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# Regional adiposity and heart failure with preserved ejection fraction

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## Abstract

The role of obesity in the pathogenesis of heart failure (HF), and in particular HF with preserved ejection fraction (HFpEF), has drawn significant attention in recent years. The prevalence of both obesity and HFpEF has increased worldwide over the past decades and when present concomitantly suggests an obese-HFpEF phenotype. Anthropometrics, including body mass index, waist circumference, and waist-to-hip ratio, are associated with incident HFpEF. However, the cardiovascular effects of obesity may actually be driven by the distribution of fat, which can accumulate in the epicardial, visceral, and subcutaneous compartments. Regional fat can be quantified using non-invasive imaging techniques, including computed tomography, magnetic resonance imaging, and dual-energy X-ray absorptiometry. Regional variations in fat accumulation are associated with different HFpEF risk profiles, whereby higher epicardial and visceral fat have a much stronger association with HFpEF risk compared with elevated subcutaneous fat. Thus, regional adiposity may serve a pivotal role in the pathophysiology of HFpEF contributing to decreased cardiopulmonary fitness, impaired left ventricular compliance, upregulation of local and systemic inflammation, promotion of neurohormonal dysregulation, and increased intra-abdominal pressure and vascular congestion. Strategies to reduce total and regional adiposity have shown promise, including intensive exercise, dieting, and bariatric surgery programmes, but few studies have focused on HFpEF-related outcomes among obese. Further understanding the role these variable fat depots play in the progression of HFpEF and HFpEF-related hospitalizations may provide therapeutic targets in treating the obese-HFpEF phenotype.

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Supplementary Information

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

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**Keywords**

Obesity; Regional adiposity; Heart failure; Heart failure with preserved ejection fraction

## Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a heterogeneous syndrome with multiple proposed mechanisms and is characterized by evidence of abnormal left ventricular (LV) relaxation and filling and an ejection fraction ≥50%.[1] Identifying effective therapies for HFpEF has been difficult due to its multiple distinct 'phenotypes', marked by diastolic dysfunction, impaired exercise reserve, abnormal ventricular–arterial coupling, inflammation and endothelial dysfunction, chronotropic incompetence, altered myocardial energetics and peripheral skeletal muscle metabolism, and renal insufficiency.[2,3] Obesity is a modifiable risk factor of HFpEF and represents excess total body adipose tissue.[2,4] The prevalence of both obesity and HFpEF has increased worldwide over the past decades.[5,6] Obesity is most commonly defined by anthropometrics, including body mass index (BMI), which is more representative of total adipose accumulation, and waist circumference (WC) and waist-to-hip ratio (WHR), which are more representative of central distribution of adiposity. While total body fat accumulation was once thought to contribute to cardiovascular risk, the deleterious cardiovascular effects of obesity may actually result from the distribution of adipose tissue within the body itself.[7] Obesity is a stronger risk factor for HF than other types of cardiovascular disease,[8] and among those who develop HF, higher BMI predicts HFpEF but not HF with reduced ejection fraction (HFrEF).[9,10] Recent trials describe that the obesity and HFpEF conditions present comorbidly,[11–17] suggesting the emergence of a distinct 'obese-HFpEF phenotype'.[18,19] Obesity is thus emerging as potentially the most important risk factor for HFpEF. While obesity contributes to the development of HFpEF, the role of regional adipose tissue distribution and its effect on HFpEF are not well understood but may play an important role in its pathophysiology. Additionally, it is not well known how regional adiposity may function differently within HFpEF groups with normal, overweight, and high BMI. In this review, we discuss the role regional adiposity has on the development and progression of HFpEF.

## Obesity and risk of heart failure with preserved ejection fraction

Obesity affects approximately 40% of the United States population and exhibits a higher prevalence in people above the age of 40 years.[20] As one ages, there is an increase in total body fat mass alongside a decrease in lean mass.[21] Obesity serves as an important risk factor for incident HF across community cohorts,[8,22] and the risk obesity confers on HF is not explained by obesity-related cardiometabolic risk factors alone.[8] Longitudinal studies have demonstrated that higher BMI confers greater risk of developing HFpEF but not HFrEF.[4,9,10,23] The association of obesity and HFpEF also appears to be stronger among older African American women than compared to White women.[24] Additionally, higher body weights in young adulthood predicts incident HF independent of BMI later in life,[25] suggesting that cumulative lifetime BMI-years drives development of HF. Average BMI has increased across HFpEF trial cohorts, as shown in Figure 1.[11–17] [Of note, PARAGON-HF

excluded morbid obesity (i.e. BMI >40 kg/m$^2$) and those with low plasma brain natriuretic peptide (BNP) at the time of enrolment, which likely reflects why the mean BMI is lower compared to other recent HFpEF trials][16].

Obesity is associated with diabetes, hypertension, LV hypertrophy, increased LV stiffness, and reduced diastolic relaxation among individuals in community populations, factors that may promote the progression of HFpEF.[26,27] Diabetes is also associated with LV remodelling, ventricular hypertrophy, and cardiac microvascular disease, likely contributing to the development of HFpEF among patients with diabetes.[28] Clinical outcomes are also worse among patients with diabetes treated with insulin in HFpEF.[29] The link between obesity and diabetes are likely driven by inhibited glucose transport and uptake into muscle cells caused by insulin resistance and reduced insulin sensitivity in the setting of glucotoxicity.[30] Central adiposity (prevalence of adipose tissue within the abdominal compartment), and particularly visceral adiposity, is a strong predictor of insulin resistance in obesity compared to normal weight individuals.[31] Visceral fat is strongly associated with increased hepatic glucose production and reduced glucose disposal,[31] and among those without diabetes, visceral but not subcutaneous fat is associated with insulin resistance.[32] Insulin resistance and its metabolic complications may contribute to HFpEF risk in obesity, although prospective studies are needed to characterize such mechanisms.

Central obesity, which is represented by the anthropometrics WC and WHR, is also associated with increased arterial stiffness, hypertension,[33,34] and HFpEF risk.[4,23] Weight loss and subsequent reduction in central adiposity has shown to reduce the degree of arterial stiffness.[35] Bariatric surgery also contributes to reduction in hypertension.[36] While regional fat is associated with arterial stiffening, observational data describe an association between obese HFpEF and lower arterial stiffness than compared to non-obese HFpEF.[37] The role of arterial vascular compliance in the development and pathophysiology of obese HFpEF is unclear and warrants further investigation. Among obese individuals, regional fat distribution may serve a pivotal role in the development of HFpEF[10] and provide insight into an obese HFpEF phenotype that may be more responsive to therapies such as weight loss (Figure 2).

## Regional distribution of adiposity and risk of heart failure with preserved ejection fraction

Fat accumulates within various body compartments, including subcutaneous, visceral, and epicardial compartments. While obesity, by measure of anthropometrics alone, contributes to risk of developing HFpEF, patterns of regional accumulation of adipose tissue within the body play a role in the development of HFpEF.[10] Although a person may be overweight or obese by anthropometrics (i.e. BMI ≥25 kg/m$^2$), regional fat accumulates disproportionately and does not equally contribute to the risk of HFpEF hospitalizations.[10]

### Visceral adipose tissue

Visceral adipose tissue (VAT) refers to the intra-abdominal adipose accumulation of omental and mesenteric adipose tissue, excluding subcutaneous and intramuscular fat (Figure 3).[38]

Visceral adipose tissue can be quantified by averaging the fat area at single or multiple levels within the abdominal cavity. These measurements can be performed at the level of the umbilicus, L2–L3, or L4–L5 using computed tomography (CT),[39] magnetic resonance imaging (MRI),[40] or dual-energy X-ray absorptiometry (DXA).[41] Various studies have looked at quantifying VAT between these imaging modalities and have found them to be comparable.[42,43]

Visceral adipose tissue is a pro-inflammatory tissue that increases cardiovascular risk by promoting diseases such as diabetes, dyslipidaemia, and hypertension.[44] While anthropometrics such as WC and WHR are intended to indirectly represent the degree of visceral adiposity by quantifying abdominal girth relative to the rest of the body, they in fact do not accurately quantify visceral fat.[38] Beyond increasing the risk of cardiometabolic disease, VAT (but not BMI) is directly associated with mortality, especially among obese people with coronary artery disease.[45] Even among those who are normal weight or overweight (i.e. BMI $<30$ kg/m$^2$), elevated VAT appears to be associated with metabolic derangements and prevalence of cardiometabolic diseases.[46]

Visceral adiposity also appears to serve an active role in the development of HF. Among ambulatory individuals, visceral adiposity is associated with increased levels of N-terminal pro-BNP, a subclinical HF-related measure of vascular congestion.[47] This correlation also appears among hospitalized individuals with HF. In a longitudinal, multi-ethnic cohort study, CT-measured VAT predicted incident hospitalized HFpEF but not HFrEF after adjusting for cardiovascular risk factors.[10] VAT also provided additional risk prediction of HFpEF among people who were overweight or obese (i.e. BMI $\geq 25$ kg/m$^2$).[10] Additionally, among people with normal BMI (i.e. BMI $<25$ kg/m$^2$), increased VAT predicted a trend towards increased incidence of hospitalized HFpEF. Excess VAT may confer risk of developing HFpEF even among people who are identified as not overweight or obese, shedding light on a limitation of anthropometrics in qualifying risk in developing HF within a ‘silent obesity’ phenotype. The longitudinal effect on changes in VAT and subsequent changes in diastolic dysfunction or prevention of incident HFpEF or HFpEF-related hospitalizations have not been studied.

## Epicardial adipose tissue

Epicardial adipose tissue (EAT) refers to regional fat surrounding the myocardium, within the pericardium. EAT is a complex, metabolically active adipose tissue that serves paracrine and exocrine functions, stores triglycerides to provide energy to the myocardium, produces pro-inflammatory adipokines and pro-oxidative substances, and may have a direct impact on cardiovascular health.[48,49] EAT can be measured by quantifying epicardial fat thickness using non-invasive imaging modalities which include two-dimensional transthoracic echocardiography,[50] CT,[51] and MRI.[52] Among these methods, CT and MRI provide the ability to quantify epicardial fat by volume and fat thickness, and MRI provides the greatest reproducibility in measurements.[53]

Epicardial fat appears to exert two key detrimental functions on the heart: (i) pro-inflammatory effects and driver of comorbid disease; (ii) cardio-mechanical interaction advancing diastolic dysfunction. EAT is associated with accelerated coronary atherosclerosis, insulin resistance, and hypertension both in obese and non-obese

individuals.[54–57] Among HF patients, EAT is associated with atrial fibrillation, diabetes, and biomarkers of myocardial injury.[58] Further, EAT thickness in itself, which trends with higher BMI, correlates with the prevalence of hypertension.[59] EAT displays different effects by sex and tends to increase disproportionately in older women.[59] The detrimental mechanical properties of EAT become apparent through a correlation with increased ventricular wall thickness, worsened LV relaxation, and diastolic dysfunction.[59–61] While epicardial fat is associated with diastolic dysfunction, no studies have investigated the role epicardial fat plays in incidence of HFpEF or whether changes in degree of EAT improves diastolic function among patients with HFpEF.

### Subcutaneous adipose tissue

Subcutaneous adipose tissue (SAT) refers to the accumulation of adipose tissue outside of the abdominal cavity. The quantification of SAT is similar to visceral adiposity, and can be measured non-invasively using CT,[39] MRI,[42] and DXA.[41] SAT appears to have different effects on cardiometabolic risk than adipose tissue in other body compartments, such as VAT. Subcutaneous adiposity is less likely associated with subclinical and clinical cardiovascular disease.[62,63] Additionally, cosmetic therapies that target and remove SAT have no effect on cardiovascular risk.[64] Among individuals without known cardiovascular disease, SAT served no role in predicting future HF, including HFpEF and HFrEF.[10] The role of altering burden of subcutaneous fat in modulating cardiovascular health remains unclear.

## Cardio-mechanical–adipose interactions

### Decreased cardiopulmonary performance

Obesity is associated with impaired cardiac energy delivery with exercise among those without HF.[65] Higher BMI also correlates with worse exercise performance among those with HF.[66] The association between obesity and poorer cardiopulmonary performance may vary by BMI as well as the distribution of fat, suggesting a distinct obese HFpEF phenotype.[19] People with obese HFpEF are different from non-obese HFpEF—they tend to have higher LV mass and develop a high output failure physiology with impaired augmentation of cardiac output during exercise despite maintaining preserved ejection fraction.[67] Peak exercise oxygen consumption ($VO_2$) drops with higher BMI among obese HFpEF.[19,68] Additionally, obese HFpEF patients have higher cardiac filling pressures with exercise,[19] worse HF symptoms, and higher metabolic cost of exertion than non-obese HFpEF.[37]

Along with excess adiposity, regional adiposity may serve a role in decreased exercise performance.[69] Higher visceral fat predicts worse peak $VO_2$, ventilatory anaerobic threshold, and 6-min walk test outcomes among obese HFpEF compared to healthy controls, and intra-abdominal adiposity predicts poorer cardiopulmonary performance than epicardial fat.[70] Visceral adiposity is also associated with reduced myocardial glucose uptake,[71] impaired efficiency of fatty acid metabolism,[72] impaired myocardial energetics, myocardial steatosis, and concentric LV hypertrophy that mediates LV diastolic dysfunction.[73] Changes in cardiac

metabolism may play a significant role in reduced cardiopulmonary performance in obese HFpEF; however, longitudinal studies are needed to characterize their mechanisms.

### Decreased left ventricular compliance

In obese HFpEF patients, one of the key underlying disorders in cardiac dysfunction is mediated by decreased LV distensibility.[19] Changes in BMI from childhood and mid-adulthood contribute to the development of LV hypertrophy and diastolic dysfunction later in life, suggesting a harmful toll that lifetime BMI-years has on cardiac function.[74,75] While the changes in weight and LV distensibility may occur concomitantly, the two are likely linked in the distinct obese HFpEF phenotype.[19] VAT is associated with increased concentric LV remodelling and impaired cardiorespiratory fitness independent of BMI, whereas SAT is associated with eccentric LV remodelling and high cardiac output.[76] Reduced LV compliance causes increased ventricular filling pressures, and higher BMI correlates with increased pulmonary and pulmonary capillary wedge pressures among individuals with HFpEF compared to those without HFpEF.[19] A proposed mechanism by which adiposity drives the dysregulation of cardiac function and LV distensibility may be through external mechanical constraint. Obese HFpEF patients have higher EAT thickness than non-obese HFpEF and healthy individuals.[19] The elevated epicardial fat develops abnormal ventricular–adipose interactions resulting in pericardial restraint: when compared to non-obese HFpEF and healthy controls, obese HFpEF demonstrates septal wall flattening by transthoracic echocardiography and higher right-sided to left-sided filling pressures along with elevated pulmonary capillary wedge pressures by invasive haemodynamics at rest and with exercise.[19] These measured parameters support pressure equalization across ventricles in different physiologic states—a constrictive pattern that correlates with increased epicardial fat within a fixed pericardial space. Epicardial fat may serve a key mechanistic role within obese HF through decreased LV compliance.

## Vascular–adipose interactions

### Inflammatory processes

Longitudinal studies are needed to identify the role of systemic inflammation as a mediator between excess regional adiposity and HFpEF. Some investigators have proposed mechanistic relationships between increased total and regional adiposity and the upregulation of local and systemic inflammation that may contribute to oxidative stress, microvascular injury, myocardial fibrosis, and cardiac dysregulation among obese HFpEF.[56,77,78] Pro-inflammatory biomarkers, interleukin-6 and tumour necrosis factor-$\alpha$, have been shown to predict HFpEF but not HFrEF in a community population.[79] Additionally, high sensitivity C-reactive protein is elevated in obese compared to non-obese HFpEF patients.[37] Thus, conceivably, obesity and excess regional adiposity may be key to producing pro-inflammatory cytokines that cause metabolic cascades leading to cardiomyocyte hypertrophy, LV remodelling, and subsequent LV diastolic dysfunction.[80] The regional variability of adipose tissue among obese individuals may play a critical role in the local and systemic cardiac and vascular function, partially mediated by inflammation.[44] Some investigators have proposed that higher VAT secretes pro-inflammatory cytokines that may contribute to microvascular endothelial dysfunction and reduced vascular compliance

among obese HFpEF; however, prospective studies confirming this relationship are lacking.[68,70,81] EAT is also a pro-inflammatory tissue that may have local paracrine effects via persistent inflammation causing coronary microvascular dysfunction and ventricular stiffness.[56,82] SAT, on the other hand, does not demonstrate these metabolically active phenomena within the abdomen.[44] Plasma volume expansion occurs more significantly in obese HFpEF compared to those who are not obese.[83] When decompensated, these obese patients tolerate decongestion less well with a greater deterioration of renal function, a process that is key to the obese HFpEF state.[84] The upregulation of systemic inflammation may result in volume expansion and adversely impair decongestive therapies in obese HFpEF. Thus, future studies investigating whether reduction in excess regional adiposity can improve systemic inflammatory dysregulation may provide potential inflammatory therapeutic targets in obese HFpEF.

### Vascular–cardiometabolic factors

Vascular–adrenergic–adipokine interactions have been proposed as pathophysiologic abnormalities seen in obese HFpEF; however, prospective studies are lacking to confirm these relationships.[85–87] Obese HFpEF individuals have higher plasma volume expansion compared to non-obese HFpEF.[83] Obesity-related insulin resistance and compensatory hyperinsulinaemia may lead to upregulation of the sympathoadrenal system and can increase blood pressure and arterial stiffness.[86] Further, dysfunctional adipose tissue triggers secretion of leptin, a hormone produced by adipocytes that regulates energy balance and modulates hunger. Leptin stimulates secretion of aldosterone,[88,89] and dysfunctional adipocytes are also stimulated by leptin-regulated increases in angiotensin II.[88,90] Obesity also is associated with increased activity of neprilysin, which rapidly degrades natriuretic peptide that otherwise would have an anti-aldosterone regulatory effect.[87] The result of increased renin–angiotensin system activation and aldosterone synthesis is volume expansion and sodium retention, a state that in the context of impaired ventricular distensibility may further lead to decompensation in obese HFpEF.[19] Prospective studies are needed to further define this relationship.

There is an inverse relationship between BMI and circulating natriuretic peptide hormone levels in obesity, although this mechanism is not well understood. Impaired cardiovascular fluid homeostasis in obese HF may be through BNP deficiency, and a correlation between higher visceral adiposity and lower BNP is possibly mediated by increased secretion of the natriuretic peptide clearance receptor (NPR-C) on adipocytes, expressing increased BNP degradation.[91] A low ratio between the BNP and the clearance receptor in obese patients may reflect a circulation dominated by BNP clearance, thus prompting this deficiency.[92] Further, adipocyte tissue renin–angiotensin–aldosterone system may attenuate the paracrine-metabolic system through additional secretion of angiotensinogen, ultimately increasing aldosterone secretion in plasma circulation.[93] Among obese compared to non-obese HFpEF patients, there is a marked reduction in transmural LV distensibility that correlates with low circulating BNP.[19] These findings lend to BNP deficiency as a marker for obese HFpEF outcomes, warranting additional studies including obese HFpEF to clarify the relationship between regional adiposity, BNP deficiency, and decompensated HFpEF.

### Vascular compliance and splanchnic coupling

Heart failure with preserved ejection fraction is characterized by decreased vascular compliance and particularly so in patients with concomitant obesity.[94,95] Decreased arterial, and equally if not more importantly venous compliance, are conceptually driven by (i) obesity-mediated neurohormonal and inflammatory activation, and (ii) possibly by pure mechanical properties of the adipose tissue.[96] The splanchnic vascular compartment is the largest reservoir of intravascular blood volume, with the majority of the blood located in the venous system. It has been proposed that inter-compartmental volume redistribution from the abdominal/splanchnic compartment into the central compartment (chest and central vasculature) could be a key determinant of cardiovascular congestion and cause of cardiac decompensation.[96,97] Since obesity (especially visceral) is associated with a higher intra-abdominal pressure (IAP),[98,99] the external vascular compression could lead to a restrictive vascular physiology that is similar to the observed epicardial fat–LV distensibility relationship. Related to this, increased IAP ≥12 mmHg has been linked to organ dysfunction in general and renal impairment specifically.[100,101] A reduction in IAP (contributed by ascites, gut oedema, and abdominal fat) via diuresis or paracentesis has been shown to improve renal function.[101,102] Finally, as recently demonstrated, a direct reduction in splanchnic vascular tone or in other words selective increase in splanchnic vascular compliance could lead to central vascular decongestion with potentially beneficial effects on cardiopulmonary performance.[103,104] The role for targeting the abdominal fat burden, elevated IAP, and modulation of vascular–splanchnic coupling in obese HFpEF remains to be studied.

## Clinical implications

The role of obesity in pathogenesis of HF, and particularly HFpEF, has drawn greater attention.[10,19,23,105] While anthropometrics are commonly used to categorize obesity at present, they are not always representative of excess regional adiposity.[38] Focus on quantifying regional distribution of adiposity may provide more insight into incidence and disease progression of an obese HFpEF phenotype.[10] The proposed mechanisms are summarized in Table 1.[19,37,67–70,74,79,82,88–90,98–104,106–109] While most people do not undergo CT, MRI, or DXA imaging for purposes of screening for HF, interpreting regional fat distribution when imaging is obtained for other purposes could shed light on subpopulations who are at increased risk of developing HFpEF. Additionally, fat distribution has important implications. A patient who has an elevated BMI, WHR, and/or WC, along with elevated visceral adiposity, may have different risk of developing HFpEF or response to therapies than an individual who has similar anthropometric measures, but lower visceral fat and higher subcutaneous fat. Additionally, higher epicardial and visceral fat among people with normal anthropometric screening may be missed and have increased HFpEF risk or HFpEF-related prognosis.

At present, the mainstay therapeutic interventions involve healthy dieting and physical activity. Reducing caloric intake and exercise improve cardiac performance among obese HFpEF.[68] However, targeting harmful fat accumulation is imperative when treating patients with obese HFpEF. Vigorous exercise reduces VAT without significant change in body

weight.[110,111] Invasive procedures also exist to reduce excess adiposity. Liposuction, which removes SAT, provides no significant cardiovascular protection or change in obesity-related metabolic abnormalities.[112,113] Alternatively, bariatric surgeries, including Roux-en-Y gastric bypass and sleeve gastrectomy, reduce VAT and provide a remarkable improvement in 10-year cardiovascular risk and remission rates for diabetes and hypertension among morbidly obese.[36] However, VAT that is surgically removed via omentectomy at time of bariatric surgery provides no significant changes in metabolic outcomes and minimal improvement in BMI compared to bariatric surgery alone.[114] Bariatric surgery has in fact demonstrated a reduction in HF incidence, with the greatest improvement in HF risk among those with the greatest weight reduction.[115] Further, there is sustained reduction in LV mass despite a plateau in BMI reduction over 2 years following bariatric surgery.[116] While weight loss initiatives such as dieting and exercise may be effective for some, surgical treatment to reduce the burden of deleterious total and regional adiposity may prove as a more successful tool in the treatment of obese HFpEF. Comparison of these strategies among obese HFpEF in the improvement of overall cardiopulmonary functional status and HFpEF-related hospitalizations and mortality is lacking.

There is certainly a role for understanding how changes in regional fat distribution affect clinical outcomes among patients with HF, including HFpEF and HFrEF. Anthropometrics predict HFpEF but not HFrEF,[10] yet there is a paradoxical relationship between BMI and HF, known as the ‘obesity paradox’.[66] When looking at HFpEF subtype only, mortality appears to increase among obese individuals with HFpEF.[117] Understanding whether regional elevations in adiposity contribute to these mortality trends may provide a better understanding of the long-term clinical outcomes following diagnosis and characterization of HF and its subtypes. Additionally, with regional distribution of adipose tissue drawing more attention, future investigations may shed additional light on new therapeutic targets.

## Future directions

The increasing burden of obesity and HFpEF poses an imperative need to understand the pathogenesis of adiposity on cardiac function and to develop effective therapies. Regional distribution of fat serves as a vast frontier for behavioural, pharmacologic, and invasive treatment options to address this need. Ongoing clinical trials are investigating therapeutic strategies for obesity and HF through behavioural modification, including dietary adherence and physical activity, and surgical weight reduction strategies. These trials’ outcomes include weight reduction, HF-related hospitalizations, LV function, and exercise capacity (online supplementary Table S1).

Weight loss interventions may advance our understanding of the development and progression of obese HFpEF and may serve as a therapeutic target. A systematic review and meta-analysis of dietary and surgical weight loss studies revealed that both interventions improve resting systemic and cardiac filling pressures among obese people without HF.[118] A prospective controlled Swedish surgical intervention study showed a marked reduction in the incidence of all HF following bariatric surgery, with the most notable HF risk reduction among those with the greatest weight loss.[115] Medical drug therapies also show promise in potentially addressing the obese HFpEF phenotype: sodium–glucose co-

transporter 2 inhibitors, which improve glucose control and cardiovascular outcomes in patients with diabetes, reduce adipose tissue mass with minimal impacts on muscle or lean mass.[119,120] Drugs affecting lipid metabolism, such as lactoferrin, reduce visceral adiposity among overweight and obese Asians without HF.[121] An ongoing prospective study aims to determine the efficacy of bariatric surgery on body weight and LV mass reduction (NCT00178633). Such surgical weight loss therapies include gastric bypass, sleeve gastrectomy, adjustable gastric banding, and biliopancreatic diversion with duodenal switch. Clinical trials of these pharmacological and surgical therapies among obese individuals are needed to help fill the gap in understanding of the change in regional adiposity and incidence of HFpEF, and among those with obese HFpEF, changes in progression of disease. Future studies can aim to answer these questions through serial imaging before and after surgical intervention, as well as serial haemodynamic assessments and serum adiposity and inflammatory biomarkers.

Among the proposed mechanisms of obese HFpEF is external pericardial constraint imposed by epicardial fat accumulation.[19] In non-obese canine and swine models, percutaneous pericardial resection was tested as a novel strategy to relieve the effect of pericardial restraint in HFpEF with reduction in LV end-diastolic pressures and increase in LV end-diastolic volumes.[122] Among individuals with excess epicardial fat thickness, novel pericardial interventions including pericardial resection and pericardiotomy could further our understanding on the direct mechanical compressive effect of regional adiposity among HFpEF, as well as determine the safety and comparative efficacy of these strategies on the outcomes of symptoms, haemodynamics, HFpEF-related hospitalizations, and adverse events. Through a separate mechanism, the REDUCE LAP-HF I trial demonstrated that a percutaneous interatrial shunt device creating left-to-right shunt flow safely reduced exercise pulmonary capillary wedge pressure in HF,[123] and the larger REDUCE LAP-HF II trial (NCT03088033) aims to provide its efficacy in HFpEF symptoms and hospitalizations.

Neuromodulation may also serve as a potential target for obese HFpEF through mechanisms such as volume redistribution. As previously mentioned, a direct reduction in splanchnic vascular tone may reduce central vascular congestion and improve cardiopulmonary performance.[103,104] The effect of neuromodulation on cardiopulmonary performance in obese HFpEF, which may theoretically have reduced vascular compliance within the abdominal compartment, increased IAP, and greater regional adiposity, has not been studied. However, future investigations are needed to understand whether neuromodulation may serve as a primary and secondary preventive strategy among obese HFpEF at risk for incident and repeat HF-related hospitalizations.

## Conclusions

With the higher prevalence trends of obesity and HF over the past several decades, there is increasing recognition of the interaction between adiposity and cardiac function in the pathophysiology of an obese HFpEF phenotype. Regional adiposity, measured by non-invasive imaging, may serve as an important driver in the incidence and pathogenesis of HFpEF among overweight and obese individuals through multiple mechanisms. Behavioural and invasive weight reduction exhibit the potential to mitigate the growing burden of obese

HFpEF and its disease progression. Future studies will further our understanding of the interactions between regional adiposity and HF, and randomized clinical trials will be essential in determining the safety and efficacy of promising preventive and therapeutic interventions for obese HFpEF.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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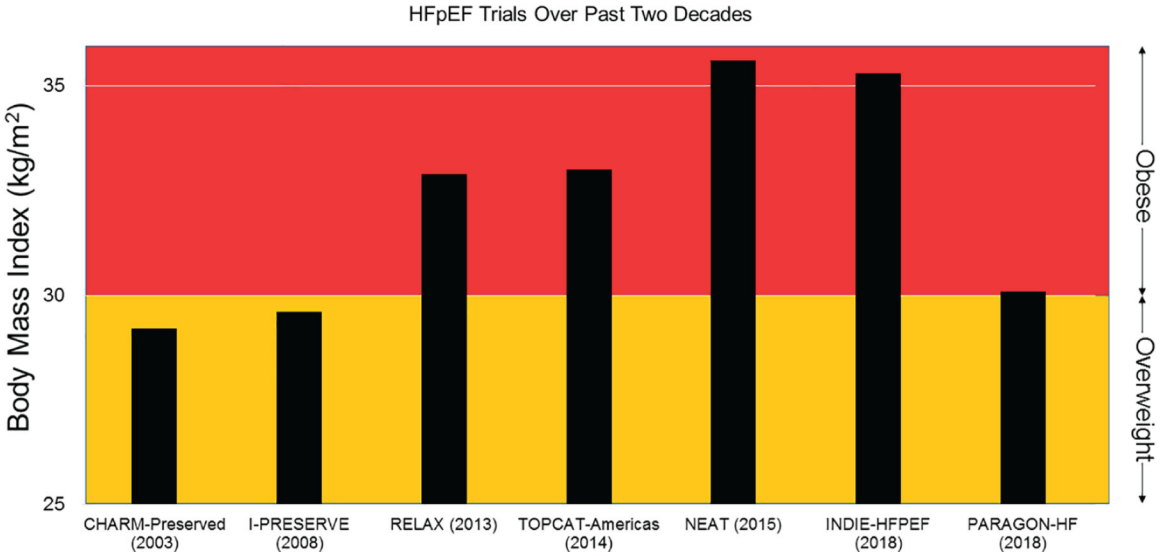


**Figure 1.**

Baseline body mass index across heart failure with preserved ejection fraction (HFpEF) cohorts over the past two decades. These examples of HFpEF trials over the past two decades demonstrate an increase in average body mass index (BMI) across HFpEF cohorts.[11–17] The lower mean BMI in PARAGON-HF was likely due to exclusion of morbid obesity (i.e. BMI >40 kg/m$^2$) and those with low plasma brain natriuretic peptide at the time of enrolment.[16]

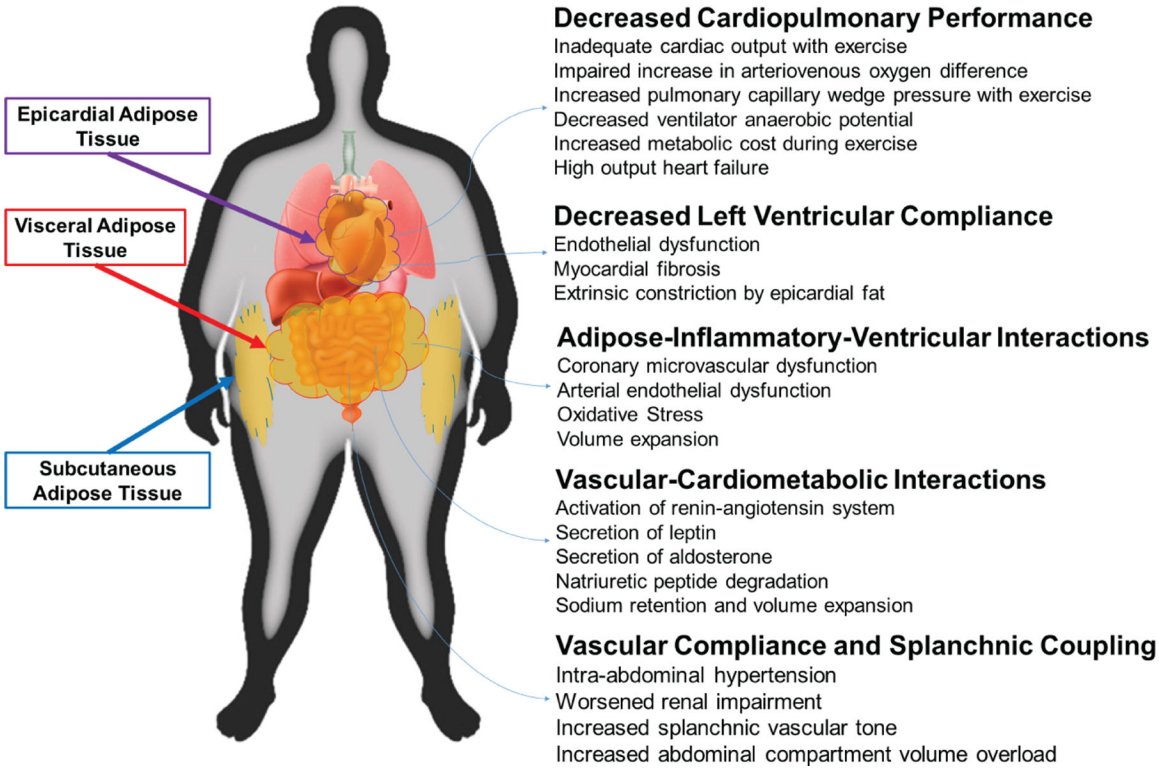


**Figure 2.**

Proposed model by which regional adiposity affects heart failure with preserved ejection fraction physiology.

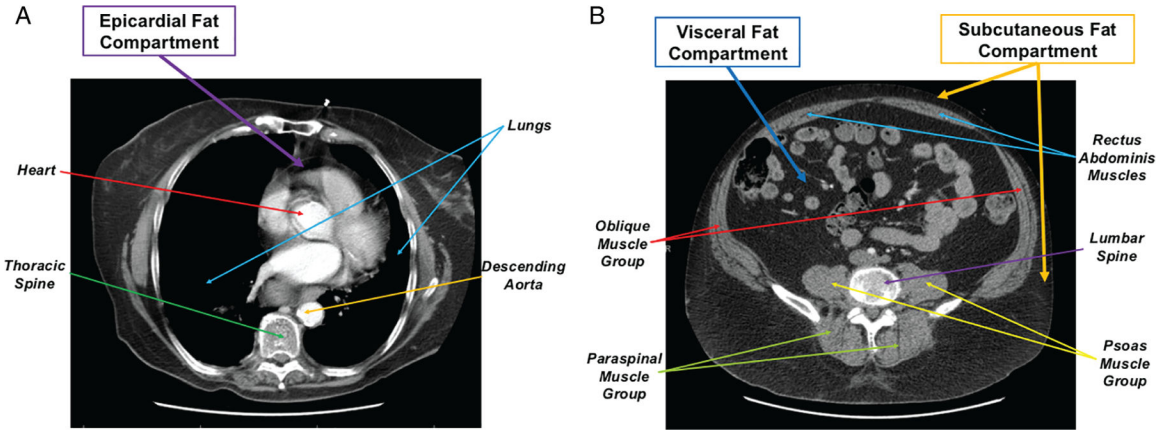


**Figure 3.**

Thoracic and abdominal computed tomography slices and regional distribution of adiposity. Thoracic and abdominal computed tomography slice at level of T5 thoracic spine (*A*) and L2–L3 lumbar spine (*B*) demonstrating distribution of epicardial, visceral, and subcutaneous abdominal fat.

**Table 1**

Summary of previous studies on excess adiposity and its effects on heart failure with preserved ejection fraction

| Findings | Mechanisms | Reference |
|---|---|---|
| Decreased cardiopulmonary performance | Inadequate cardiac output with exercise<br>Impaired increase in $AVO_2$ difference<br>Increased PCWP with exercise<br>Decreased ventilator anaerobic potential<br>Increased metabolic cost during exercise<br>High output heart failure | Obokata *et al.*[19]<br>Reddy *et al.*[37]<br>Mohammed *et al.*[67]<br>Kitzman *et al.*[68]<br>Li *et al.*[69]<br>Haykowsky *et al.*[70]<br>Haykowsky *et al.*[106]<br>Reddy *et al.*[107]<br>Abudiab *et al.*[108] |
| Decreased left ventricular compliance | Endothelial dysfunction<br>Myocardial fibrosis<br>Extrinsic constriction by epicardial fat | Obokata *et al.*[19]<br>Khan *et al.*[74] |
| Adipose–inflammatory–ventricular interactions | Coronary microvascular dysfunction<br>Arterial endothelial dysfunction<br>Oxidative stress<br>Volume expansion | Reddy *et al.*[37]<br>Kalogeropoulos *et al.*[79]<br>Nerlekar *et al.*[82] |
| Vascular–cardiometabolic interactions | Activation of renin–angiotensin system<br>Secretion of leptin<br>Secretion of aldosterone<br>Natriuretic peptide degradation<br>Sodium retention and volume expansion | Xue *et al.*[88]<br>Huby *et al.*[89]<br>Briones *et al.*[90]<br>Clerico *et al.*[109] |
| Vascular compliance and splanchnic coupling | Intra-abdominal hypertension<br>Worsened renal impairment<br>Increased splanchnic vascular tone<br>Increased abdominal compartment volume overload | Varela *et al.*[98]<br>Lambert *et al.*[99]<br>Malbrain *et al.*[100]<br>Mullens *et al.*[101]<br>Mullens *et al.*[102]<br>Fudim *et al.*[103]<br>Fudim *et al.*[104] |

$AVO_2$, arteriovenous oxygen difference; PCWP, pulmonary capillary wedge pressure.

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