

The Obesity Paradox in Patients with Significant Tricuspid Regurgitation: Effects of Obesity on Right Ventricular Remodeling and Long-Term Prognosis



Marlieke F. Dietz, MD, Edgard A. Prihadi, MD, Pieter van der Bijl, MB, ChB, MMed, Nina Ajmone Marsan, MD, Jeroen J. Bax, MD, and Victoria Delgado, MD, *Leiden, the Netherlands; and Antwerp, Belgium*

Background: Obesity may cause right ventricular (RV) remodeling due to volume overload. However, obesity is also associated with better prognosis compared with normal weight in patients with various cardiac diseases. The aim of this study was to assess the impact of obesity on RV remodeling and long-term prognosis in patients with significant (moderate and severe) tricuspid regurgitation (TR).

Methods: A total of 951 patients with significant TR (median age, 70 years; interquartile range, 61–77 years; 50% men) were divided into three groups according to body mass index (BMI): normal weight (BMI 18.5–24.9 kg/m²), overweight (BMI 25–29.9 kg/m²), and obese (BMI ≥ 30 kg/m²). Patients with congenital heart disease, peripheral edema, active endocarditis, and BMI < 18.5 kg/m² were excluded. RV size and function for each group were measured using transthoracic echocardiography and compared with reference values of healthy study populations. The primary end point was all-cause mortality. Event rates were compared across the three BMI categories.

Results: Four hundred seventy-six patients (50%) with significant TR had normal weight, 356 (37%) were overweight, and 119 (13%) were obese. RV end-diastolic and end-systolic areas were larger in overweight and obese patients compared with normal-weight patients. However, no differences in RV systolic function were observed. During a median follow-up period of 5 years, 358 patients (38%) died. Five-year survival rates were significantly better in overweight and obese patients compared with patients with normal weight (65% and 67% vs 58%, respectively, $P < .001$ and $P = .005$). In multivariate analysis, overweight and obesity were independently associated with lower rates of all-cause mortality compared with normal weight (hazard ratios, 0.628 [95% CI, 0.493–0.800] and 0.573 [95% CI, 0.387–0.848], respectively).

Conclusions: In patients with significant TR, overweight and obese patients demonstrated more RV remodeling compared with patients with normal weight. Nevertheless, a higher BMI was independently associated with better long-term survival, confirming the obesity paradox in this context. (*J Am Soc Echocardiogr* 2021;34:20-9.)

Keywords: Obesity paradox, Tricuspid regurgitation, Body mass index, Prognosis, Right ventricular remodeling

Obesity is a rapidly growing problem in modern society and a known risk factor for the development of heart failure.¹ Hemodynamic and metabolic changes due to excessive adipose tissue in patients with high body mass index (BMI) may increase total blood volume and

cardiac output.² The resulting pressure and volume overload are associated with various changes in cardiac morphology and function in the general community, including right ventricular (RV) dilation and dysfunction.³ By a similar mechanism, significant (moderate or

From the Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands (M.F.D., E.A.P., P.v.d.B., N.A.M., J.J.B., V.D.); and Hartcentrum, Ziekenhuis Netwerk Antwerpen Middelheim, Antwerp, Belgium (E.A.P.).

This work was funded by an unrestricted research grant from Edwards Lifesciences (IISUSTHV2018017).

Conflicts of Interest: The department of Cardiology has received unrestricted research grants from Abbott Vascular, Bayer, Bioventrix, Biotronik, Boston Scientific, Edwards Lifesciences, GE Healthcare, and Medtronic. Dr. Delgado has received speaking fees from Abbott Vascular, Edwards Lifesciences, Merck Sharpe & Dohme, GE Healthcare, and Medtronic. Drs. Ajmone Marsan and Bax have received speaking fees from Abbott Vascular.

Jordan B. Strom, MD, served as guest editor for this report.

Reprint requests: Victoria Delgado, MD, Department of Cardiology, Heart Lung Center, Albinusdreef 2, 2300 RC Leiden, the Netherlands (E-mail: v.delgado@lumc.nl).

0894-7317

Copyright 2020 by the American Society of Echocardiography. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

<https://doi.org/10.1016/j.echo.2020.07.022>

Abbreviations
ARIC = Atherosclerosis Risk in Communities
BMI = Body mass index
HR = Hazard ratio
IQR = Interquartile range
LV = Left ventricular
RV = Right ventricular
TAPSE = Tricuspid annular plane systolic excursion
TR = Tricuspid regurgitation

severe) tricuspid regurgitation (TR) causes volume overload of the right ventricle and is often associated with RV dilation and/or dysfunction at first presentation.⁴ Whether a high BMI enhances RV remodeling and dysfunction in patients with significant TR has never been investigated.

Several studies have demonstrated the independent influence of RV dysfunction on prognosis in patients with significant TR.^{4,5} The association between high BMI and RV

dysfunction in different patient populations would suggest that obesity enhances the development of RV dysfunction and has a negative effect on prognosis in patients with significant TR.^{3,6} However, in patients with certain established cardiovascular diseases, a higher BMI is associated with lower mortality, known as the obesity paradox.⁷ No studies to date have investigated if the obesity paradox exists in patients with significant TR.

More insight into the effects of BMI on RV remodeling and function and the influence on prognosis in patients with significant TR is needed. Therefore, the aim of the present study was to assess the impact of overweight and obesity on RV remodeling and long-term prognosis in a large cohort of patients with significant TR.

METHODS

Patients

A query was performed in the departmental echocardiographic database of the Leiden University Medical Center (Leiden, the Netherlands) in which 1,598 patients with significant (moderate and severe) TR between June 1995 and September 2016 were selected. TR was diagnosed using a multiparametric approach in agreement with current recommendations, including qualitative, semiquantitative, and quantitative data of the regurgitant jet, tricuspid valve characteristics, and right atrial and RV size.^{8,9} Patients with congenital heart disease, previous tricuspid valve surgery, or endocarditis of the tricuspid valve at baseline were excluded. For inclusion in the present study, patients were required to have height and weight data documented at the time of first echocardiographic diagnosis of significant TR to derive baseline BMI by the following formula: body weight (kg) divided by height squared (m²). Those patients with peripheral edema at baseline, which could lead to incorrect BMI measurements, were excluded. Patients were divided into BMI categories according to current guidelines.¹⁰ Because of the small

number of underweight patients in the present database, three BMI categories were examined and compared in the final study population: patients with normal weight (BMI 18.5–24.9 kg/m²), overweight (BMI 25–29.9 kg/m²), and obesity (BMI ≥ 30 kg/m²; Figure 1).

The first transthoracic echocardiogram indicating significant (moderate or severe) TR marked the baseline time point for the subsequent survival analyses. Demographic and clinical data at baseline were collected retrospectively in the departmental cardiology information system (EPD-Vision, Leiden University Medical Center). Clinical characteristics included New York Heart Association functional class, cardiovascular risk factors, relevant comorbidities, laboratory values, and medication use. The institutional review board of the Leiden University Medical Center approved the observational design of the present retrospective study of clinically acquired anonymized data and waived the need to obtain written informed consent from patients.

Echocardiography

Transthoracic two-dimensional echocardiography was performed according to current recommendations.^{8,11} Commercially available ultrasound systems (Vivid 7, E9, and E95; GE Vingmed Ultrasound, Horten, Norway) equipped with 3.5-MHz or M5S transducers were used. Images were digitally stored for offline analysis using EchoPAC version 113.0.3 and 202 software (GE-Vingmed). M-mode, bidimensional and color, continuous- and pulsed-wave Doppler data were obtained from parasternal long- and short-axis, apical and subcostal views. Left ventricular (LV) ejection fraction was derived from LV end-diastolic and end-systolic volumes measured in apical two- and four-chamber views using the Simpson method.¹¹ The peak velocities of early diastolic flow (E) and late diastolic flow (A) across the mitral valve in patients in sinus rhythm were measured, and the E/A ratio was derived.¹² Significant (moderate or severe) aortic stenosis was defined by an aortic valve area ≤ 1.5 cm² as calculated using the continuity equation.¹³ Mitral regurgitation and TR were assessed on the basis of qualitative, semiquantitative, and quantitative measurements evaluated on bidimensional, color, continuous-wave, and pulsed-wave Doppler data and graded according to current recommendations.⁸ All dimensions and areas of the right atrium, right ventricle, and tricuspid valve annulus were measured in the RV-focused apical four-chamber view. RV systolic pressure was estimated on the basis of the TR peak jet velocity with continuous-wave Doppler using the modified Bernoulli equation.¹⁴ RV systolic function was assessed by tricuspid annular plane systolic excursion (TAPSE), which was measured on M-mode recordings of the lateral tricuspid annulus in an RV-focused apical four-chamber view. Additionally, fractional area change was derived from RV end-diastolic and end-systolic areas.¹¹ From the RV-focused apical view, two-dimensional RV free wall longitudinal strain was measured and calculated as the mean of the RV lateral basal, mid, and apical segments, and values are presented as absolute values.¹⁵ All left and right atrial and ventricular

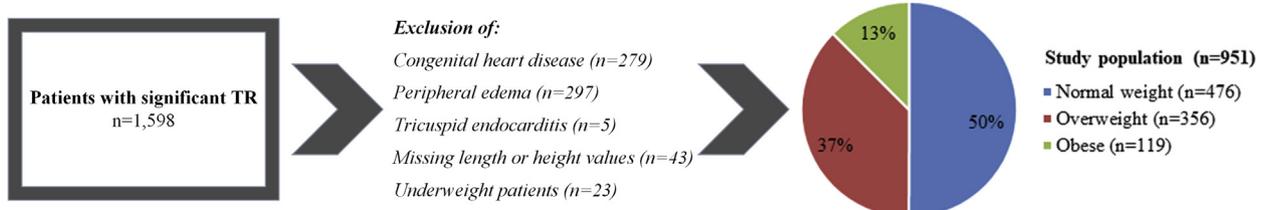


Figure 1 Flowchart of the selection of the study population and the distribution of BMI categories in patients with significant TR.

HIGHLIGHTS

- Obesity is associated with RV dilation in patients with TR.
- RV function is similar across BMI groups.
- Higher BMI is related to fewer events in patients with significant TR.
- This confirms the obesity paradox in patients with TR.

dimensions, areas, and volumes were corrected for height for comparison across BMI categories. Furthermore, median RV end-diastolic areas of all groups were compared with reference values of the current recommendations, the Atherosclerosis Risk in Communities (ARIC) study, and the Coronary Artery Risk Development in Young Adults study to define RV remodeling in patients with TR.^{3,11,16}

Outcomes

Patient follow-up started on the day of first diagnosis of significant TR by echocardiography. The primary end point for the present study was all-cause mortality. Date of death was ascertained from the departmental cardiology information system and the Social Security Death Index and was available for all patients. Secondary end points were hospitalization for heart failure, tricuspid valve surgery, and any other valve surgery and were obtained from the departmental cardiology information system.

Statistical Analysis

Continuous variables with Gaussian distribution are presented as mean \pm SD. Skewed continuous variables are presented as median (interquartile range [IQR]). Categorical variables are presented as frequencies and percentages. Differences among BMI categories were analyzed using one-way analysis of variance for continuous variables in case of Gaussian distribution, the Kruskal-Wallis test for continuous variables in case of non-Gaussian distribution, and the Pearson χ^2 test for categorical variables. Post hoc correction for multiple comparisons between groups was performed using the Bonferroni method.

Kaplan-Meier curves were used to estimate cumulative 1- and 5-year survival rates. Differences among BMI categories were compared using the log-rank test. Likewise, Kaplan-Meier curves were composed for the combined end point of all-cause mortality and hospitalization for heart failure. Cox proportional-hazards models were used to investigate the independent associates of all-cause mortality and of the combined end point of all-cause mortality and hospitalization for heart failure. Clinical and echocardiographic variables that were different among BMI categories at baseline and possible confounders for the association between BMI and mortality in patients with TR were included in the univariate analysis. Variables with P values $< .10$ in the univariate analysis were considered significant for entry in the multivariate analysis. A tolerance level of $> .50$ was set to avoid multicollinearity among the univariate determinants. No collinearity was detected; thus all parameters that were significantly associated with all-cause mortality in univariate analysis were included in the multivariate model. The proportional-hazards assumption was confirmed using statistics and graphs on the basis of the Schoenfeld residuals. Hazard ratios (HR) and 95% CIs were calculated. All tests were two-sided, and P values $< .05$ were considered to indicate statistical significance. Statistical analyses were performed using SPSS for Windows version 25 (IBM, Armonk, NY).

RESULTS

After the exclusion of patients with congenital heart disease ($n = 279$), tricuspid valve endocarditis ($n = 5$), peripheral edema ($n = 297$), missing length or height values ($n = 43$), and BMI < 18.5 kg/m² ($n = 23$), a total of 951 patients with significant TR were included in the final study population. In 49%, the patient was hospitalized at the time of the first diagnosis of significant TR. At the time of first diagnosis of significant TR, 476 patients (50%) had normal weight, 356 patients (37%) were overweight, and 119 patients (13%) were obese (Figure 1).

Clinical Characteristics

The clinical characteristics of all patients and according to BMI categories are summarized in Table 1. The median age was 70 years (IQR, 61–77 years), and 477 patients (50%) were men. Patients with significant TR were often limited in their physical activity, with 336 patients (39%) presenting with New York Heart Association functional class III and IV heart failure symptoms. Preexisting hypertension was common (81%), and approximately half of the patients had atrial fibrillation (48%).

In per-group analysis, obese patients were more often women (63%) and less tall (168 ± 9 cm) than those with normal weight (50% and 171 ± 10 cm, $P = .002$ and $P = .003$, respectively). Overweight and obese patients were more likely to have hypercholesterolemia and diabetes mellitus compared with those with normal weight ($P = .009$ and $P < .001$, respectively). Furthermore, use of diuretics and statins was more prevalent in patients with higher BMI ($P = .022$ and $P = .015$, respectively). No significant differences across BMI categories were observed in hemoglobin, creatinine, and urea level.

Echocardiographic Characteristics

Table 2 summarizes the echocardiographic characteristics of the total population and the comparisons across BMI categories. The mean LV ejection fraction of the overall population was $45 \pm 15\%$ and was highest in obese patients ($48 \pm 14\%$, $P = .041$). Concomitant significant aortic stenosis or mitral regurgitation was present in 180 (21%) and 249 (26%) patients, respectively.

After correction for height, overweight patients had larger LV end-diastolic and end-systolic volumes compared with patients with normal weight and obesity ($P = .006$ and $P = .003$, respectively). In contrast, RV end-diastolic and end-systolic areas were significantly larger in both overweight and obese patients compared with those with normal weight ($P < .001$). RV systolic function as measured by TAPSE was reduced in the overall study population (16 ± 5 mm) and did not differ significantly across BMI categories ($P = .153$). In contrast, RV free wall strain was significantly more impaired in obese patients compared with those with normal weight and overweight. The tricuspid annular diameter and RV linear diameters as well as the left and right atria were largest in obese patients.

Quantitative data on TR severity were available for 852 patients. Overweight and obese patients had more severe TR compared with normal-weight patients on the basis of quantitative parameters, but not according to the multiparametric approach (Table 2). A sensitivity analysis was performed to assess the relationship between BMI and RV size in different TR grades on the basis of effective regurgitant orifice area. In patients with quantitatively assessed severe TR (effective regurgitant orifice area ≥ 40 mm²), a similar progression of RV

Table 1 Baseline clinical characteristics of the overall population of patients with significant TR and according to BMI

Variables	Overall (N = 951)	Normal weight (n = 476)	Overweight (n = 356)	Obese (n = 119)	P-value
Age, y	70 (61–77)	71 (60–78)	69 (61–77)	69 (59–75)	.282
Sex, male	477 (50)	236 (50)*	197 (55)*	44 (37) ^{†,‡}	.002
Weight, kg	75 ± 14	67 ± 10 ^{*,‡}	80 ± 9 ^{*,†}	94 ± 12 ^{†,‡}	<.001
Height, cm	171 ± 10	171 ± 10*	172 ± 10*	168 ± 9 ^{†,‡}	.003
BSA, m ²	1.9 ± 0.2	1.8 ± 0.2 ^{*,‡}	2.0 ± 0.2 ^{*,†}	2.1 ± 0.2 ^{†,‡}	<.001
BMI, kg/m ²	26 ± 4	23 ± 2 ^{*,‡}	27 ± 1 ^{*,†}	33 ± 3 ^{†,‡}	<.001
NYHA functional class > II	336 (39)	160 (38)	126 (38)	50 (47)	.175
Hypertension	714 (81)	354 (80)	266 (80)	94 (85)	.532
Hypercholesterolemia	419 (47)	187 (42) ^{*,‡}	171 (52) [†]	61 (55) [†]	.009
Diabetes mellitus	148 (17)	51 (12) ^{*,‡}	59 (18) ^{*,†}	38 (34) ^{†,‡}	<.001
(Ex-)smoker	271 (31)	131 (30)	109 (33)	31 (28)	.571
Coronary artery disease	362 (38)	169 (36)	147 (42)	46 (39)	.264
Pacemaker/ICD	348 (37)	167 (36)	138 (39)	43 (36)	.625
Atrial fibrillation	421 (48)	204 (46)	159 (48)	58 (52)	.528
Chronic obstructive pulmonary disease	114 (13)	58 (13)	42 (13)	14 (13)	.987
Hemoglobin, mmol/L	8.0 (6.9–8.8)	8.1 (7.1–8.8)	8.0 (6.9–8.9)	7.7 (6.4–8.6)	.071
Creatinine, μmol/L	89 (73–116)	89 (72–114)	90 (77–117)	88 (69–123)	.145
Urea, mmol/L	8.1 (6.0–11.3)	8.1 (6.0–11.3)	8.2 (6.3–11.5)	7.8 (5.7–10.9)	.446
Diuretics	495 (54)	226 (49)	199 (57)	70 (60)	.022
Statins	401 (46)	180 (41) [‡]	164 (50) [†]	57 (53)	.015

BSA, Body surface area; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association.

Data are expressed as median (IQR), number (percentage), or mean ± SD. P values by Kruskal-Wallis test or one-way analysis of variance for non-Gaussian- and Gaussian-distributed continuous variables, respectively. P values by χ^2 test for categorical variables (Bonferroni correction). Bold text indicates statistically significant P values.

*P < .05 vs obese.

[†]P < .05 vs normal weight.

[‡]P < .05 vs overweight.

end-diastolic area along with increasing BMI was demonstrated as in the overall population (Supplemental Table 1).

RV Remodeling According to BMI in Patients with Significant TR

According to the most recent recommendations, the normal range for RV end-diastolic area when indexed to body surface area is 4.5 to 11.5 cm²/m² for women and 5 to 12.6 cm²/m² for men.¹¹ Similar 95% reference limits were reported in the Coronary Artery Risk Development in Young Adults study by Ogunyankin *et al.*,¹⁶ including a large population of healthy young adults. In the present study of patients with significant TR, RV dilation was frequent: median RV end-diastolic area was 11.5 cm²/m² (IQR, 9.3–14.0 cm²/m²) among women and 12.9 cm²/m² (IQR, 10.8–16.0 cm²/m²) among men. Linear dimensions also showed RV basal (47 ± 8 mm) and midventricular (36 ± 9 mm) dilation, compared with current limits of normality (25–41 and 19–35 mm, respectively).¹¹ In contrast, the mean longitudinal diameter of the right ventricle in patients with significant TR (75 ± 12 mm) was within the normal range summarized in the guidelines (59–83 mm).¹¹

To the best of our knowledge, only the substudy of the ARIC trial³ considered BMI to correct for cardiac abnormalities independent of comorbidities in obese patients in a population of 4,343 patients aged 69 to 82 years who were free of coronary artery disease and

heart failure. Overall, RV end-diastolic areas were larger in our population with significant TR (normal-weight men, 25 cm² [IQR, 20–31 cm²]; normal-weight women, 19 cm² [IQR, 16–24 cm²]) compared with patients in the ARIC study (normal-weight men, 22 ± 5 cm²; normal weight women, 16 ± 4 cm²). The association between increasing BMI and larger RV end-diastolic area demonstrated in the ARIC study for both sexes is comparable with our findings: RV end-diastolic area in overweight men was 26 cm² (IQR, 22–31 cm²) in patients with TR compared with 22 ± 5 cm² in patients in the ARIC substudy, and RV end-diastolic area in obese men was 28 cm² (IQR, 23–37 cm²) compared with 23 ± 5 cm², respectively. In the present study, RV end-diastolic area was significantly larger in overweight and obese patients compared with normal-weight patients in both men and women (P = .005 and P < .001, respectively).

Long-Term Follow-Up

During a median follow-up period of 5 years (IQR, 29–60 months), 358 patients (38%) died. In this period, 144 patients (15%) were hospitalized for heart failure. Only 76 patients (8%) underwent tricuspid valve annuloplasty or replacement, while 111 of 429 patients with concomitant valvular disease in this cohort underwent other valvular surgery during follow-up (Table 3). In the evaluation of outcomes according to BMI categories, the Kaplan-Meier analysis demonstrated significantly better survival for patients with overweight and obesity

Table 2 Baseline echocardiographic characteristics of the overall population of patients with significant TR and according to BMI

Variables	Overall (N = 951)	Normal weight (n = 476)	Overweight (n = 356)	Obese (n = 119)	P
Heart rate, beats/min	78 ± 18	79 ± 17	77 ± 18	80 ± 19	.183
LV end-diastolic volume/height, mL/m	65 (47–97)	63 (45–91)*	69 (50–104) [†]	65 (46–94)	.006
LV end-systolic volume/height, mL/m	34 (22–58)	32 (21–54)*	38 (24–68) [†]	31 (23–51)	.003
LV ejection fraction, %	45 ± 15	46 ± 15	44 ± 15 [‡]	48 ± 14*	.041
E/A ratio	1.5 (1.0–2.6)	1.3 (0.9–2.5)	1.6 (1.1–2.7)	1.8 (1.2–2.8)	.026
LA maximum volume/height, mL/m	53 (34–75)	49 (33–74)	57 (36–74)	60 (39–78)	.029
Significant aortic stenosis	180 (21)	94 (22)	65 (20)	21 (19)	.715
Significant mitral regurgitation	249 (26)	128 (27)	97 (28)	24 (20)	.273
Tricuspid annular diameter/height, mm/m	24 ± 4	24 ± 5 [‡]	25 ± 4	25 ± 4 [†]	.006
RV basal diameter/height, mm/m	26 ± 5	26 ± 5	26 ± 4	27 ± 4	.143
RV midventricular diameter/height, mm/m	20 ± 5	20 ± 5 [‡]	20 ± 5	21 ± 5 [†]	.034
RV longitudinal diameter/height, mm/m	42 ± 7	41 ± 6** [‡]	42 ± 7 [†]	43 ± 7 [†]	<.001
RV end-diastolic area/height, cm ² /m	13 (11–17)	13 (10–16)** [‡]	14 (11–17) [†]	15 (11–18) [†]	<.001
RV end-systolic area/height, cm ² /m	8 (6–11)	8 (6–11)** [‡]	9 (7–12) [†]	9 (7–12) [†]	<.001
RV systolic pressure, mm Hg	32 (25–42)	31 (25–41)	33 (25–42)	33 (25–44)	.615
RA maximum area/height, cm ² /m	15 (12–19)	15 (11–18)** [‡]	16 (12–20) [†]	16 (12–20) [†]	.001
TAPSE, mm	16 ± 5	16 ± 5	15 ± 5	16 ± 5	.153
RV fractional area change, %	36 ± 13	37 ± 13	35 ± 13	37 ± 12	.310
RV free wall longitudinal strain (%)	15.6 ± 7.4	16.6 ± 7.3	15.5 ± 7.4	12.4 ± 7.1	<.001
Severe TR	188 (20)	101 (21)	62 (17)	25 (20)	.370
Leaflet tenting height, mm	10 (0–14)	8 (0–13)** [‡]	10 (0–15) [†]	12 (6–16) [†]	<.001
PISA radius (mm)	12 ± 4	11 ± 4** [‡]	12 ± 4 [†]	13 ± 4 [†]	<.001
EROA (mm ²)	68 (45–102)	61 (42–93)** [‡]	72 (47–109) [†]	75 (49–131) [†]	.001
RVol (mL/beat)	66 (41–102)	58 (37–91)** [‡]	71 (45–108) [†]	77 (47–120) [†]	<.001

EROA, Effective regurgitant orifice area; LA, left atrial; PISA, proximal isovelocity surface area; RA, right atrial; RVol, regurgitant volume; TAPSE, tricuspid annular plane systolic excursion.

Data are expressed as mean ± SD, median (IQR), or number (percentage). P values by Kruskal-Wallis test or one-way analysis of variance for non-Gaussian- and Gaussian-distributed continuous variables, respectively. P values by χ^2 test for categorical variables (Bonferroni correction). Bold text indicates statistically significant P values.

*P < .05 vs overweight.

[†]P < .05 vs normal weight.

[‡]P < .05 vs obese.

compared with those with normal weight (overall log-rank $\chi^2 = 10.05$, $P = .007$; Figure 2A). One- and 5-year survival rates were 81% and 58% in patients with normal weight, 87% and 65%

in overweight patients, and 90% and 67% in obese patients, respectively. The Kaplan-Meier curves for the combined end point of all-cause mortality and hospital admissions for heart failure were similar

Table 3 Occurrence of the outcome parameters in the overall population and according to BMI during follow-up

Variables	Overall (N = 951)	Normal weight (n = 476)	Overweight (n = 356)	Obese (n = 119)	P
Death	358 (38)	200 (42)	120 (34)	38 (32)	.019
Hospital admission for heart failure	144 (15)	66 (14)	61 (17)	17 (14)	.412
Tricuspid valve surgery	76 (8)	36 (8)	27 (8)	13 (11)	.451
Any valve surgery	111 (12)	55 (12)	38 (11)	18 (16)	.439

Data are expressed as number (percentage). Bold text indicates statistically significant P values.

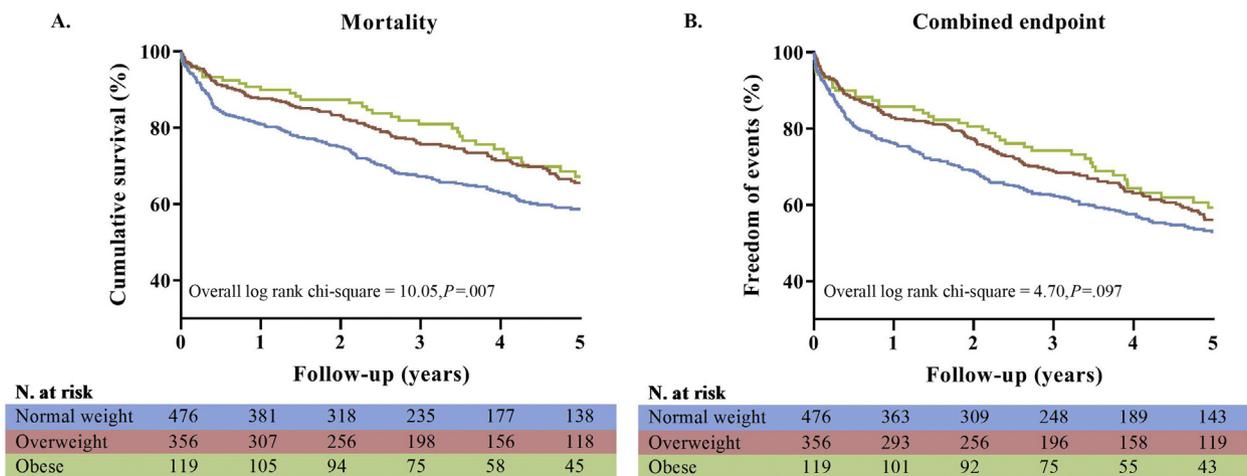


Figure 2 Kaplan-Meier curves for survival (A) and the combined end point of hospital admissions for heart failure and survival (B) according to BMI in patients with significant TR.

across the BMI categories (overall log-rank $\chi^2 = 4.70$, $P = .097$; Figure 2B).

Univariate and multivariate Cox proportional-hazards models for the primary end point are presented in Table 4. In multivariate analysis, overweight and obesity were independently associated with better survival compared with normal weight (HRs, 0.628 [95% CI, 0.493–0.800; $P < .001$] and 0.573 [95% CI, 0.387–0.848; $P = .005$], respectively). When introducing BMI as a continuous variable, higher BMI was also independently associated with better survival (HR, 0.934; 95% CI, 0.903–0.965; $P < .001$). Additionally, older age, higher creatinine, diuretic use, larger LV end-diastolic volume, and lower TAPSE were independently associated with all-cause mortality. Regarding the composite end point, multivariate analysis showed an independent association between overweight and obesity with better prognosis compared with normal weight (HRs, 0.716 [95% CI, 0.573–0.895; $P = .003$] and 0.685 [95% CI, 0.483–0.971; $P = .034$], respectively; Supplemental Table 2).

DISCUSSION

The main findings of the present study of a large population of patients with moderate and severe TR are that higher BMI is associated with larger RV end-diastolic area, while no differences in RV systolic function were observed across BMI groups. In addition, overweight

and obesity were independently associated with lower all-cause mortality compared with normal weight, confirming the existence of the obesity paradox in this cardiac condition. No significant differences in hospitalization for heart failure during follow-up were observed between patients with normal weight, overweight, and obesity.

Association between RV Remodeling and Obesity in Patients with Significant TR

Significant TR is often associated with RV dilation and dysfunction due to volume overload of the right ventricle.⁴ Accordingly, the RV size of the overall population in the present study was larger compared with reference values of healthy study populations.^{11,16,17} Obesity may also affect RV structure and function by a multifactorial mechanism of increased RV afterload, increased circulating blood volume, metabolic and neuroendocrine influences, and direct obesity-related myocardial effects.^{2,18} The additional impact of obesity on RV dilation and dysfunction in patients with significant TR has not previously been investigated.

Most studies to date have investigated RV size in obesity without cardiovascular comorbidities using cardiovascular magnetic resonance imaging.^{19–21} Foppa *et al.*¹⁹ demonstrated in 1,794 participants of the Framingham Heart Study that increased BMI was associated with larger RV end-diastolic volume indexed for height in both men and women. In contrast, in 739 subjects without cardiovascular risk factors, women displayed increased RV end-diastolic volume per

Table 4 Univariate and multivariate Cox proportional-hazards models for mortality in patients with TR with BMI in categories (model 1) and BMI as continuous variable (model 2)

Variables	Univariate analysis		Multivariate analysis: model 1		Multivariate analysis: model 2	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age	1.024 (1.015–1.033)	<.001	1.027 (1.017–1.037)	<.001	1.026 (1.016–1.036)	<.001
Sex, male	1.290 (1.048–1.589)	.016	1.010 (0.796–1.282)	.936	0.988 (0.779–1.254)	.924
Diabetes mellitus	1.702 (1.322–2.192)	<.001	1.270 (0.951–1.696)	.105	1.301 (0.977–1.733)	.072
Hypercholesterolemia	1.074 (0.868–1.327)	.512				
Creatinine	1.004 (1.003–1.005)	<.001	1.003 (1.002–1.004)	<.001	1.003 (1.002–1.004)	<.001
Diuretics	1.931 (1.545–2.413)	<.001	1.439 (1.118–1.852)	.005	1.425 (1.106–1.836)	.006
LV end-diastolic volume/ height	1.006 (1.004–1.008)	<.001	1.004 (1.002–1.007)	.001	1.004 (1.002–1.007)	.001
LV ejection fraction	0.983 (0.977–0.990)	<.001	0.994 (0.985–1.002)	.132	0.994 (0.986–1.002)	.159
E/A ratio	1.005 (0.989–1.022)	.530				
TA diameter/height	1.031 (1.007–1.056)	.013	1.008 (0.982–1.035)	.562	1.010 (0.983–1.037)	.472
RV end-diastolic area/height	1.010 (1.003–1.017)	.005	1.006 (0.997–1.015)	.190	1.006 (0.997–1.015)	.226
TAPSE	0.952 (0.931–0.974)	<.001	0.971 (0.948–0.995)	.017	0.973 (0.950–0.997)	.026
RV free wall longitudinal strain (each 1% decrease)	1.037 (1.020–1.054)	<.001				
Severe TR	1.197 (0.933–1.535)	.157				
BMI groups		.007		<.001	—	—
Normal weight (reference)	—	—	—	—	—	—
Overweight	0.734 (0.585–0.920)	.007	0.628 (0.493–0.800)	<.001	—	—
Obese	0.669 (0.473–0.947)	.023	0.573 (0.387–0.848)	.005	—	—
BMI (continuous)	0.951 (0.923–0.979)	.001	—	—	0.932 (0.901–0.964)	<.001

TA, Tricuspid annular; TAPSE, tricuspid annular plane systolic excursion. Bold text indicates statistically significant *P* values.

BMI point increase, while in men, no association between RV end-diastolic volume and BMI was demonstrated.²⁰ The MESA-Right Ventricle Study²¹ is the largest study to date evaluating the association between BMI and RV dimensions. In 4,127 individuals without clinical heart disease, overweight and obesity were independently associated with greater RV end-diastolic volume on cardiovascular magnetic resonance imaging, even after adjustment for respective LV parameters. Studies using echocardiography to assess RV size in obese individuals are scarce. The only published data comparing RV end-diastolic area measured using two-dimensional echocardiography across various BMI categories in a healthy population originate from a substudy of the ARIC trial by Bello *et al.*,³ which demonstrated significantly larger RV end-diastolic area with increasing BMI. Tadic *et al.*²² reported similar results for indexed RV volumes measured by three-dimensional echocardiography in 127 patients with untreated hypertension.

The present study extends these findings by demonstrating the additive effect of overweight and obesity on RV dilation in both men and women with significant TR. Similar to the results presented by Chahal *et al.*,²¹ changes in RV size were more pronounced than changes in LV size, suggesting that RV dilation is more than a generalized cardiac adaptation to a larger body size in obese patients. In our population, this difference could be explained by the additional impact of TR on volume overload of the thin-walled right ventricle, which is already more susceptible to dilation than the left ventricle.

Despite the association between RV remodeling and obesity, RV systolic function as measured by TAPSE and RV fractional area change was not more impaired in patients with increasing BMI in our data. However, when using speckle-tracking echocardiography to assess RV free wall strain, we observed more impaired RV systolic function in patients with larger BMI. Previous studies on the influence of BMI on RV function in different patient populations have yielded conflicting results. Interestingly, the studies that reported RV dilation in individuals without structural heart disease, discussed previously, also reported a significant reduction in RV systolic function in higher BMI groups.^{3,21,22} Likewise, Wong *et al.*²³ demonstrated a reduction of RV free wall strain in overweight and obese subjects compared with normal-weight subjects without overt heart disease. In contrast, 153 obese participants of the Obesity Weight Reduction and Remodeling Study had similar TAPSE as age- and gender-matched healthy control subjects.²⁴ Additionally, Takiguchi *et al.*²⁵ reported no significant differences in RV fractional area change among all BMI groups in a population of 648 patients hospitalized for decompensated heart failure. In the context of acute myocardial infarction, obese patients even had a better RV function measured by TAPSE than nonobese patients.²⁶ The heterogenous results of these studies may be explained by factors that were not accounted for, such as duration of obesity, or by differences between study populations. In our population, the enhanced RV dilation in obese patients may be an initial adaptive response to increased circulating blood volume in order to preserve RV function by the Frank-Starling mechanism. As

this mechanism may become maladaptive over time, prospective trials with systematic RV function analysis during follow-up are needed to elucidate if targeting obesity could prevent or reverse RV remodeling and dysfunction.

Association of Prognosis and Obesity in Patients with Significant TR

Obesity is associated with the development of various cardiovascular diseases due to hemodynamic, metabolic, and neuroendocrine effects of adipose tissue that lead to an unfavorable profile.¹ Concordant with these mechanisms, overweight and obese patients in our population had a higher prevalence of obesity-related comorbidities (hypercholesterolemia, diabetes mellitus) and larger left and right atrial and LV and RV volumes and areas. Notwithstanding, the present study demonstrated better long-term survival in overweight and obese patients compared with normal-weight patients with significant TR. This “obesity paradox” for mortality has been described in various patient populations, but the mechanism remains unclear.^{7,27,28} Investigators have suggested several hypotheses, such as the production of protective cytokines by the adipose tissue.²⁹ Moreover, obese patients may have a greater metabolic reserve or could become symptomatic at less severe stages of heart failure and thus present earlier.²⁹ Others have suggested that the prognosis might be affected by unmeasured confounding factors, such as unintentional weight loss, leading to worse survival in patients with a lower BMI.^{29,30} Banack *et al.*³¹ suggested that the obesity paradox in cardiovascular diseases may be entirely explained by collider stratification bias (a correlation between an exposure and an unmeasured confounder due to selection on a third variable [collider] that is caused by both, which induces a false association between the exposure and outcome in case the confounder also influences the outcome). However, in the present population of patients with significant TR, the role of collider bias is uncertain. Firstly, collider bias can occur only if obesity causes TR. Although obesity is known to increase the risk for cardiovascular diseases such as myocardial infarction, hypertension, and atrial fibrillation, there is no evidence that obesity causes TR. In subjects in the Framingham Heart Study,³² the severity and prevalence of TR even decreased as a function of increasing BMI. This reverse association makes the hypothesis that obesity causes TR unlikely. However, despite lacking evidence, one may argue that obesity can cause TR by the pathophysiologic mechanism of volume overload, which leads to RV dilation and tricuspid annular dilation, thereby causing secondary TR. Assuming that obesity does cause TR, collider bias is still not the only explanation for the obesity paradox. As demonstrated by Sperrin *et al.*,³³ for obesity as collider to reverse the harmful effect, the unmeasured confounders must have a very strong effect on TR and mortality. It is unlikely that confounders with such strong associations with TR and mortality are still unknown to medicine and therefore were not included in the analysis. Consequently, a true physiologic protective effect of obesity on mortality in patients with significant TR is more plausible. Preclinical trials, clinical studies, and bias analyses might further elucidate the mechanisms for the obesity paradox.

Interestingly, in the present population of patients with significant TR, higher BMI was not associated with higher risk for heart failure hospitalization during follow-up but was independently associated with a lower risk for the combined end point of all-cause mortality and heart failure hospitalization. This in contrast to the increased risk for heart failure in overweight and obese subjects as demonstrated in 5,881 participants in the Framingham

Heart Study.¹ These contrasting results suggest that even though obesity is a risk factor for heart failure in healthy populations, higher BMI in the presence of established cardiovascular disease such as significant TR is associated with a lower risk for heart failure hospitalization, confirming the presumption of an obesity paradox for heart failure as well.

To the best of our knowledge, the present study is the first to demonstrate the independent association between obesity and prognosis in patients with significant TR. These counterintuitive findings emphasize the need for further studies to confirm our results. Better understanding of the favorable phenotype of obese patients and the mechanism behind the obesity paradox may help clinicians in applying risk-reducing treatment in this patient population.

Study Limitations

The present study is subject to limitations inherent to the retrospective and single-center design. No information was available on physical activity, the duration of obesity, the distribution of adipose tissue and weight loss, all of which could influence RV remodeling and prognosis.^{7,21} BMI, even though it is a surrogate for true body adiposity, is highly correlated to anthropometric measures of body fat^{3,21} and is an easy-to-use parameter for caregivers in risk stratification.

The presence of obstructive sleep apnea was not documented, even though this disease is associated with obesity and may increase afterload of the right ventricle and thereby enhance RV remodeling due to pulmonary arterial hypertension.³⁴ However, Wong *et al.*²³ found no relationship between sleep apnea severity and RV characteristics. Furthermore, pulmonary pressures were assessed in our study and did not differ significantly across BMI groups.

No healthy control subjects were included in the present study. To assess the impact of significant TR and obesity on RV remodeling compared with normal subjects, reference values of RV measurements in healthy subjects from the largest studies to date were used.^{3,11,16,17} However, data on RV size are challenging to compare because data are inconsistently presented with and without indexing for body surface area or height. Current recommendations differentiate normal values for men and women but do not specify different normal ranges for higher BMI groups.¹¹ We chose to index RV parameters to height to correct for a generalized cardiac adaptation to a larger body size, but to prevent overcorrection for the effects of obesity. After correction for height, RV size was similar in both sexes in the present study. Explicit guidelines on how to present reference values on RV size could improve comparability across studies.

Measuring RV function using two-dimensional echocardiography is challenging. Given the higher blood volume and compensatory mechanisms that initially lead to increased stroke volume in obese patients, load-dependent measurements such as TAPSE are not ideal to assess RV systolic function in patients with higher BMI. However, TAPSE is the most validated method and most used in clinical practice.¹⁴ Furthermore, similar results were observed with RV fractional area change. Longitudinal data from sequential echocardiograms over time were not analyzed, as the data were not gathered systematically (only at the discretion of the treating physician), which may introduce a significant bias.

CONCLUSION

In a large cohort of patients with moderate or severe TR, overweight and obesity were associated with more pronounced RV dilation

compared with normal-weight patients. This RV remodeling appears to be adaptive, as no significant differences across BMI groups were observed in RV systolic function. Additionally, higher BMI was independently associated with better survival during long-term follow-up, supporting the concept of the “obesity paradox” being applicable to patients with significant TR.

SUPPLEMENTARY DATA

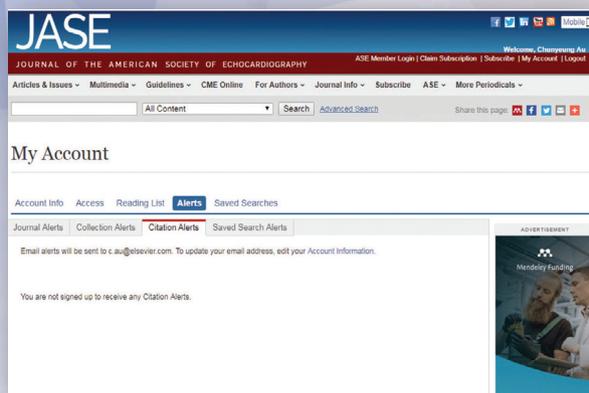
Supplementary data to this article can be found online at <https://doi.org/10.1016/j.echo.2020.07.022>.

REFERENCES

1. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, et al. Obesity and the risk of heart failure. *N Engl J Med* 2002;347:305-13.
2. Alpert MA, Karthikeyan K, Abdullah O, Ghadban R. Obesity and cardiac remodeling in adults: mechanisms and clinical implications. *Prog Cardiovasc Dis* 2018;61:114-23.
3. Bello NA, Cheng S, Claggett B, Shah AM, Ndumele CE, Roca GQ, et al. Association of weight and body composition on cardiac structure and function in the ARIC study (Atherosclerosis Risk in Communities). *Circ Heart Fail* 2016;9:e002978.
4. Dietz MF, Prihadi EA, van der Bijl P, Goedemans L, Mertens BJA, Guroy E, et al. Prognostic implications of right ventricular remodeling and function in patients with significant secondary tricuspid regurgitation. *Circulation* 2019;140:836-45.
5. Kammerlander AA, Marzluf BA, Graf A, Bachmann A, Kocher A, Bonderman D, et al. Right ventricular dysfunction, but not tricuspid regurgitation, is associated with outcome late after left heart valve procedure. *J Am Coll Cardiol* 2014;64:2633-42.
6. Obokata M, Reddy YNV, Melenovsky V, Pislaru S, Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. *Eur Heart J* 2019;40:689-97.
7. Elagizi A, Kachur S, Lavie CJ, Carbone S, Pandey A, Ortega FB, et al. An overview and update on obesity and the obesity paradox in cardiovascular diseases. *Prog Cardiovasc Dis* 2018;61:142-50.
8. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;30:303-71.
9. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;14:611-44.
10. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al. European guidelines for obesity management in adults. *Obes Facts* 2015;8:402-24.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1-39.e14.
12. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF III, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;29:277-314.
13. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr* 2017;30:372-92.
14. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23:685-713.
15. Badano LP, Koliaas TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to Standardize Deformation Imaging. *Eur Heart J Cardiovasc Imaging* 2018;19:591-600.
16. Ogunyankin KO, Liu K, Lloyd-Jones DM, Colangelo LA, Gardin JM. Reference values of right ventricular end-diastolic area defined by ethnicity and gender in a young adult population: the CARDIA study. *Echocardiography* 2011;28:142-9.
17. Grunig E, Biskupek J, D'Andrea A, Ehlken N, Egenlauf B, Weidenhammer J, et al. Reference ranges for and determinants of right ventricular area in healthy adults by two-dimensional echocardiography. *Respiration* 2015;89:284-93.
18. Tadic M, Ivanovic B, Cuspidi C. Metabolic syndrome and right ventricle: an updated review. *Eur J Intern Med* 2013;24:608-16.
19. Foppa M, Arora G, Gona P, Ashrafi A, Salton CJ, Yeon SB, et al. Right ventricular volumes and systolic function by cardiac magnetic resonance and the impact of sex, age, and obesity in a longitudinally followed cohort free of pulmonary and cardiovascular disease: the Framingham Heart Study. *Circ Cardiovasc Imaging* 2016;9:e003810.
20. Rider OJ, Lewis AJ, Lewandowski AJ, Ntusi N, Nethononda R, Petersen SE, et al. Obese subjects show sex-specific differences in right ventricular hypertrophy. *Circ Cardiovasc Imaging* 2015;8:e002454.
21. Chahal H, McClelland RL, Tandri H, Jain A, Turkbey EB, Hundley WG, et al. Obesity and right ventricular structure and function: the MESA-Right Ventricle Study. *Chest* 2012;141:388-95.
22. Tadic M, Cuspidi C, Vukomanovic V, Kocijancic V, Celic V, Stanisavljevic D. The association between obesity, blood pressure variability, and right ventricular function and mechanics in hypertensive patients. *J Am Soc Echocardiogr* 2016;29:802-11.
23. Wong CY, O'Moore-Sullivan T, Leano R, Hukins C, Jenkins C, Marwick TH. Association of subclinical right ventricular dysfunction with obesity. *J Am Coll Cardiol* 2006;47:611-6.
24. Zeller J, Strack C, Fenk S, Mohr M, Loew T, Schmitz G, et al. Relation between obesity, metabolic syndrome, successful long-term weight reduction, and right ventricular function. *Int Heart J* 2016;57:441-8.
25. Takiguchi M, Yoshihisa A, Miura S, Shimizu T, Nakamura Y, Yamauchi H, et al. Impact of body mass index on mortality in heart failure patients. *Eur J Clin Invest* 2014;44:1197-205.
26. Alhamshari YS, Alnabelsi T, Mulki R, Cepeda-Valery B, Figueredo VM, Romero-Corral A. Right ventricular function measured by TAPSE in obese subjects at the time of acute myocardial infarction and 2 year outcomes. *Int J Cardiol* 2017;232:181-5.
27. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J* 2008;156:13-22.
28. Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-Dehoff RM, Zhou Q, et al. Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med* 2007;120:863-70.
29. Horwich TB, Fonarow GC, Clark AL. Obesity and the obesity paradox in heart failure. *Prog Cardiovasc Dis* 2018;61:151-6.
30. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, et al. Prognostic importance of weight loss in chronic heart failure and the effect

- of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* 2003;361:1077-83.
31. Banack HR, Kaufman JS. The obesity paradox: understanding the effect of obesity on mortality among individuals with cardiovascular disease. *Prev Med* 2014;62:96-102.
 32. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* 1999;83:897-902.
 33. Sperrin M, Candlish J, Badrick E, Renehan A, Buchan I. Collider bias is only a partial explanation for the obesity paradox. *Epidemiology* 2016;27:525-30.
 34. Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. *Am J Med Sci* 2001;321:225-36.

Did you know?



You can track the impact of your article with citation alerts that let you know when your article (or any article you'd like to track) has been cited by another Elsevier-published journal.

Visit onlinejase.com today!