/height^{2.7}$) | 39 (33–45) | 45 (39–54) | 0.0002 |
| Ejection fraction (%) | 64 ± 6 | 62 ± 7 | 0.2 |
| Mitral annular e′ (cm/s) | 7.5 ± 2.6 | 6.8 ± 1.9 | 0.03 |
| E/e′ ratio | 12 (10–18) | 13 (10–15) | 0.7 |
| LA volume (ml) | 66 (51–99) | 71 (60–91) | 0.3 |
| LA volume index ($ml/height^{2.7}$) | 17 (13–24) | 17 (14–22) | 0.9 |

Values are mean ± standard deviation, $n$ (%), or median (interquartile range).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; NT-proBNP, N-terminal pro B-type natriuretic peptide.

greater in the high WC group than in the low WC group (*Table 3*, *Figure 2A* and *2B*). In contrast, none of these variables differed significantly as a function of WC in men with HFpEF. In linear regression analyses, WC exhibited positive associations with fasting glucose, LDL cholesterol, in women, but not men (*Figure 2C*), but there were no significant sex interactions for any of these analyses (online supplementary *Table S6*). Significant associations of WC with HDL cholesterol and triglycerides were observed in both women and men with HFpEF. Women with HFpEF and high WC displayed greater LV mass index compared to those with low WC, but this difference was not apparent in men (*Table 3*).

Right atrial pressure, PA pressure, and PCWP at rest did not significantly differ between the low and high WC groups for either sex (*Table 4*). However, with exercise, RA and PA pressure were higher in the high WC group than in the low WC group

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**Table 2 Baseline and peak exercise haemodynamics in heart failure with preserved ejection fraction with and without central obesity**

| | HFpEF without central obesity ($n = 52$) | HFpEF with central obesity ($n = 177$) | $p$-value |
|---|---|---|---|
| Baseline | | | |
| Heart rate (bpm) | 63 ± 12 | 66 ± 12 | 0.2 |
| Systolic blood pressure (mmHg) | 147 ± 25 | 145 ± 27 | 0.7 |
| RA pressure (mmHg) | 9 ± 4 | 10 ± 4 | 0.2 |
| PA systolic pressure (mmHg) | 40 ± 12 | 40 ± 12 | 0.6 |
| PA mean pressure (mmHg) | 26 ± 8 | 26 ± 8 | 0.7 |
| PCWP (mmHg) | 16 ± 5 | 17 ± 6 | 0.5 |
| CO (L/min) | 4.6 ± 1.3 | 5.1 ± 1.5 | 0.02 |
| Cardiac index (L/min/m$^2$) | 2.5 ± 0.7 | 2.4 ± 0.6 | 0.4 |
| Peak exercise | | | |
| Workload (W) | 53 ± 27 | 45 ± 26 | 0.06 |
| Duration of exercise (min) | 11 ± 4 | 10 ± 5 | 0.1 |
| Heart rate (bpm) | 101 ± 27 | 100 ± 21 | 0.8 |
| Systolic blood pressure (mmHg) | 181 ± 32 | 174 ± 31 | 0.3 |
| RA pressure (mmHg) | 17 ± 6 | 20 ± 7 | 0.005 |
| PA systolic pressure (mmHg) | 57 ± 15 | 66 ± 16 | <0.0001 |
| PA mean pressure (mmHg) | 40 ± 11 | 46 ± 10 | 0.0003 |
| PCWP (mmHg) | 29 ± 6 | 32 ± 6 | 0.001 |
| PCWP/W (mmHg/W) | 0.71 ± 0.40 | 0.95 ± 0.54 | 0.005 |
| PCWL (mmHg*kg/W) | 42 (28–67) | 76 (49–120) | <0.0001 |
| CO (L/min) | 8.2 ± 2.7 | 8.7 ± 3.1 | 0.3 |
| Cardiac index (L/min/m$^2$) | 4.5 ± 1.4 | 4.1 ± 01.4 | 0.1 |
| PCWP/CO slope | 3.7 (2.0–7.2) | 4.7 (2.6–7.9) | 0.3 |
| Supine peak $VO_2$ (ml/min*kg)[a] | 11.6 ± 3.4 | 8.9 ± 2.9 | <0.0001 |
| Supine peak $VO_2$ (ml/min)[a] | 828 ± 44 | 852 ± 24 | 0.6 |
| Supine RER[a] | 1.08 ± 0.14 | 1.00 ± 0.12 | 0.0003 |
| Upright peak $VO_2$ (ml/min*kg)[b] | 17.1 ± 5.2 | 15.1 ± 4.7 | 0.01 |
| Upright peak $VO_2$ (ml/min)[b] | 1237 ± 71 | 1475 ± 523 | 0.004 |
| % Predicted peak $VO_2$ | 83 ± 23 | 91 ± 24 | 0.04 |
| Upright RER[b] | 1.13 ± 0.15 | 1.10 ± 0.11 | 0.2 |

Values are mean ± standard deviation, or median (interquartile range).
CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PCWL, ratio of pulmonary capillary wedge pressure at peak exercise to workload normalized to body weight; RA, right atrial; RER, respiratory exchange ratio; $VO_2$, oxygen consumption.
[a]Measured during supine invasive exercise testing.
[b]Measured during non-invasive upright exercise testing at separate visit.

among women with HFpEF, but these haemodynamics were not significantly different in men with HFpEF (*Table 4*). Conversely, CO during exercise was greater in the high WC group than in the low WC group among men with HFpEF, but did not vary with WC in women with HFpEF. Women with HFpEF in the high WC group demonstrated significantly higher PCWP as CO increased compared to women with HFpEF in the low WC group (*Figure 3A*, *Table 4*). Among men, exercise PCWP did not significantly differ between the high and low WC groups (*Figure 3B*, *Table 4*). PCWP/CO slope was associated with WC only in women, but not in men (*Table 4*). When tested using linear regression analysis, we found that peak exercise workload decreased as a function of increasing WC in women, but not in men; the sex interaction term was not statistically significant (*Figure 3C*, *Table 5*). RA and PA pressures during exercise were associated with WC in women only. Although there was no significant sex interaction, the impairment in PCWP/W was significantly greater in women with HFpEF and increased WC but not in men (interaction $p = 0.08$, online supplementary *Figure S3*). The strength of correlation between PCWP/W and WC was also significantly more robust in women with HFpEF as compared to men (Meng's test $p = 0.0008$). The impairment in PCWL was significantly greater in women with HFpEF and increased WC as compared to men (interaction $p = 0.02$, *Figure 3E*). With supine exercise, the peak RER was lower in patients with high WC than low WC in women, but it was not significantly different in men (*Table 4*). In both sexes, supine and upright peak $VO_2$ indexed to body weight were lower in the high WC group, indicating poorer aerobic capacity. However, absolute peak $VO_2$ (i.e. not indexed to body weight) was similar during supine exercise in the two groups, and in fact higher (or tending to be higher) in those with central obesity during upright exercise.

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**Table 3 Cardiometabolic and cardiac structure-function data stratified by sex and waist circumference**

| | Women with HFpEF | | | Men with HFpEF | | |
|---|---|---|---|---|---|---|
| | Low WC ($n = 63$) | High WC ($n = 61$) | *p*-value | Low WC ($n = 55$) | High WC ($n = 50$) | *p*-value |
| Age (years) | 67 ± 15 | 66 ± 9 | 0.7 | 71 ± 10 | 64 ± 12 | 0.002 |
| Height (cm) | 162 ± 7 | 164 ± 7 | 0.3 | 175 ± 6 | 178 ± 7 | 0.01 |
| Weight (kg) | 72 ± 10 | 100 ± 19 | <0.0001 | 88 ± 11 | 113 ± 17 | <0.0001 |
| Body surface area ($m^2$) | 1.79 ± 0.14 | 2.08 ± 0.21 | <0.0001 | 2.05 ± 0.15 | 2.32 ± 0.20 | <0.0001 |
| BMI ($kg/m^2$) | 27.2 (24.6–31.2) | 36.2 (32.7–41.5) | <0.0001 | 28.4 (26.7–31.4) | 35.5 (32.3–37.3) | <0.0001 |
| General obesity (BMI >30 $kg/m^2$), *n* (%) | 18 (29) | 58 (95) | <0.0001 | 19 (35) | 47 (94) | <0.0001 |
| Body fat (%, available in $n = 146$) | 33 ± 5 | 37 ± 3 | <0.0001 | 24 ± 4 | 29 ± 4 | <0.0001 |
| Comorbidities, *n* (%) | | | | | | |
| Hypertension | 52 (82) | 56 (92) | 0.1 | 49 (89) | 46 (92) | 0.6 |
| Diabetes mellitus | 6 (10) | 19 (31) | 0.002 | 14 (25) | 19 (38) | 0.2 |
| Atrial fibrillation | 24 (38) | 17 (28) | 0.2 | 22 (40) | 16 (32) | 0.4 |
| Dyslipidaemia | 40 (63) | 47 (77) | 0.1 | 44 (80) | 43 (86) | 0.4 |
| COPD | 5 (8) | 11 (18) | 0.09 | 8 (15) | 7 (14) | 0.9 |
| Laboratory data | | | | | | |
| Fasting glucose (mg/dl) | 96 (87–105) | 107 (95–127) | 0.0004 | 104 (92–129) | 106 (95–135) | 0.5 |
| LDL-C (mg/dl) | 82 (62–105) | 104 (72–135) | 0.02 | 79 (61–100) | 82 (60–113) | 0.5 |
| HDL-C (mg/dl) | 63 (50–73) | 51 (45–64) | 0.009 | 45 (38–55) | 40 (34–50) | 0.07 |
| Triglyceride (mg/dl) | 93 (73–140) | 163 (98–214) | <0.0001 | 109 (72–154) | 161 (110–208) | 0.02 |
| Echocardiography | | | | | | |
| LV diastolic dimension (mm) | 46.8 ± 4.4 | 47.9 ± 4.5 | 0.2 | 49.9 ± 5.0 | 51.7 ± 5.2 | 0.08 |
| LV mass (g) | 148 (128–175) | 171 (148–203) | 0.0001 | 188 (170–235) | 230 (187–264) | 0.008 |
| LV mass index ($g/height^{2.7}$) | 41 (33–47) | 45 (39–56) | 0.001 | 43 (38–51) | 46 (40–56) | 0.1 |
| Ejection fraction (%) | 64 ± 6 | 65 ± 4 | 0.3 | 61 ± 8 | 61 ± 7 | 0.9 |
| Mitral annular e′ (cm/s) | 7.2 ± 2.5 | 6.8 ± 1.8 | 0.4 | 6.5 ± 2.0 | 7.1 ± 2.0 | 0.2 |
| E/e′ ratio | 11 (9–17) | 13 (11–16) | 0.1 | 12 (10–18) | 12 (9–15) | 0.6 |
| LA volume (ml) | 62 (46–81) | 67 (57–86) | 0.1 | 75 (66–114) | 78 (66–107) | 0.9 |
| LA volume index ($ml/height^{2.7}$) | 17 (14–23) | 17 (14–23) | 0.4 | 17 (15–24) | 17 (13–22) | 0.3 |

Values are mean ± standard deviation, *n* (%), or median (interquartile range).
BMI, body mass index; COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; WC, waist circumference.

# Discussion

We found that central adiposity is even more common in HFpEF than general obesity. Patients with HFpEF and central obesity displayed greater prevalence of diabetes and dyslipidaemia, more severe haemodynamic perturbations during exercise, and more severe impairments in aerobic capacity. Associations of central obesity with metabolic abnormalities including glucose, lipids, as well as haemodynamic perturbations such as peak workload and RA, PA pressure, PCWP/W were significant only in women with HFpEF but not in their male counterparts. These findings might suggest that associations between central obesity and metabolic abnormalities and haemodynamic perturbations were more profound in women with HFpEF than in their male counterparts.

## Obesity and central fat distribution in HFpEF

Obesity is one of the most common and clinically important comorbidities among patients with HFpEF, affecting 60%–80% of patients.[10] Patients with HFpEF and general obesity display poorer exercise capacity, more profound haemodynamic abnormalities during exercise, and impaired pulmonary vasodilatation, which lead to more severe symptoms and worse quality of life compared to non-obese HFpEF patients.[4,10,21–24] Excess adipose content in the form of visceral adipose tissue has been identified as a key risk factor, mediator and prognostic factor of HFpEF with obesity.[3,4,25]

In the present study, we showed that these abnormalities were strongly related to the presence of central adiposity (*Table 2*). While the most common pattern was combined central and general obesity (*Figure 1*), it is notable that prevalence of central obesity as a stand-alone diagnosis was higher than general obesity defined conventionally by BMI (77% vs. 62%, $p < 0.0001$). The independent relevance of central adiposity is further supported by analyses restricted to patients with normal BMI or overweight (<30 $kg/m^2$), of whom 38 (44%) had a central, upper body fat distribution. This group displayed higher prevalence of diabetes, dyslipidaemia, and worse exercise haemodynamics compared to HFpEF without central obesity (online supplementary *Tables S2* and *S3*). This indicates that the overall differences between patients

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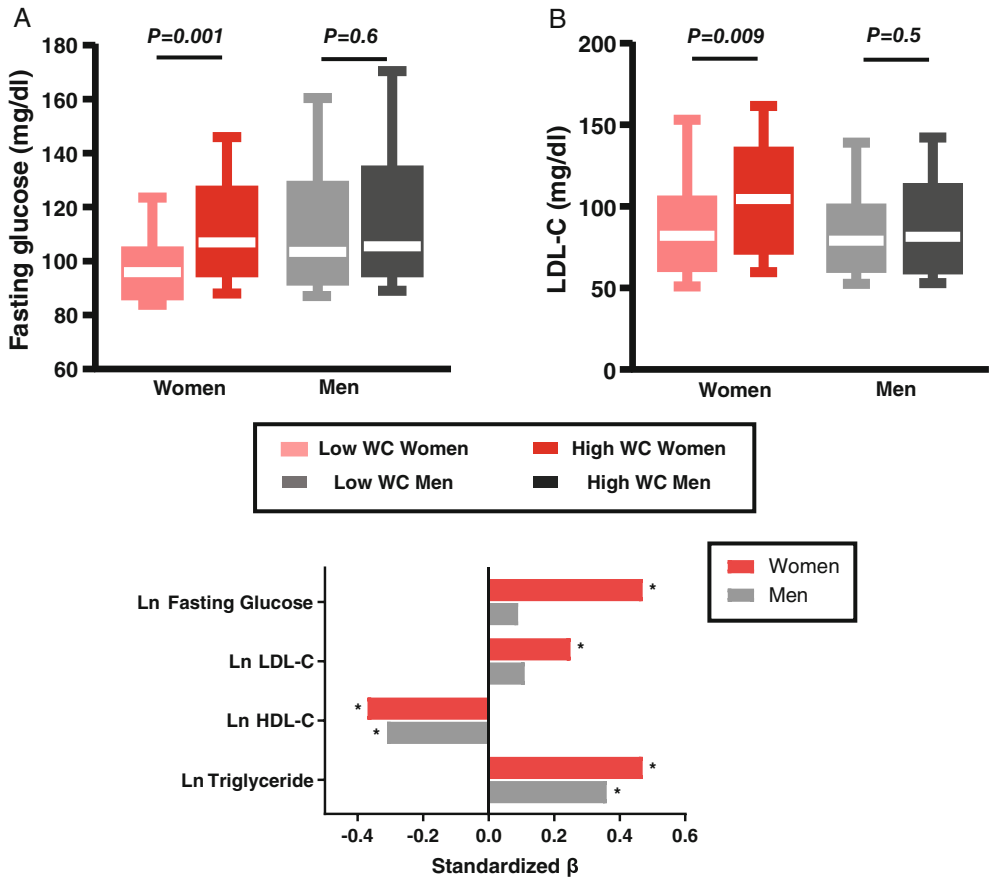


**Figure 2** Metabolic and Inflammatory marker relationships with waist circumference. (WC) fasting glucose (*A*) and low-density lipoprotein cholesterol (LDL-C) levels (*B*) were higher in the high WC group than in the low WC group in women, but they were not significantly different between the low and high WC groups in men. (*C*) WC was associated with fasting glucose, and LDL-C in women only. WC was significantly associated with high-density lipoprotein cholesterol (HDL-C) and triglyceride levels in both women and men. *Significance was defined as $p < 0.05$.

with and without central obesity are not simply ascribable to general obesity, further emphasizing the limitations of BMI as an index of adiposity.

Body mass index does not distinguish between fat and lean mass, nor does it consider differences in body fat distribution. In this regard WC provides a more robust method to estimate body composition when more direct measures such as imaging are not available.[26] A prior study has shown that higher WC is associated with an increased risk of all-cause mortality in HFpEF, whereas BMI conversely associated with lower mortality in keeping with the obesity paradox.[9] Here we demonstrate clinically relevant associations between central obesity and cardiometabolic abnormalities typical of HFpEF, further emphasizing the importance for therapies targeting obesity and visceral adipose excess in this cohort. Collectively, these data suggest that focusing solely on BMI to phenotype HFpEF patients may underestimate the impact of adiposity, particularly among those HFpEF patients with a BMI <30 kg/m$^2$.

The mechanism pathways connecting central body fat distribution to HFpEF pathophysiology are not yet clear. Adipose tissue is an active endocrine organ and produces proinflammatory cytokines, leading to chronic cardiac remodelling.[27] Adipose tissue may contribute to sodium retention and plasma volume expansion directly through the adipocyte-dependent elaboration of leptin, neprilysin, and aldosterone,[28] or indirectly by inducing insulin resistance leading to hyperinsulinaemia, which also has potent anti-natriuretic effects that may contribute to volume expansion.[29]

Patients with HFpEF and obesity also exhibit impairments in venous function such as a reduction in systemic venous capacity and compliance, resulting in higher LV filling pressure on exertion,[23] and this may be amplified even greater in central obesity. Patients with increases in upper body adipose tissue (as in central obesity) also display higher plasma free fatty acid levels,[30] and multiple studies have suggested that excess free fatty acid delivery to the heart impairs cardiac function and efficiency,[31] which may be associated with energetic abnormalities that contribute to diastolic dysfunction,[32] or even frank myocardial lipotoxicity due to excess myocellular fat accumulation.[33]

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**Table 4 Baseline and exercise haemodynamic data in heart failure with preserved ejection fraction stratified by sex and waist circumference**

| | Women with HFpEF | | | Men with HFpEF | | |
|---|---|---|---|---|---|---|
| | Low WC ($n = 63$) | High WC ($n = 61$) | *p*-value | Low WC ($n = 55$) | High WC ($n = 50$) | *p*-value |
| Baseline | | | | | | |
| Heart rate (bpm) | 66 ± 12 | 67 ± 12 | 0.6 | 63 ± 12 | 66 ± 14 | 0.4 |
| Systolic blood pressure (mmHg) | 142 ± 30 | 150 ± 26 | 0.2 | 147 ± 21 | 142 ± 27 | 0.4 |
| RA pressure (mmHg) | 9 ± 4 | 10 ± 4 | 0.4 | 9 ± 4 | 11 ± 4 | 0.06 |
| PA systolic pressure (mmHg) | 38 ± 11 | 41 ± 11 | 0.2 | 40 ± 13 | 41 ± 14 | 0.7 |
| PA mean pressure (mmHg) | 25 ± 7 | 27 ± 7 | 0.1 | 26 ± 9 | 26 ± 9 | 0.9 |
| PCWP (mmHg) | 16 ± 5 | 17 ± 6 | 0.5 | 15 ± 5 | 18 ± 6 | 0.06 |
| CO (L/min) | 4.5 ± 1.4 | 5.1 ± 1.3 | 0.02 | 4.9 ± 1.0 | 5.6 ± 1.7 | 0.009 |
| Peak exercise haemodynamics | | | | | | |
| Workload (W) | 45 ± 23 | 37 ± 18 | 0.04 | 52 ± 30 | 53 ± 30 | 0.9 |
| Duration of exercise (min) | 10 ± 4 | 9 ± 4 | 0.3 | 11 ± 5 | 11 ± 5 | 0.7 |
| Heart rate (bpm) | 108 ± 24 | 100 ± 23 | 1.0 | 93 ± 22 | 98 ± 20 | 0.3 |
| Systolic blood pressure (mmHg) | 175 ± 33 | 178 ± 32 | 0.7 | 175 ± 30 | 175 ± 32 | 1.0 |
| RA pressure (mmHg) | 17 ± 7 | 20 ± 7 | 0.03 | 20 ± 6 | 21 ± 7 | 0.3 |
| PA systolic pressure (mmHg) | 59 ± 14 | 66 ± 16 | 0.02 | 64 ± 17 | 68 ± 16 | 0.2 |
| PA mean pressure (mmHg) | 41 ± 10 | 47 ± 11 | 0.002 | 44 ± 10 | 46 ± 9 | 0.2 |
| PCWP (mmHg) | 29 ± 6 | 34 ± 8 | 0.0004 | 30 ± 5 | 32 ± 5 | 0.1 |
| PCWP/W (mmHg/W) | 0.81 ± 0.40 | 1.14 ± 0.59 | 0.0007 | 0.79 ± 0.48 | 0.84 ± 0.53 | 0.6 |
| PCWL (mmHg*kg/W) | 58 ± 29 | 120 ± 78 | <0.0001 | 70 ± 44 | 94 ± 61 | 0.02 |
| CO (L/min) | 8.1 ± 3.2 | 8.3 ± 3.0 | 0.8 | 8.3 ± 2.5 | 9.8 ± 3.2 | 0.009 |
| Cardiac index (L/min/m$^2$) | 4.5 ± 1.6 | 4.0 ± 1.4 | 0.06 | 4.0 ± 1.3 | 4.3 ± 1.4 | 0.4 |
| PCWP/CO slope | 4.1 (1.9–7.4) | 5.4 (4.0–8.5) | 0.02 | 3.7 (2.3–9.3) | 3.3 (1.9–5.6) | 0.5 |
| Supine peak $VO_2$ (ml/min*kg)[a] | 10.7 ± 2.8 | 8.1 ± 2.9 | <0.0001 | 10.2 ± 3.5 | 8.7 ± 2.8 | 0.03 |
| Supine peak $VO_2$ (ml/min)[a] | 774 ± 217 | 791 ± 275 | 0.7 | 890 ± 305 | 966 ± 341 | 0.3 |
| Supine RER[a] | 1.06 ± 0.13 | 0.99 ± 0.11 | 0.005 | 1.02 ± 0.12 | 1.00 ± 0.13 | 0.5 |
| Upright peak $VO_2$ (mL/min*kg)[b] | 15.8 ± 4.6 | 13.1 ± 4.0 | 0.0006 | 17.8 ± 5.2 | 15.6 ± 4.6 | 0.03 |
| Upright peak $VO_2$ (mL/min)[b] | 1152 ± 417 | 1299 ± 426 | 0.06 | 1555 ± 513 | 1775 ± 503 | 0.03 |
| % Predicted peak $VO_2$ | 91 ± 22 | 90 ± 25 | 0.8 | 86 ± 25 | 91 ± 24 | 0.3 |
| Upright RER[b] | 1.12 ± 0.15 | 1.09 ± 0.14 | 0.3 | 1.11 ± 0.08 | 1.11 ± 0.10 | 0.9 |

Values are mean ± standard deviation, or median (interquartile range).
CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PCWL, ratio of pulmonary capillary wedge pressure at peak exercise to workload normalized to body weight; RA, right atrial; RER, respiratory exchange ratio; $VO_2$, oxygen consumption; WC, waist circumference.
[a]Measured during supine invasive exercise testing.
[b]Measured during non-invasive upright exercise testing at separate visit.

## Sex differences in central obesity in HFpEF

HFpEF is the most common subtype of HF in women.[3,4] Recent studies have shown that obesity is a stronger risk factor for HFpEF in women than in men.[6] From an analysis of 105 patients with HFpEF (63 women) and 105 age- and BMI-matched control participants, we found that excess visceral adipose as measured using computed tomography was associated with haemodynamic abnormalities in women but not in men.[4] In the present study, which includes an independent cohort of patients from the prior study, we corroborated this finding in a larger sample using the more pragmatic measure of WC and extend these associations to include cardiometabolic abnormalities.

Consistent with a prior study,[4] we showed associations between central obesity and haemodynamic derangements during exercise were more profound in women with HFpEF than in men. In addition, patients with central obesity, particularly women, had lower respiratory exchange ratio at peak supine exercise, which likely contributed to their lower peak $VO_2$, indicating earlier cessation of exercise prior to onset of anaerobic metabolism. Indeed, many patients with HFpEF are not able to attain a respiratory exchange ratio >1.0–1.1, and this may be related to inability to tolerate the discomfort associated with elevated PCWP during stress.

In this study, peak $VO_2$ indexed to body weight and absolute peak $VO_2$ had different relationships with central obesity. During supine and upright exercise, peak $VO_2$ indexed to body weight was lower

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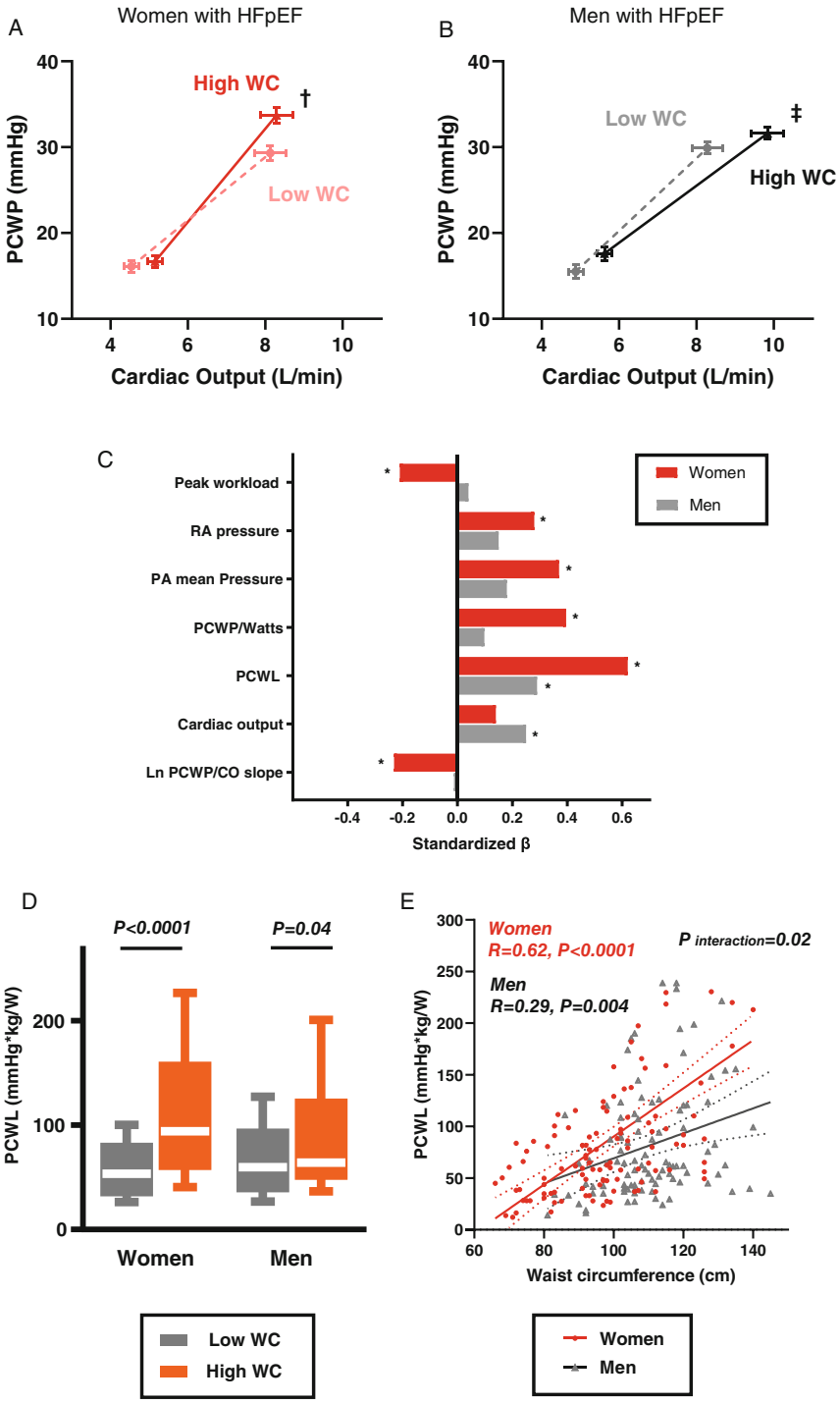


**Figure 3** Despite greater increases in pulmonary capillary wedge pressure (PCWP), women with high waist circumference (WC) exhibited less of an increase in cardiac output (CO) than women with low WC (*A*). In men, the high WC group exhibited a less substantial increase in PCWP than the low WC group, but CO increased more than in men with heart failure with preserved ejection fraction (HFpEF) and low WC (*B*). Linear regression for the associations of WC with exercise haemodynamics (*C*). Peak workload, right atrial (RA) pressure, and pulmonary artery (PA) pressure during exercise, PCWP/W and PCWP/CO slope were associated with WC in women only. The ratio of PCWP at peak exercise to workload normalized to body weight (PCWL) was associated with WC in both sexes. CO was associated with WC in men only. For both sexes, PCWL was higher in the high WC group than in the low WC group (*D*). We observed an interaction effect of sex on the association between WC and PCWL (*E*). Ln, log transformed. $^{\dagger}p < 0.05$ vs. low WC in PCWP in (*A*). $^{\ddagger}p < 0.05$ vs. low WC in CO in (*B*). *Significance was defined as $p < 0.05$ in (*C*).

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**Table 5 Associations with waist circumference (per 10 cm) by sex**

| | Women ($n$ = 124) | | Men ($n$ = 105) | | $p$ for sex interaction |
|---|---|---|---|---|---|
| | β (95% CI) | $p$-value | β (95% CI) | $p$-value | |
| Baseline | | | | | |
| RA pressure (mmHg) | 0.46 (0.99, 0.92) | 0.049 | 0.45 (−0.13, 1.03) | 0.1 | 1.0 |
| PA mean pressure (mmHg) | 0.54 (−0.20, 1.28) | 0.2 | 0.12 (−1.17, 1.40) | 0.9 | 0.6 |
| PCWP (mmHg) | 0.33 (−0.26, 0.92) | 0.3 | 0.86 (0.01, 1.70) | 0.047 | 0.3 |
| CO (L/min) | 0.32 (0.17, 0.47) | <0.0001 | 0.35 (0.15, 0.56) | 0.0008 | 0.3 |
| Exercise | | | | | |
| Ln Peak workload (W) | −0.06 (−0.11, −0.01) | 0.01 | 0.01 (−0.08, 0.09) | 0.7 | 0.2 |
| RA pressure (mmHg) | 1.15 (0.36, 1.93) | 0.005 | 0.72 (−0.33, 1.78) | 0.2 | 0.5 |
| PA mean pressure (mmHg) | 2.41 (1.32, 3.50) | <0.0001 | 1.33 (−0.10, 2.76) | 0.07 | 0.2 |
| PCWP (mmHg) | 1.80 (1.11, 2.49) | <0.0001 | 1.23 (0.50, 1.97) | 0.001 | 0.3 |
| PCWP/W (mmHg/W) | 0.12 (0.07, 0.17) | <0.0001 | 0.04 (−0.04, 0.12) | 0.3 | 0.08 |
| PCWL (mmHg*kg/W) | 23.3 (17.8, 28.8) | <0.0001 | 12.1 (3.97, 20.2) | 0.004 | 0.02 |
| CO (L/min) | 0.26 (−0.08, 0.61) | 0.1 | 0.56 (0.11, 1.02) | 0.02 | 0.3 |
| Ln PCWP/CO slope | 0.14 (0.03, 0.23) | 0.02 | −0.01 (−0.15, 0.13) | 0.9 | 0.1 |
| Supine peak $VO_2$ (ml/min*kg) | −0.94 (−1.26, −0.63) | <0.0001 | −0.81 (−1.34, −0.29) | 0.003 | 0.7 |
| Supine peak $VO_2$ (ml/min)[a] | 14,5 (−14.1, 43.0) | 0.3 | 36.5 (−17.0, 90.2) | 0.2 | 0.4 |
| Supine RER[a] | −0.03 (−0.04, −0.01) | 0.0002 | −0.02(−0.04, 0.00) | 0.1 | 0.3 |
| Upright peak $VO_2$ (ml/min*kg) | −0.88 (−1.34, −0.41) | 0.0003 | −1.30 (−2.03, −0.57) | 0.0006 | 0.3 |
| Upright peak $VO_2$ (ml/min)[b] | 72.5 (27.8, 117.1) | 0.002 | 78.1 (−0.03, 156.2) | 0.05 | 0.9 |
| % Predicted peak $VO_2$ | 0.21 (−2.38, 2.80) | 0.9 | 2.51 (−1.23, 6.25) | 0.2 | 0.3 |
| Upright RER[b] | −0.01 (−0.02, 0.01) | 0.3 | 0.00 (−0.02, 0.01) | 0.5 | 0.8 |

CI, confidence interval; CO, cardiac output; Ln, log transformed; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PCWL, ratio of pulmonary capillary wedge pressure at peak exercise to workload normalized to body weight; RA, right atrial; RER, respiratory exchange ratio; $VO_2$, oxygen consumption; WC, waist circumference.
[a]Measured during supine invasive exercise testing.
[b]Measured during non-invasive upright exercise testing at separate visit.

in HFpEF with central obesity, indicating poorer aerobic capacity. However, absolute peak $VO_2$ and percent-predicted peak $VO_2$ during upright exercise were higher in patients with central obesity (*Table 2*). While this could be interpreted as signifying better fitness in patients with central obesity, this more likely reflects the importance of accounting for body weight when considering peak $VO_2$ as a measure of aerobic capacity rather than using regression equations to predict normal responses. Indeed, a prior study has shown that percent-predicted peak $VO_2$ concealed group differences between individuals with HFpEF and non-cardiac causes of dyspnoea.[35] In the SECRET trial,[36] it was shown that diet-induced weight loss improved the primary endpoint of peak $VO_2$ indexed to body weight in patients with HFpEF (16.1 vs. 14.8 ml/kg/min, estimated treatment effect 1.3 ml/kg/min, $p < 0.001$ compared to attention control). However, if one were to instead substitute absolute peak $VO_2$ as the primary endpoint of the very same trial, the reader would conclude that there was no effect of weight loss (1537 vs. 1519 ml/min, $p = 0.44$). Therefore, based upon the prior literature and the known deleterious effects of central adiposity in non-HFpEF cohorts, we interpret the present findings to indicate that central obesity was associated with reduced, not greater, aerobic capacity.

We found that men displayed a worse metabolic risk profile and a higher prevalence of dyslipidaemia, higher fasting glucose, and lower HDL cholesterol than women, despite similarities in age and BMI (online supplementary *Table S4*), mirroring what is observed in the general population. However, central obesity was significantly correlated with metabolic markers in women but not men without significant sex interactions. These findings might imply that central obesity confers a greater risk of metabolic disorder in women with HFpEF than in their male counterparts, consistent with other studies.[7]

Insulin resistance, hyperinsulinaemia, and hyperglycaemia lead to changes in substrate metabolism and cardiac lipotoxicity, advanced glycated end-product deposition, endothelial and microvascular dysfunction, inappropriate neurohormonal responses, oxidative stress, and subcellular component abnormalities, which may result in LV remodelling.[37,38] The present findings are consistent with the nearly three-fold greater causal effect of visceral adiposity among women for type 2 diabetes with increases in visceral fat from a recent Mendelian randomization analysis.[7]

Compared with men, women are more prone to the systemic metabolic disorders that cause adipose tissue inflammation, and they show a heightened systemic inflammatory response to the accumulation of body fat. Circulating adipokines and inflammatory markers such as leptin and C-reactive protein are higher in women than men.[28,39,40] Women may also be more susceptible to developing coronary microvascular dysfunction along with myocardial structural and functional abnormalities in response to increases in visceral adiposity and systemic inflammation,[41,42] consistent with

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relationships between central obesity and haemodynamic and functional impairments among women with central obesity in the present study.

## Clinical implications

Exercise intolerance, the primary symptom in HFpEF and major contributor to reduced quality of life, is significantly correlated with increased adiposity.[22] In a prospective randomized trial in patients with HFpEF and obesity, diet-induced weight loss was found to improve peak $VO_2$ in tandem with substantial reductions in visceral fat and decreases in inflammation.[36] In addition, in a meta-analysis of obese patients without HF, therapeutic weight loss was found to be associated with reductions in RA pressure, PA pressure and PCWP.[43] It is well established that increased WC, a marker of visceral adiposity, is a stronger correlate of metabolic disruptions and inflammation than general obesity.[44,45] Viewed in tandem with the published literature, the present findings relating haemodynamic severity to excess upper body fat provide further support for the emerging hypothesis that treatments targeting central obesity may be effective to improve clinical status in patients with HFpEF, particularly in women.

## Limitations

This was a single-centre study conducted at a tertiary referral centre, introducing selection and referral bias. The cross-sectional nature of the study limits ability to make inferences regarding causality. There were a number of baseline differences that were not adjusted for that may influence group differences. The sample size was reduced owing to the requirement for WC measurements in patients undergoing invasive exercise testing to define the presence or absence of central obesity, which may have limited power to detect sex interactions in multivariable linear regression analysis, and the attainment of these measurements may also introduce additional selection bias, though baseline characteristics of the groups with and without WC were similar. The most common form of obesity still appears to be concurrent central and general obesity. Although we attempted to address whether those metabolic and haemodynamic abnormalities are observed in the subgroup with central obesity but without general obesity (online supplementary *Tables S2* and *S3*), the small numbers also decrease statistical power. Given the focus on pathophysiology and mechanisms rather than treatment, correction for multiple hypothesis testing was not performed. We did not assess fat composition directly, and measurement of WC cannot discriminate between visceral fat and subcutaneous fat.

# Conclusions

Central obesity is even more common than general obesity in HFpEF, affecting 77% of patients overall, and 44% of patients with BMI falling in the non-obese range. The presence of central obesity in HFpEF with or without general obesity is associated with greater metabolic abnormalities, poorer exercise capacity, and more profound haemodynamic impairments during exercise, and these effects might be more prominent in women than men. Further studies are required to evaluate the mechanisms underlying the relationships between central obesity and HFpEF in women and men, along with clinical trials targeting central adiposity in this patient population for whom few treatments exist.

# Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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