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Evidence and temporality of the obesity paradox in coronary bypass surgery: an analysis of cause-specific mortality†

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Abstract

OBJECTIVES: We evaluated the presence of an ‘obesity paradox’ in coronary artery bypass grafting (CABG) patients, determined its time course and ascertained whether it is associated with improved cardiovascular (CV) survival versus non-CV survival.

METHODS: A retrospective analysis of 3 prospectively collected databases was conducted. A fifteen-year Kaplan–Meier analysis in 7091 CABG patients was performed and repeated in 5 body mass index [BMI (kg/m²)] cohorts [Normal (18.5–24.99 kg/m²), Overweight (25–29.99 kg/m²), Obese I (30–34.99 kg/m²), Obese II (35–39.99 kg/m²) and Obese III (>40 kg/m²)]. Mortality hazard ratios {HR [95% confidence interval (CI)]} were derived using comprehensive multivariable competing risk Cox regression, accounting for BMI categories for overall (0–15), Early (0–1), Intermediate (1–8) and Late (8–15) postoperative years, to relax the proportional hazards assumption. The regression was repeated using BMI as a continuous variable. Mortality was classified into any, CV and non-CV.

RESULTS: Obese patients were younger with more comorbidities. Fifteen-year survival was improved in the Overweight and Obese I groups ($P < 0.001$). Adjusted 15-year mortality was reduced in the Overweight [HR (95% CI) = 0.88 (0.79–0.98)] and Obese I [HR = 0.88 (0.78–0.99)] groups driven by improved CV and non-CV survival. This trend was noted in the early (Overweight) and intermediate postoperative periods (Overweight and Obese I) with no significance in the late period. Higher mortality in the Obese III [HR = 1.28 (1.06–1.55)] group was driven by a decreased CV survival. Using BMI as a continuous variable, a BMI of 29 kg/m² was associated with optimal survival.

CONCLUSIONS: We identified a protective partial obesity paradox in the early and intermediate postoperative periods among Overweight and mildly obese (Obese I) patients with improved CV and non-CV survival. The morbidly obese (the Obese III group) had higher early and late CV mortality.

Keywords: Obesity • Coronary artery bypass grafting • Obesity paradox

INTRODUCTION

Obesity is a global health challenge of epidemic proportions. The World Health Organization (WHO) estimates that the rate of obesity has doubled worldwide within the last 3 decades, and currently, over 70% of American adults are either overweight or obese compared to fewer than 25% 40 years ago [1–3]. Obesity is a risk factor for cardiovascular (CV) disease including atherosclerosis, diabetes, hypertension, heart failure and atrial fibrillation [4, 5]. The estimated direct annual cost of treating obesity is \$51.6 billion and another \$30 billion is spent on weight reduction programmes [6, 7]. Obesity is an independent predictor of long-term

morbidity and mortality due in part to its association with the cardiometabolic syndrome and likely through yet unrecognized mechanisms [8]. Although obesity is a risk factor for CV disease, it has been suggested, paradoxically, that obese patients with established CV disease may have a more favourable prognosis than the non-obese patients. This ‘obesity paradox’ has been identified in patients with renal and pulmonary disease [9, 10], patients with peripheral arterial disease [11] and patients undergoing coronary revascularization [12]. There are conflicting reports on whether an obesity paradox exists in cardiac surgery [13–22] with some studies documenting improved, equivalent or worse outcomes in the obese compared to their non-obese counterparts. A number of plausible mechanisms behind the obesity paradox have been suggested [4, 23], and although some have postulated that the obesity paradox may be explained by

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the observation that obese patients undergoing coronary artery bypass grafting (CABG) may have less complex coronary artery disease [24, 25], we are unaware of any studies specifically assessing whether the reported improved survival of obese CABG patients is attributable to diminished CV mortality versus non-CV mortality. Moreover, only few studies [14] have investigated the possible survival benefit of obesity after long-term follow-up (>8–10 years).

Within this conceptual framework, the aim of this study is to ascertain whether an obesity paradox exists in CABG patients and, if present, determine its time course and whether it is attributable to improved CV and/or non-CV survival.

METHODS

Patients

This investigation is a retrospective analysis of prospectively collected registries from 3 Ohio cardiac surgical centres. The centres collected data in accordance with the Society of Thoracic Surgeons (STS) Cardiac Surgery Database. The study was approved by the respective institutional review board, and informed consent was waived. No patient contact or additional review of patient records was needed.

Primary CABG patients with multivessel disease receiving 2 or more bypass grafts including a left internal thoracic artery (LITA) graft were studied (1996–2012). Patients were excluded in case of a single graft, no LITA, concomitant cardiac or aortic surgery, salvage surgery, preoperative renal failure, reoperation and BMI <18.5 kg/m² or those without a valid Social Security number. Patients undergoing concurrent carotid endarterectomy or atrial fibrillation ablation surgery were included. Patients were divided into body habitus cohorts per WHO criteria [26] based on body mass index [BMI (kg/m²): Normal (18.5–24.99 kg/m²), Overweight (25–29.99 kg/m²), Obese I (30–34.99 kg/m²), Obese II (35–39.99 kg/m²) and Obese III (≥40 kg/m²). The operative techniques and perioperative management have been previously described [27]. Briefly, on-pump techniques were utilized in 95% of patients. Forty-one percent of patients received multiarterial grafting using the radial artery in addition to the LITA. Aortocoronary grafting was used in more than 95% of patients.

End points and follow-up

The primary outcome was all-cause mortality with secondary analysis of cause-specific mortality (CV and non-CV) after competing risk adjustment across the BMI groups. Outcomes were categorized into 3 time intervals (years) [Early (0–1 year), Intermediate (1–8 years) and Late (8–15 years)] defined by inspection of the 15-year hazard rate plots. Mortality data were secured from institutional follow-up and verified from recurrent queries of the US Social Security Death Index (<http://ssdi.genealogy.rootsweb.com>—last checked November 2011, following which this platform was no longer a valid research tool). Death data were also obtained from the 1994–2013 Ohio Death Index for verification for determining death status after November 2011 and for derivation of the primary cause of death. Causes of death were allocated to CV category: {Cerebrovascular-[ICD10-(I60–I69), ICD9-(430–434, 436–438)]}; {Cardiovascular-[ICD10-(I00–I09, I11, I13, I20–I51), ICD9-(390–398, 402, 404, 410–429)]} and {Other Vascular-[ICD10-(I10, I12, I15, I70, I71–78, I80–I99),

ICD9-(401, 403, 404, 441–448, 451–459)]} and non-CV category (all other ICD9/ICD10 codes). Patients with an unknown cause of death were analysed within all-cause mortality.

Statistical analysis

Continuous variables for the BMI-based cohorts are expressed as mean ± standard deviation and compared pairwise versus the Normal group (reference) using the independent *t*-test or the Mann–Whitney *U*-test based on normality. Categorical variables are expressed as counts (percentages) and compared using the χ^2 test. Time-to-event analyses were truncated after 15 years due to the small number of patients who were followed up beyond 15 years. Time zero for longitudinal follow-up was defined as the time of surgery. Cumulative incidence of mortality based on all-cause, CV and non-CV deaths were estimated using the Kaplan–Meier analysis and compared for the different body habitus study groups. Hazard ratios were calculated [±95% confidence intervals (CIs)] using the competing risk Cox regression models which were applied to all patients without adjustment (unadjusted HR) and then in all patients with comprehensive risk adjustment (covariate adjusted). Demographic and risk factors were significantly different between the comparison cohorts (Table 1). Thus, covariate adjustment was done by building a non-parsimonious competing risk Cox regression model that included patient demographics and risk factors and other surgical factors included in Table 1, except for highly correlated variables (e.g. body surface area which correlates with BMI category—see the legend of Table 1). Interaction terms between BMI categorical variables and a number of patient demographic and risk factors were attempted but none were found to be significant. Revascularization index was defined as the number of grafts minus the number of diseased principal coronary arterial systems. The regression model was utilized across the BMI groups for the overall follow-up duration and then separately for each of the 3 time periods. For validation of our results, the association between mortality and BMI was also analysed using BMI as a continuous variable. On the basis of visual interpretation of the results of the primary analysis with BMI categories, we established that the relationship between BMI and mortality is non-linear as in previous studies [28]. The best fit for the relationship between overall (0–15 years) all-cause mortality and CV mortality and continuous BMI after covariate adjustment was a cubic function model. A higher 4th-order polynomial was attempted but was not justified. The relationship was plotted using beta covariates of BMI (linear, quadratic and cubic orders) after the non-parsimonious competing risk Cox regression. This model was used to study the association between BMI and mortality for the overall follow-up duration (15 years) and for the aforementioned time periods using time segmentation to relax to proportional hazard assumption.

A 2-sided *P*-value <0.05 was used uniformly to indicate significance. Statistical analysis was conducted using the IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp. and StataCorp. 2017) and the Stata Statistical Software: Release 15 (College Station, TX: StataCorp LLC) for competing risk analysis.

RESULTS

The study population consisted of 7091 patients including 1312 patients in the Normal group (18.6%), 2786 patients in the

Table 1: Patient characteristics and operative data for the 5 body habitus (BMI category) groups

	Normal (BMI 18.5– 24.99 kg/m ²)	Overweight (BMI 25– 29.99 kg/m ²)	Obese I (BMI 30– 34.99 kg/m ²)	Obese II (BMI 35– 39.99 kg/m ²)	Obese III (BMI ≥40 kg/ m ²)
Categorical variables, counts (%)					
Number of patients ^a	1312 (18.5)	2786 (39.3)	1866 (26.3)	729 (10.3)	398 (5.6)
Female	462 (35.2)	672 (24.1)*	531 (28.5)*	280 (38.4)	188 (47.2)*
Smoking	836 (63.7)	1722 (61.8)	1133 (60.7)***	445 (61)	237 (59.5)
Diabetes	315 (24)	839 (30.1)*	785 (42.1)*	359 (49.2)*	249 (62.6)*
Insulin dependence	99 (7.5)	260 (9.3)***	247 (13.2)*	132 (18.1)*	97 (24.4)*
Hypercholesterolaemia	816 (62.2)	1994 (71.6)*	1365 (73.2)*	565 (77.5)*	294 (73.9)*
Hypertension	977 (74.5)	2196 (78.8)*	1572 (84.2)*	615 (84.4)*	360 (90.5)*
Peripheral vascular disease	261 (19.9)	442 (15.9)*	280 (15)*	91 (12.5)*	65 (16.3)
Cerebrovascular disease	357 (27.2)	641 (23)*	412 (22.1)*	129 (17.7)*	74 (18.6)*
Chronic lung disease	339 (25.8)	491 (17.6)*	325 (17.4)*	153 (21)**	92 (23.1)
Myocardial infarction	703 (53.6)	1544 (55.4)	1018 (54.6)	367 (50.3)	218 (54.8)
Congestive heart failure	143 (10.9)	265 (9.5)	203 (10.9)	97 (13.3)	70 (17.6)*
2-Vessel disease	290 (22.1)	580 (20.8)	415 (22.2)	169 (23.2)	86 (21.6)
3-Vessel disease	1022 (77.9)	2206 (79.2)	1451 (77.8)	560 (76.8)	312 (78.4)
Left main disease	336 (25.6)	658 (23.6)	403 (21.6)*	140 (19.2)*	79 (19.8)**
Percutaneous coronary intervention	203 (15.5)	517 (18.6)**	365 (19.6)*	157 (21.5)*	66 (16.6)
Emergency	76 (5.8)	155 (5.6)	100 (5.4)	35 (4.8)	22 (5.5)
CABG + other surgeries	132 (10.1)	256 (9.2)	176 (9.4)	61 (8.4)	34 (8.5)
Other non-cardiac surgeries	101 (7.7)	165 (5.9)**	109 (5.8)**	158 (21.5)*	21 (5.3)
Other cardiac surgeries	38 (2.9)	100 (3.6)	77 (4.1)***	40 (5.5)*	14 (3.5)
Off-pump	85 (6.5)	158 (5.7)	91 (4.9)***	41 (5.6)	28 (7)
Surgery era ^b			**	*	*
1995–2000	562 (42.8)	1114 (40)	717 (38.4)	224 (30.7)	104 (26.1)
2000–2005	619 (47.2)	1345 (48.3)	918 (49.2)	397 (54.5)	224 (56.3)
2005–2012	131 (10)	327 (11.7)	231 (12.4)	108 (14.8)	70 (17.6)
Stroke	104 (7.9)	226 (8.1)	148 (7.9)	48 (6.6)	22 (5.5)
All arterial grafts	77 (5.9)	210 (7.5)**	172 (9.2)*	65 (8.9)**	48 (12.1)*
Bilateral internal mammary graft	31 (2.4)	87 (3.1)	55 (2.9)	12 (1.6)	2 (0.5)**
Radial artery graft	387 (29.5)	1110 (39.8)*	823 (44.1)*	369 (50.6)*	228 (57.3)*
Ejection fraction <35% ^b	119 (9.1)	247 (8.9)	164 (8.8)	65 (8.9)	49 (12.3)***
Continuous variables, mean ± SD					
Age (years)	67.1 ± 10.8	65.2 ± 10.6*	62.9 ± 10.0*	60.4 ± 9.9*	58.9 ± 9.3*
BSA (m ²) ^b	1.78 ± 0.17	1.98 ± 0.17*	2.13 ± 0.19*	2.25 ± 0.21*	2.41 ± 0.23*
Ejection fraction (%)	49.2 ± 11.2	49.1 ± 11.2	49.2 ± 11.1	49.2 ± 10.9	47.8 ± 11.8**
Perfusion time (min)	79 ± 34	82 ± 35*	83 ± 34*	85 ± 35*	84 ± 43**
Cross-clamp time (min) ^b	49 ± 23	52 ± 25*	53 ± 25*	54 ± 25*	54 ± 29*
Revascularization index	0.59 ± 0.77	0.67 ± 0.79*	0.67 ± 0.81**	0.74 ± 0.84*	0.63 ± 0.78
Number of grafts	3.37 ± 0.84	3.46 ± 0.86*	3.44 ± 0.90**	3.50 ± 0.90*	3.42 ± 0.88
Arterial ^b	1.39 ± 0.64	1.55 ± 0.71*	1.60 ± 0.72*	1.69 ± 0.78*	1.72 ± 0.72*
Vein ^b	1.98 ± 0.94	1.92 ± 0.97**	1.85 ± 0.99*	1.82 ± 0.95*	1.70 ± 0.99*
Year of surgery ^c	7.31 ± 4.07	7.7 ± 4.13*	7.81 ± 4.10*	8.58 ± 4.10*	9.04 ± 3.99*

*P-value <0.01.

**P-value = 0.01–0.05.

***P-value = 0.05–0.10.

^aReflect percentage of the overall study population (%).^bVariables were not used in multivariable risk adjustment as they are highly correlated with other model variables.^cYear of surgery: 1 = 1994, 2 = 1996, . . . , 19 = 2012.

BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass grafting; SD: standard deviation.

Overweight group (39.3%), 1866 patients in the Obese I group (26.3%), 729 patients in the Obese II group (10.3%) and 398 patients in the Obese III group (5.6%). Prevalence of diabetes, hypertension and heart failure [Normal (10.9%) vs Obese III (17.6%)] was progressively higher with increasing BMI despite age being systematically lower [Normal (67.1 ± 10.8) vs Obese III (58.9 ± 9.3); years] (Table 1). Multiarterial grafts were frequently used in this series, and the rate increased with BMI given their younger age [Normal (29.5%) vs Obese III (57.3%)].

Mean follow-up was 9.5 ± 4.6 years. A total of 4063 (57.3%) deaths were documented overall, of which CV deaths accounted for 20.3%, non-CV deaths for 28.4% and 8.6% of

deaths were of unknown cause. Unadjusted 30-day mortality was 1.38% and was similar across BMI categories [Normal (1.68%), Overweight (1.29%), Obese I (1.23%), Obese II (1.23%) and Obese III (1.37%)].

Overall and cause-specific mortality cumulative incidence functions

Figure 1 shows the cumulative incidence functions for all-cause mortality partitioned to its CV, non-CV and unknown cause components for the entire population and then for the Normal,

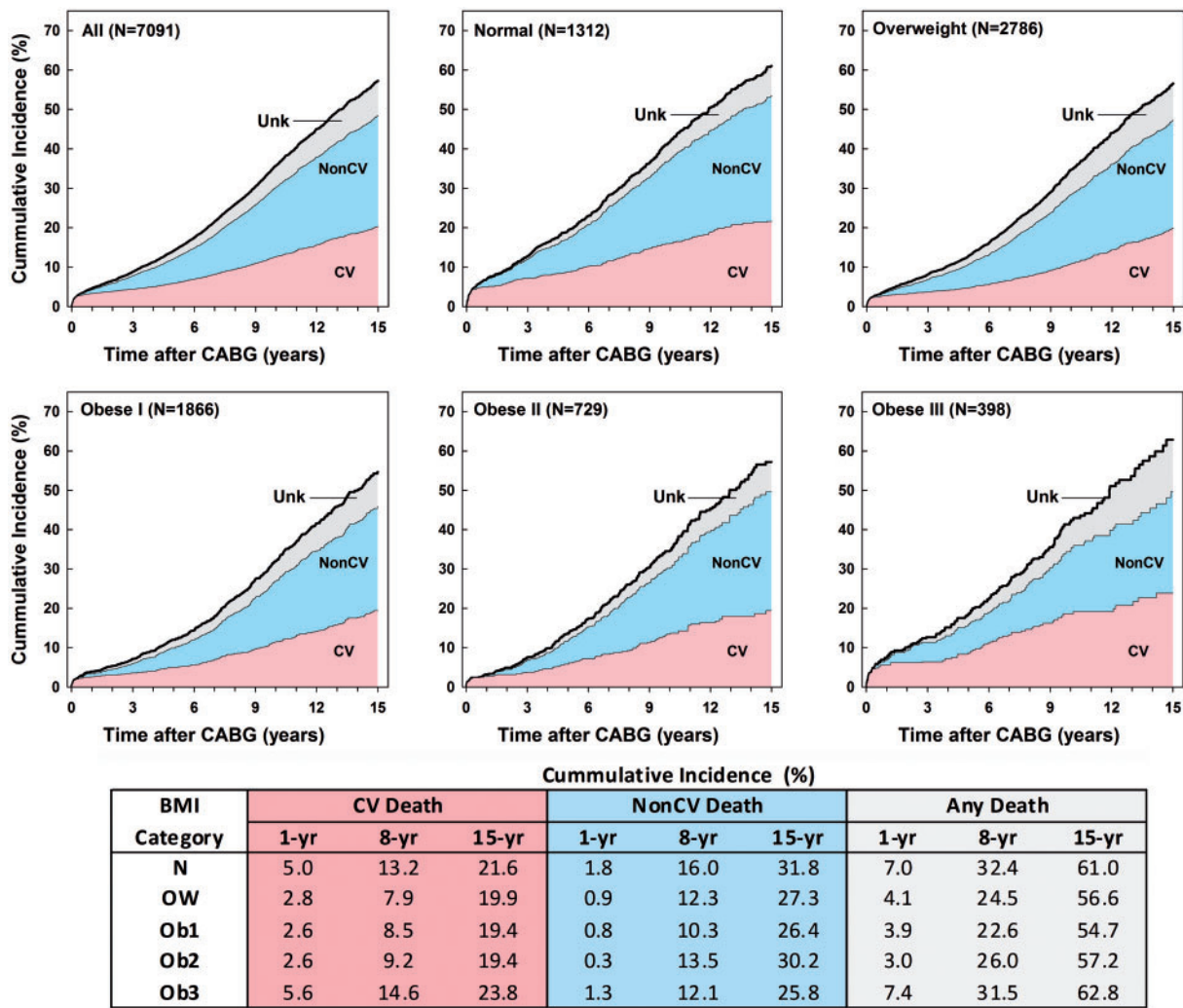


Figure 1: Fifteen-year cumulative incidence functions showing all-cause mortality and cause-specific mortality for all patients ($n = 7091$) and for all the 5 body habitus sub-cohorts. CABG: coronary artery bypass grafting; CV: cardiovascular; non-CV: non-cardiovascular; Unk: unknown cause of death.

Overweight, Obese I, Obese II and Obese III subgroups. Compared to Normal (61.0%), the estimated 15-year unadjusted all-cause mortality was significantly lower for the Overweight [(56.6%), $P < 0.001$], Obese I [(54.7%), $P < 0.001$] and Obese II [(57.2%), $P = 0.007$] groups, whereas it was similar for the Obese III [(62.8%), $P = 0.91$] group.

The unadjusted and comprehensively covariate-adjusted hazard ratios across BMI categories are summarized in Fig. 2—with ‘Normal’ designated as the reference group and accounting for competing risks in case of cause-specific (CV and non-CV) mortality calculations. Figure 2 also shows results assuming proportional hazard over the entire 15-year follow-up (overall) and after relaxing this assumption by time segmenting the analysis to Early mortality, Intermediate mortality and Late mortality. Generally, the unadjusted all-cause, CV and non-CV death data showed a significant and appreciable partial obesity paradox [Fig. 2 (left panels)] whereby Overweight and Obese I and Obese II groups showed superior outcomes (mortality hazard ratios < 1), whereas the Obese III group had unadjusted hazard ratios similar to the Normal group. This paradox was (i) the largest in case of early outcomes, (ii) present but relatively

reduced in the intermediate term (1–8 years) and (iii) absent in the late term.

Risk-adjustment modified the mortality outcome–BMI relationships such that the magnitude of the paradoxical (improved) outcomes at higher BMI were generally reduced in magnitude and limited to Overweight and Obese I patients, whereas severely obese patients (Obese III) showed significantly worse outcomes than Normal BMI. The complementary time-segmented and cause-specific analysis suggested that a higher BMI paradox was mostly due to superior intermediate survival. The overall 15-year mortality demonstrated the presence of the J-shaped protective partial ‘obesity paradox’ in the Overweight and Obese I showing lower mortality as evidenced by the following adjusted hazard ratios (AHR): [AHR (95% CI) = 0.88 (0.79–0.98), $P = 0.017$ and AHR = 0.88 (0.78–0.99), $P = 0.032$, respectively]. The morbidly obese patients (Obese III) had a higher mortality [AHR = 1.28 (1.06–1.55), $P = 0.012$]. The Obese II group showed an increased trend for overall mortality, but this did not reach statistical significance [AHR = 1.13 (0.97–1.33)]. The protective nature of the Overweight and Obese I category was driven by decreased CV mortality and non-CV mortality although this trend did not reach significance in

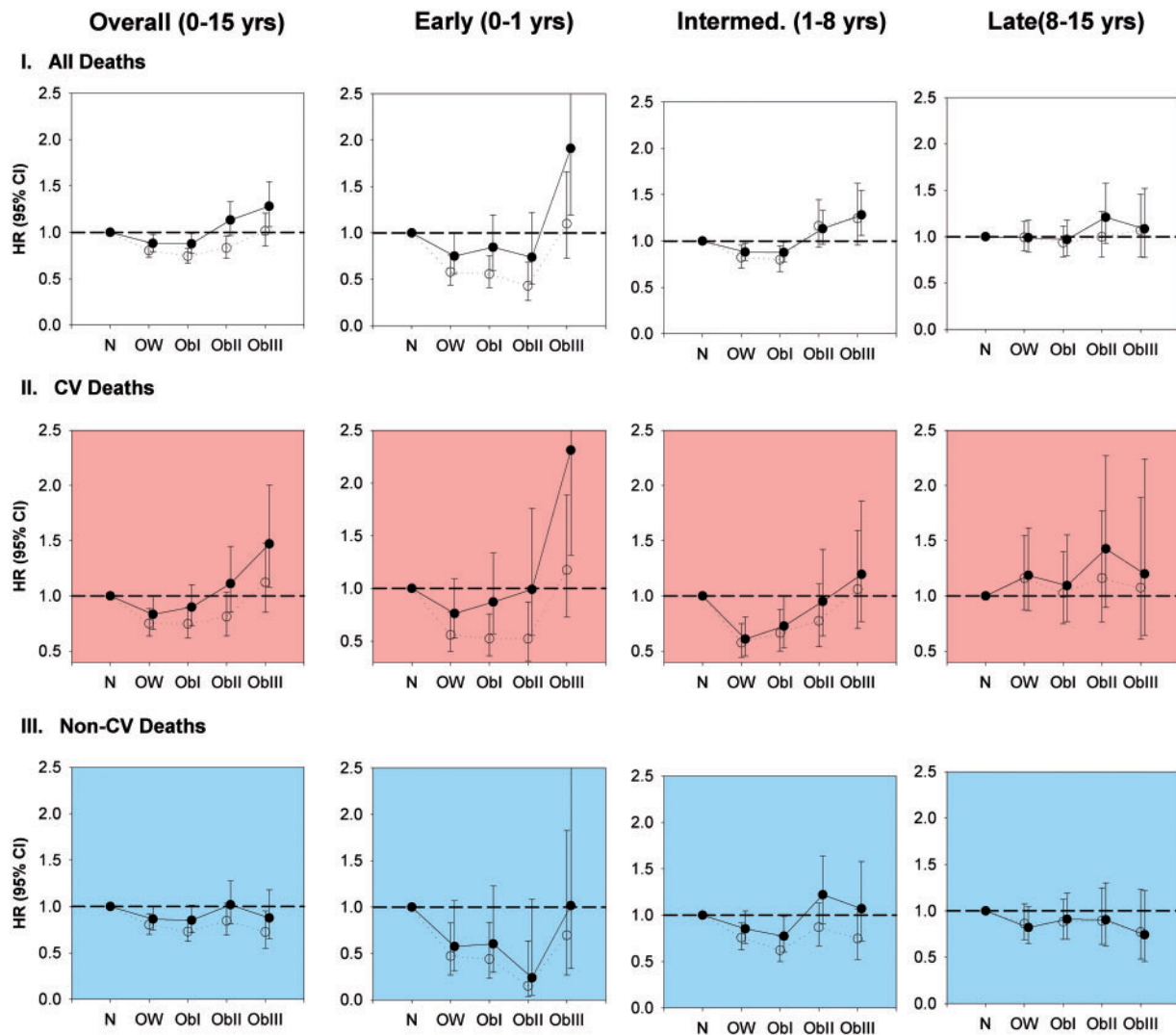


Figure 2: Comparison of mortality risk stratified by the body habitus groups for all-cause, CV and non-CV deaths shown for entire follow-up [overall (0–15 years) and for time-segmented follow-up (Early: 0–1 year, Intermediate: 1–8 years and Late: 8–15 years)]. Open symbols indicate unadjusted hazard ratios with or without accounting for competing risk of death, closed symbols indicate comprehensive risk-adjusted hazard ratios with or without accounting for competing risk of death and error bars represent 95% CIs. CI: confidence interval; CV: cardiovascular; HR: hazard ratio; Ob: obese; OW: overweight.

the Obese I patients (Fig. 2). The detrimental impact on survival in the Obese III category was driven by increased CV mortality only [AHR = 1.47 (1.08–2.00), $P = 0.015$] (Table 2; Fig. 2).

Comprehensive multivariable Cox regression model analyses using BMI as a continuous non-linear variable corroborated the 5 BMI category analyses (Fig. 3). A cubic function was found to be the best fit for the overall follow-up analysis; however, a quadratic function was the best fit for some of the time-segmented and cause-specific death analyses. The late follow-up time period showed no significant correlation with BMI as continuous function regardless of the function used (linear, quadratic and cubic). In the overall (0–15 years), early (0–1 year) and intermediate (1–8 years) analyses, there was evidence of the consistent obesity paradox with the adjusted hazard ratios at slightly above normal BMI [25–30], being less than 1. Also, with the exception of early non-CV mortality, it appears that a higher BMI (>37 kg/m²) is associated with worse outcome (Fig. 3). Based on the continuous model, a BMI between 28.5 and 29 kg/m² is associated with the best outcomes, mostly due to less early mortality and intermediate-term mortality.

DISCUSSION

Our study supports the existence of a long-term (15 years) protective partial obesity paradox in CABG patients as evidenced by improved survival in the Overweight and Obese I cohorts, which appeared in the Early postoperative period in Overweight patients and in the Intermediate postoperative period in both the Overweight and Obese I patients. Using the competing risk analysis, the obesity paradox was associated with both CV and non-CV mortality risk reduction during the entire 0–15-year follow-up period in Overweight patients and during the Intermediate postoperative time period in Obese I patients. The morbidly obese patients (Obese III) were found to have increased mortality risk primarily due to worse CV survival in the early postoperative time interval.

These results agree with previous reports documenting an obesity paradox after CABG in higher BMI patients [15, 16, 18, 19, 28] and worse survival in the morbidly obese patients [13, 18]. Stamou *et al.* [15] identified an obesity paradox among cardiac surgery patients noting a decreased short-term mortality and intermediate-term mortality among overweight patients. van

Table 2: Overall and time-segmented risk-adjusted hazard ratios for all-cause and cause-specific mortality across the BMI groups

	PH regression, HR (95% CI)	Time-segmented analysis, HR (95% CI)		
	Overall (0–15 years)	Early (0–1 year)	Intermediate (1–8 years)	Late (8–15 years)
All deaths				
N (ref)	1	1	1	1
Overweight	0.88 (0.79–0.98)	0.75 (0.56–1.00)	0.82 (0.71–0.96)	0.99 (0.83–1.18)
Obese I	0.88 (0.78–0.99)	0.84 (0.6–1.19)	0.80 (0.67–0.95)	0.97 (0.80–1.18)
Obese II	1.13 (0.97–1.33)	0.74 (0.44–1.22)	1.16 (0.94–1.44)	1.21 (0.93–1.57)
Obese III	1.28 (1.06–1.55)	1.91 (1.19–3.06)	1.24 (0.95–1.62)	1.08 (0.77–1.52)
CV deaths				
N (ref)	1	1	1	1
Overweight	0.83 (0.70–1.00)	0.76 (0.53–1.09)	0.61 (0.46–0.81)	1.19 (0.87–1.62)
Obese I	0.90 (0.73–1.10)	0.87 (0.57–1.34)	0.73 (0.53–1.00)	1.09 (0.77–1.55)
Obese II	1.11 (0.85–1.45)	0.99 (0.56–1.76)	0.95 (0.64–1.42)	1.43 (0.90–2.27)
Obese III	1.47 (1.08–2.00)	2.31 (1.31–4.07)	1.20 (0.77–1.86)	1.20 (0.64–2.24)
Non-CV deaths				
N (ref)	1	1	1	1
Overweight	0.86 (0.74–1.00)	0.57 (0.31–1.07)	0.85 (0.69–1.04)	0.82 (0.64–1.04)
Obese I	0.85 (0.72–1.01)	0.60 (0.30–1.23)	0.77 (0.61–0.98)	0.91 (0.69–1.19)
Obese II	1.02 (0.81–1.28)	0.24 (0.05–1.08)	1.22 (0.91–1.64)	0.90 (0.62–1.30)
Obese III	0.88 (0.65–1.18)	1.01 (0.34–3.04)	1.07 (0.72–1.58)	0.74 (0.45–1.22)

CI: confidence interval; CV: cardiovascular; HR: hazard ratio; PH: proportional hazard.

Bold values indicate significance at P -value = 0.05.

Straten *et al.* [18] noted a long-term survival advantage in overweight CABG patients. In a Veterans Administration CABG population, Wagner *et al.* [28] noted optimal acute perioperative survival in patients with a BMI of 30 kg/m².

The identified partial obesity paradox characterized by a 'J'-shaped relationship between our 5 BMI groups and long-term survival conflicts with other reports [12, 14, 17, 21] that found no such protective effect of increased BMI on survival. The discrepant findings between those studies and ours could be due to multiple factors including small sample sizes and short follow-up periods in the other studies [17], as well as using different BMI categorization [14] and not taking into account the continuous but non-linear relationship between outcome and BMI. Gurm *et al.* [12] analysed the impact of obesity on acute mortality and 5-year mortality in patients undergoing CABG and percutaneous intervention in the Bypass Angioplasty Revascularization Investigation (BARI) trial. In contrast to our observation, they identified that among overweight and mildly obese patients, CV mortality risk was increased, whereas all-cause mortality was unaffected by increasing BMI, suggesting, in fact, that non-CV mortality was reduced. Importantly, the BARI cohort did not reflect contemporary treatment modalities (low LITA use rate of 75–86%) as it included patients from the 1990s, and operative deaths were not included in the analysis. Le-Bert *et al.* [17], despite claims of identifying an obesity paradox in a small cohort of elderly CABG patients, did not find an association between BMI and acute in-hospital mortality. Prabhakar *et al.* [21], using the Society of Thoracic Surgeons Database and relying only on a small number of covariates for a logistic regression analysis, found an increased perioperative mortality risk among mildly obese patients [HR = 1.21 (1.45–1.73)]. Long-term mortality was not analysed, and their patient population was characterized by low LITA utilization. As our study population included only LITA-based CABG with an appreciable rate of multiarterial grafting (41.6%), the 2 study populations are not comparable. Importantly, our outcomes were adjusted for the number of

arterial grafts and the revascularization index, both of which were generally higher with rising BMI. Not doing so would have further exaggerated the protective effects of the obesity paradox. Benedetto *et al.* [14] found no effect of obesity on acute perioperative mortality, an observation that agrees with our findings. In propensity-matched groups, an overweight BMI was not protective against long-term mortality [HR = 1.05 (0.90–1.08)], and in contrast to our study, mildly obese patients (our Obese I cohort) had an increased risk of mortality [HR = 1.22 (1.07–2.66)] during a mean follow-up period of 7.6 years. The covariates in the propensity matching algorithm used by Benedetto *et al.* were limited to those included in the EuroSCORE and did not include specific grafting strategies (single arterial or multiarterial) or the revascularization index. They were unable to corroborate their outcomes in a subsequent Cox regression analysis, noting that overweight patients had decreased risk of long-term mortality [HR = 0.88 (0.80–0.97)], whereas mild obesity and morbid obesity did not influence long-term survival. They only all-cause peri-operative and long-term mortality without details on specific causes of death.

The physiological basis of the obesity paradox remains undefined and is beyond the scope of this study, but a number of possible hypotheses have been proposed. Among these are the development of earlier but less complex coronary artery disease [24] (less left main coronary disease with increasing BMI in our series), altered cytokine and neuroendocrine profiles among obese patients with a favourable CV profile, increased adipose-tissue-derived soluble tumour necrosis factor (TNF) receptor production with a resultant decrease in the pathogenic effects of TNF, lower levels of atrial natriuretic peptides, attenuated sympathetic and renin-angiotensin activity, decreased systemic vascular resistance and enhanced metabolic reserves that maybe beneficial during stress-induced catabolic states such as the postoperative period [23]. The fact that weight-loss programmes have been associated with increased adverse outcomes maybe considered as indirect evidence for the existence of an obesity paradox [29].

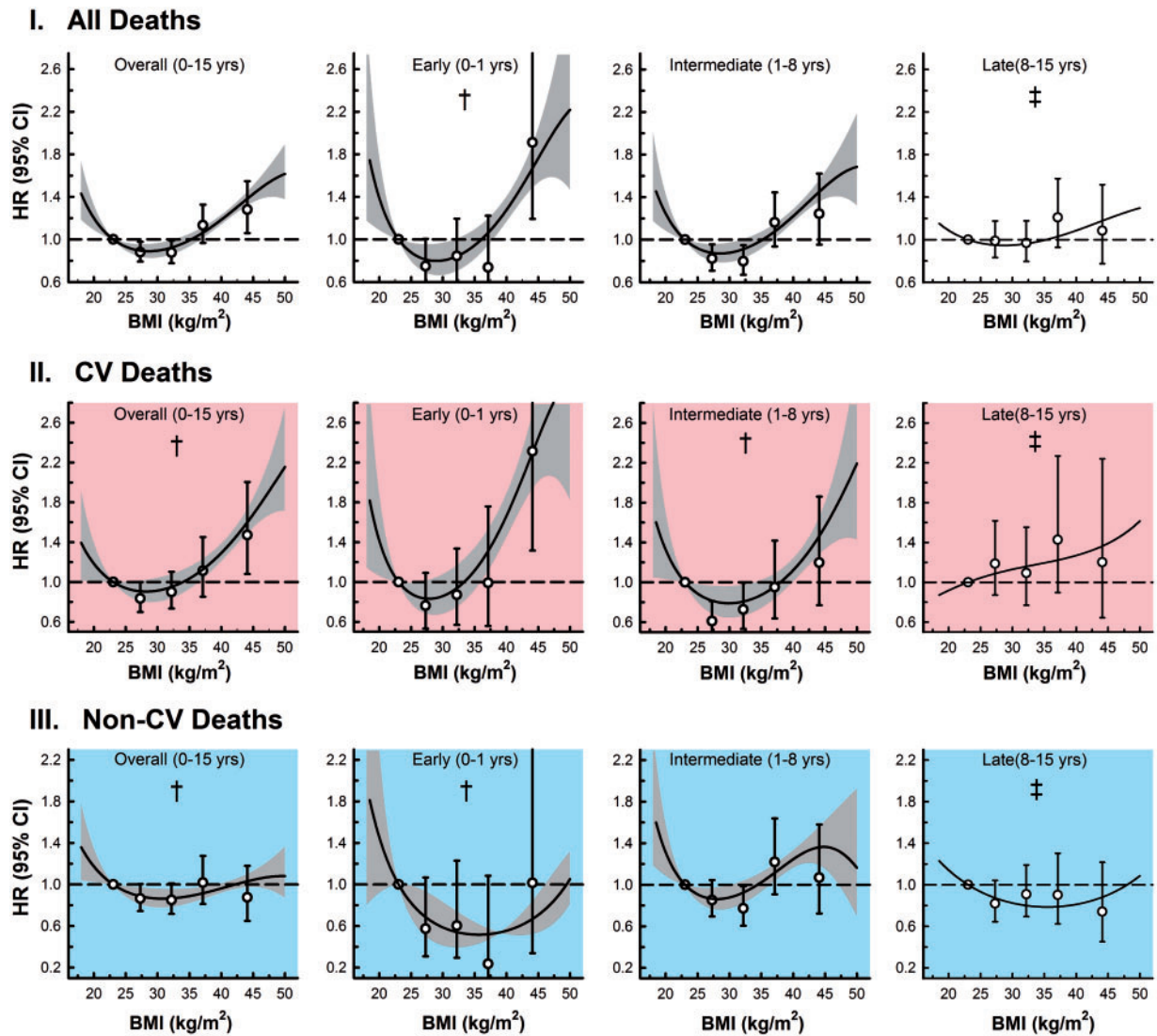


Figure 3: Association between BMI and mortality (all-cause, CV and non-CV) across the BMI spectrum (continuous variable with cubic outcome association) for overall and time-segmented follow-up periods following multivariable competing risk regression. Shaded area represents 95% CI. Symbol with error bars represent HR with 95% CIs for BMI when categorized into the body habitus groups (same as risk-adjusted data in Fig. 2). Dagger represents results of model fit with a forced BMI cubic function ($a_1 \cdot \text{BMI} + a_2 \cdot \text{BMI}^2 + a_3 \cdot \text{BMI}^3$), where the model coefficient a_3 (for BMI^3) was not significant, whereas a_2 (for BMI^2) was significant and double dagger indicates that the BMI outcome association is not significant for any order. BMI: body mass index; CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Our findings of increased mortality in the morbidly obese (Obese III) CABG patients confirms those of multiple other reports [12–14, 18, 21, 30], and this was principally driven by increased CV mortality within the first postoperative year. The pathophysiology behind this observation is also undefined and beyond the scope of this study but is unlikely related to postoperative complications, as the acute perioperative outcomes were equivalent and uniformly excellent across all BMI categories.

When survival was analysed as a function of BMI as a continuous variable, we identified a BMI of 29 kg/m² corresponding to the lowest overall mortality rate (Fig. 3). In such an analysis, rather than a 'J'-shaped relationship between survival and the 5 distinct BMI groups, the survival curves showed a U-shaped relationship between BMI and mortality with increased risk at both extremes, a finding that we have reported on earlier [13]. Benedetto *et al.* [14] similarly identified a BMI range of 27–29 kg/m² as being maximally protective for late mortality. Wagner *et al.* [28] noted a similar U-shaped relationship

between acute perioperative mortality and BMI with a nadir mortality point at a BMI of 30 kg/m². A question that remains unanswered is whether delaying surgery to affect weight reduction may ameliorate the increased mortality risk among the morbidly obese patients.

Limitations

Our study has a number of limitations. As this is a retrospective analysis, only associations can be established, and we are unable to assess the specific physiological mechanisms that may account for our findings. All observational studies are subject to well-recognized biases including patient selection bias, and conclusions might be altered by exclusion of covariates that may be pertinent to the analysis but, nevertheless, are not included in the study data set. In addition, although BMI is a convenient and widely used parameter to assess obesity, other parameters of obesity such as adiposity, body fatness, waist circumference and weight-to-height

ratio, all of which have been shown to impact mortality [23], were not used in our analysis, and it is not known how, or if at all, the inclusion of these measures of obesity may have impacted our conclusions. Furthermore, it is important to note that body mass index is not a static patient characteristic and is subject to change over time. Any changes in BMI over the study period were unavailable to us, and only the values at the index operation were utilized in the analysis. Also, we are unable to assess the patients' long-term medication use and risk reduction strategies on long-term survival. The impact of any repeat revascularization strategies on long-term survival was not included in our study. Finally, BMI does not provide a distinction between all obese patients and metabolically healthy obese patients who may have a distinctly different prognosis for any given BMI [23].

CONCLUSION

In conclusion, our study demonstrates the presence of a partial obesity paradox up to 15 years postoperatively in CABG patients. Patients who are overweight and mildly obese show improved survival, with a decreased risk of CV mortality and non-CV mortality in the entire 0–15-year postoperative period and in the 1–8-year postoperative period, respectively. Conversely, morbidly obese patients had significantly worse survival driven by increased CV mortality within a year of the index operation.

Conflict of interest: none declared.

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