Impact of body mass index on diastolic function in patients with normal left ventricular ejection fraction

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BACKGROUND: Obesity is a major public health epidemic and is associated with increased risk of heart failure and mortality. We evaluated the impact of body mass index (BMI) on the prevalence of diastolic dysfunction (DD).

METHODS: We reviewed clinical records and echocardiograms of patients with baseline echocardiogram between 1996 and 2005 that showed normal left ventricular ejection fraction (LVEF). Diastolic function was labeled as normal, stage 1, stage 2 or stage 3/4 dysfunction. Patients were categorized as normal weight (BMI < 25 kg m\(^{-2}\)), overweight (25–29.9 kg m\(^{-2}\)), obese (30–39.9 kg m\(^{-2}\)) and morbidly obese (≥ 40 kg m\(^{-2}\)). Multivariable ordinal and ordinary logistic regression were performed to identify factors associated with DD, and evaluate the independent relationship of BMI with DD.

RESULTS: The cohort included 21 666 patients (mean (s.d.) age, 57.1 (15.1); 55.5% female). There were 7352 (33.9%) overweight, 5995 (27.6%) obese and 1616 (7.4%) morbidly obese patients. Abnormal diastolic function was present in 13 414 (61.9%) patients, with stage 1 being the most common. As BMI increased, the prevalence of normal diastolic function decreased (P < 0.0001). Furthermore, there were 1733 patients with age < 35 years; 460 (26.5%) and 407 (23.5%) were overweight and obese, respectively, and had higher prevalence of DD (P < 0.001). Using multivariable logistic regression, BMI remained significant in both ordinal (all stages of diastolic function) and binary (normal versus abnormal). Also, obesity was associated with increased odds of DD in all patients and those aged  < 35 years.

CONCLUSIONS: In patients with normal LVEF, higher BMI was independently associated with worsening DD.

KEYWORDS: diastolic function; body mass index; outpatients; normal ejection fraction

INTRODUCTION

Obesity is a major public health epidemic and has been increasing at alarming rates worldwide and in all age groups.\(^1,2\) It is associated with increasing risk of heart failure,\(^3,4\) and cardiac death.\(^5\) Excess body fat has been associated with inflammation,\(^5\) increase preload and afterload,\(^6\) insulin resistance,\(^7\) hypertension and left ventricular (LV) hypertrophy.\(^8,9\) The precise mechanisms by which body mass index (BMI) affects cardiac function, nevertheless, are not well understood. Diastolic dysfunction (DD) and its progression are independent predictors of incident heart failure.\(^10\) A recent study showed that overweight and obesity were independent predictors of DD after adjustment for potential confounders.\(^11\) However, the study was performed in an elderly cohort of patients (mean age 72 years), the majority of which were hypertensive, and limited to mostly Hispanics from the North Manhattan Study. There are limited data, however, and with small-sample-size studies assessing the impact of BMI on DD in young normotensive patients.

We sought to evaluate the association between BMI and DD in a large cohort of patients with normal left ventricular ejection fraction (LVEF) undergoing outpatient echocardiograms.

MATERIALS AND METHODS

Study design

The study cohort consisted of patients who underwent an outpatient echocardiogram test with normal LV systolic function (LVEF ≥ 55%), at the Cleveland Clinic or its satellite facilities between 1 January 1996 and 31 December 2005. For patients with more than one echocardiogram, only the first one was included and analyzed. These data were derived from a previous study of diastolic function and the original data set was used.\(^12\) Patients were excluded if diastolic function could not be assessed or was not reported, if severe mitral valve disease or prior mitral valve surgery were present, or if BMI could not be calculated. Inability to assess diastolic function was common in certain clinical scenarios such as in patients with tachycardia, atrial fibrillation, poor acoustic window and in limited echocardiogram performed on an urgent basis.

Using the above algorithm, 21 666 patients were included from a total of 65 696 echocardiograms performed.

Echocardiographic methods

Patients were imaged in the left lateral decubitus position with commercially available systems, and images were acquired per standard protocol. Diastolic function was assessed in our institution in a standardized method, and in accordance with the published and relevant guidelines by using a combination of echocardiographic variables including transmitral inflow pattern, pulmonary venous flow pattern, and beginning in the late 1990s and almost uniformly after 2001, mitral annular velocities assessed by tissue Doppler imaging.\(^13\) In patients with atrial fibrillation, if diastolic function was assessed, it was based on deceleration time of mitral E wave velocity\(^14\) and tissue Doppler imaging if available (that is, peak early mitral inflow velocity/diastolic early tissue velocity (E/E′)).\(^15\)

Diastolic function was then labeled as normal or abnormal (DD). DD was then categorized as mild (stage 1, impaired relaxation), moderate (stage 2, pseudo-normal) and severe (stage 3/4, restrictive).\(^16\) Systolic function was

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Received 6 July 2012; accepted 8 July 2012
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assessed by quantitative and/or visual evaluation of the LVEF in accordance with published guidelines.\(^\text{17}\) LV mass and LV mass index were calculated based on the formula: LV mass (g): 0.8 \times (1.04 [(LVIDD + PWTD + IVS)/2] - (LVIDD)^2) + 0.6g; LV mass index = LV mass/height\(^2\).\(^\text{3,4}\)

All echocardiograms were interpreted by experienced and board-certified readers who over-read and approved measurements made by the sonographers. The interobserver agreement of reproducibility and DD classification extrapolated from our ongoing quality assurance effort was on average 83%, and intraobserver agreement was 94%.

Clinical data
Clinical data were obtained from review of the electronic medical records from a period starting 6 months before the first echocardiographic testing and ending 6 months afterward. The indications for echocardiograms were previously published.\(^\text{12}\) The clinical diagnosis of conditions, including coronary artery disease, peripheral vascular disease, diabetes mellitus, hypertension, atrial fibrillation, congestive heart failure, hyperlipidemia, chronic obstructive pulmonary disease and chronic renal insufficiency, was established by reviewing records documented by a health-care provider in an electronic medical record system (EpicCare; Epic Systems Corporation, Madison, WI, USA) that was linked to relevant International Classification of Diseases, Ninth Revision (ICD-9) codes, as previously described.\(^\text{12}\) Patients’ blood pressure, height and weight were obtained and recorded at the time the echocardiograms were performed.

Hypertension was defined as systolic blood pressure \(\geq 140\) mm Hg or diastolic blood pressure \(\geq 90\) mm Hg at the time of the echocardiogram, or the use of antihypertensive medications. Diabetes mellitus was defined as fasting glucose \(\geq 126\) mg dl\(^{-1}\), or self-reported history or the use of diabetic medications. Hyperlipidemia was defined as low-density lipoprotein, high-density lipoprotein and non-high-density lipoprotein greater than those recommended by ATP III guidelines, self-reported history or the use of antihyperlipidemic medications. Chronic renal insufficiency was defined as glomerular filtration rate <60 ml min\(^{-1}\), BMI was calculated using standard formula (weight (kg) divided by height-squared (m\(^2\))), and was classified as \(<25\) kg m\(^{-2}\) (normal weight), \(25-29.9\) kg m\(^{-2}\) (overweight), \(30-39.9\) kg m\(^{-2}\) (obese) and \(\geq 40\) kg m\(^{-2}\) (morbidly obese).\(^\text{2,3}\) The study was approved by the Cleveland Clinic Institutional Review Board with waiver of consent.

Statistical analysis
Continuous data were expressed as mean \(\pm\) s.d. or median (interquartile range). \(t\)-tests or Fisher exact tests were used to assess the differences for the continuous data. This non-parametric test accommodated for highly skewed variables such as BMI. Categorical data were displayed as frequencies and percentages, and comparisons were made using \(\chi^2\) tests or \(t\)-tests as appropriate.

Multivariable ordinal and ordinary logistic regression were performed to identify factors associated with DD, and to evaluate the independent relationship of BMI with DD. Variables that were considered in this analysis were age, gender, race, body size (height, weight, BMI and body surface area), atrial fibrillation, diabetes mellitus, hypertension, systolic and diastolic blood pressures, LV mass index, left atrial (LA) size, hyperlipidemia, chronic obstructive pulmonary disease, chronic renal insufficiency, congestive heart failure, serum creatinine, hemoglobin and date of the echocardiogram performed. Utilizing the final model, nomograms of the relationship between DD and BMI were plotted allowing the adjustment of variables that were considered in this analysis.

RESULTS
Clinical data
The study population consisted of 21 666 patients (mean (s.d.) age, 57.1 (15.1); 55.5% female; 82.9% Caucasians; 13% with diabetes mellitus, mean (s.d.) BMI 29.1 (7.5) 25 kg m\(^{-2}\). There were 6703 (30.9%) normal weight (BMI \(<25\) kg m\(^{-2}\)), 7352 (33.9%) overweight (BMI 25-29.9 kg m\(^{-2}\), 5995 (27.6%) obese (BMI 30-39.9 kg m\(^{-2}\)) and 5437 (25.2%) morbidly obese (BMI \(\geq 40\) kg m\(^{-2}\)) patients. The clinical, demographic and echocardiographic data of the study cohort stratified by BMI are described in Table 1.

BMI and cardiovascular risk factors
Obese and morbidly obese patients were younger, and had higher prevalence of cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, LV hypertrophy (LV mass index) and elevated blood pressure as compared with those with normal or overweight (Table 1).

BMI and DD
Abnormal diastolic function was prevalent in 13 414 (61.9%) patients with stage 1 being the most common with 12 497 (93.2%), 867 (6.5%) stage 2 DD, 50 (0.4%) stage 3, 4 DD. The BMI increased across diastolic stages, with a median of 26.6 kg m\(^{-2}\) in normal diastolic function and 28.7 kg m\(^{-2}\) in stage 3, 4 (\(P<0.001\)) (Table 2). Furthermore, more patients with normal diastolic function had normal weight (37.8%), while those with DD were predominately either overweight (35.1% and 32.6% for stage 1 and 2, respectively) or obese (42% for stage 3, 4) (\(P<0.0001\)) (Table 2). On the other hand, as BMI increased the prevalence of normal diastolic function decreased (47% in normal weight patients; 36% in overweight; and 32% in obese and morbidly obese), while the prevalence of DD increased (\(P<0.0001\)) (Figure 1). In fact, the prevalence of stage 1 DD increased from 50% in normal weight to 60% in overweight, 63% in obese and 61% in morbidly obese patients (\(P<0.0001\)). Similarly, the prevalence of stage \(\geq 2\) DD were 3.9%, 4.0%, 4.5% and 5.5% for normal, overweight, obese and morbidly obese patients, respectively (\(P<0.0001\)) (Figure 1a).

Normotensive patients without diabetes
There were 16 482 normotensive patients and without diabetes mellitus; 5685 (34.5%) were overweight, 4088 (24.8%) obese and 992 (6.0%) morbidly obese. DD was presented in 9357 (56.8%) patients, and was more prevalent in overweight and obese patients versus those with normal weights (58.8% and 62.6%, respectively, versus 49.5%, \(P<0.0001\)).

DD in patients <35 years old
Analysis of patients <35 years old included 1733 patients (mean (s.d.) age 27.5 (4.8) years; 2.7% hypertensive; 0.0% coronary artery disease; 0.5% with heart failure; and 2.8% diabetes mellitus). 866 (50%) had normal weight, 460 (26.5%) were overweight and 407 (23.5%) were obese. Obese patients had significantly higher prevalence of hypertension (5.2% versus 1.3%, \(P<0.001\)), diabetes (6.2% versus 1.3%, \(P<0.001\)), mean systolic (s.d.) and diastolic (s.d.) blood pressure (133.1 (17.9) versus 120.1 (15.3) mm Hg, and 83.6 (11.1) versus 75.8 (10.4) mm Hg, respectively, \(P<0.001\) for both) and mean LA size (s.d.) (3.6 (0.5) versus 3.1 (0.5) cm, \(P<0.001\) as compared with those with normal weights. 109 (6.3%) had DD. The prevalence of DD increased from 3.8% in

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normal weight to 5.2% in overweight and 12.8% in obese patients ($P<0.0001$) (Figure 1b).

Multivariable analysis

Using multivariable logistic regression to assess for the effect of BMI on diastology and after accounting for the factors mentioned above, BMI remained significant in both ordinal (all stages of diastolic function: normal, stage 1, 2 and 3/4) and binary (normal versus abnormal) with a nonlinear association. The model had good discriminatory power between normal and abnormal groups depicting the probability of DD across values of BMI and stratified on three hypothetical age groups for illustration purposes (Figure 2). At any given BMI, the probability of DD was higher for older patients. Conversely, for any given age group, the probability of DD increased with higher BMI.

Using BMI as categorical groups (Supplementary Appendix A), being overweight, obese and morbidly obese were associated with increased odds of DD as compared with those with normal weights (odds ratio (95% confidence interval) 1.30 (1.20–1.42), 1.88 (1.71–2.06), 2.16 (1.87–2.49), respectively, $P<0.0001$ for all) (Figure 3a). Reclassifying obesity into class I, II and III yielded 1.88 (1.71–2.06), 2.16 (1.87–2.49), respectively, $P=0.0001$ for all). Using BMI as categorical groups (Supplementary Appendix A), being overweight, obese and morbidly obese were associated with increased odds of DD as compared with those with normal weights (odds ratio (95% confidence interval) 1.30 (1.20–1.42), 1.88 (1.71–2.06), 2.16 (1.87–2.49), respectively, $P<0.0001$ for all) (Figure 3a). Reclassifying obesity into class I, II and III yielded 1.88 (1.71–2.06), 2.16 (1.87–2.49), respectively, $P=0.0001$ for all).

### Table 1. Baseline patient characteristics stratified by BMI

| Variable | Normal weight BMI (<25 kg m⁻²) (n = 6703) | Overweight BMI (25–29.9 kg m⁻²) (n = 7352) | Obese BMI (30–39.9 kg m⁻²) (n = 5995) | Morbidly obese BMI (≥40 kg m⁻²) (n = 1616) | P  |
|----------|----------------------------------------|-----------------------------------------|---------------------------------|---------------------------------|-----|
| Age, mean (s.d.), years | 56.1 (17.3) | 58.5 (14.6) | 57.1 (13.2) | 54.6 (12.7) | <0.0001 |
| Male sex | 2373 (35.4%) | 3931 (53.5%) | 2825 (47.1%) | 512 (31.7%) | <0.0001 |
| Caucasians | 4343 (82.9%) | 4774 (83.0%) | 3858 (82.9%) | 1009 (82.1%) | 0.89 |
| Coronary artery disease | 35 (0.5%) | 37 (0.5%) | 30 (0.5%) | 8 (0.5%) | 0.99 |
| Atrial fibrillation | 356 (5.3%) | 425 (5.8%) | 367 (19.3%) | 88 (5.4%) | <0.0001 |
| Diabetes mellitus | 356 (5.3%) | 777 (10.6%) | 1154 (19.3%) | 441 (27.3%) | <0.0001 |
| Hypertension | 729 (10.9%) | 1086 (14.8%) | 1102 (18.4%) | 319 (19.6%) | <0.0001 |
| Hyperlipidemia | 1806 (27.0%) | 3176 (43.2%) | 2803 (46.8%) | 685 (42.4%) | <0.0001 |
| BMI, mean (s.d.), kg m⁻² | 26.1 (4.0) | 2.59 (0.40) | 2.61 (0.40) | 2.66 (0.42) | <0.0001 |
| Systolic BP, mean (s.d.), mm Hg | 136 (22) | 141 (21) | 144 (20) | 147 (20) | <0.0001 |
| Diastolic BP, mean (s.d.), mm Hg | 80 (11) | 83 (10) | 85 (11) | 86 (11) | <0.0001 |

Abbreviations: BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease. P-value comparing means or proportions of baseline characteristics across different BMI ranges. aCould be measured in 16876 patients for race; 21653 for coronary artery disease, atrial fibrillation, diabetes mellitus, hypertension, hyperlipidemia, peripheral vascular disease, congestive heart failure, COPD and chronic renal insufficiency; 15673 for serum creatinine and hemoglobin; 15795 for systolic blood pressure; and 15954 for diastolic blood pressure. bCould be measured in 20672 patients for end-diastolic and end-systolic diameter/height; 19397 for relative wall thickness; 19397 for left ventricular mass index; and 20731 for left atrial size.

### Table 2. Diastolic function and BMI

| Diastolic function | Normal (n = 8252) | Stage 1 (n = 12497) | Stage 2 (n = 867) | Stage 3, 4 (n = 50) |
|-------------------|------------------|------------------|-----------------|-----------------|
| BMI, mean (s.d.), kg m⁻² | 28.26 (7.58) | 29.67 (7.43) | 29.84 (7.87) | 29.59 (6.10) |
| BMI, median (25th, 75th), kg m⁻² | 26.6 (23.1, 31.0) | 28.3 (24.8, 32.7) | 28.2 (24.5, 33.4) | 28.7 (24.2, 33.6) |
| BMI < 25 kg m⁻² | 3123 (37.8%) | 3260 (26.6%) | 246 (28.4%) | 14 (28.0%) |
| BMI 25–29.9 kg m⁻² | 2674 (32.4%) | 4381 (35.1%) | 283 (32.6%) | 14 (28.0%) |
| BMI 30–39.9 kg m⁻² | 1917 (23.2%) | 3806 (30.5%) | 251 (29%) | 21 (42%) |
| BMI ≥40 kg m⁻² | 538 (6.5%) | 990 (7.9%) | 87 (10.0%) | 1 (2.0%) |

Abbreviation: BMI, body mass index. $P<0.0001$. 

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grade severity increased (normal diastolic function decreased while the prevalence of DD and higher for obese (2.95 (1.81–4.83), aged 0-35 years, obesity was associated with increased odds of DD for all patients. In those with BMI >40, there was a 3-fold increase in the prevalence of DD (P<0.0001 for all patients). As BMI increased, the prevalence of normal diastolic function decreased while the prevalence of DD and stage severity increased (P<0.0001). A BMI of 30 kg/m² was an independent and strong predictor of DD with a continuous relationship. Also, being overweight, obese and morbidly obese was associated with increased odds of DD for all patients. In those aged <35 years, obesity was associated with ~3-fold increase in odds of having DD.

In patient’s age <35 years, the odds of abnormal DD were higher for obese (2.95 (1.81–4.83), P<0.0001), morbidly obese (1.76 (0.80–3.90), P = 0.16), but not for overweight (1.04 (0.60–1.81), P = 0.89) (Supplementary Appendix B, Figure 3b).

DISCUSSION

This is the largest study to our knowledge to assess the impact of BMI on diastolic function, and focused only on patients with normal LVEF. After adjusting for age, hypertension, diabetes, LA size, LV mass index and other covariates, BMI remains an independent and strong predictor of DD with a continuous relationship. Also, being overweight, obese and morbidly obese was associated with increased odds of DD for all patients. In those aged <35 years, obesity was associated with ~3-fold increase in odds of having DD.

Obesity has become an epidemic. In our cohort, less than one-third of all patients and less than half of those younger than 35 years old had normal weights. These numbers reflect a cohort from a decade ago, and are probably worse now. There is also increased prevalence of cardiovascular risk factors such as hypertension, diabetes mellitus and LV hypertrophy with higher BMI (Table 1). In addition, obesity is associated with heart failure, cardiovascular complications and mortality, but so is DD. The latter has been proposed as one of the pathophysiological links between obesity and heart failure. With increasing body adiposity, changes in cardiac metabolism occur, leading to myocardial fatty infiltration, inflammation and cardiac toxicity, with the end result of DD. Indeed, Kuznetsova et al. showed that BMI was associated with DD in 539 patients from the general community in Europe. However, the prevalence of DD was much lower (only 25% had DD), the mean BMI was significantly smaller (26 kg m⁻² vs. 29 kg m⁻², P<0.0001) and with virtually no patients with BMI ≥35 kg m⁻² while our cohort had >3400 patients. Another study showed that BMI was associated with DD independent of LV mass and other confounders. However, the studied cohort consisted of elderly patients (mean age 72 years) and with >72% having hypertension and high prevalence of coronary artery disease. Our current cohort was on average 15 years younger (mean age 57 years), had a much lower prevalence of hypertension (14.9%) and included a large number of morbidly obese patients (N=1616) who are in most studies under-represented. Also, the cohort studied by Russo et al. was from the North Manhattan Study, a predominately Hispanic community, while our cohort was more representative of the general US population. Furthermore, 1733 patients of our cohort were younger than 35 years old.

Table 3. Predictors of abnormal diastolic function in all patients using BMI

| Parameter       | Estimate | s.e. | Wald χ² | P-value |
|-----------------|----------|------|---------|---------|
| Age             | 0.1499   | 0.0108| 193     | <0.0001 |
| Age (exp)       | −0.5687  | 0.1717| 11      | 0.0009  |
| BMI (log)       | 2.1880   | 0.1946| 126     | <0.0001 |
| BMI (squared)   | −0.7170  | 0.1219| 34      | <0.0001 |
| AFib            | −0.3559  | 0.0779| 21      | <0.0001 |
| Diabetes        | 0.3044   | 0.0586| 27      | <0.0001 |
| Hypertension    | 0.2765   | 0.0542| 26      | <0.0001 |
| COPD            | 0.5478   | 0.1175| 22      | <0.0001 |
| Creatinine (log)| 0.4907   | 0.0601| 67      | <0.0001 |
| BP diastolic    | 0.0192   | 0.00194| 98      | <0.0001 |
| Interceptor     | −14.6015 | 0.6086| 576     | <0.0001 |

Abbreviations: AFib, atrial fibrillation; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease. C = 0.86.
The epidemic of obesity is now affecting younger age groups. Hence, the recognition of DD at such young age group is of great interest from a cardiovascular epidemiological standpoint. There have been several studies evaluating DD in young patient cohorts showing the association between BMI and DD; however, all these studies were of small sample size, and none of them graded the severity of diastolic function. Furthermore, the causation has often been confounded by other processes found in obesity such as hypertension. In 1999, Carroll et al. showed in an animal model of obesity that diastolic compliance is reduced early in the development of obesity, and may contribute to reduced cardiac reserve. DD has clinical, prognostic and therapeutic ramifications. Hypertension, LV hypertrophy, diabetes mellitus and insulin resistance are complications of obesity and have all been associated with worsening of DD. In fact, these cardiovascular risk factors were much more prevalent in the obese and morbidly obese patients than those with normal BMI for all patients and those aged <35 years (Table 1). After adjusting for these confounders, BMI was still independently associated with DD in our cohort. 26–30 The financial impact of morbid obesity on society is overwhelming. Not only was the prevalence of hypertension and diabetes 2 and 5 times, respectively, higher than those with normal weights (Table 1), but so was DD, particularly in those aged <35 years old (Figure 1).

DD is a dynamic phenomenon. Not only can it progress and worsen with time, but can also improve. Recent data from our group have shown that in patients with normal LVEF, diastolic function changed in 27% of patients (1.1 years mean time between echoes) (16% had worsening and 11% had improvement). Worsening of DD was an independent predictor of all-cause mortality with similar hazard ratio to worsening of systolic function, irrespective of baseline diastolic function. In a similar study, worsening of DD was associated with new incidence of heart failure. Furthermore, Achong et al. showed that improvement in DD has been associated with trend toward better survival. The effect of weight loss on DD in morbidly obese patients has been evaluated in small studies with evidence of improvement of diastolic parameters, although other studies showed no significant change. It is of interest to evaluate in a large cohort of patients whether reduction of BMI is associated with improvement of DD.

### Table 1

| BMI Category          | Odds Ratio [95% CI] | P value |
|-----------------------|---------------------|---------|
| Normal weight (BMI <25 kg/m²) | Reference | |
| Overweight (BMI 25-29.9 kg/m²) | 1.30 [1.20;1.42] | <0.0001 |
| Obese (BMI 30-39.9 kg/m²) | 1.88 [1.71;2.06] | <0.0001 |
| Morbidly Obese (BMI ≥40kg/m²) | 2.16 [1.87;2.49] | <0.0001 |

**All patients (N=21666)**

### Table 2

| BMI Category          | Odds Ratio [95% CI] | P value |
|-----------------------|---------------------|---------|
| Normal weight (BMI <25 kg/m²) | Reference | |
| Overweight (BMI 25-29.9 kg/m²) | 1.04 [0.60;1.81] | 0.89 |
| Obese (BMI 30-39.9 kg/m²) | 2.95 [1.81;4.83] | <0.0001 |
| Morbidly Obese (BMI ≥40kg/m²) | 1.76 [0.80;3.90] | 0.16 |

**Patients age <35 years (N=1733)**

Figure 3. Odds ratio of having DD. Forest plot illustrating the odds ratios (95% confidence interval) of having DD in all patients (a) and those aged <35 years (b) based on categorical BMI groups. Patients with normal weights were used as reference.
with improvement in DD after adjusting for improvement in blood pressure, diabetes and LV mass.

Strengths and limitations
This is the largest study to our knowledge that evaluates the association between obesity and DD across different age groups, and underlines the unexpectedly high prevalence of DD even in young obese patients (age < 35 years), who are not spared. With the growing epidemic of obesity, additional research is warranted to evaluate whether significant weight loss may indeed reverse DD early on. However, we acknowledge several limitations. This is a retrospective study from a single tertiary center with selection and referral bias, particularly given the large number of patients who were excluded for various reasons; hence, a large study validating these findings in the general US community is warranted. Given the cross-sectional nature of the study, the direction of the relationship between BMI and DD needs to be interpreted cautiously; perhaps DD leads to less exercise tolerance, sedentary lifestyle and weight gain. A prospective study is warranted to validate these findings, assess cause–effect relationship and perform a causal modeling to determine to what extent changes in BMI are associated with worsening DD. Patients aged > 35 years, who are not spared either. While the exact mechanism linking obesity to DD is still not well understood, further studies are warranted, particularly given the obesity epidemic and the likely increased incidence in the United States. It will be interesting to evaluate whether significant weight loss may indeed reverse DD early on, and if so affects outcomes.

CONCLUSION
In our study of relatively young and middle age patients with normal LVEF, higher BMI was independently associated with worsening DD. Patients aged < 35 years were not spared either. While the exact mechanism linking obesity to DD is still not well understood, further studies are warranted, particularly given the obesity epidemic and the likely increased incidence in the United States. It will be interesting to evaluate whether significant weight loss may indeed reverse DD early on, and if so affects outcomes.

AUTHOR CONTRIBUTIONS
Dr s AlJaroudi, Houghtaling and Jaber had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: AlJaroudi, Halley, Thomas and Jaber. Acquisition of data: AlJaroudi and Jaber. Analysis and interpretation: AlJaroudi, Houghtaling, Agarwal and Jaber. Drafting of the manuscript: AlJaroudi, Agarwal, Halley, Grimm, Rodriguez, Menon, Thomas and Jaber. Critical revision of the manuscript for important intellectual content: AlJaroudi, Rodriguez, Halley, Agarwal, Grimm, Menon, Thomas and Jaber. Administrative, technical and material support: AlJaroudi, Rodriguez, Grimm, Thomas and Jaber. Study supervision: AlJaroudi and Jaber.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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