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ASSOCIATION OF BODY MASS INDEX WITH SHORT-TERM OUTCOMES AFTER CARDIAC SURGERY: RETROSPECTIVE STUDY AND META-ANALYSIS

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Abstract The relationship between higher body mass index (BMI), decreased morbidity and mortality is known as the "obesity paradox", and has been described in cohorts of patients with hypertension, diabetes, heart failure, coronary and peripheral artery diseases, non-cardiac surgery, and end-stage renal disease. Here we investigated the relationship between BMI and short-term outcomes after adult cardiac surgery to explore the existence of an obesity paradoxical effect. A secondary objective was to perform an updated systematic review to further analyze the association between BMI and 30-day in-hospital mortality after cardiac surgery. A retrospective analysis was performed from a consecutive series of 1823 adult patients who underwent cardiac surgery, that were assigned to five BMI groups: normal weight (18.5-24.9 kg/m²), overweight (25-29.9 kg/m²), class I obese (30-34.9 kg/m²), class II obese (35-39.9 kg/m²), and class III obese or morbidly obese (40-49.9 kg/m²). A systematic review search was performed including controlled trials and observational studies identified in *MEDLINE*, *Embase*, *SCOPUS*, and the Cochrane library (to the end of June 2017). In the present series, overweight and obese patients had similar or slightly lower in-hospital mortality rates after cardiac surgery compared with normal-weight individuals. Conversely, postoperative complication rates increased with higher BMI levels. Most studies included in the review showed that overweight and obese patients had at least the same mortality rate as normal-weight patients, or even a lower death risk. Pooled-data of the meta-analysis provided evidence on the association between higher BMI levels and a lower all-cause in-hospital mortality rate after cardiac surgery.

Key words: obesity, operative risk, cardiac surgery, meta-analysis

Resumen ***Asociación entre índice de masa corporal y resultados a corto plazo después de la cirugía cardíaca: estudio retrospectivo y metaanálisis.*** La relación entre mayor índice de masa corporal (IMC) y menor morbilidad y mortalidad se conoce como "paradoja de la obesidad". Se ha descrito en cohortes de pacientes con hipertensión, diabetes, insuficiencia cardíaca, enfermedad coronaria y arterial periférica, cirugías no cardíacas y enfermedad renal en etapa terminal. Aquí se investigó la relación entre IMC y resultados a corto plazo después de cirugía cardíaca en adultos, y la manifestación de la paradoja de la obesidad. También se realizó una revisión sistemática sobre asociación entre IMC y mortalidad a 30 días de la cirugía cardíaca. Se hizo un análisis retrospectivo de una serie consecutiva de 1823 adultos con cirugía cardíaca, asignados a cinco grupos de IMC: peso normal (18.5-24.9 kg/m²), sobrepeso (25- 29.9 kg/m²), obesidad clase I (30-34.9 kg/m²), clase II (35-39.9 kg/m²), y clase III (40-49.9 kg/m²), y una búsqueda sistemática de ensayos controlados y estudios observacionales en *MEDLINE*, *Embase*, *SCOPUS* y Cochrane (hasta 30/6/2017). En la serie, las tasas de mortalidad hospitalaria fueron similares o ligeramente menores en pacientes con sobrepeso y obesidad comparados con aquellos de peso normal. Pero también las tasas de complicaciones postoperatorias aumentaron con el IMC. La mayoría de los estudios observacionales revisados mostraron que los pacientes con sobrepeso y obesidad tenían al menos similar tasa de mortalidad que aquellos con peso normal, o menor riesgo de muerte. Los datos combinados del metaanálisis evidenciaron asociación entre los niveles de IMC mayores y tasa de mortalidad hospitalaria más baja después de cirugía cardíaca.

Palabras clave: obesidad, riesgo operatorio, cirugía cardíaca, metaanálisis

Obesity has been described as a risk factor for the development of coronary artery disease, stroke, cancer, renovascular disease, and other physical and psychological comorbidities[1-5]. Conversely, several other epidemiological and observational studies on different diseases have shown better outcomes and survival rates in overweight and obese patients than in those with normal body mass index (BMI)[6]. This counter-intuitive relationship between higher BMI and decreased morbidity and mortality is known as the "obesity paradox"[7], and has been observed in patients with hypertension, diabetes, heart failure, coronary and peripheral artery diseases,

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non-cardiac surgery, and end-stage renal disease[8-10]. However, studies examining the association between obesity and adverse outcomes after cardiac surgery still remain controversial[11-15]. For instance, the *EuroSCORE* II model does not include BMI as a predictive variable for stratification of perioperative death risk[16]. Some studies have demonstrated that overweight and moderately obese patients have better early hospital outcomes in terms of mortality[11, 12, 17], and a lower incidence of major adverse cardiac and cerebrovascular events[12, 17, 18]. Other studies have not found any clear protective effect of overweight and obesity on mortality or adverse events after cardiac surgery[19-21]; or they have even demonstrated a deleterious effect for sternal wound infection[22-25], leg infection[26], sternal dehiscence[27], renal failure[23, 28], atrial fibrillation[26, 29], venous thromboembolism[29], and pulmonary and gastrointestinal complications[30]. In general, studies with negative evidence for the "obesity paradox" have tended to include far fewer patients than reports with positive evidence, a difference possibly related to the power analysis of sample size. Nevertheless, outcomes from large samples may in turn exaggerate the clinical value of a statistical difference.

The aim of this study was to investigate the relationship between BMI and short-term outcomes after adult cardiac surgery and to explore the existence of an obesity paradoxical effect. A secondary objective was to perform an updated systematic review to further analyze the association between BMI and 30-day in-hospital mortality after cardiac surgery.

Materials and methods

A retrospective analysis was performed on prospectively collected data (ambispective design) from a consecutive series of 1823 adult patients who underwent different types of cardiac surgery at the Buenos Aires University Hospital and its associated clinics over a 6-year period (2011-2016). All types of on-pump and off-pump elective cardiac surgery were included, except transplantation and transcatheter aortic valve implantation. Baseline and operative data were prospectively collected in a clinical registry, which included the variables needed to estimate the operative risk mortality based on *EuroSCORE* II[16]. Additional information on other risk factors and comorbidities was added in the computerized database. In-hospital major postoperative complications (stroke, cardiac arrest, myocardial infarction, renal dialysis, permanent pacemaker implantation, ventricular arrhythmias, reoperation for bleeding, low cardiac output, sternal dehiscence, deep sternal wound infection or mediastinitis, sepsis, prolonged ventilation, and pneumonia), and in-hospital mortality were compared among various BMI groups after cardiac surgery. BMI was automatically recorded in the operation theatre before surgery. Postoperatively, patients were assigned to five BMI groups[31]: normal weight (18.5 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²), class I obese (30 to 34.9 kg/m²), class II obese (35 to 39.9 kg/m²), and class III obese or morbidly obese (40 to 49.9 kg/m²). Underweight (BMI < 18.5 kg/m²) (n = 3) and class IV or "super obese" (BMI ≥ 50 kg/m²) (n = 1) groups were excluded from the study due to the low number of patients.

Baseline preoperative clinical variables and in-hospital outcome data were recorded and analyzed with the approval of the local Institutional Review Board which waived the need for a written informed consent.

The systematic review search strategy was performed using controlled trials and observational studies identified in *MEDLINE*, *Embase*, *SCOPUS*, and the Cochrane library (to the end of June 2017). Reference lists of primary studies, review articles, and previous meta-analyses were reviewed with no language, age or type of cardiac surgery restrictions. The inclusion criteria required studies to separately report mortality in normal, overweight and obese patients using traditional World Health Organization BMI categories. Studies comparing obese versus non-obese patients (i.e. normal and overweight patients grouped together), and studies published only in abstract form were excluded from the analysis. Articles were also excluded if the total number of deaths was < 3. Two reviewers (R.A.B. and C.A.I.) independently reviewed citations and performed data retrieval, and disagreements were resolved through consensus. No additional data were requested from the primary study authors. The primary endpoint was all-cause mortality. Odds ratios (OR) with 95% confidence intervals (95% CI) and forest plots were calculated with *EPIDAT*, Version 3.1 (Xunta de Galicia-PAHO/WHO) using fixed and random effect models. Heterogeneity among studies was examined using the χ^2 test and the Higgins I^2 test (25%, 50%, and 75% I^2 values were interpreted as low, moderate, and high heterogeneity). A funnel plot was used as a graphical method to identify studies affecting heterogeneity, and the Begg test to assess publication bias.

Categorical data were expressed as absolute frequencies and percentages, and continuous variables as mean and standard deviation (SD). The Kolmogorov-Smirnov (K-S) goodness-of-fit test was used to analyze normal distributions. Univariate comparison of discrete variables was performed using χ^2 or Yates' corrected χ^2 test. Analysis for linear trends in proportions for postoperative complications was done with χ^2 test for trend. One-way analysis of variance (ANOVA) was used to compare more than two means and post hoc multiple comparisons were done with Tukey's test assuming equal variances. The Snedecor *F*-test was used to assess variance equality. Observed-to-expected operative mortality ratios within groups was also calculated and compared with the χ^2 test. A propensity-score analysis was used to adjust for preoperative and operative confounding factors in order to minimize baseline differences between the BMI groups. Characteristics independently associated with normal and overweight or obese patients after propensity-score matching were assessed in a multivariate binary logistic regression model with backward stepwise conditional method. Covariates used in the regression model included all the preoperative and operative variables, and final results were expressed as odds ratio (OR) with the associated 95% CI. Non-linear regression analysis and the corresponding coefficient of determination (R^2) were used to find the best fit for postoperative complications and mortality rates between BMI groups. Statistical analysis was performed with IBM SPSS 23.0 Statistics (IBM Corporation, Armonk, NY). A 2-tailed p value ≤ 0.05 was considered statistically significant.

Results

Classification and proportional distribution of patients based on preoperative BMI is shown in Table 1, where 22.7% (n = 413) was classified as obese, independently of class. For purpose analysis, all types of obesity were considered as a single group (aggregated BMI 30.0-49.9 kg/m²). Table 2 lists preoperative baseline characteristics of the BMI groups. Univariate analysis revealed younger age and higher rates of male sex and diabetes in overweight and obese patients compared with normal-weight individuals. Conversely, the normal-weight group showed higher rates of heart failure, pulmonary hypertension and heart valve endocarditis.

Distribution of operative variables and outcomes are shown in Table 3. Isolated coronary surgery and shorter cross-clamping time were more frequent in overweight and obese patients. Overall postoperative complications increased through BMI groups with a slight decrease in overweight patients (Table 3, Fig. 1). Postoperative ventricular arrhythmias were significantly more common in obese patients when complications were disaggregated.

In-hospital mortality rate was slightly higher in the normal-weight group than in the other BMI groups, though differences were not significant (normal versus overweight OR: 1.17, 95% CI: 0.70-1.95, p = 0.554; normal versus obese OR: 1.09, 95% CI: 0.59-2.00, p = 0.789) (Fig. 2). There was no statistical difference between observed and

TABLE 1.– *Classification and proportional distribution of patients based on preoperative body mass index (BMI)*

BMI (kg/m²)	Classification	Denomination	Number	Percent
18.5-24.9	Normal	Normal	502	27.5%
25.0-29.9	Overweight	Overweight	908	49.8%
30.0-34.9	Obese Class I	Obese	328	18.0%
35.0-39.9	Obese Class II	Severely obese	64	3.5%
40.0-49.9	Obese Class III	Morbidly obese	21	1.2%
		Total	1823	100.0%

TABLE 2.– *Distribution of preoperative variables according to body mass index*

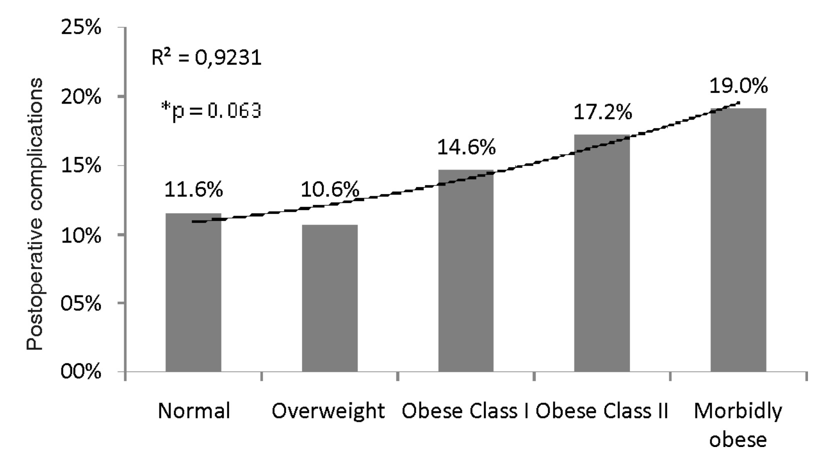
Variable	Total (18.5-49.9 kg/m²) n = 1823	Normal weight (18.5-24.9 kg/m²) n = 502	Overweight (25.0-29.9 kg/m²) n = 908	Obese (30.0-49.9 kg/m²) n = 413	p value
BMI (kg/m²)	27.5±3.9	23.6±1.3	27.0±1.4	33.2±3.2	<0.0001
Age (years)	66.4±10.8	67.5±11.9	66.6±10.6	64.7±9.6	0.0003
Male sex	1321 (74.5%)	311 (62.0%)	704 (77.5%)	306 (74.1%)	<0.0001
Hypertension	1014 (55.6%)	259 (51.6%)	514 (56.6%)	241 (58.4%)	0.086
Dyslipidemia	597 (32.7%)	160 (31.9%)	294 (32.4%)	143 (34.6%)	0.640
Diabetes (I-II)	418 (22.9%)	89 (17.7%)	212 (23.3%)	117 (28.3%)	0.0007
Active smoker	200 (11.0%)	53 (10.6%)	104 (11.5%)	43 (10.4%)	0.804
COPD	94 (5.2%)	22 (4.4%)	48 (5.3%)	24 (5.8%)	0.604
Peripheral vascular disease	56 (3.1%)	14 (2.8%)	30 (3.3%)	12 (2.9%)	0.845
Stroke	42 (2.3%)	10 (2.0%)	23 (2.5%)	9 (2.2%)	0.796
Myocardial infarction	140 (7.7%)	43 (8.6%)	75 (8.3%)	22 (5.3%)	0.122
Atrial fibrillation	96 (5.3%)	28 (5.6%)	49 (5.4%)	19 (4.6%)	0.781
Pulmonary hypertension	81 (4.4%)	36 (7.2%)	31 (3.4%)	14 (3.4%)	0.002
Heart failure	43 (2.4%)	20 (4.0%)	18 (2.0%)	5 (1.2%)	0.013
Chronic renal failure (dialysis or eCrCl < 30ml/min)	25 (1.4%)	12 (2.4%)	9 (1.0%)	4 (1.0%)	0.070
Previous cardiac surgery	37 (2.0%)	10 (2.0%)	20 (2.2%)	7 (1.7%)	0.830
LVEF (%)	57.3±10.9	56.6±10.9	57.2±11.2	57.7±10.1	0.461
Emergency	60 (3.3%)	17 (3.4%)	33 (3.6%)	10 (2.4%)	0.514
Unstable angina	54 (3.0%)	8 (1.6%)	35 (3.9%)	11 (2.7%)	0.052
Valve endocarditis	57 (3.1%)	27 (5.4%)	20 (2.2%)	10 (2.4%)	0.003

BMI: body mass index; COPD: chronic obstructive pulmonary disease; eCrCl: Cockcroft-Gault estimated creatinine clearance; LVEF: left ventricular ejection fraction

TABLE 3.– Distribution of operative variables and outcomes according to body mass index

Variable	Total (18.5-49.9 kg/m²) n = 1823	Normal weight (18.5-24.9 kg/m²) n = 502	Overweight (25.0-29.9 kg/m²) n = 908	Obese (30.0-49.9 kg/m²) n = 413	p value
Type of surgery:					
CABG alone	954 (52.3%)	235 (46.8%)	480 (52.9%)	239 (57.9%)	0.004
Heart valve surgery alone	491 (26.9%)	153 (30.5%)	230 (25.3%)	108 (26.2%)	
Combined	258 (14.2%)	84 (16.7%)	136 (15.0%)	38 (9.2%)	
Miscelaneous	120 (6.6%)	30 (6.0%)	62 (6.8%)	28 (6.8%)	
Off pump surgery*	258 (27.0%)	67 (28.5%)	124 (25.8%)	67 (28.0%)	0.385
Cross-clamping time (min)	39.3 ± 14.1	40.6 ± 15.0	38.8 ± 13.6	38.3 ± 13.8	0.039
Perfusion time (min)	64.8 ± 16.6	65.2 ± 17.3	64.5 ± 16.6	64.5 ± 15.6	0.744
Postoperative complications:					
Stroke	17 (0.9%)	8 (1.6%)	4 (0.4%)	5 (1.2%)	0.078
Myocardial infarction	16 (0.9%)	3 (0.6%)	9 (1.0%)	4 (1.0%)	0.731
Dialysis	17 (0.9%)	4 (0.8%)	9 (1.0%)	4 (1.0%)	0.933
Mediastinitis	26 (1.4%)	4 (0.8%)	13 (1.4%)	9 (2.2%)	0.214
Sternal dehiscence	5 (0.3%)	1 (0.2%)	3 (0.3%)	1 (0.2%)	0.894
Reoperation for bleeding	28 (1.5%)	10 (2.0%)	12 (1.3%)	6 (1.5%)	0.611
Cardiac arrest	11 (0.6%)	2 (0.4%)	5 (0.6%)	4 (1.0%)	0.519
Low cardiac output	41 (2.2%)	9 (1.8%)	20 (2.2%)	12 (2.9%)	0.524
Prolonged ventilation	22 (1.2%)	6 (1.2%)	11 (1.2%)	5 (1.2%)	0.999
Pneumonia	18 (1.0%)	6 (1.2%)	7 (0.8%)	5 (1.2%)	0.648
Permanent pacemaker	9 (0.5%)	4 (0.8%)	2 (0.2%)	3 (0.7%)	0.250
Ventricular arrhythmias	7 (0.2%)	1 (0.2%)	1 (0.1%)	5 (1.2%)	0.008
Overall complications	217 (11.9%)	58 (11.6%)	96 (10.6%)	63 (15.3%)	0.049
Death	83 (4.6%)	25 (5.0%)	39 (4.3%)	19 (4.6%)	0.951
Combined events (death + complications)	300 (16.5%)	83 (16.6%)	135 (14.9%)	82 (19.9%)	0.077

CABG: Coronary artery bypass grafting
**Percent calculated exclusively for coronary artery surgery*



*p-value: χ² test for trend.

Fig. 1.– Overall postoperative complications observed in patients undergoing all types of cardiac surgery according to their body mass indexes (BMI). BMI showed a near quadratic relationship with the risk of postoperative complications (R^2 = 0.923)

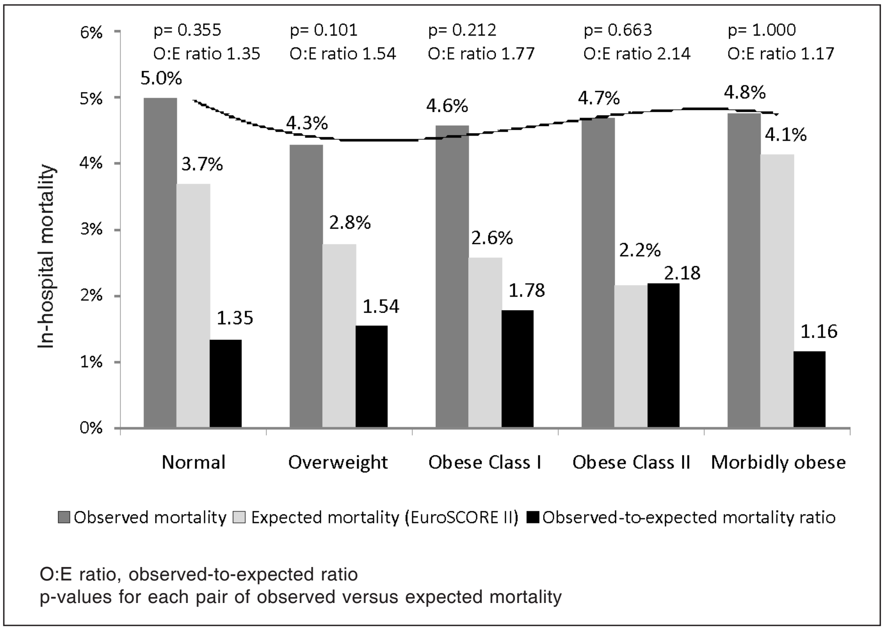


Fig. 2.– In-hospital mortality, *EuroSCORE* II mortality risk and observed-to-expected mortality ratio of patients undergoing all types of cardiac surgery according to their body mass indexes (BMI). BMI showed a near quadratic (reverse J-shaped) association with in-hospital mortality risk (R^2 = 0.912)

expected mortality for each individual BMI group; nevertheless, the expected mortality risk according to *EuroSCORE* II was significantly different among BMI groups (ANOVA F = 2.98, p = 0.018; Tukey's test p = 0.046 for post hoc comparison between normal and overweight groups), with the normal-weight group showing the highest expected risk.

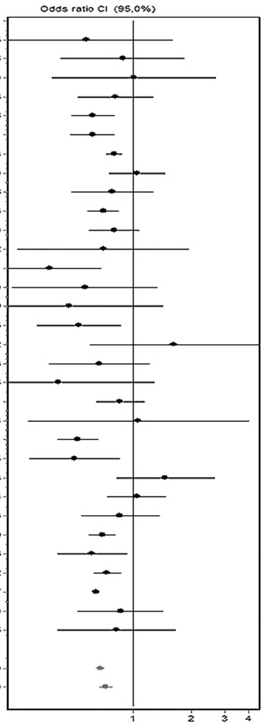
After adjusting by propensity score, a total of 806 patients for normal versus overweight comparison and 460 patients for normal versus obese comparison showed no systematic differences in the distribution of covariates.

Differences in in-hospital mortality rates were preserved, and complications rates became similar after propensity score-matched normal versus overweight groups were compared (mortality rate 4.2% versus 3.5%, OR: 1.22, 95% CI: 0.59-2.52, p = 0.583, and complications 8.4% versus 8.4%, OR: 1.00, 95% CI: 0.61-1.64, p = 1.000). Conversely, when comparing normal versus obese groups, differences in in-hospital mortality and complications rates were preserved after propensity score matching (mortality rate 3.5% versus 2.2%, OR: 1.62, 95% CI: 0.52-5.03, p = 0.399, and complications 6.5% versus 11.7%, OR: 0.52, 95% CI: 0.27-1.01, p = 0.052).

Out of 4410 initial independent references obtained through various search strategies comprising cardiac surgery and obesity, 30 eligible cohort observational studies were identified and included in the meta-analysis[11, 12, 17-19, 22, 29, 31-53]. When the data from our study before and after propensity score matching were included, the final meta-analysis population comprised 451 300 patients for the normal/overweight comparison (32 studies), and 289 214 patients for the normal/obese comparison (20 studies). The meta-analysis demonstrated the obesity paradox. Compared with overweight patients, the random observed global OR was 0.71 (95% CI, 0.66-0.77) for normal-weight individuals (Fig. 3.a), whereas compared with obese patients, the random observed global OR was 0.73 (95% CI, 0.65-0.83) for normal-weight patients (Fig. 3.b). Funnel plots revealed no evidence of publication bias in both mortality comparisons (Begg test Z = 0.60, p = 0.549 for overweight versus normal groups, and Z = 0.29, p = 0.770 for obese versus normal groups). Between-study heterogeneity was statistically significant in the analysis of both overweight versus normal-weight patients (I^2 = 61.0%, Q = 62.0, p = 0.0008) and in obese versus normal-weight patients (I^2 = 74.4%, Q = 44.3, p = 0.0009).

Discussion

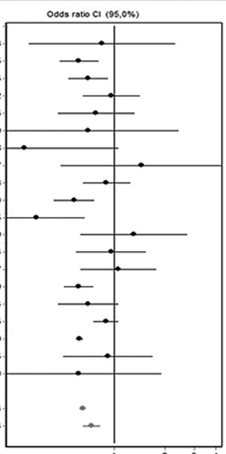
The initial unadjusted comparison of in-hospital mortality rates after cardiac surgery between the different BMI groups revealed the incipient reverse J-shaped distribution described in the obesity paradoxical effect, with overweight and class I obese patients showing the lowest mortalities. Nevertheless, the higher mortality rate found in patients with normal BMI can be easily explained by a greater expected risk according to *EuroSCORE* II. This expected risk was significantly higher than that predicted for the



Study (Year)	n	Overweight event	Overweight total	Normal event	Normal total	OR	95% CI	Type of surgery
Gurm [44] (2002)	945	9	683	6	262	0.57	0.20-1.62	CABG
Reeves [38] (2003)	3336	18	2170	11	1166	0.88	0.41-1.87	CABG
Orhan [53] (2004)	950	12	632	6	318	1.01	0.37-2.71	CABG
Brat [48] (2005)	3126	51	2139	29	987	0.81	0.51-1.28	All
Jin [40] (2005)	10158	129	6683	108	3475	0.61	0.47-0.80	CABG
Pan [39] (2006)	6441	125	4257	103	2184	0.61	0.47-0.80	CABG
Wagner [45] (2007)	52193	1090	34063	725	18130	0.79	0.72-0.87	CABG
Rahmanian [47] (2007)	4330	75	2289	64	2041	1.05	0.75-1.47	Combine
Shirzad [50] (2009)	7988	34	4809	29	3179	0.77	0.47-1.27	CABG
Sun [46] (2009)	9313	228	5551	218	3762	0.70	0.58-0.84	All
van Straten [37] (2010)	8130	105	5234	73	2896	0.79	0.59-1.07	CABG
Le-Bert [34] (2011)	302	7	167	8	135	0.69	0.25-1.97	CABG
Stamou [11] (2011)	1521	17	965	26	556	0.37	0.20-0.68	Combine
Atalan [51] (2012)	530	12	371	9	159	0.56	0.23-1.35	CABG
Zalewska-Adamiec [52] (2012)	109	7	72	7	37	0.46	0.15-1.43	CABG
Vaduganathan [49] (2012)	1885	25	1020	40	865	0.52	0.31-0.86	Valve
Ho [29] (2013)	1462	14	924	5	538	1.64	0.59-4.58	All
van Straten [42] (2013)	1313	23	829	20	484	0.66	0.36-1.22	Valve
Chang [32] (2013)	295	4	130	12	165	0.40	0.13-1.29	All
Zittermann [18] (2014)	6491	107	3937	81	2554	0.85	0.64-1.14	All
Cemerlic-Adjic [43] (2014)	544	8	389	3	155	1.03	0.28-4.06	CABG
Benedetto [33] (2014)	9931	133	6662	125	3269	0.51	0.40-0.66	CABG
Allama [22] (2014)	2205	22	1261	33	944	0.49	0.28-0.85	CABG
Caliskan [35] (2014)	2793	40	1802	15	991	1.48	0.81-2.69	CABG
Ranucci [41] (2014)	4054	65	2086	59	1968	1.04	0.73-1.49	All
Lopez-Delgado [19] (2015)	1673	51	1150	27	523	0.85	0.53-1.38	All
Johnson [12] (2015)	51759	356	34597	256	17162	0.69	0.58-0.81	CABG
Gao [17] (2016)	2918	43	1774	45	1144	0.61	0.40-0.93	All
Hartrumpf [36] (2017)	10242	344	6608	254	3634	0.73	0.62-0.86	All
Mariscalco [31] (2017)	242147	4283	150769	4014	91378	0.64	0.61-0.66	All
Current study (2017)	1410	39	908	25	502	0.86	0.51-1.43	All
Current (porpensity) (2017)	806	14	403	17	403	0.82	0.40-1.68	All
GLOBAL (Fixed Eff.)	451300	7490	285334	6453	165966	0.67	0.65-0.70	
GLOBAL (Random Eff.)	451300	7490	285334	6453	165966	0.71	0.66-0.77	

a. Overweight versus normal

OR: Odds ratio; CI: Confidence interval; CABG: Coronary artery bypass grafting



Study (Year)	n	Obese event	Obese total	Normal event	Normal total	OR	95% CI	Type of surgery
Reeves [38] (2003)	1913	6	747	11	1166	0.85	0.31-2.31	CABG
Jin [40] (2005)	9445	116	5970	108	3475	0.62	0.47-0.81	CABG
Pan [39] (2006)	5605	115	3421	103	2184	0.70	0.54-0.92	CABG
van Straten [37] (2010)	4582	41	1686	73	2896	0.96	0.65-1.42	CABG
Stamou [11] (2011)	1475	34	919	26	556	0.78	0.46-1.32	Combine
Le-Bert [34] (2011)	229	4	94	8	135	0.72	0.21-2.41	CABG
Chang [32] (2013)	298	3	133	12	165	0.29	0.08-1.07	All
Ho [29] (2013)	1207	9	669	5	538	1.45	0.48-4.36	All
Zittermann [18] (2014)	4923	68	2369	81	2554	0.90	0.65-1.25	All
Benedetto [33] (2014)	7090	86	3821	125	3269	0.58	0.44-0.77	CABG
Allama [22] (2014)	1915	12	971	33	944	0.35	0.18-0.67	CABG
Caliskan [35] (2014)	1699	14	708	15	991	1.31	0.63-2.74	CABG
Ranucci [41] (2014)	2834	25	866	59	1968	0.96	0.60-1.55	All
Lopez-Delgado [19] (2015)	1147	34	624	27	523	1.06	0.63-1.78	All
Johnson [12] (2015)	35309	168	18147	256	17162	0.62	0.51-0.75	CABG
Gao [17] (2016)	2904	49	1760	45	1144	0.70	0.46-1.06	All
Hartrumpf [36] (2017)	8615	314	4981	254	3634	0.90	0.75-1.06	All
Mariscalco [31] (2017)	196649	2928	105271	4014	91378	0.62	0.59-0.65	All
Current study (2017)	915	19	413	25	502	0.92	0.50-1.70	All
Current (propensity) (2017)	460	5	230	8	230	0.62	0.20-1.91	All
GLOBAL (Fixed Eff.)	289214	4050	153800	5288	135414			
GLOBAL (Random Eff.)	289214	7490	285334	6453	165966	0.65	0.63-0.68	
						0.73	0.65-0.83	

b. Obese versus normal

OR: Odds ratio; CI: Confidence interval; CABG: Coronary artery bypass grafting

Fig. 3.– Forest plots of studies estimating 30-day-in-hospital mortality post-cardiac surgery. Comparison between overweight and normal groups (a), and between obese and normal groups (b)

other BMI groups, and even the observed-to-expected mortality ratio of the normal BMI cohort was closer to one. Therefore, this observation plus outcomes obtained from the propensity score analysis helped to question a clear obesity paradoxical effect on mortality when contrasting matched data of normal and overweight groups. Nonetheless, after propensity score analysis, obese patients presented a lower mortality rate compared with normal patients, but a higher complication rate. In short, relative to non-obese patients, overweight and obese individuals showed comparable or lower in-hospital mortality rates after cardiac surgery. On the contrary, the overall complication rates were similar in overweight and higher in obese patients compared with normal-weight individuals.

Evaluation relative to previous research becomes difficult because some studies bring together overweight and normal-weight patients in a single set of data[20, 21, 23, 25, 28, 30], and adjustment by confounders was rarely done. The analysis of 4172 patients from the ARIAM registry[21] demonstrated that after adjusting for severity and perfusion time, obese patients had mortality rate, complication rate, and length-of-stay similar to non-obese patients (BMI < 30 kg/m^2). Ho el al.[29] did not observe any "obesity paradox" in mortality rate assessment after adjusting data for the principal confounders. In a short series of 637 patients, obesity did not increase in-hospital mortality; however, it increased pulmonary and gastrointestinal complications after adjusting for age, sex, and comorbidities[30]. Conversely, in a cohort analysis with propensity score matching of 2440 patients, Stamou el al.[11] communicated that overweight patients had a lower operative mortality than normal BMI patients (OR: 0.4, 95% CI: 0.2-0.9), whereas obese individuals had a comparable risk with respect to normal-weight patients.

As in other studies[12, 19, 22], we found that overweight and obese patients were younger and with higher rates of male sex and diabetes compared with normal-weight patients. However, the higher rates of heart failure, pulmonary hypertension and valve endocarditis found in normal-weight patients had not been previously observed or considered.

Some considerations must be taken into account to evaluate the obesity paradox effect. Firstly, a normal BMI in a healthy person might be protective in a public health setting in which mortality is assessed in the long-term[54]. By contrast, an overweight or obese BMI might be protective in critical illnesses when comorbidities are frequent because mortality is high and is assessed in the short-term rather than years[55-57]. It is important to consider additional sources of bias for the "obesity paradox" phenomenon. Obese patients consistently undergo revascularization surgical procedures at a younger age than their non-obese counterparts and, consequently, may present with lower risk coronary anatomy[58]. Outcomes of the present study were consistent with this last observation, since obese patients were significantly younger, and coronary surgery was more common. On the other hand, the paradox may be due to selection bias if only a subgroup of the "healthiest" obese patients were selected for cardiac surgery[59-60].

The present systematic review of observational studies suggested that overweight and obesity were associated with a neutral or beneficial effect on all-cause mortality after cardiac surgery. Meanwhile, pooled analysis of the 32 studies in the meta-analysis demonstrated a definite protective effect of overweight and obesity in general, on 30-day-in-hospital mortality rates post-cardiac surgery. Though moderate to high statistical heterogeneity was found in the analyses of overweight or obese versus normal-weight patients, nearly all studies reported a neutral or protective effect of higher BMI levels on mortality, providing supportive evidence that the summary effect sizes were the product of consistent results. Nevertheless, the pooled effect size found in the meta-analysis should be considered small (OR > 0.66)[61].

Previously, two other meta-analyses reported similar outcomes. Oreopoulos et al.[62] analyzed the effect of BMI only after coronary artery bypass grafting in 12 observational studies (nearly 75 000 patients). After coronary surgery, both overweight and obese patients had lower in-hospital mortality risks compared with normal-weight individuals (OR: 0.70, 95% CI: 0.63-0.77 and OR: 0.63, 95% CI: 0.56-0.71, respectively). Recently, Mariscalco et al.[31] studied approximately 558 000 patients undergoing all types of cardiac surgery in 26 observational studies. They reported lower in-hospital mortality in overweight (OR: 0.79, 95% CI: 0.76-0.83), obese class I (OR: 0.81, 95% CI: 0.76-0.86) and obese class II (OR: 0.83; 95% CI: 0.74-0.94) patients relative to normal-weight individuals.

This study has some limitations. Since in most patients, BMI was calculated from self-reported weight and height, a systematic bias may arise when comparing with BMI calculated from objectively measured data. Nevertheless, in large studies[54], self-reported and measured BMI differed on average by only 3%, with a 95% correlation coefficient between them. It is possible that overweight or obese patients with a more severe profile of comorbidities and considered at high risk for a cardiac operation were excluded from surgery. Isolated BMI used as a marker of obesity also has limitations, since other aspects of body composition such as visceral fat distribution were not explored in this study. Finally, early reductions in mortality observed in obese patients may not be sustained in the mid- and long-term.

In conclusion, this study showed that overweight and obese patients had similar or slightly lower in-hospital mortality rates after cardiac surgery compared with normal-weight individuals. Conversely, postoperative complication rates systematically increased with higher BMI levels. Most observational studies included in the systematic review showed that overweight and obese patients had at least the same mortality rate as normal-weight patients, or even a lower death risk. Pooled-data of the meta-analysis provided evidence on the association between higher BMI levels and a lower all-cause in-hospital mortality rate after cardiac surgery.

Conflict of interests: None to declare

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