Body mass index and early outcomes following mitral valve surgery for degenerative disease

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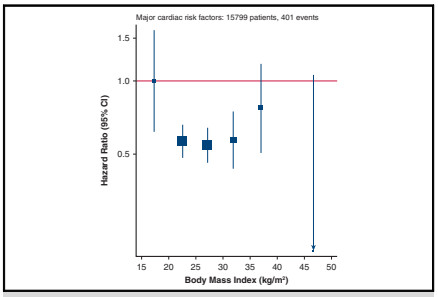
ABSTRACT

Objective: Using a large national database, we sought to better define the relationship between obesity measures and early clinical outcomes following mitral valve surgery for degenerative disease.

Methods: For the outcomes of in-hospital mortality, postoperative cerebrovascular event (CVA), and deep sternal wound infection (DSWI), a retrospective cohort study was performed using data acquired from the United Kingdom National Adult Cardiac Surgery Audit. Multivariable Cox proportional hazard regression modeling was used to investigate associations with individual measures of obesity. Progressively adjusted body mass index (BMI)-specific hazard ratios (HRs) were plotted against mean BMI values in each World Health Organization category using floated variances to investigate specific shapes of association.

Results: Multivariable Cox proportional hazard modeling failed to demonstrate an association between mortality and an increase in BMI of 5 points (HR, 0.93, 95% confidence interval [CI], 0.81-1.07), a BMI quintile increase (HR, 0.98; 95% CI, 0.90-1.07), or being classed "obese" by World Health Organization standards (HR, 1.03; 95% CI, 0.74-1.42). A 5-point BMI increase was associated with an increased hazard of DSWI (HR, 1.38; 95% CI, 1.08-1.77) but was not associated with perioperative CVA (HR, 1.05; 95% CI, 0.91-1.21). The shape of association between BMI and mortality appeared approximately U-shaped. DSWI appeared linear, whereas CVA demonstrated an inverted U, or a possible hourglass.

Conclusions: Although individual measures of obesity were not associated with an increased mortality risk on regression modeling, the U-shaped relationship between mortality and increasing BMI demonstrates lower mortality risks in lower obesity classes. Increasing BMI was associated with an increased hazard for DSWI. (J Thorac Cardiovasc Surg 2021;161:1765-73)



Adjusted shape of association for incident in-hospital mortality and mean body mass index.

CENTRAL MESSAGE

With a demonstrated U-shaped relationship, body mass index values outside the extreme margins may confer a mortality benefit when undergoing mitral valve surgery for degenerative etiologies.

PERSPECTIVE

For mitral valve surgery for degenerative etiologies, the effect of BMI on outcomes remains undefined. A mortality benefit can be seen outside the extreme margins of BMI, whereas sternal complications appear to increase proportionally. The relationship between BMI and cerebrovascular events is less clear. This may represent a target for preoperative intervention and optimization.

See Commentary on page 1774.

The prevalence of obesity in developed countries has been consistently increasing.[1] Obesity is strongly associated with several cardiovascular and metabolic diseases, including atherosclerosis, hypertension, heart failure, and diabetes mellitus, and has been shown to increase mortality in the general population.[2-4] Moreover, obesity has been shown to be both increasing within the cardiac surgery population and conferring an excess risk of perioperative morbidity.[5,6]

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Abbreviations and Acronyms

BMI = body mass index
CABG = coronary artery bypass graft
CI = confidence interval
CVA = cerebrovascular event
DSWI = deep sternal wound infection
HR = hazard ratio
NACSA = National Adult Cardiac Surgery Audit
WHO = World Health Organization

Scanning this QR code will take you to the table of contents to access supplementary information.

However, the relationship between obesity and outcomes following cardiac surgery is still under debate, with inconsistent evidence demonstrated. Some large analyses have demonstrated obesity to be a risk factor for mortality,[5,7] whereas others have demonstrated no association or a procedure-specific association.[8] Further complicating matters is that large analyses have suggested a U-shaped relationship between increasing body mass index (BMI) and mortality, a so-called obesity paradox.[6,9,10] These studies have focused on heterogeneous cardiac surgery populations, consisting predominantly of patients undergoing coronary artery bypass grafting (CABG). A differential effect of obesity on distinct subpopulations of cardiac surgery patients remains understudied.

Patients with a degenerative mitral valve represent a specific cardiac surgery subpopulation, with the relationship between obesity and early clinical outcomes following mitral valve surgery remaining controversial. A recent attempt to understand the effects of obesity in this population has failed to show an analogous U-shaped association, although this was a small single-center study.[11] Given the disparity between these recent results and the associations demonstrated in more heterogeneous populations, the aim of our study was 2-fold. First, we sought to describe the shape of association between increasing BMI and the outcomes of in-hospital mortality, deep sternal wound infection (DSWI), and postoperative cerebrovascular events (CVA) in the degenerative mitral valve population. Second, we sought to investigate whether individual measures of BMI or obesity were associated with the same outcomes after multivariable adjustment. We hypothesized that the degenerative mitral disease population would exhibit a different shape of association and hazard when compared with analyses on a more heterogeneous and CABG-focused surgical population.

METHODS

Data Acquisition

A retrospective cohort study was performed using National Adult Cardiac Surgery Audit (NACSA) data, maintained by the National Institute for Cardiovascular Outcomes Research, with specialist knowledge and leadership from the Society for Cardiothoracic Surgery. This United Kingdom national database contains clinical information on all patients undergoing cardiac surgery under the National Health Service. Maintenance and validation are regularly undertaken by the use of reproducible cleaning and maintenance algorithms, with return to individual centers for local validation.[12,13]

Access was solicited from National Institute for Cardiovascular Outcomes Research, under approval from the University Hospitals Bristol National Health Service Foundation Trust Clinical Audit and Effectiveness Team, to examine the relationship between changes in BMI and early clinical outcomes. Data were requested in March of 2016, with access granted in March of 2018, understanding its novel use in the mitral valve-specific population. Identifiable patient information was removed, the requirement for patient informed consent was waived, and the dataset was adapted for use with statistical analysis software. The dataset was resurveyed for nonadult or duplicate results, with removal planned as appropriate. Ambiguously coded, conflicting, or extreme outlying values were recoded as missing data. There was no attempt to replace missing data. Missingness was potentially the result of being related to the true value (not recorded when a variable was absent or normal rather than coding a zero value) and could not be considered missing at random. To prevent systematic error due to misclassification, missing data for binary or categorical variables were treated as missing rather than a "no."

Patient Population, Exposure, and Outcomes

Patients were ≥18 years old and had undergone mitral valve surgery for degenerative disease as classified in the NACSA database. January 1, 2000, was the lower date limit. Patients were required to have nonmissing data for both mitral procedure and BMI. Exclusions included concomitant aorta or aortic valve procedures, patients requiring preoperative hemodialysis, mechanical assistance, intra-aortic balloon pump use, or classified as in preoperative cardiogenic shock.

The exposure of interest was BMI, defined by the following World Health Organization (WHO) categories: underweight (<18.5 kg/m^2), normal (20-24.9 kg/m^2), overweight (25-29.9 kg/m^2), obese class 1 (30-34.9 kg/m^2), obese class 2 (35-39.9 kg/m^2), and obese class 3 (>40 kg/m^2).[14] For purposes of demographic comparison, patients were classified with obesity if their BMI was ≥30. To help fully understand the relationship between BMI and postoperative outcomes, we modeled BMI per 5-point increase, per-quintile increase, as a binary variable (obesity: yes/no), and as a continuous variable. This mitigates issues relating to the artificial nature of BMI categories, with potentially little clinical difference between the extremes of each subsequent range, while remaining pragmatic for interpretation. The primary outcome event was all cause in-hospital mortality. Secondary outcome events were postoperative in-hospital DSWI and CVA.

Statistical Analysis

All parameters were checked for normality. Normally distributed continuous variables were reported as mean ± standard deviation and compared by the 2-sample *t*-test. Non-normally distributed variables were reported as median and first to third quartile (Q1-Q3), and compared by the 2-sample Wilcoxon rank-sum test. Binary variables were reported as proportions and compared using the χ^2 test.

TABLE 1. Preoperative patient demographics

Clinical variable	Nonobese (13,460)	Obese (2792)	*P* value	Missing
BMI, mean (SD)	24.6 (3.0)	33.4 (4.2)	<.0001	0
Age, median (Q1-Q3)	69.8 (61.3-76.2)	67.7 (59.7-74.1)	<.0001	2
Male	8779 (65.2)	1735 (62.1)	.0019	2
Active smoking	551 (4.1)	126 (4.5)	.33	139
Diabetes	847 (6.3)	382 (13.7)	<.0001	80
Hypertension	6314 (46.9)	1710 (61.2)	<.0001	149
NYHA class			<.0001	107
1	1814 (13.5)	257 (9.2)		
2	5290 (39.3)	945 (33.8)		
3	5273 (39.2)	1335 (47.8)		
4	991 (7.4)	240 (8.6)		
Previous MI	1009 (7.5)	300 (10.8)	<.0001	171
Creatinine, median (Q1-Q3)	86 (74-101)	89 (76-105)	.0001	9792
Obstructive lung disease	1500 (11.1)	397 (14.2)	<.0001	73
Atrial fibrillation	4831 (35.9)	1003 (35.9)	.97	556
CVA history	787 (5.8)	171 (6.1)	.57	429
Peripheral vascular disease	577 (4.3)	128 (4.6)	.48	111
Pulmonary hypertension	4977 (37.0)	1057 (37.9)	.38	8940
Nonelective	1728 (12.8)	349 (12.5)	.63	2
Reoperation	799 (5.9)	189 (6.8)	.094	1529
LVEF, median (Q1-Q3)	55 (50-60)	55 (50-60)	.091	192
Coronary disease	3101 (23.0)	722 (25.9)	.0014	2130

Values as n (%) unless otherwise noted. *BMI*, Body mass index; *SD*, standard deviation; *Q1-Q3*, first to third quartile; *NYHA*, New York Heart Association; *MI*, myocardial infarction; *CVA*, cerebrovascular event; *LVEF*, left ventricular ejection fraction.

First, a Cox proportional hazard regression model was planned to assess the association between mortality and BMI. The proportional hazard assumption was tested by log-log plots and Schoenfeld residuals. A complete case analysis was planned, whereby only patients with an absence of missing data were included. Univariable models were generated for the following prespecified confounders: 5-year age increase, sex, smoking history, previous myocardial infarction, diabetes, hypertension, chronic pulmonary disease, previous CVA, peripheral vascular disease, coronary artery disease, left ventricular ejection fraction, redo-sternotomy, mitral valve replacement, perioperative return to the operating room (noninfectious), postoperative hemodialysis, postoperative CVA, and DSWI. Statistically significant univariable predictors of mortality were included in the full multivariable model. Because of the loss of data due to missingness in the multivariable model, we then reanalyzed the univariable associations using the subsequent smaller population, free of missing data. The change in population is shown in Figure E1. Multivariable model fit was assessed by the likelihood ratio test relative to the unadjusted model.

We then characterized the shape of association with mortality across WHO-defined BMI categories. The log hazard ratio (HR) for mortality in each category was derived and exponentiated. Confidence intervals (CIs) were estimated using floated variances, assigning a less intercorrelated variance to each BMI category, including the reference group, permitting the valid comparison of any exposure groups by describing the uncertainty in risk without reference to another level.[15,16] The category-specific HRs were plotted against the mean BMI value for each WHO category, allowing the characterization of the shape of association between BMI and in-hospital mortality. The shape of association was graphed for the unadjusted population as well as after adjustment for major cardiac risk factors. As a sensitivity analysis, BMI was modeled using a population of isolated mitral valve patients, and as a continuous variable using a restricted cubic spline function with 4 knots.

Secondary outcomes were modeled by Cox regression for 5-point BMI increase in the same manner as mortality. The shapes of association were characterized using the aforementioned method. Additional analyses for secondary outcomes were also completed using restricted cubic splines as mentioned previously.

All statistical analysis was performed using Stata 13.1 (StataCorp LP, College Station, Tex). The α level was set at 0.05, with a 95% CI. All *P* values were 2-sided and considered statistically significant if <.05. When possible, exact *P* values have been reported.

RESULTS

Patient Characteristics

The base population included 16,252 patients. The nonobese group contained 13,460 patients, whereas the obese group contained 2792 patients. The mean BMI in the obese group was 33.4 kg/m^2 versus 24.6 in the nonobese group ($P < .0001$). Patients without obesity were older, more commonly male, and had a lower presenting New York Heart Association functional class. Patients with obesity had more hypertension, diabetes, and a greater baseline creatinine. Patients with obesity were

TABLE 2. Perioperative details

Clinical variable	Nonobese (13,460)	Obese (2792)	*P* value	Missing
Cardiopulmonary bypass, min, median (Q1-Q3)	115 (89-148)	123 (96-159)	<.0001	444
Crossclamp, min, median (Q1-Q3)	85 (65-112)	91 (70-118)	<.0001	431
Mitral replacement	4333 (32.2)	1022 (36.6)	<.0001	0
Mechanical valve	4202 (31.2)	992 (35.5)	<.0001	11,027
Ablation	787 (5.8)	157 (5.6)	.65	5452
ASD repair	336 (2.5)	66 (2.4)	.68	5452
Tricuspid repair	2188 (16.3)	431 (15.4)	.28	13,500
CABG	3233 (24.0)	749 (26.8)	.0017	2311
BIMA	19 (0.14)	4 (0.14)	.98	12,460
Sternal wound infection	48 (0.36)	24 (0.86)	.0003	1062
CVA	209 (1.6)	50 (1.8)	.36	220
Take-back*	802 (6.0)	134 (4.8)	.017	1076
Dialysis	363 (2.7)	90 (3.2)	.12	1653
Hospital stay, d, median (Q1-Q3)	10 (7-15)	10 (8-16)	<.0001	204

Values as n (%) unless otherwise noted. *Q1-Q3*, First to third quartile; *ASD*, atrial septal defect; *CABG*, coronary artery bypass graft; *BIMA*, bilateral internal mammary artery; *CVA*, cerebrovascular event. *Take-back defined as a return to the operating room for noninfectious reasons (bleeding, sternal re-wiring, pericardial effusion, cardiac).

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also found to more commonly suffer from coronary artery disease, previous myocardial infarction, and obstructive lung disease. Complete details regarding patient demographics, including missing values, are included in Table 1.

Patients with obesity had increased median cardiopulmonary bypass (123 [96-159] vs 115 [89-148] minutes, $P < .0001$) and aortic crossclamp times (91 [70-118] vs 85 [65-112] minutes, $P < .0001$), relative to patients without obesity. Patients with obesity more often received a mitral valve replacement (36.6 vs 32.2%, $P < .0001$), as well as a mechanical mitral valve (35.5 vs 31.2%, $P < .0001$). Apart from a 2.8% greater incidence of CABG ($P = .0017$), there were no significant differences detected in concomitant procedures performed between groups. The use of bilateral internal mammary arteries was identical between patients with obesity and patients without obesity (0.14%, $P = .98$). Patients without obesity had a slightly lower incidence of sternal wound infection, a slightly shorter length of hospital stay, and a greater incidence of take-back procedures not related to sternal infection. Full perioperative details are reported in Table 2.

Regression Analyses

The proportional hazard assumption was valid. After removal of missing data, uni- and multivariable analysis included a population of 10,928 patients with 267 mortality events. Preoperative characteristics independently predicting in-hospital mortality were 5-year age increase (HR, 1.25; 1.15-1.36, $P < .001$) and hypertension (HR, 1.41, 1.08-1.85, $P = .013$). Male sex demonstrated a decreased hazard for mortality (HR, 0.72; 0.56-0.92, $P = .01$). Perioperative factors independently predicting in hospital mortality were return to the operating room (HR, 1.92, 1.44-2.56, $P < .001$), postoperative dialysis (HR, 6.63, 5.02-8.77, $P < .001$), postoperative CVA (HR, 1.03, 1.01-1.05, $P = .001$), and mitral valve replacement (HR, 1.62, 1.26-2.09, $P < .001$). No manner of describing BMI yielded a non-null result. Complete uni-/multivariable modeling results are presented in Table 3.

For DSWI, the multivariable model was composed of 10,928 patients and 46 DSWI events. A 5-point increase in BMI was independently associated with an increased hazard for DSWI (HR, 1.38; 1.08-1.77, $P = .009$), as was male sex (HR, 2.14; 1.08-4.25, $P = .030$). For postoperative CVA, the multivariable model was composed of 10,928 patients and 202 CVA events. Only ejection fraction <30% was found to be independently protective for postoperative CVA (HR, 0.39; 0.16-0.95, $P = .039$). Mitral valve replacement approached, but did not achieve, statistical significance for the postoperative CVA endpoint (HR, 1.31; 0.99-1.75, $P = .063$). A 5-point increase in BMI was not associated with an increased hazard of postoperative CVA (HR, 1.05; 0.91-1.21, $P = .48$). Complete multivariable results for the secondary outcomes are presented in Table 4.

Shape of Association

The shape of association between BMI and in-hospital mortality was approximately U-shaped. Figure 1 demonstrates the relative stability of this association. Normal weight, preobese, and obesity class 1 were shown to be at a decreased hazard for early mortality. This shape was consistent when analyzed by a restricted cubic spline function (Figure 2) and when only isolated mitral valve patients were included (Figure E2).

TABLE 3. Uni-/multivariable associations with mortality

Clinical variable	Univariable (n = 10,928), Events = 267		Multivariable (n = 10,928), Events = 267	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
BMI (per 5-point increase)	0.93 (0.82-1.06)	.26	0.93 (0.81-1.07)	.34
BMI (per quintile increase)	0.97 (0.90-1.06)	.54	0.98 (0.90-1.07)	.69
Obese	1.00 (0.74-1.36)	.99	1.03 (0.74-1.42)	.88
Age (per 5-y increase)	**1.35 (1.25-1.46)**	**<.001**	**1.25 (1.15-1.36)**	**<.001**
Male	**0.71 (0.55-0.90)**	**.005**	**0.72 (0.56-0.92)**	**.01**
Previous MI	**1.43 (1.05-1.94)**	**.023**	1.08 (0.76-1.52)	.67
Diabetes	**1.43 (1.03-1.98)**	**.032**	0.86 (0.59-1.25)	.43
Hypertension	**1.71 (1.32-2.20)**	**<.001**	**1.41 (1.08-1.85)**	**.013**
Active smoker	0.60 (0.30-1.22)	.16	–	–
Obstructive lung disease	1.30 (0.96-1.76)	.095	–	–
CVA history	1.36 (0.91-2.02)	.13	–	–
Pulmonary hypertension	1.72 (0.90-3.29)	.10	–	–
Peripheral vascular disease	**1.81 (1.26-2.60)**	**.001**	1.40 (0.96-2.06)	.084
Coronary disease	**1.69 (1.32-2.16)**	**<.001**	1.24 (0.94-1.62)	.13
Ejection fraction				
>50%	Reference		Reference	
30%-50%	**1.46 (1.13-1.88)**	**.003**	1.15 (0.89-1.50)	.29
<30%	**1.72 (1.05-3.142.82)**	**.032**	1.35 (0.80-2.27)	.25
Reoperation	**1.67 (1.19-2.34)**	**.003**	1.10 (0.77-1.56)	.60
Mitral replacement	**1.91 (1.50-2.45)**	**<.001**	**1.62 (1.26-2.09)**	**<.001**
Take-back*	**2.74 (2.08-3.62)**	**<.001**	**1.92 (1.44-2.56)**	**<.001**
Postoperative dialysis	**9.46 (7.24-12.37)**	**<.001**	**6.63 (5.02-8.77)**	**<.001**
Sternal wound infection†	1.01 (0.99-1.04)	.29	–	–
Postoperative CVA†	**1.01 (1.00-1.04)**	**.036**	**1.03 (1.01-1.05)**	**.001**
Nonelective	1.05 (0.79-1.39)	.74	–	–

Bold indicates statistical significance. *HR*, Hazard ratio; *CI*, confidence interval; *BMI*, body mass index; *MI*, myocardial infarction; *CVA*, cerebrovascular event. *Take-back defined as a return to the operating room for noninfectious reasons (bleeding, sternal re-wiring, pericardial effusion, cardiac). †Time-varying.

The secondary outcomes of DSWI and postoperative CVA were modeled on the same population of 10,928. DSWI demonstrated a linear association with increasing BMI. CVA demonstrated an inverted U, or possible hourglass, shape with increasing BMI. However, wider 95% CIs and fewer events, especially at the greater BMI levels, precluded definitively ruling out a linear relationship between BMI and CVA (Figure 3). Spine-based analysis revealed comparable shapes for each secondary outcome (Figure E3).

DISCUSSION

The results of this study failed to demonstrate an association between increasing BMI and all cause in-hospital mortality when different methods of characterizing BMI were analyzed by Cox proportional hazard modeling. However, subsequent analysis of the shape association demonstrated a U-shaped relationship between BMI and all cause in-hospital mortality. This characteristic shape demonstrates different HRs at different regions of the graph, which may make it challenging to detect an effect with a conventional regression model. A 5-point BMI increase was associated with an increased hazard for DSWI but not postoperative CVA. DSWI demonstrated a linear association with increasing BMI, whereas a linear association could not be ruled out for CVA. These findings may represent the potential opportunity for targeted preoperative intervention for risk mitigation, such as nutritional optimization of a patient with a low BMI, or targeted weight loss/lifestyle-modification strategies in a patient with a high BMI, if possible and clinically feasible. Such an intervention would necessarily be limited by the patient's functional capacity and would likely be limited to elective patients with normal ventricular function.

Although cardiopulmonary bypass and aortic crossclamp times were increased in the obese population, the median increase was less than 10 minutes and did not translate to

TABLE 4. Multivariable associations with secondary outcomes

Clinical variable	Deep sternal wound infection, Events = 46		Cerebrovascular event, Events = 202	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
BMI (per 5-point increase)	**1.38 (1.08-1.77)**	**.009**	1.05 (0.91-1.21)	.48
Age (per 5-y increase)	0.98 (0.85-1.13)	.77	1.0 (0.93-1.07)	.94
Male	**2.14 (1.08-4.25)**	**.030**	1.10 (0.82-1.47)	.54
Previous MI	0.35 (0.11-1.09)	.070	0.91 (0.59-1.39)	.65
Diabetes	1.06 (0.46-2.43)	.90	1.06 (0.69-1.62)	.79
Hypertension	0.72 (0.39-1.34)	.30	0.87 (0.65-1.16)	.34
Peripheral vascular disease	0.92 (0.27-3.13)	.89	1.12 (0.67-1.87)	.68
Coronary disease	0.62 (0.30-1.28)	.20	0.93 (0.67-1.29)	.68
Ejection fraction				
>50	Reference		Reference	
30%-50%	0.98 (0.52-1.82)	.95	0.80 (0.58-1.08)	.15
<30	0.58 (0.13-2.61)	.48	**0.39 (0.16-0.95)**	**.039**
Reoperation	0.85 (0.31-2.30)	.75	0.97 (0.61-1.53)	.89
Mitral replacement	1.12 (0.60-2.07)	.73	1.31 (0.99-1.75)	.063
Take-back*	0.86 (0.40-1.83)	.69	0.71 (0.45-1.10)	.13
Postoperative dialysis	0.97 (0.43-2.20)	.94	0.90 (0.56-1.44)	.65
Postoperative CVA†	1.04 (0.98-1.10)	.16	–	–
Sternal wound infection†	–	–	1.03 (0.99-1.07)	.15

HR, Hazard ratio; *CI*, confidence interval; *BMI*, body mass index; *MI*, myocardial infarction; *CVA*, cerebrovascular event. *Take-back defined as a return to the operating room for noninfectious reasons (bleeding, sternal re-wiring, pericardial effusion, cardiac). †Time-varying.

an increased hazard for mortality or CVA. Patients with obesity more often received a mitral valve replacement. This may indicate selection bias due to a patient with obesity carrying an elevated comorbidity profile with the surgeon desiring a more expedient replacement procedure. Replacement could also be related to surgical exposure, with the mitral valve being more difficult to access and/or visualize, leading the surgeon toward a less technically demanding procedure. The obese group had a 4.3% greater incidence of mechanical mitral valves. Mitral replacement did not confer an excess hazard of CVA on multivariable analysis, although this difference may have influenced the shape of association. The reason for the 1.2% difference in incidence of take-back procedures is unclear and difficult to explain beyond speculation.

Our results are inconsistent with a recent large American study of more than 6 million patients. This study demonstrated that patients with obesity were at a decreased risk for in-hospital mortality and CVA while having an increased risk of DSWI.[5] This study population consisted of approximately 60% patients undergoing CABG, with fewer than 10% undergoing isolated valve procedures, and an undefined amount undergoing mitral valve surgery for degenerative disease. Another American study of 2440 patients demonstrated a similarly improved mortality in patients with overweight.[17] This study population was again predominantly CABG, with only 9.5% of the overall population undergoing a mitral valve procedure, alone or in combination. Our current study population is distinct, as it is from a national United Kingdom database, with all patients having undergone mitral valve surgery for degenerative disease. These populations may systematically differ, potentially accounting for our different results.

In a recent landmark analysis, Mariscalco and colleagues[9] also demonstrated a U-shaped association between BMI and all-cause in hospital mortality for patients undergoing cardiac surgery. This study sourced its data from the same base NACSA population. However, this analysis included all cardiac operations and all underlying cardiac etiologies (with salvage procedures, critical preoperative state, preoperative hemodialysis excluded), with CABG being predominant at 58%. More complicated or urgent operations may have a different association than those that are more straightforward, with different underlying disease processes potentially differentially affecting the final result when pooled together. Because of this potential differential effect, it was surprising to demonstrate the same relationship between BMI and in-hospital mortality, especially after demonstrating a null association in a previous analysis.[11] Other factors, apart from underlying etiology and surgical procedure, may therefore influence the postoperative course. Our population included commonly associated procedures, such as tricuspid repair, ablation, or coronary artery bypass.

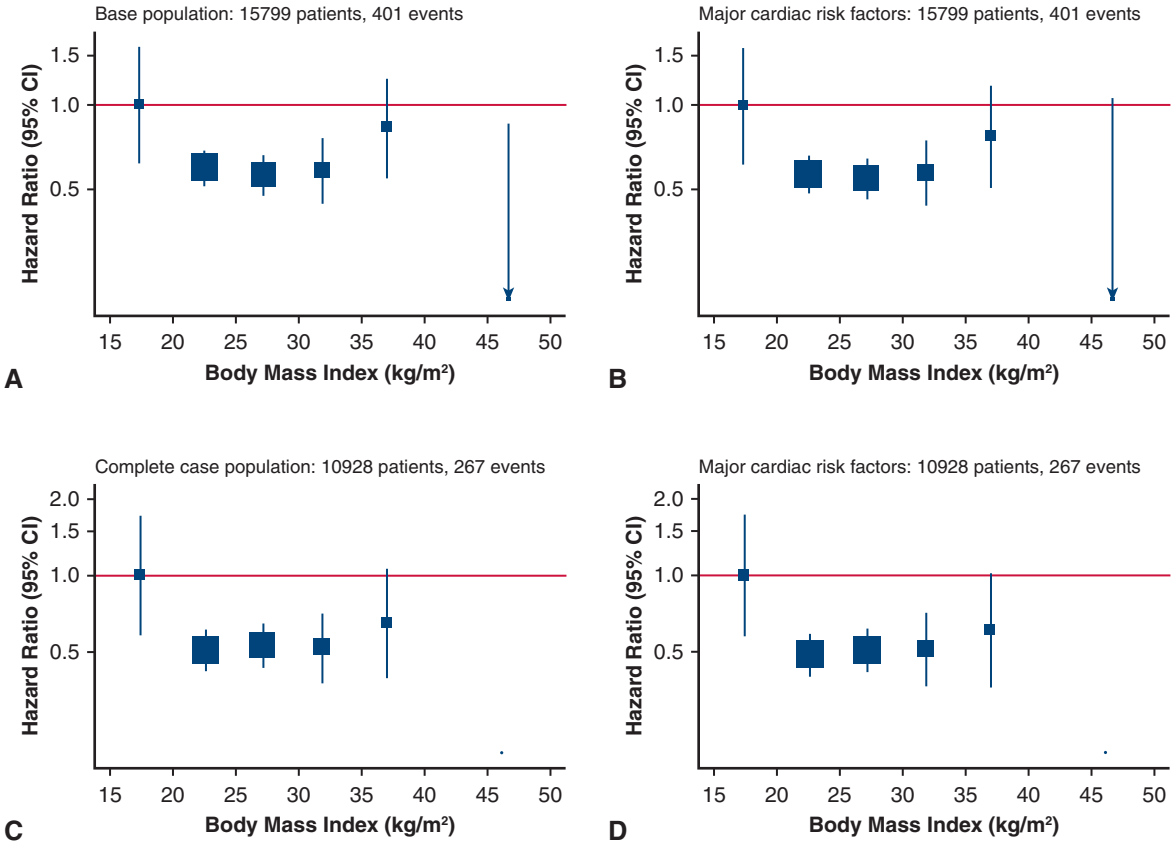

FIGURE 1. Hazard ratios for incident in-hospital mortality by class-specific mean body mass index. A, Unadjusted base population; B, base population adjusted for major cardiac risk factors; C, unadjusted complete case population; D, complete case population adjusted for major cardiac risk factors. *CI*, Confidence interval.

However, exclusion of these patients did not change the relationship with mortality (Figure E2).

BMI does not account for body composition, distribution of adiposity, or lean body mass, all of which may influence a patient's overall health. High lean body mass has been demonstrated as inversely related to mortality in cardiac patients.[18] Therefore, a patient with increased BMI because of increased lean mass having a positive outcome is not paradoxical. Lower BMI may also be a manifestation of occult illness, poorly controlled disease, or cachexia/frailty, giving the appearance of improved outcomes in the greater BMI groups.[19] Similarly, conditioning on a variable affected by exposure that shares common causes with the outcome (a collider) can distort the association, leading to an apparent protective effect in the specific disease group.[20] The collider bias, however, may only introduce small discrepancies.[21]

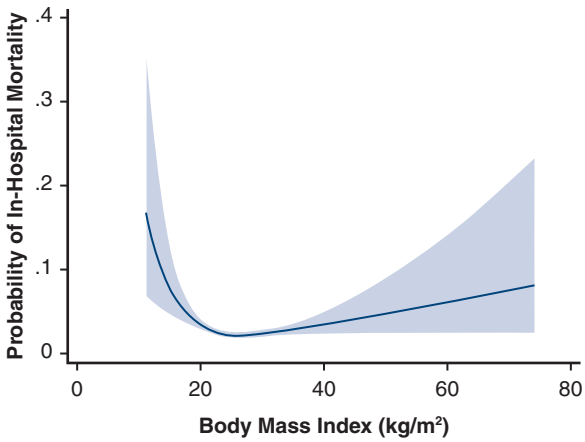

FIGURE 2. Probability of in-hospital mortality expressed by restricted cubic spline.

The strengths of our study are the sample size, the prospective collection of data, and a robust analysis plan, investigating the influence of BMI by several methods. However, our results must be interpreted in the context of certain important limitations. All database research suffers from the nonrandomized, retrospective study design. Although every effort was made to exclude nondegenerative causes of mitral valve disease, such as ischemic, rheumatic, and infective, there remains the possibility of incorrect coding or differential misclassification

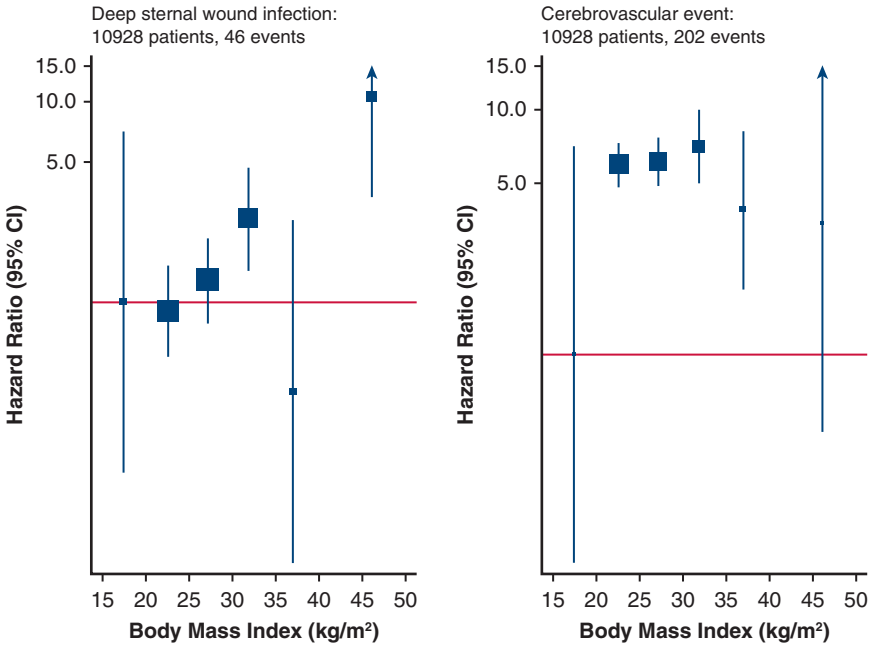

FIGURE 3. Hazard ratios for incident deep sternal wound infection and cerebrovascular event by class-specific mean body mass index. *CI*, Confidence interval.

influencing our results. Although the NACSA database undergoes regular validation and maintenance efforts, it remains possible that data have been reported or entered incorrectly prior to data submission taking place. We unfortunately did not have access to data regarding the complexity of mitral valve pathology. Although there is no reason to expect a differential distribution of complexity across BMI, it nonetheless is a potential residual confounder.

Missing data accounted for the loss of 5324 patients from the multivariable analysis. Although a substantial population of 10,928 patients remained, meaningful information and analytical efficiency was certainly lost. We can see this at the extreme end of panels *C* and *D* in Figure 1. Fewer patients and events present in the greatest level of BMI have resulted in less precise estimates, with a nonestimable result due to lack of events present. Although we have no reason to suspect that this would impose a differential effect, this nevertheless remains a possibility. Fewer events at the greatest level of BMI may also be indicative of selection bias. Unfortunately, the source data cannot be considered to be missing at random. Methods of missing data analysis, such as multiple imputation, can be considered heavily biased in such a scenario. Although the NACSA database is comprehensive, several key parameters are not captured, potentially limiting our analysis in terms of interpretability and generalizability. Mortality risk stratification scores, minimally invasive approaches, complexity of mitral pathology, left atrial appendage procedures, postoperative atrial fibrillation, prolonged intubation, and other potential clinical parameters of interest are not captured. Although several adjustment methods were employed, there may be systematic differences in mortality risk between BMI categories. The increased risk of sternal wound infection in greater BMI groups brings up the question of selection bias, where patients with obesity would be more likely to have a sternotomy-based approach, placing them at a systematically greater risk of sternal wound complications. Although a left atrial appendage exclusion presumably accompanied ablation procedures, and should not be differentially distributed, we cannot guarantee this.

With any observational study, no matter how robust and comprehensive the model, there remains a risk of residual confounding from measured and unmeasured confounders. Finally, as in-hospital outcomes were used, it is possible that a subset of patients discharged to respite facilities (327 patients, 2.01%) or home hospitals (854 patients, 5.25%) may have suffered from complications related to their cardiac surgery but have failed to be captured by our endpoints.

In patients undergoing mitral valve surgery for degenerative disease, increasing BMI appears to confer an increased hazard of DSWI and possibly CVA, although it does not appear to confer an increased hazard of mortality in this patient population. This suggests that the patient with an elevated BMI is not necessarily at an excess risk of in-hospital mortality. However, postoperative DSWI

and CVA remain concerning in this patient population as BMI increases. Given the limitations addressed previously, further targeted research into this patient population is certainly warranted.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

References

1. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet*. 2011;377:557-67.
2. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association scientific statement on obesity and heart disease from the obesity committee of the council on nutrition, physical. *Circulation*. 2006;113:898-918.
3. Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB. Annual deaths attributable to obesity in the United States. *JAMA*. 1999;282:1530-8.
4. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013;309:71-82.
5. Vargo PR, Steffen RJ, Bakaeen FG, Navale S, Soltesz EG. The impact of obesity on cardiac surgery outcomes. *J Card Surg*. 2018;33:588-94.
6. Ghanta RK, LaPar DJ, Zhang Q, Devarkonda V, Isbell JM, Yarboro LT, et al. Obesity increases risk-adjusted morbidity, mortality, and cost following cardiac surgery. *J Am Heart Assoc*. 2017;6:1-8.
7. Benedetto U, Danese C, Codispoti M. Obesity paradox in coronary artery bypass grafting: myth or reality? *J Thorac Cardiovasc Surg*. 2014;147:1517-23.
8. Rahmanian PB, Adams DH, Castillo JG, Chikwe J, Bodian CA, Filsoufi F. Impact of body mass index on early outcome and late survival in patients undergoing coronary artery bypass grafting or valve surgery or both. *Am J Cardiol*. 2007;100:1702-8.
9. Mariscalco G, Wozniak MJ, Dawson AG, Serraino GF, Porter R, Nath M, et al. Body mass index and mortality among adults undergoing cardiac surgery: a nationwide study with a systematic review and meta-analysis. *Circulation*. 2017;135:850-63.
10. Johnson AP, Parlow JL, Whitehead M, Xu J, Rohland S, Milne B. Body mass index, outcomes, and mortality following cardiac surgery in Ontario, Canada. *J Am Heart Assoc*. 2015;4:1-13.
11. Rapetto F, Bruno VD, King M, Benedetto U, Caputo M, Angelini GD, et al. Impact of body mass index on outcomes following mitral surgery: does an obesity paradox exist? *Interact Cardiovasc Thorac Surg*. 2018;26:590-5.
12. Hickey GL, Grant SW, Cosgriff R, Dimarakis I, Pagano D, Kappetein AP, et al. Clinical registries: governance, management, analysis and applications. *Eur J Cardiothorac Surg*. 2013;44:605-14.
13. Hickey GL, Cosgriff R, Grant SW, Cooper G, Deanfield J, Roxburgh J, et al. A technical review of the United Kingdom national adult cardiac surgery governance analysis 2008-11. *Eur J Cardiothorac Surg*. 2014;45:225-33.
14. World Health Organization. *Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation*. Geneva: World Health Organization; 2000.
15. Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med*. 1991;10:1025-35.
16. Plummer M. Improved estimates of floating absolute risk. *Stat Med*. 2004;23:93-104.
17. Stamou SC, Nussbaum M, Stiegel RM, Reames MK, Skipper ER, Robicsek F, et al. Effect of body mass index on outcomes after cardiac surgery: is there an obesity paradox? *Ann Thorac Surg*. 2011;91:42-7.
18. Lavie CJ, De Schutter A, Patel DA, Romero-Corral A, Artham SM, Milani RV. Body composition and survival in stable coronary heart disease: impact of lean mass index and body fat in the "obesity paradox." *J Am Coll Cardiol*. 2012;60:1374-80.
19. Preston SH, Stokes A. Obesity paradox: conditioning on disease enhances biases in estimating the mortality risks of obesity. *Epidemiology*. 2014;25:454-61.
20. Banack HR, Kaufman JS. The "obesity paradox" explained. *Epidemiology*. 2013;24:461-2.
21. 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.

Key Words: mitral valve, obesity, clinical outcomes, perioperative risk

ADULT

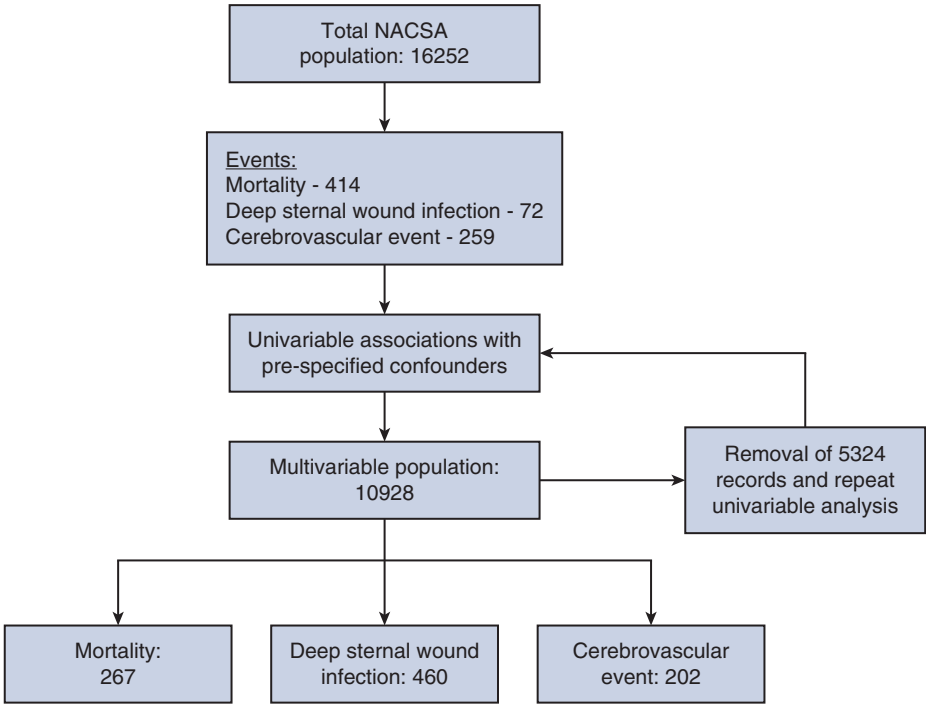

FIGURE E1. Patient population flow diagram. *NACSA*, National Adult Cardiac Surgery Audit.

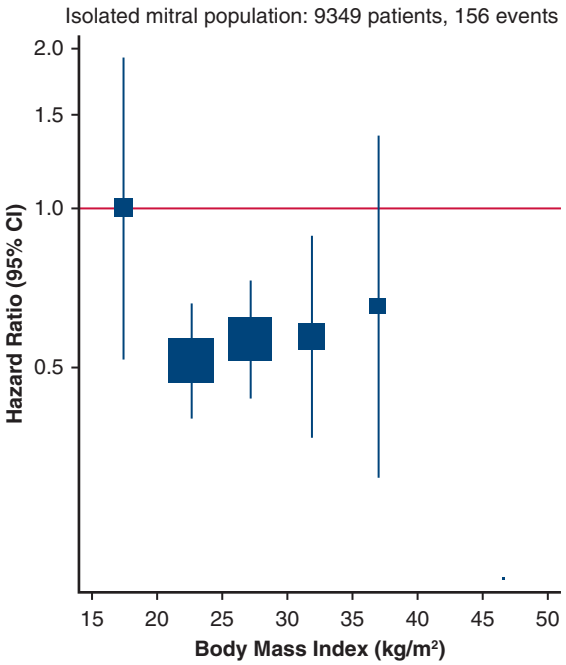

FIGURE E2. Shape of association for an isolated mitral valve population.
CI, Confidence interval.

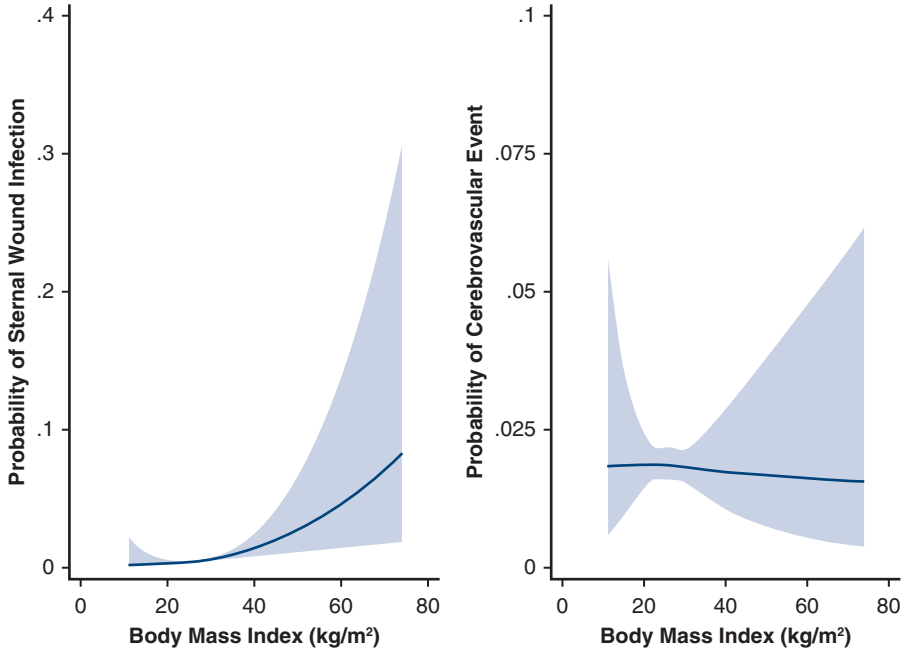

FIGURE E3. Probability of sternal wound infection and cerebrovascular event.