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ORIGINAL ARTICLE

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 echocardiogram 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 $<25\,\mathrm{kg\,m^{-2}}$), overweight (25–$29.9\,\mathrm{kg\,m^{-2}}$), obese ($30$–$39.9\,\mathrm{kg\,m^{-2}}$) and morbidly obese ($\geqslant 40\,\mathrm{kg\,m^{-2}}$). 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.

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] and cardiac death.[4] 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 $\geqslant 55\%$), 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 to 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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assessed by quantitative and/or visual evaluation of the LVEF in accordance with published guidelines.[17] LV mass and LV mass index were calculated based on the formula: LV mass (g): $0.8 \times (1.04 ([LVIDD + PWTD + IVS]^3 - [LVIDD]^3)) + 0.6g$; LV mass index = LV mass/height$^{2.7}$ $(g\,m^{-2.7})$.[18,19]

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.[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.[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 $\geqslant 140\,mm\,Hg$ or diastolic blood pressure $\geqslant 90\,mm\,Hg$ at the time of the echocardiogram, or self-reported history of hypertension, or the use of antihypertensive medications. Diabetes mellitus was defined as fasting glucose $\geqslant 126\,mg\,dl^{-1}$, or self-reported history or the use of diabetic medications. Hyperlipidemia was defined as lipid panel (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 $\geqslant 40\,kg\,m^{-2}$ (morbidly obese).[20] The study was approved by the Cleveland Clinic Institutional Review Board with waiver of consent.

Statistical analysis

Continuous data were expressed as mean ± s.d. or median (interquartile range). Kruskal–Wallis tests were used to analyze group 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 χ^2 tests or Fisher exact 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 association between DD and BMI were plotted allowing the adjustment of other factors. Owing to the low numbers in the moderate and severe DD groups, the final logistic model combined these groups and the model predicted normal versus abnormal diastolic function. The model was also rerun using categorical BMI groups (that is, normal, overweight, obese and morbidly obese) for all patients and the subgroup of patients aged <35 years old (a group of patients generally not expected to have DD). Given the high number of patients with stage 1 DD that could overwhelm the logistic model, we preformed another binary logistic regression looking at the associations with DD stage 2 or greater compared with the remainder. Finally, because of possible attenuation effect of BMI, we categorized obesity class I (BMI $30–34.99\,kg\,m^{-2}$), class II (BMI $35–39.99\,kg\,m^{-2}$) and class III (BMI $\geqslant 40\,kg\,m^{-2}$), and looked at the association with DD. Compared with normal weights, odds ratio for predicting abnormal diastolic function for the categorical BMI groups were expressed with 95% confidence interval. The discriminatory ability of the test was assessed using C-statistics.

All statistical tests were two sided. A P-value <0.05 was set a priori and considered statistically significant. All statistical analyses were performed using SAS statistical software, version 9 (SAS Institute Inc., Cary, NC, USA).

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 1616 (7.4%) morbidly obese (BMI $\geqslant 40\,kg\,m^{-2}$) patients. The clinical, demographic and echocardio-graphic 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 $\geqslant 2$ 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%, $P<0.001$).

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% 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 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

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 $\geqslant40\,kg\,m^{-2}$ (n = 1616)	P
Demographic/clinical data[a]					
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 (6.1%)	88 (5.4%)	0.25
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 (19.8%)	<0.0001
Hyperlipidemia	1806 (27.0%)	3176 (43.2%)	2803 (46.8%)	685 (42.4%)	<0.0001
Peripheral vascular disease	93 (0.9%)	89 (1.2%)	65 (1.1%)	15 (0.9%)	0.43
Congestive heart failure	192 (2.9%)	206 (2.8%)	275 (4.6%)	91 (5.6%)	<0.0001
COPD	249 (3.7%)	246 (3.3%)	176 (2.9%)	60 (3.7%)	0.090
Chronic renal insufficiency	101 (1.5%)	123 (1.7%)	114 (1.9%)	29 (1.8%)	0.38
Creatinine, mean (s.d.), $mg\,dl^{-1}$	0.96 (0.39)	1.01 (0.37)	1.01 (0.39)	0.99 (0.41)	<0.0001
Hemoglobin, mean (s.d.), $g\,dl^{-1}$	12.1 (2.7)	12.7 (2.6)	12.7 (2.6)	12.3 (2.4)	<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
Echocardiographic data[b]					
End-diastolic diameter/height, mean (s.d.), $cm\,m^{-1}$	2.61 (0.40)	2.59 (0.40)	2.61 (0.40)	2.66 (0.42)	<0.0001
End-systolic diameter/height, mean (s.d.), $cm\,m^{-1}$	1.60 (0.36)	1.59 (0.35)	1.60 (0.35)	1.63 (0.37)	<0.001
Relative wall thickness, mean (s.d.)	0.51 (0.13)	0.51 (0.14)	0.51 (0.14)	0.51 (0.13)	0.70
Left ventricular mass/height$^{2.7}$, mean (s.d.), $kg\,m^{-2.7}$	40.9 (14.5)	41.4 (14.1)	42.2 (14.6)	43.9 (14.8)	<0.0001
Left atrium size, mean (s.d.), cm	3.44 (0.65)	3.71 (0.61)	3.88 (0.58)	3.92 (0.63)	<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. [a]Could be measured in 16 876 patients for race; 21 653 for coronary artery disease, atrial fibrillation, diabetes mellitus, hypertension, hyperlipidemia, peripheral vascular disease, congestive heart failure, COPD and chronic renal insufficiency; 15 673 for serum creatinine and hemoglobin; 15 795 for systolic blood pressure; and 15 954 for diastolic blood pressure. [b]Could be measured in 20 672 patients for end-diastolic and end-systolic diameter/height; 19 397 for relative wall thickness; 19 397 for left ventricular mass index; and 20 731 for left atrial size.

Table 2. Diastolic function and BMI

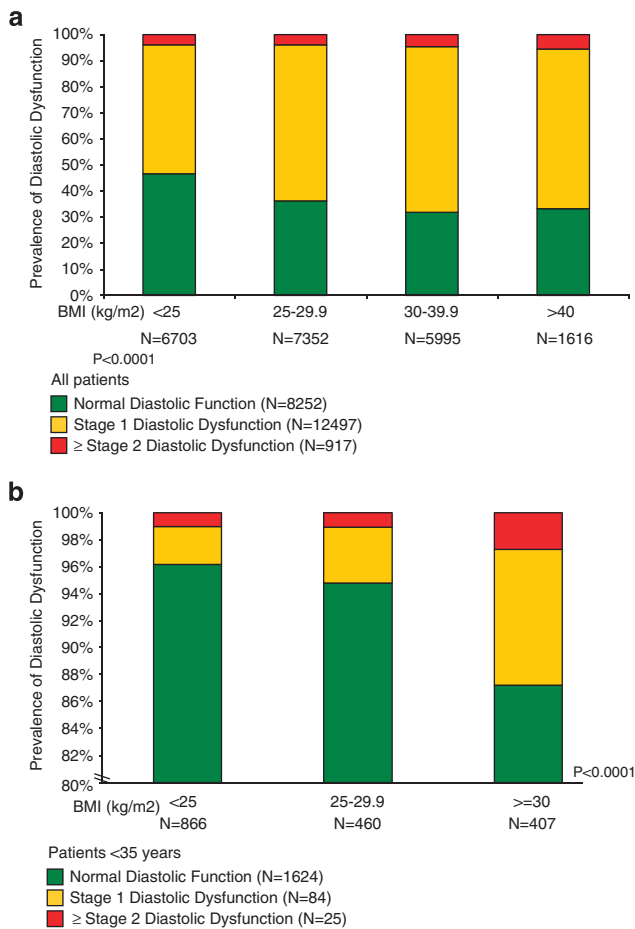|	Diastolic function			
	Normal (n = 8252)	Stage 1 (n = 12 497)	Stage 2 (n = 867)	Stage 3, 4 (n = 50)
BMI, mean (s.d.), $kg\,m^{-2}$	28.26 (7.58)	29.67 (7.43)	29.84 (7.87)	29.59 (6.10)
BMI, median (25th, 75th), $kg\,m^{-2}$	26.6 (23.1, 31.0)	28.3 (24.8, 32.7)	28.2 (24.5, 33.4)	28.7 (24.2, 33.6)
BMI $<25\,kg\,m^{-2}$	3123 (37.8%)	3320 (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 $\geqslant40\,kg\,m^{-2}$	538 (6.5%)	990 (7.9%)	87 (10.0%)	1 (2.0%)

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

normal weight to 5.2% in overweight and 12.8% in obese patients ($P<0.001$) (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 with C-statistic of 0.86 (Table 3). DD was associated with patient's age, BMI (shaped with terms for both older and younger age, greater and lower BMI), diabetes mellitus, hypertension, chronic obstructive lung disease, creatinine, diastolic blood pressure and atrial fibrillation. LV mass and LA size were not independent predictors and did not influence the strength of the observed

association. Using this model, a normogram was produced depicting the probability of DD across values of BMI and stratified based 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 similar results. Also, after rerunning the model and looking at predictors of DD stage $\geqslant2$, obesity (1.39 (1.04–1.86), $P=0.026$) and morbid obesity (2.07 (1.37–3.14), $P=0.001$) were independent predictors, as well as class II and class III obesity.

Figure 1. Prevalence of DD stratified by BMI. Bar histograms illustrating the prevalence of DD with higher BMI in all patients (**a**) and those < 35 years old (**b**). As BMI increased, the prevalence of normal diastolic function decreased while the prevalence of DD and grade severity increased (P < 0.0001 for all patients (**a**) and those < 35 years old (**b**)).

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.[1,2] 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,[4] cardiovascular complications and mortality[3], but so is DD.[10,12] The latter has been proposed as one of the pathophysiological links between obesity and heart failure.[11] With increasing body

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

Analysis of maximum likelihood estimates				
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
Intercept	− 14.6015	0.6086	576	<0.0001

Abbreviations: AFib, atrial fibrillation; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease. $C = 0.86$.
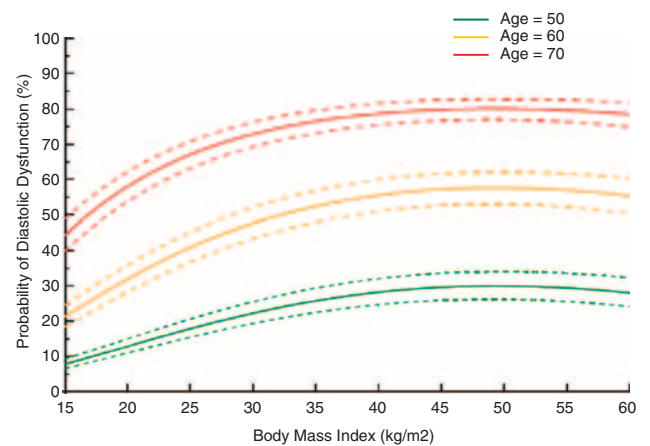
Figure 2. Probability of DD by BMI. Utilizing the final model in Table 3, nomograms with 95% confidence intervals of the association between DD and BMI are plotted and stratified based on three hypothetical age groups. For any given age, the prevalence of DD increased with increasing BMI. For example, the probability of DD for a 50-year-old patient with normal systolic function is ≈15% if he has a normal weight, 20% if overweight, 25% if obese and 28% if morbidly obese.

adiposity, changes in cardiac metabolism occur, leading to myocardial fatty infiltration, inflammation and cardiac toxicity, with the end result of DD.[5] Indeed, Kuznetsova et al.[21] 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 than our cohort (mean (s.d.), 26 kg m⁻² (ref. 4) versus 29 kg m⁻²,[8] 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.[11] 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.[11] 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.
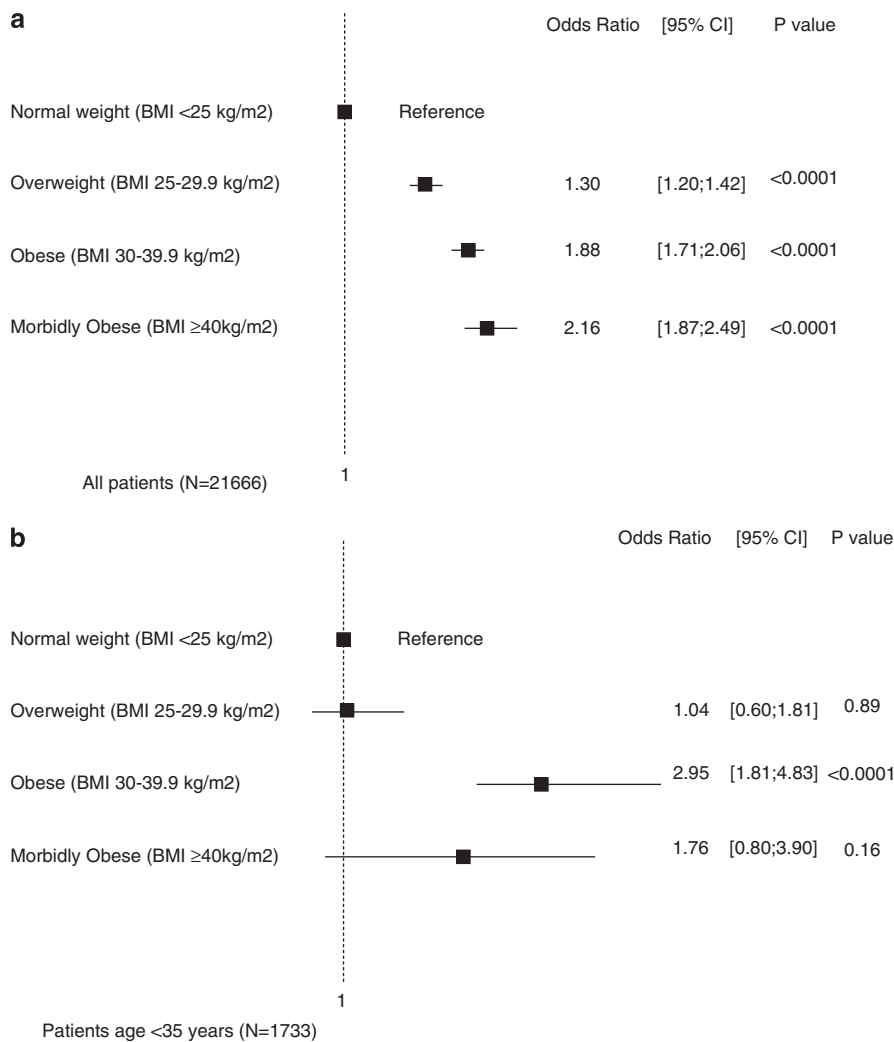
Figure 3. Odds ratio of having DD. Forest plot illustrating the odds ratios (95% confidence interval) of having DD in all patients (**a**) and those aged <35 years (**b**) based on categorical BMI groups. Patients with normal weights were used as reference.

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.[22] 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.[23–27] Hypertension, LV hypertrophy, diabetes mellitus and insulin resistance are complications of obesity and have all been associated with worsening of DD.[10] 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 <35 years old (Table 1). After adjusting for these confounders, BMI was still independently associated with DD (Table 3). Our results were further strengthened by the fact that the majority of patients did not have hypertension, and that the cohort was much younger than presented by Russo et al. Of particular interest are patients who are <35 years old. In this group of patients with normal LVEF and minimal cardiovascular disease, DD should be quite uncommon.

Yet, DD was three times more prevalent in obese versus normal weight patients (12.8% versus 3.8%, P<0.0001) (Figure 1b).

In addition, data on DD in morbidly obese patients are limited to few studies, the largest with <100 patients as compared with ~1600 patients in our cohort.[28–30] 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 <35 years old (Figure 1).

DD is a dynamic phenomenon. Not only can it progress and worsen with time, but can also improve.[31] 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.[31] In a similar study, worsening of DD was associated with new incidence of heart failure.[10] Furthermore, Achong et al.[32] 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,[33,34] although other studies showed no significant change.[35] It is of interest to evaluate in a large cohort of patients whether reduction of BMI is associated

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 some of the known factors might mediate this effect. In addition, the readers were unblinded to the medical history of patients, and LV systolic function was assessed using quantitative and/or visual LVEF (cutoff LVEF $\geqslant 55\%$ was used for normal systolic function), which is not perfect, but universally accepted. Furthermore, there was no systematic review of the echocardiograms to reassess diastolic function or concordance between different methods that were available or evolved over the 10-year study period, but rather the data were extracted from prior reads, which is comparable to what is done in clinical practice. Although the assessment of diastology is performed in a standard manner at our institution, the use of tissue Doppler imaging only began in the late 1990s. Also, the proper archiving of the echocardiographic measurements, particularly diastolic parameters, did not start until recently; hence most of the diastolic parameters (LA volumes, transmitral filling and tissue velocities) were not available in the database. The echo-Doppler indices of LV filling pressures that were measured and intrinsic myocardial DD are not universally accepted as interchangeable; yet, they are still fairly accepted and adopted. While the intra- and interobserver agreements were not ideal, there were a large number of patients, and a lack of precision in the determination of DD would only tend to underestimate the magnitude of the observed association. In addition, the list of medications was not available; however, there has been no single proven medication that impacts directly diastolic function. Other unmeasured or unobserved variables, including rate of weight gain, chronicity of obesity, waist circumference, insulin levels, malignancy and pulmonary hypertension, were not accounted for. Finally, while several pathophysiological links between obesity and DD have been proposed, a clear mechanism still needs to be identified.

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 expected increase in the incidence of DD. It will be interesting to evaluate whether significant weight loss may indeed reverse DD early on, and if so affects outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Nutrition and Diabetes website (http://www.nature.com/nutd)