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Body-Mass Index and Mortality Among Adults Undergoing Cardiac Surgery: A Nationwide Study with a Systematic Review and Meta-Analysis

Running Title: *Mariscalco et al.; The Obesity Paradox in Cardiac Surgery*

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Abstract

Background **—**In an apparent paradox morbidity and mortality are lower in obese patients undergoing cardiac surgery, although the nature of this association is unclear. We sought to determine whether the obesity paradox observed in cardiac surgery is attributable to reverse epidemiology, bias, or confounding.

Methods **—**Data from the National Adult Cardiac Surgery registry for all cardiac surgical procedures performed between April 2002 and March 2013 were extracted. A parallel systematic review and meta-analysis (MEDLINE, Embase, SCOPUS, Cochrane Library) through June 2015 was also accomplished. Exposure of interest was body mass index (BMI) categorised into 6 groups according to the World Health Organisation classification.

Results **—** A total of 401 227 adult patients in the cohort study, and 557 720 patients in the systematic review were included. A "U-shape" association between mortality and BMI classes was observed in both studies, with lower mortality in overweight (adjusted odds ratio [OR], 0.79; 95% confidence interval [CI], 0.76-0.83) and obese class I and II (OR, 0.81; 95%CI, 0.76-0.86 and OR, 0.83; 95%CI, 0.74-0.94) patients relative to normal weight patients and increased mortality in underweight individuals (OR, 1.51; 95%CI 1.41-1.62). In the cohort study, a "U-shaped" relationship was observed for stroke and low cardiac output syndrome, but not for renal replacement therapy or deep sternal wound infection. Counter to the reverse epidemiology hypotheses the protective effects of obesity were less in patients with severe chronic renal, lung or cardiac disease and greater in older patients, and in those with complications of obesity including the metabolic syndrome and atherosclerosis. Adjustments for important confounders did not alter our results.

Conclusions —Obesity is associated with lower risks after cardiac surgery, with consistent effects noted in multiple analyses attempting to address residual confounding and reverse causation.

Key-words: obesity; surgery; morbidity/mortality

Clinical Perspective

What is new?

- In a nationwide cohort study of 401 227 adult patients, and a systematic review of 557 720 patients from 13 countries we demonstrated that overweight and obese patients had improved outcomes after cardiac surgery compared to normal weight patients.
- Sub-group and sensitivity analyses designed to mitigate the effects of likely sources of bias and confounding did not affect our estimates that demonstrated reductions in mortality with increasing levels of obesity.
- Analysis of secondary outcomes indicated that obesity also had divergent associations with important causes of death.

What are the clinical implications?

- The present findings do not support common practice where weight loss is recommended prior to surgery, or where very obese patients are refused surgery in the morbidly obese.
- These results suggest a new area for research into strategies that may minimize organ failure in cardiac surgery and other clinical settings characterised by acute surgical metabolic stress.

Introduction

In an apparent paradox obesity, an important risk factor for cardiovascular death,[1,2] is associated with reduced mortality following cardiac surgery.[3] Similar observations have been described in patients with acute coronary syndromes,[4] heart failure,[5] or requiring dialysis.[6] It is unclear whether this simply reflects the limitations of epidemiological analyses or whether there may be actual protective factors associated with obesity that contribute to improved outcomes. The obesity paradox has been attributed to reverse epidemiology (causation), or collider bias where the survival benefit associated with obesity actually reflects worse outcomes in underweight patients that also have frailty, cachexia or severe chronic disease.[7] Alternate hypotheses are that obese patients are selected for surgery only if they are subjectively at lower risk, they have high body mass index (BMI) but no metabolic syndrome with its related complications.[8] We report the results of two related studies in cardiac surgery patients: a cohort study of United Kingdom (UK) and Ireland cardiac surgery audit data and a systematic review with meta-analysis of this and other similar studies that have considered the relationship between BMI and mortality. The aim of these studies was to assess whether the obesity paradox in cardiac surgery can be attributed to reverse epidemiology, bias and confounding, or other mechanisms.

Methods

Observational Study Cohort

Prospectively collected data were extracted from the National Institute for Cardiovascular Outcomes Research (NICOR) National Adult Cardiac Surgery Audit (NACSA) registry (version 4.1.2) on 1 December 2014 for all cardiac operations performed in the UK and Ireland. These data are collected prospectively and undergoes robust validation and checking procedures to

maintain data quality.[9-12] Duplicate records and non-adult cardiac surgery entries were removed, transcriptional discrepancies harmonised and clinical and temporal conflicts and extreme values corrected or removed.[11] No attempt to replace missing values was made. The need to obtain informed consent was waived since patient identifiable information was either removed or pseudonymized. The study was approved by the NICOR NACSA Research Board (study reference 14-ACS-29), and complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting requirements for observational studies (Supplemental Appendix 1).[13]

Study Design

We performed a retrospective observational cohort study encompassing all adult cardiac surgical procedures performed in the UK and Ireland between 1 April 2002 and 31 March 2013. For each operation, data were recorded on patient characteristics and demographics, comorbidities, intraoperative factors, and postoperative outcomes. Administrative data were also extracted. The analysis dataset was obtained by including all cases with complete data on a set of key preoperative, intraoperative and postoperative variables as follows: age, BMI, sex, left ventricular ejection fraction (EF) category, history of myocardial infarction, renal impairment, diabetes on medication, previous cardiac surgery, operation type and cardiopulmonary bypass (CPB) use. Patients undergoing salvage surgical procedures (cardiac arrest prior to induction), patients with critical preoperative state (ventilated, cardiogenic shock, inotropic support, intra-aortic balloon pump [IABP]) and stage 5 chronic kidney disease (dialysis) were excluded. Patients for whom it was not possible to calculate the BMI, or where the sex of the patient or operation type or discharge status was missing were also excluded.

Study Outcomes, Exposures and Confounding

BMI was defined as the weight in kilograms divided by the square of the height in metres (kg/m^2).[14] According to the World Health Organization (WHO) classification,[15] BMI was further categorised in six classes: underweight (BMI<18.5 Kg/m^2), normal weight (BMI 18.5-<25), overweight (BMI 25-<30), obese class I (BMI 30-<35), obese class II (BMI 35-<40), and obese class III (BMI ≥ 40). The primary end-point was in-hospital mortality, defined as death in hospital following the index surgical procedure and prior to transfer from the cardiac surgery unit as per the definition used in the national audit. Potential confounders pre-specified in our analyses included severe chronic disease: chronic lung disease, chronic renal impairment, neurological dysfunction, NYHA class III/IV symptoms, as well as gender, increasing age, EF category, Canadian Cardiovascular Society (CCS) class, diabetes, extracardiac arteriopathy, social deprivation index, and metabolic syndrome; a composite of increased BMI, hypertension and diabetes. Secondary end-points were: low cardiac output, defined by the new use of an IABP postoperatively; re-exploration for bleeding/tamponade; postoperative stroke; severe acute kidney injury, defined as need for new postoperative renal replacement therapy (RRT); and occurrence of deep sternal wound infection (DSWI). Variables and outcomes were defined according to the NACSA registry.[10]

Systematic Review and Meta-Analysis

The review protocol was developed and complete details including electronic search strategy, objectives, criteria for study selection, eligibility, data collection, and assessment of study quality were published online and registered in PROSPERO (CRD42015024232).[16] The review adhered to MOOSE and PRISMA guidelines (Supplemental Appendix 2 and 3).[17,18]

Briefly, literature searches were systematically performed using electronic databases (MEDLINE (PubMed and Ovid), Embase, SCOPUS, and Cochrane Library) without date or language restriction from inception to the end of June 2015. Keywords and MeSH terms pertinent to the exposure of interest were used in relevant combinations: "*body mass index*", "*obesity*", "*overweight*", "*underweight*", "*cardiac surgery*", "*adult*", "*coronary artery bypass grafting*", "*valve surgery*", "*aortic surgery*", *"cardiac transplant", "ventricular assist device", "mortality", "morbidity", and "patient outcome"*. References of all eligible studies and review articles were also screened to identify relevant resources that were not previously identified. The exposure of interest was obesity stratified into the six BMI groups according to the WHO classification.[15] Studies with alternate BMI definitions of the underweight class were also included and defined as modified WHO classification. All adult cardiac surgical procedures were considered. Studies in which BMI was expressed as a continuous variable or in which BMI classes were merged were excluded. The primary outcome of interest was all-cause mortality in hospital or within 30 days from index admission or procedure. Inclusion and exclusion criteria for qualitative/quantitative analyses were summarized according to PICOS approach (Supplemental Table 1). Year of publication, study design, country, sample size, recruitment period, number of patients in each treatment group, inclusion and exclusion criteria, measured outcomes, obesity classification, baseline patient demographics, cardiac status, comorbidities, and outcomes among relevant subgroups of patients were extracted. The Newcastle-Ottawa Scale (NOS) for cohort and case-control studies was used to assess study quality.[19]

Statistical Analysis

Statistical analysis methods are fully reported in the Supplement Material.

Briefly, baseline characteristics, operative factors, and univariate outcomes were described as median (25^{th}-75^{th} percentiles), and counts and percent, and compared among BMI groups with the Kruskall-Wallis test and the chi-square test, respectively. To adjust the effect of BMI (6 categories) for potential confounders, multivariable logistic regression models of the primary and secondary outcomes were fitted. Sensitivity analyses evaluated the effects of inclusion or exclusion of suggested confounders identified in previous analyses of the obesity paradox.[3,20-44] Subgroup analyses assessed the interaction in the full model between pre-specified known risk factors for adverse outcomes in cardiac surgery on the associations between BMI and mortality. Propensity score analysis (propensity for being overweight) was also performed. Effect estimates were presented as Odds Ratios (OR; and 95% confidence intervals [CI]). Stata version 13.1 (Stata Corp, College Station, TX, USA) was used for computation. The meta-analysis was performed using R version 3.2.2 (R Core Team, 2015) with metafor package version 1.9-8.[45,46] Random/mixed-effects models were adopted to summarize the results expressed as Relative Risks (RR) (95%CI).[47,48] The contribution of study level covariates to heterogeneity was assessed using mixed effects models. Publication bias was assessed using funnel plots and Egger's test.[49] Statistical tests were 2-sided with a significance threshold of $P<0.05$.

Results

Observational Study Cohort

Of the 401 227 records identified in the NACSA registry, 350 800 (87.4%) had complete case data and were included in the analysis dataset. The final cohort presented a median age of 59 years (25^{th}-75^{th} percentile, 18-67) and 27% were women. Median BMI was 27.5 kg/m^2 (25^{th}-75^{th}

percentile, 24.8-30.7), and 3 382 (1%) patients were classified as underweight, 91 378 (26%) as normal weight,

150 769 (43%) as overweight, 77 614 (22%) as obese class I, 21 610 (6%) as obese class II, and 6 047 (2%) as obese class III, respectively. Preoperative and operative characteristics are summarized in Table 1.[50,51] Patients with higher BMI were younger and had a higher prevalence of hypertension and/or diabetes. A higher prevalence of women was observed in the underweight and the morbidly obese patients. Key variable comparison of the cohort with incomplete data to the complete case cohort, suggested that the missing at random mechanism was applicable (Supplemental Table 2).

Primary Endpoint

Overall 11 511 patients died in hospital (3.29%; 95% CI, 3.23-3.34). Mortality was 8.5% in underweight patients, 4.4% in normal weight patients, 2.7% in overweight patients, 2.8% in obese class I-II patients, and 3.7% in obese class III patients, respectively (Supplemental Table 3). This "U-shaped" relationship was confirmed after adjustment for baseline differences (Figure 1A). There were multiple additional baseline predictors of mortality that differed in frequency across the BMI groups (Supplemental Table 4). After adjustment for differences in baseline risk, OR for hospital mortality was 1.51 (95% CI, 1.41-1.62) for underweight *versus* normal weight patients (Supplemental Tables 3 and 4). Compared to normal weight, the adjusted ORs for hospital mortality were 0.79 (95% CI, 0.76-0.83) for overweight, 0.81 (95% CI, 0.76-0.86) for obese class I, 0.83 (95% CI, 0.74-0.94) for obese Class II, and 0.99 (95% CI, 0.80-1.22) for obese class III patients, respectively.

Sensitivity and Subgroup Analyses

Fractional polynomial, restricted cubic spline, and propensity score analyses demonstrated similar findings to our primary analysis (Supplemental Tables 4 and 5, and Supplemental Figure 1). Sensitivity analyses that excluded patients with low BMI (underweight patients), poor exercise tolerance (NYHA Class III/IV), and severe chronic cardiac, neurological, renal, or respiratory diseases also did not materially alter our findings (Figure 1B). Analyses of subgroup interactions indicated that the relative reductions in mortality in obese/overweight patients *versus* normal weight individuals were less in patients with atrial fibrillation, chronic lung disease, kidney disease or poor left ventricular function (Figures 1 C-E; Supplemental Table 6 and Supplemental Figure 2). In contrast, the protective associations seen with obesity were greater in older patients and in those with coronary disease undergoing coronary artery bypass grafting (CABG), extracardiac arteriopathy, or the metabolic syndrome. (Figures 1F-H; Supplemental Table 6 and Supplemental Figure 2). The interaction between smoking status, BMI and mortality was statistically significant but demonstrated mixed increases and decreases in odds of death by BMI class for each smoking category; never, ex- and current. Nonetheless each category demonstrated a "U" shaped relationship between BMI and mortality as per the primary analyses. The differences in mortality between obesity classes were also consistent over time (Supplemental Table 6).

Secondary Endpoints

To explore processes that could underlie the results of our primary analysis we also evaluated the associations between BMI and important causes of death. Low cardiac output was observed in 3 155 patients (1.0%), re-exploration for bleeding/tamponade in 14 509 (4.6%), stroke in 3 120 (1.0%), RRT in 10 814 (3.6%), and DSWI in 681 (0.2%) (Supplemental Table 3). Similarly to

the primary end-point of hospital mortality, a “U-shape” relationship was demonstrated between increasing BMI class and postoperative RRT and stroke (Figure 2). An inverse “U-shape” was observed for low cardiac output (postoperative IABP). In contrast, the rate of re-exploration for bleeding/tamponade decreased stepwise with increasing BMI, whereas the rate of DSWI increased with BMI class. These relationships were not altered after adjustment for baseline differences. Additional analyses are reported in the Results section in the Data Supplemental Material.

Systematic Review and Meta-analysis

Of the 4 788 records identified by our searches, 26 eligible cohort observational studies were identified and included in the meta-analysis (Supplemental Figure 3).[8,26-50] When the data from the NACSA registry were included, the final meta-analysis population comprised 557 720 patients. Regions of origin of participants included Europe (n=14), the Unites States (n=9), and Asia (n=3) and included patients from 13 countries (Supplemental Table 7). Study characteristics and collected outcomes for each BMI group are summarized in Supplemental Tables 8-10. Five comparisons among BMI groups were considered: normal weight *versus* overweight patients (27 studies), normal weight *versus* obese class I patients (17 studies), normal weight *versus* obese class II patients (4 studies), normal weight *versus* obese class III patients (5 studies), and finally normal weight *versus* underweight patients (19 studies) (Supplemental Table 11). Normal weight patients were classified according to either the standard (BMI, 18.5 -<25 kg/m^2) or the modified WHO classification introduced by Gurm and colleagues[26] (BMI, 20 -<25 kg/m^2). Other studies considering other classifications of the underweight class (18 or 19 Kg/m^2) were considered and pooled within the standard or the modified WHO classifications, respectively (full Methods

section in the Supplemental Material).[31,36,37] Newcastle Ottawa Scale assessment of study quality is reported in Supplemental Table 12.

As per our cohort study, we demonstrated the "obesity paradox" in our meta-analysis. When compared to normal weight patients, the observed RRs were 0.73 (95%CI, 0.66-0.81) for overweight, 0.76 (95%CI, 0.67-0.86) for obese class I, 0.65 (95%, 0.60-0.71) for obese class II, and 0.83 (95%CI, 0.74-0.94) for obese class III patients, respectively (Figures 3 and 4). Underweight patients had significantly increased mortality (RR, 1.77; 95% CI, 1.30-2.42) compared to normal weight individuals (Figure 3). Sensitivity analyses showed that the survival benefit for overweight/obese patients was greater when studies with significant methodological limitations (NOS score <8), or studies that used modified WHO definitions of obesity were excluded (Supplemental Table 13). Subgroup analysis demonstrated that the reductions in mortality with increasing obesity were greatest in patients undergoing isolated CABG compared to other types of surgical procedure (Figures 3 and 4). Funnel plots revealed no evidence of publication bias in any of the mortality comparisons (Supplemental Figure 4). Between-study heterogeneity was statistically significant in the analyses of normal weight *versus* overweight patients (I^2=62.3%, Q=59.99, P<0.001) and in normal weight *versus* obese class I patients (I^2=62.1%, Q=42.25, P<0.001). Meta-regression analysis identified several covariates that contributed to the observed heterogeneity, although a significant model effect was observed only in the obese class I comparison with reference to the average age and the use of the modified WHO classification for BMI (Age, R^2=82.35%, P=0.005; WHO classification, R^2=53.87%, P=0.026) (Supplemental Tables 14-16 and Supplemental Figure 5). Heterogeneity was also observed in the analysis of underweight *versus* normal weight patients (I^2=77.7%, Q=59.29, P<0.001) where meta-regression identified prior myocardial infarction (R^2=61.55%, P =0.004)

and chronic lung disease (R^2=43.86% P=0.017) as contributing significantly to the model heterogeneity. Additional analyses including publication bias assessment are reported in the Results section in the Supplemental Material.

Discussion

In large cohorts of UK and Irish cardiac surgery patients we found that overweight and obese patients had lower in-hospital mortality compared with normal BMI patients, while underweight patients had increased mortality. This relationship was unchanged when patients with low BMI and/or severe chronic disease, or severe limitation of exercise tolerance were excluded. Reductions in mortality associated with increasing BMI class were greater in older patients and in those with clinical complications of obesity. The relationship between obesity and secondary outcomes demonstrated heterogeneity; obesity was associated with a reduction of primarily ischemic complications such as low cardiac output and stroke, but not for RRT or infections. In a systematic review of 27 studies that included patients from 13 countries we observed similar results. Subgroup and meta-regression analyses also demonstrated greater reductions in mortality associated with obesity in the elderly and in patients with coronary artery disease.

Our cohort study was significantly larger than all previous evaluations of the obesity paradox in cardiac surgery combined. We used high quality prospectively collected data that are used as part of a national quality control program in UK and Irish cardiac surgery. The study cohort included all patients undergoing cardiac surgery in every UK and Irish unit. Our analysis population included 87.4% of all patients and we demonstrated that data missingness was likely to be random, reducing the likelihood of sampling bias. The study limitations were those of any retrospective analysis, notably the likelihood that unmeasured confounders will have introduced unknown bias. For example, it is possible that obese patients with a more severe profile of

comorbidities and considered at high risk for a cardiac operation were excluded from surgery. The sample size of the cohort will have mitigated this source of bias as there were large numbers of patients with significant comorbidity in each BMI group thereby allowing accurate estimation of the interaction between obesity and known risk factors for adverse outcome. The use of BMI as a marker of obesity also has significant limitations, and other important aspects of body composition such as visceral fat or fat distribution were not explored.

Our systematic review had important strengths. We used a comprehensive search strategy and contemporary assessments of study quality. We found that 17 out of 27 studies had significant limitations. Studies of low quality and those that used non-standard definitions of obesity were more likely to conclude that there was no obesity paradox. We also used detailed statistical methods to explore the independent contribution of potential confounders. This demonstrated that risks factors contributing to heterogeneity in the analysis of underweight patients (chronic lung disease and history of MI), differed to those contributing to heterogeneity in the analyses of the obese (age and coronary artery disease). The meta-analysis also had limitations. Principally, the analysis relied on the reported information on confounding variables that were controlled for; consistent analyses of all studies can be done only when data on individual patients are combined. A limitation is that our studies consider data with a different time interval (March 2013 *vs* December 2015). NACSA registry allowed us to collect and analyze validated data through March 2013 only.[10,11] Another limitation of both analyses is that they considered only short-term mortality. Given that obesity is a principal etiological factor in cardiovascular disease and premature death,[1,52,53] it is possible that early reductions in mortality observed in obese patients may not be sustained in the mid to long-term. This has been reported in a previous study, where the short term reduction in mortality observed in overweight and

obese patients were no longer evident at 5 years.[54] Acute weight loss is also known to reduce major adverse cardiovascular event rates in patients with coronary artery disease in the longer term.[55,56] A final limitation, is that observational analyses, including in the current study, cannot prove or disprove the reverse epidemiology hypothesis for the obesity paradox; greater survival benefit attributable to increasing weight may equally represent increased mortality with lower body mass. It is intuitive that cachexia in cardiac patients, commonly associated with chronic diseases affecting the heart, lung and kidneys, will contribute to adverse outcomes.[57] Alternatively, patients with severe symptomatic coronary artery disease in the absence of obesity may represent a more aggressive phenotype and consequently have a worse outcome. However, both subgroup and sensitivity analyses suggested that patients with low BMI (<18.5 kg/m^2) and/or severe chronic lung, cardiac, neurological, and renal disease did not explain our findings. In fact the effect of increasing obesity, or inversely lower body mass, on mortality, was significantly less in these groups. This is in complete contrast to the interactions observed for increasing age, metabolic syndrome and atherosclerotic disease. We also observed heterogeneity in the relationships between BMI and the principal causes of in-hospital death in cardiac surgery. These are key findings; if the relationship between obesity and mortality were simply the result of reverse epidemiology or confounding, then it should be expected that there would be a consistent effect on the estimate of the association between BMI and mortality across all risk factors for adverse outcome, or important causes of death. A common example of this phenomenon is red cell transfusion that is strongly associated with mortality as well all important causes of mortality in cardiac surgery in cohort studies, but has different and divergent effects on these events in randomized trials that consider causation.[58,59]

These findings highlight knowledge gaps that must be addressed by further research. They identify a high risk cohort, patients with low BMI, who could potentially benefit from targeted weight gain interventions prior to surgery. They also challenge current practice where obese patients are rejected for, or advised to lose weight prior to, major surgery. The current analyses included large cohorts of obese class III (BMI≥40 kg/m^2) patients that are considered to have significantly higher morbidity and mortality, and to use significantly more resources than other patient groups.[60] However, neither the NICOR analysis, nor the systematic review demonstrated an increase in mortality in these patients relative to normal weight. Divergent associations between obesity and important causes of death were most marked in this group; obese class III patients had less perioperative cardiac failure or bleeding, but higher rates of DSWI and RRT. The overall effects on resource use remains unclear as NICOR does not capture resource use data. Further research should consider whether strategies focused on the prevention of wound infection or acute kidney injury will have specific benefits in these morbidly obese patients.

In summary, we explored the basis of the obesity paradox in two related studies in cardiac surgery patients. Mitigation of the effects of potential bias and confounding did not substantially affect our estimates that demonstrated reductions in mortality with increasing levels of obesity. Moreover, analysis of sub-group interactions and secondary outcomes did not support a reverse epidemiology hypothesis. These findings highlight a knowledge gap with respect to the perioperative management of body mass and obesity in cardiac surgery patients.

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Author Contributions

Mariscalco and Murphy had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Mariscalco, Porter, Wozniak and Murphy.

Acquisition of data: Mariscalco, Wozniak, Dawson, Serraino and Kumar.

Analysis and interpretation of data: Mariscalco, Wozniak, Nath, Klersy and Murphy.

Drafting of the manuscript: Mariscalco, Wozniak, Klersy and Murphy.

Critical revision of the manuscript for important intellectual content: Mariscalco, Wozniak, Dawson, Serraino, Porter, Nath, Klersy, Kumar and Murphy.

Paper Supervision: Mariscalco, Wozniak, Dawson, Serraino, Porter, Nath, Klersy, Kumar and Murphy.

Statistical analysis: Nath, Klersy and Wozniak.

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Disclosures

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Table 1. Distribution of Prognostic Variables among Increasing BMI Groups

Variables*	Overall	Underweight	Normal	Overweight	Obese Class I	Obese Class II	Obese Class III	*P* value†	*P*-trends
BMI class (kg/m^2)		**<18.5**	**18.5-<25**	**25-<30**	**30-<35**	**35-<40**	**≥40**		
N.Pts	**350800**	**3382**	**91378**	**150769**	**77614**	**21610**	**6047**		
Demographics									
Age, y	67 (59-74)	68 (55-76)	69 (50-76)	68 (60-74)	66 (59-73)	64 (57-71)	62 (55-69)	0.0001	0.0001
BMI, Kg/m^2	27.47 (24.76-30.74)	17.58 (16.79-18.08)	23.23 (21.85-24.22)	27.38 (26.20-28.57)	31.77 (30.81-33.08)	36.65 (35.70-37.92)	42.28 (40.90-44.62)	0.0001	0.0001
Female, %	94997 (27)	1956 (58)	29704 (33)	33394 (22)	19649 (25)	7559 (35)	2735 (45)	0.0001	0.0001
Presentation									
Urgent/Emergent, %	106706 (30)	1461 (43)	31931 (35)	44678 (30)	2091 (27)	5850 (27)	1885 (31)	0.0001	0.0001
Reoperation, %	21817 (7)	459 (15)	7296 (9)	8863 (6)	3915 (6)	1020 (5)	264 (5)	0.0001	0.0001
Nitrates IV, %	17389 (5)	224 (1)	5025 (6)	7355 (5)	3517 (5)	947 (4)	321 (5)	0.0001	0.0001
NYHA class, %								0.0001	0.0001
Class I	85603 (25)	737 (22)	24145 (27)	39378 (26)	16820 (22)	3652 (17)	871 (14)		
Class II	144961 (41)	1101 (33)	35646 (39)	63981 (43)	33271 (43)	8782 (41)	2180 (36)		
Class III	96380 (28)	1081 (33)	24021 (27)	38246 (26)	22973 (30)	7604 (35)	2445 (41)		
Class IV	20077 (6)	417 (12)	6362 (7)	7489 (5)	3883 (5)	1415 (7)	511 (9)		
CCS class III/IV, %	113168 (33)	667 (20)	25148 (29)	49154 (34)	27761 (37)	8155 (39)	2283 (39)	0.0001	0.0001
Cardiac status									
CAD, %	275516 (80)	1952 (59)	66022 (74)	122025 (82)	63939 (83)	17169 (80)	4409 (74)	0.0001	0.0001
LMS, %	65148 (21)	378 (14)	15647 (19)	29424 (22)	14812 (21)	3857 (19)	1030 (19)	0.0001	0.0001
Previous MI, %	121859 (35)	783 (23)	28838 (32)	53754 (36)	28483 (37)	7872 (36)	2129 (35)	0.0001	0.0001
Previous PCI, %	27366 (8)	168 (5)	6100 (7)	11837 (8)	6736 (9)	1987 (10)	538 (9)	0.0001	0.0001
Preoperative AF, %	33845 (10)	602 (19)	10984 (13)	13251 (9)	6500 (9)	1951 (9)	557 (10)	0.0001	0.0001
Ejection fraction, %								0.0001	0.0001
Good (LVEF >50%)	241634 (69)	2217 (66)	62355 (68)	104727 (69)	53429 (69)	14734 (68)	4172 (69)		
Fair (LVEF 30-50%)	87300 (25)	883 (26)	22390 (25)	37125 (25)	19742 (25)	5638 (26)	1522 (25)		
Poor (LVEF <30%)	21866 (6)	282 (8)	6633 (7)	8917 (6)	4443 (6)	1238 (6)	353 (6)		
Comorbidities									

Hypertension, %	230388 (66)	1474 (44)	51594 (57)	99162 (66)	56591 (73)	16819 (78)	4748 (79)	0.0001	0.0001
Diabetes, %	71217 (20)	265 (8)	11878 (13)	27899 (19)	20899 (27)	7729 (36)	2457 (41)	0.0001	0.0001
Lung disease, %	46328 (13)	684 (20)	12298 (13)	18159 (12)	10422 (13)	3614 (17)	1151 (19)	0.0001	0.0001
Extracardiac arteriopathy, %	41471 (12)	412 (12)	10597 (12)	17729 (12)	9516 (12)	2618 (12)	599 (10)	0.0001	0.105
History of CVA, %	25613 (8)	313 (10)	6977 (8)	10773 (7)	5602 (8)	1565 (8)	383 (7)	0.0001	0.0001
Creat > 2.26 mg/dl, %	8905 (2)	162 (5)	2775 (3)	3426 (2)	1802 (2)	558 (3)	182 (3)	0.0001	0.0001
Smoking status, %								0.001	0.0001
Never smoked	123976 (36)	1524 (46)	37134 (41)	52166 (35)	24260 (31)	6796 (32)	2096 (35)		
Ex-smoker	185993 (53)	1181 (35)	41740 (46)	82297 (55)	45134 (59)	12390 (58)	3251 (54)		
Current smoker	36598 (11)	633 (19)	11298 (13)	14519 (10)	7329 (10)	2189 (10)	630 (11)		
Index of Multiple Deprivation (IMD), score‡	16.38 (9.59-28.67)	18.33 (10.05-18.70)	15.59 (9.06-27.50)	15.84 (9.38-27.42)	17.37 (10.24-30.27)	19.5 (11.20-33.72)	20.57 (11.78-35.19)	0.0001	0.0001
Operative									
CPB use, %	308757 (88)	3472 (93)	89157 (89)	143730 (88)	73946 (87)	20630 (88)	5860 (88)	0.0001	0.0001
CPB time, min	54 (38-75)	96 (72-130)	92 (70-123)	90 (69-118)	89 (69-116)	90 (69-117)	91 (69-120)	0.0001	
ACC time, min	90 (69-119)	60 (42-84)	56 (39-78)	53 (37-74)	53 (37-73)	54 (38-74)	56 (38-76)	0.0001	0.0001
Type of Operation, %								0.001	0.0001
CABG isolated	203547 (58)	899 (27)	43999 (48)	92326 (61)	49769 (64)	13252 (61)	3302 (55)		
Valve(s) isolated	66175 (19)	1321 (39)	22301 (24)	25183 (17)	12037 (16)	3890 (18)	1443 (24)		
CABG+valve	41407 (12)	457 (13)	11880 (13)	17499 (12)	8657 (11)	2302 (11)	612 (10)		
Major aortic surgery	13099 (4)	236 (7)	4343 (5)	5290 (3)	2339 (3)	685 (3)	206 (3)		
Other procedures	26572 (7)	469 (14)	8855 (10)	10471 (7)	4812 (6)	1481 (7)	484 (8)		
Number of grafts, n	3 (2-3)	3 (2-3)	3 (2-3)	3 (2-3)	3 (2-3)	3 (2-3)	3 (2-3)	0.0001	0.004

ACC indicates aortic cross clamp; AF, atrial fibrillation; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CPB, cardiopulmonary bypass; creat, creatinine; CVA, cerebrovascular accident; IMD, Index of Multiple Deprivation (score); IQR, interquartile range; IV, intravenous; NYHA, New York Heart Association; LMS, left main stem; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

*Continuous data are presented as median and IQR; categorical variables as number (percent).

†*P* values for the Kruskall-Wallis test and the chi-square test for group comparisons among continuous and categorical variables.

‡The IMD score is a calculated deprivation score for geographical area inhabited by at least 1000 people, and is used for investigating social deprivation and cardiovascular disease outcomes. The IMD score is based on: 1) income deprivation; 2) employment deprivation; 3) health deprivation and disability; 4) education, skills and training deprivation; 5) barriers to housing and services; 6) crime and disorder; 7) living environment.

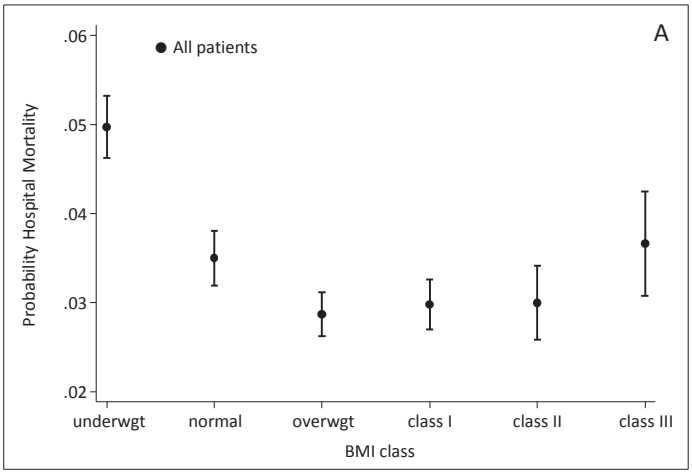
Figure Legends

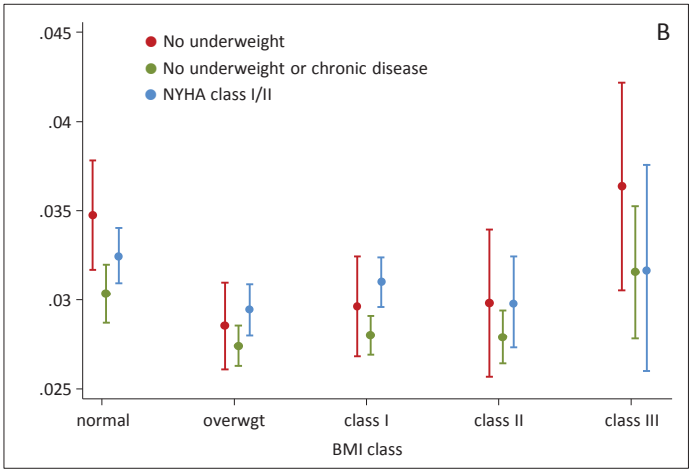
Figure 1. Probability of in-hospital mortality among enrolled patients according to body mass index (BMI) class. Bars represent the effect estimate probability with 95% confidence intervals. Panel A shows the results for the total study population. Panel B shows the results of the analysis excluding underweight patients, underweight or chronic disease patients, and patients with NYHA class III/IV. Panel C shows the results of the analysis according to the EF category (*P* value for interaction <0.001). Panel D shows the results of the analysis according to the presence of chronic kidney disease (*P* value for interaction <0.001). Panel E shows the results of the analysis according to the presence of chronic lung disease (*P* value for interaction =0.008). Panel F shows the results of the analysis according to the presence of metabolic syndrome (*P* value for interaction <0.001). Panel G shows the results of the analysis according to the presence of CABG operation performed (*P* value for interaction <0.001). Panel H shows the results of the analysis by age group (*P* value for interaction <0.001). Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; EF, ejection fraction; NYHA, New York Heart Association.

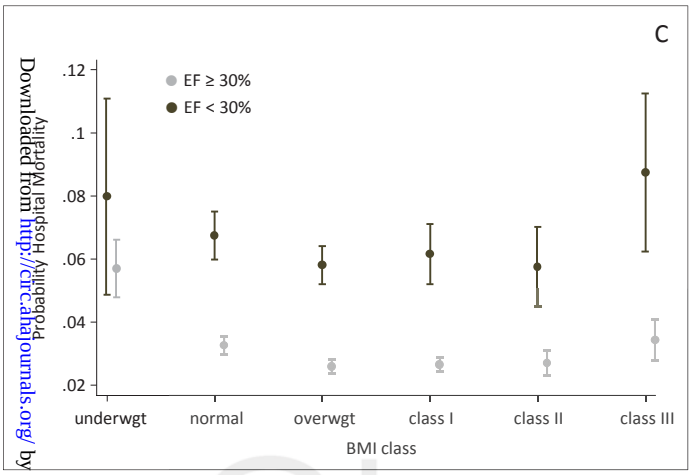
Figure 2. Probability of secondary outcomes among enrolled patients according to body mass index (BMI) class. Bars represent the effect estimate probability with 95% confidence intervals. The likelihood ratio test for linearity of risk is show. As the null hypothesis assumes linearity, a significant *P* value (<0.05) rejects the linearity of risk hypothesis. Abbreviations: DSWI, deep sternal wound infection; IABP, intra-aortic balloon pump; RRT, renal replacement therapy.

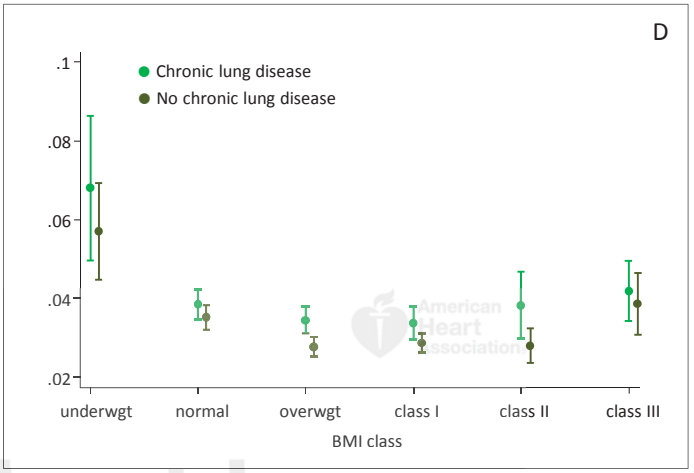
Figure 3. Forest plot with relative risks for in-hospital/30-day mortality relative to normal weight patients compared with overweight (upper panel) and underweight individuals (lower panel). For each patient sub-group, "*" denotes a statistically significant difference between the considered weight categories. Abbreviations: AHA, American Heart Association (definition of body mass index class); All, all type of cardiac operations; CABG, coronary artery bypass grafting; iCABG, isolated CABG; NOS, New Ottawa Scale; RE, random effect; VAD, ventricular assist device; WHO, World Health Organization (definition of body mass index class).

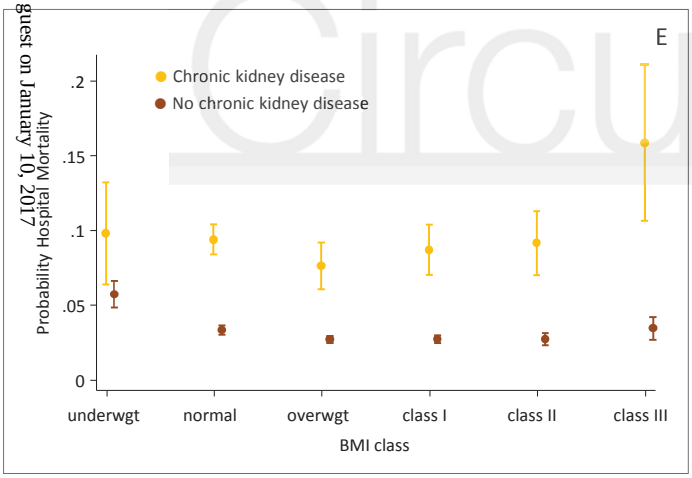
Figure 4. Forest plot with relative risks for in-hospital/30-day mortality relative to normal weight patients compared with obese class I, II and III patients, respectively. For each patient sub-group, "*" denotes a statistically significant difference between the considered weight categories. Abbreviations: AHA, American Heart Association (definition of body mass index class); All, all type of cardiac operations; CABG, coronary artery bypass grafting; iCABG, isolated CABG; NOS, New Ottawa Scale; RE, random effect; VAD, ventricular assist device; WHO, World Health Organization (definition of body mass index class)

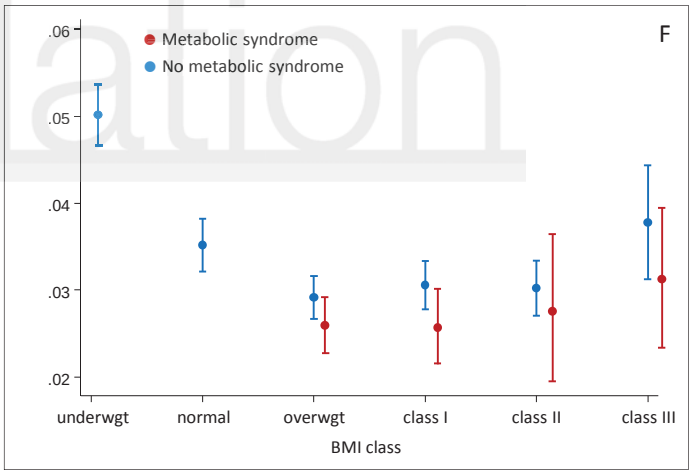


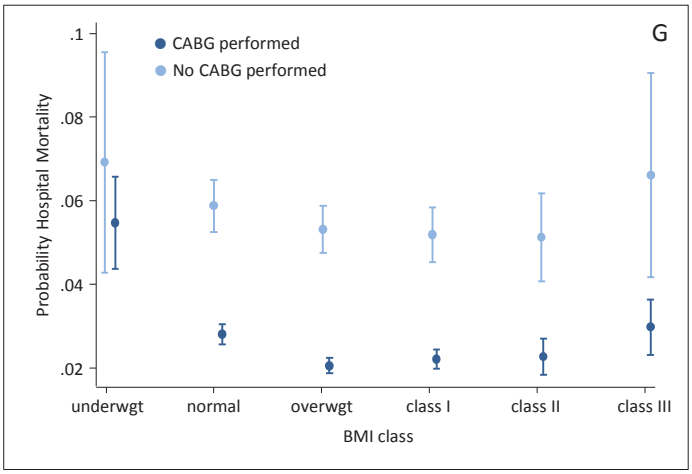


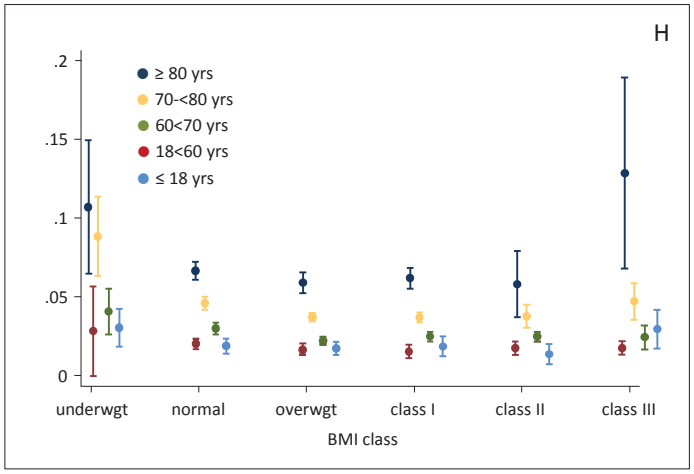


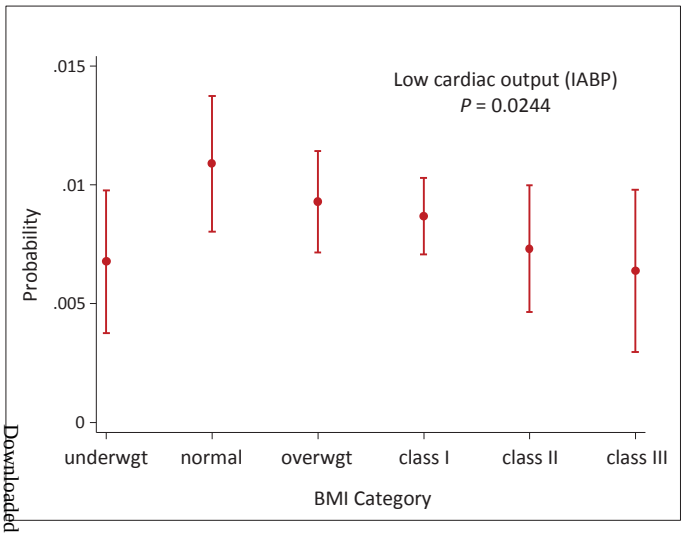


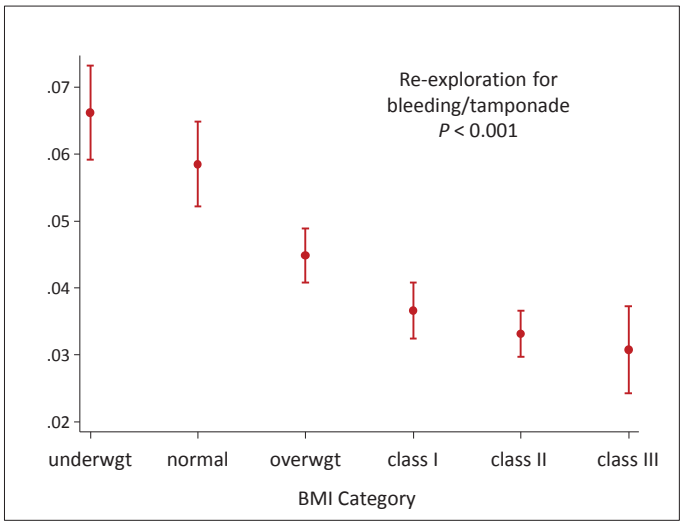


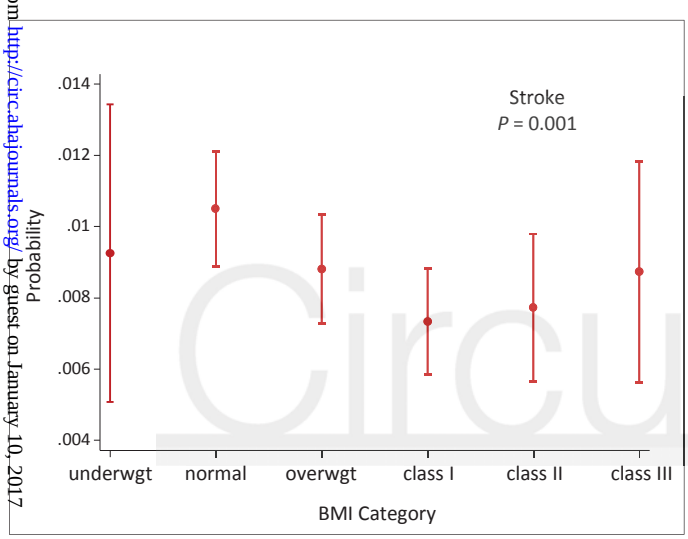


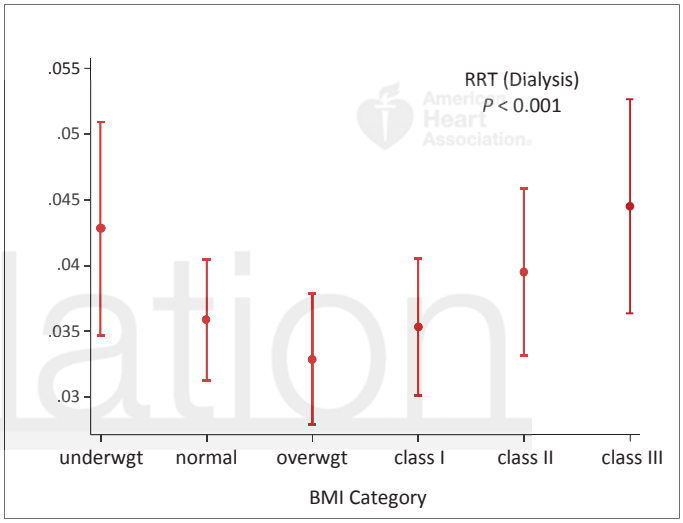


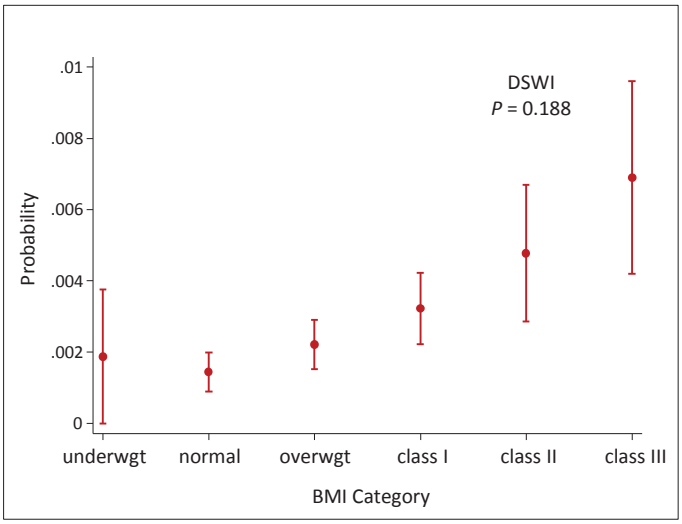


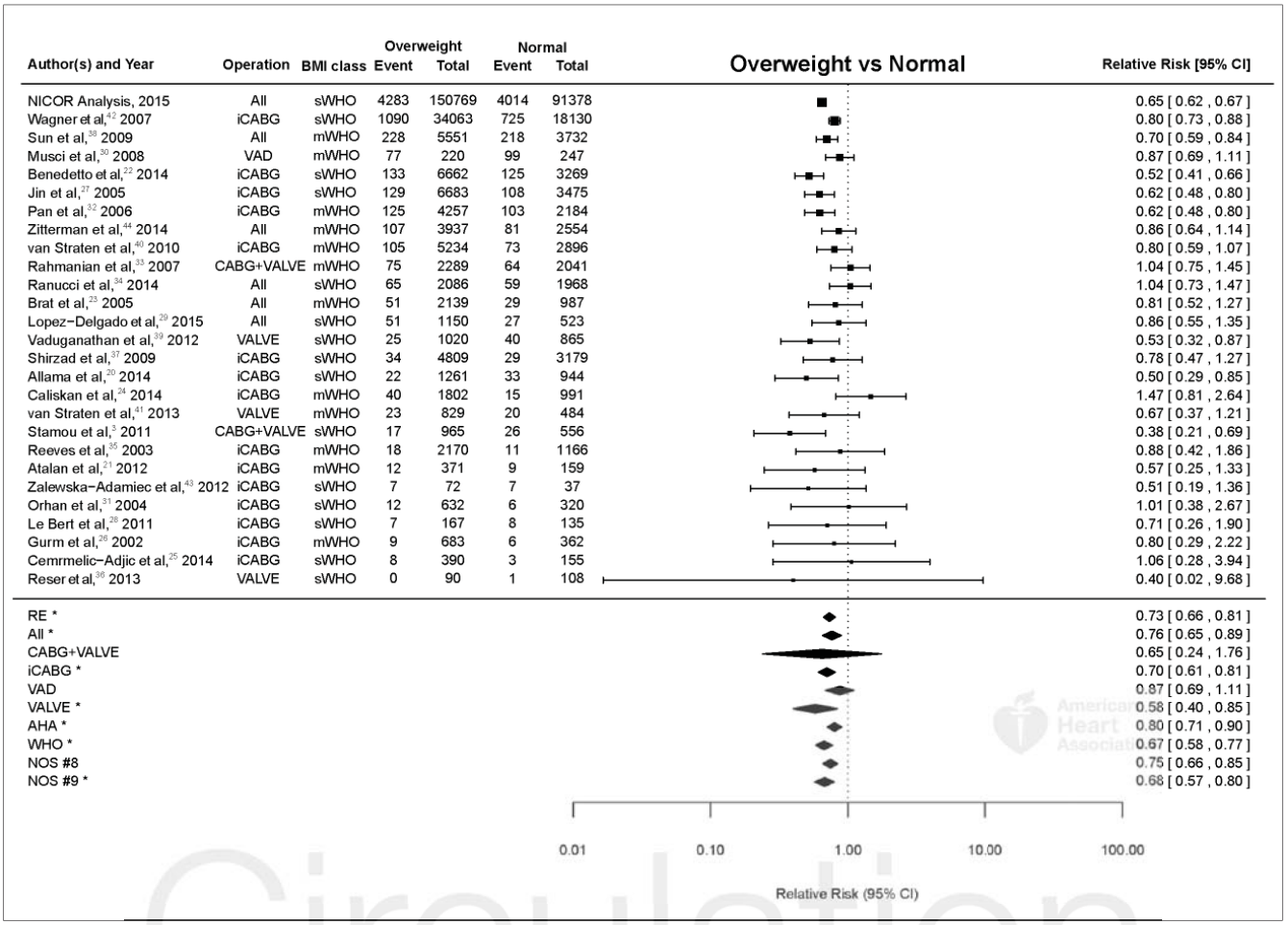


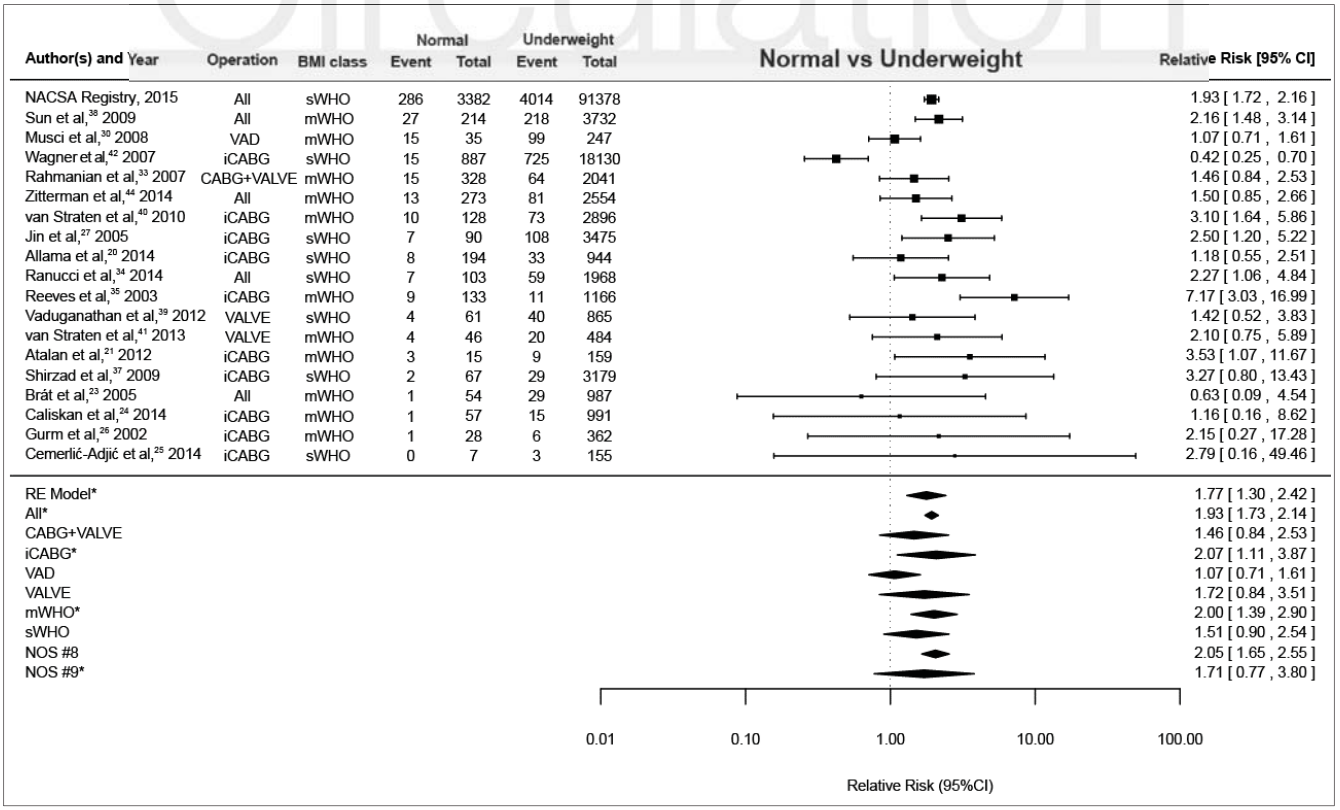


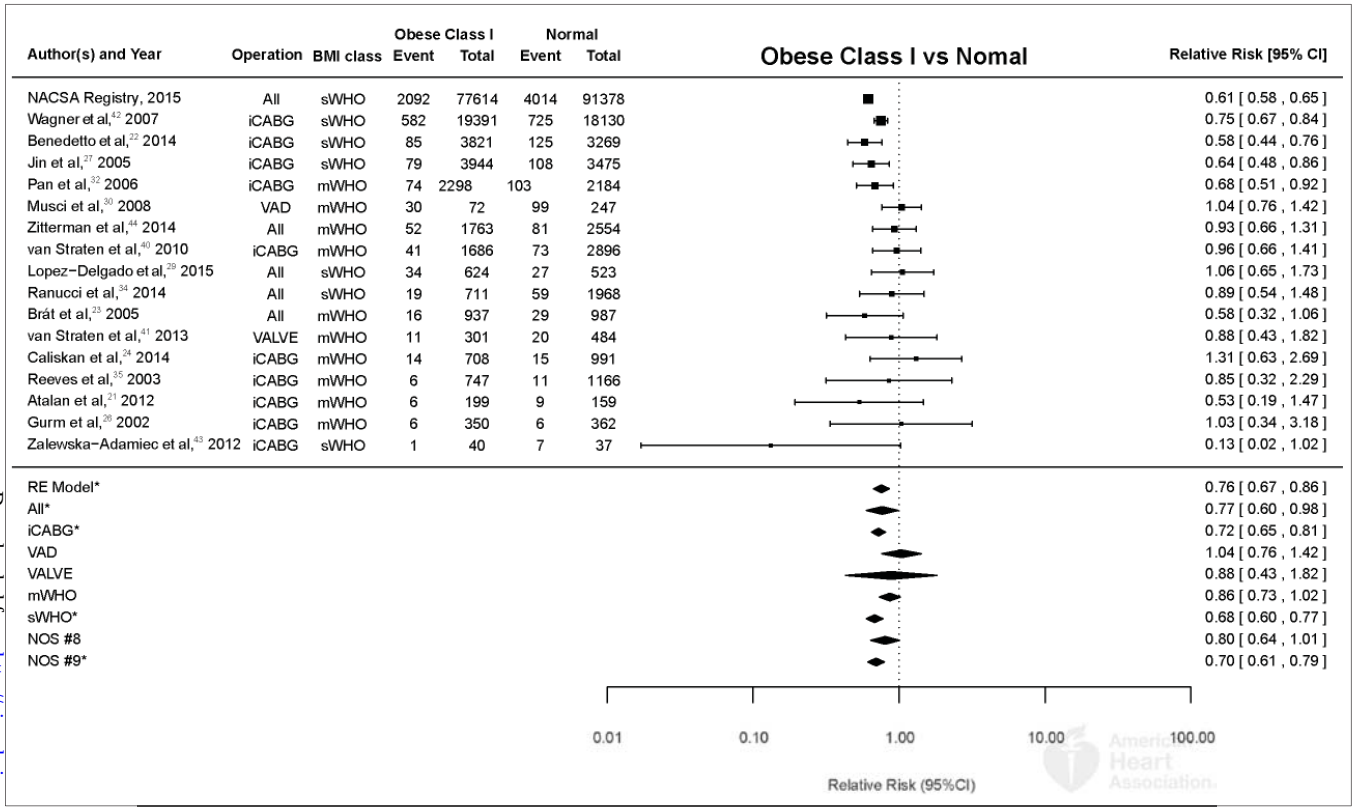


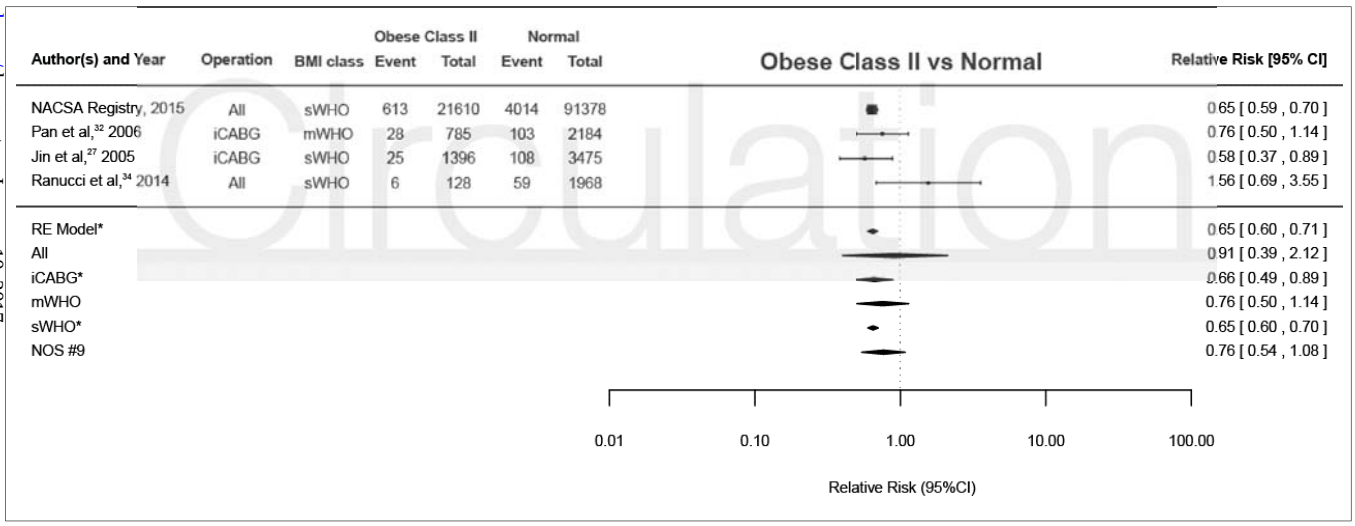


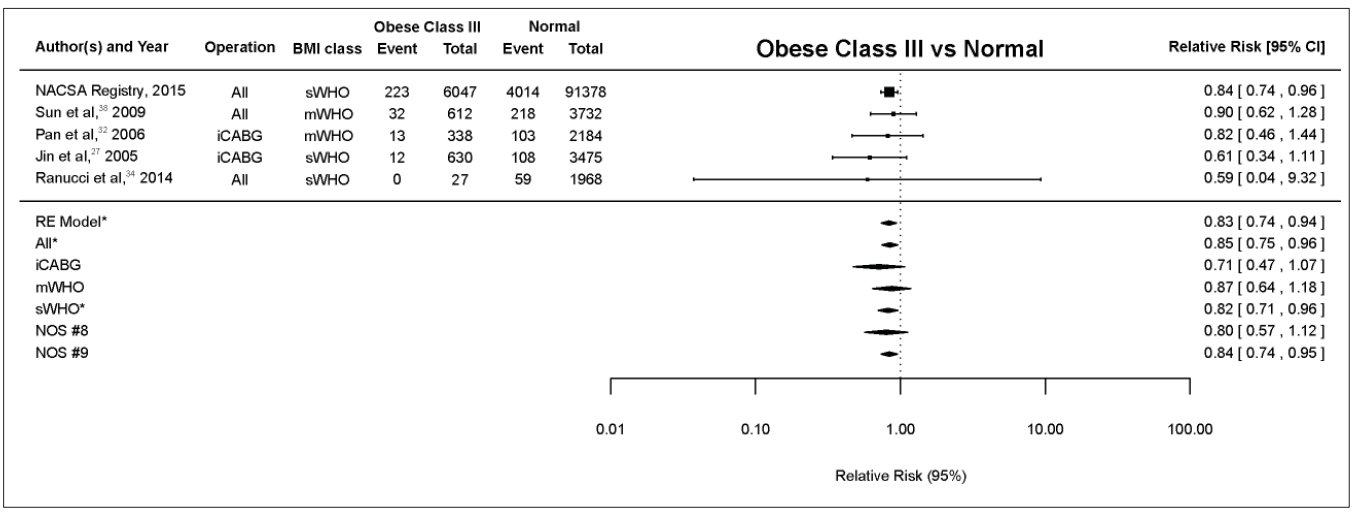












Body-Mass Index and Mortality Among Adults Undergoing Cardiac Surgery:A Nationwide Study with a Systematic Review and Meta-Analysis

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SUPPLEMENTAL MATERIAL

Mariscalco G, Wozniak M, Dawson AG, Serraino GF, Porter R, Nath M, Klersy C, Kumar T, Murphy GJ. Body-Mass Index and mortality among adult patients undergoing cardiac surgery a nationwide study with a systematic review and meta-analysis.

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplemental Methods

Statistical Analysis

NACSA Cohort Study

Clinical data were recorded and tabulated with Microsoft Excel (Microsoft Corporation, Redmond, WA). Baseline characteristics, operative factors, and univariate outcomes were described as median (25^{th}-75^{th} percentiles), and counts and percent, respectively. They were compared among body mass index (BMI) groups with the Wilcoxon rank-sum test and the chi-square test, respectively. Differences between complete case and missing data were assessed by the Mann Whitney *U* test for continuous variables and the chi-square test for categorical variables. To adjust the effect of BMI (6 categories according the World Health Organization [WHO] classification)[1] for potential confounders, multivariable logistic regression models of the primary and secondary outcomes were fitted. The full list of variables considered in the multivariable models are listed in Supplemental Tables 3 and 4. Collinearity between candidate predictors was evaluated by computing the correlation. If R>0.40, variables were considered collinear and the more clinical meaningful variable was chosen. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated. Huber-White robust standard errors were computed while clustering on regions. Discrimination was assessed through the model area under the receiver operating characteristic curve (AUC-ROC). We tested the robustness of our primary analysis by an additional analysis that used fractional polynomials where BMI was fitted as a continuous variable, as well as propensity scoring, with propensity of being overweight/obese *versus* normal weight. Underweight patients were not considered in our analysis. The propensity for being overweight/obese was computed through a logistic model, using all the confounders listed at the bottom of Supplemental Table 3 (included in the multivariable analysis). The *pscore* command in Stata was used with the common support option. The risk difference was computed with the *attnd* command in Stata, which uses nearest neighbour matching. We also repeated the propensity analysis by measuring the propensity of being classified in either of the 6 categories of BMI, using the multivalued *teffects* command implemented in Stata and a multinomial logit model, with the AIPW (Augmented inverse-probability weighting) option to account for confounding when assessing the risk of hospital death. Further sensitivity analyses evaluated the effects of inclusion or exclusion of suggested confounders identified in previous analyses, specifically low BMI (<18.5 kg/m^2) an index of cachexia, poor exercise tolerance (New York Heart Association [NYHA] class III/IV) or severe chronic lung or renal disease. Subgroup analyses assessed the interaction between pre-specified known risk factors for adverse outcomes in cardiac surgery on the associations between BMI and mortality. The following baseline and operative variables were considered: decades of age, left ventricular ejection fraction (EF), diabetes, lung disease, gender, renal impairment, coronary artery bypass grafting (CABG) performed, angina class (according to the Canadian Cardiovascular Society classification), coronary artery disease, metabolic syndrome, extracardiac arteriopathy, and NYHA classification. Effect estimates were presented as OR (95% CIs). Leave-one-center-out cross-validation and rolling epoch analyses were performed to check for the influence of misclassification. A two-sided *P* value <0.05 was considered statistically significant. Stata version 13.1 (Stata Corp, College Station, TX, USA) was used for computation.

Systematic Review and Meta-analysis

The meta-analysis of the identified studies[2-27] was performed using R version 3.2.2 (R Core Team, 2015) and metafor package version 1.9-8.[28,29] Since our assumptions about included studies were not functionally identical (different operation types and different definition of the underweight group in

term of BMI range) it was unlikely that the studies shared a common effect size, therefore, random/mixed-effects models were more appropriate and were fitted with *REML* heterogeneity estimator using *rma function* (metafor) to summarize the overall and within subgroups results.[30,31] Between studies heterogeneity was assessed with Cochran's Q-test in random models without moderators.[32] For mixed models with moderators QE test for residual heterogeneity was used (included in the standard output of the *rma* metafor function). Heterogeneity is reported as Q with *P* value (Q-test), τ^2 (estimated mount of residual heterogeneity), I^2 (percentage of total variability due to heterogeneity between true effects) and H^2 (percentage of total variability and sampling variability).[33,34] To compensate for uncertainty in the estimate of heterogeneity, Knapp-Hartung adjustment was included in the models.[35] Since there was no difference in heterogeneity estimation with and without the adjustment, only data without it is reported. Whenever the heterogeneity Q-test was statistically significant ($P<0.05$), meta-regression was done with year of publication and clinical demographics (operation type; normal BMI classification; comparison's average: age and left ventricular EF; comparison's fraction of males and current smokers; comparison's fraction of patients with NYHA class III and IV, prior myocardial infraction (MI), hypertension, diabetes, dyslipidaemia, chronic obstructive pulmonary disease (COPD), cerebrovascular accident, peripheral vascular disease (PVD) and chronic kidney disease) used as moderators. The results are presented in plots (R, graphics package) of relative risks (RR) as a function of the moderator with fitted mixed model estimates and 95%CI.[29,36,37] To assess whether operation type, definition of the underweight BMI range, Newcastle-Ottawa Scale (NOS)[38] and study size could have acted as potential confounders, the interaction term was included in the mixed model, which were then re-fitted after the confounders were removed.

The influence of individual studies on the fitted random-effects model was tested with *influence* and *leave1out* functions (metafor), as described in the metafor package manual.[29,39]

Any publication bias was visualised in funnel plots and analysed with *regtest function* (metafor), which is based on Egger's regression test.[40]

Finally, cumulative analysis of the selected studies was done with *cumul function* (metafor) with publication years, cohort size and NOS as ordering vectors.

Supplemental Results

NACSA Cohort Study: Sensitivity Analyses

A series of sensitivity analyses of the primary endpoint were performed to address the issues of missingness, misclassification and inconsistent data definitions, selection bias and reverse epidemiology.

Data Quality and Missingness

About 13% of patients had incomplete data for any of the key variables (Supplemental Figure 6). Missingness was highest for creatinine and lowest for the type of operation. In most cases only one of these variables had missing data (10% of patients), few had 2 variables, and almost none had 3 or more variables with missing data. Missingness varied among regions (from 0.8% to 31%), but remained fairly constant over years (Supplemental Figure 7). When comparing the cohort with incomplete data in the key variables to the complete case cohort (Supplemental Table 2), minor differences were present both in the exposure variables and in the primary and secondary outcome variables, with no clear differential inclusion of patient more compromised or less compromised in the complete case cohort which was analyzed. Given the absence of any clear selection process in the generation of missingness,

and also the consistency of the several sensitivity analyses of the primary endpoint (see below), we considered the missing at random mechanism to be applicable.

Misclassification and Inconsistent Data Definition

Retrospective analyses of routinely collected data have limitations with respect to data quality, specifically misclassification and inconsistent data definitions between individuals and sites. Leave-one-centre-out cross-validation was used to assess whether inconsistent data definitions between regions will have influenced our results. For that purpose, we first assessed discrimination (AUC-ROC) of the original model, which was 0.818, then we computed the cross validated AUC-ROC, that with a value 0.816 was consistent with no influence of region on the results.

In addition, we assessed the likelihood that definitions and classifications will have altered over time by assessing goodness of fit in 6 year rolling epochs starting from 2002-2007 and finishing in 2008-2013. This will also address the high likelihood that clinical outcomes have changed over time regardless of the BMI. Mortality was slightly higher in 2002-2007 than in 2008-2013 (3.5%; 95%CI, 3.4-3.6 *versus* 3.1%; 95%CI, 3.0-3.1; $P<0.001$). However, discrimination of the multivariable logistic model was comparable and was respectively 0.824 and 0.82, and so was the magnitude of the association of BMI with in-hospital mortality (Supplemental Table 17). These observations were consistent with no indication of epoch on the results.

Selection Bias and Unmeasured Confounders

If "fat fit" patients, or patients with high BMI attributable to a high muscle mass have been preferentially selected for surgery this will introduce bias attributable to these unmeasured confounders. To address the effects of these and other unmeasured confounders, as well as imbalances in the distribution of prognostic factors among BMI groups, we compared the outcomes obtained in propensity matched normal weight and overweight/obese patients. The propensity score was computed via a logistic regression including the demographic, presentation, cardiac status and comorbidity variables listed in Table 1. The *pscore* command in Stata was used with the common support option (comprised between 0.308 and 0.960); 56,285 and 160,554 patients were included in the normal and overweight groups respectively. The risk difference was computed with the *attnd* command in Stata, which uses nearest neighbour matching. After propensity score matching, the normal weight group reduced to 44,325 patients. The resulting average treatment effect on the treated (ATT) was 0.007 (standard error 0.001) (Supplemental Table 5). The same difference was obtained when fitting a general linear model for binomial variables and identity link with being overweight as the independent variable and either using the propensity score either as an inverse probability weight in the model, or using it as a covariate (continuous and categorized into deciles). A similar confirmation was obtained for the secondary endpoints (data not shown). Finally a propensity score analysis for multivalued treatment effect (in this case BMI classes) was also performed for confirmation of results.

Reverse Epidemiology

To address the likely bias attributable to patients with cachexia or late stage chronic diseases affecting the heart, lungs and kidneys we assessed the goodness of fit of the models after exclusion of patients with very low BMI (<18.5 kg/m^2), patients with metabolic syndrome, patients with chronic disease (patients with NYHA Class IV dyspnoea, serum creatinine >200 µmol/l, pulmonary disease or history of neurological dysfunction). As shown in Figure 1, the same behaviour is present as in the complete case analysis, with the lowest mortality observed for overweight patients ($P<0.001$ with respect to normal weight in all cases).

Systematic Review and Meta-analysis

No randomized controlled trials evaluating the effect of obesity on hospital mortality were retrieved. All of the included studies were observational cohort studies (prospective n=2; retrospective n=24) published between 2002 and 2014. Study characteristics and collected outcomes for each BMI group are summarized in Supplemental Table 7. With reference to the definition of the underweight group in relation to BMI range, 12 studies followed the standard WHO classification (underweight definition level: <18.5 kg/m^2), and 14 the modified WHO classification proposed by Gurm and colleagues (underweight definition level: <20 kg/m^2).[1,2] In addition, 2 studies defined the underweight class <18 kg/m^2, and one <19 kg/m^2.[3-5] Study characteristics and collected outcomes for each BMI group are reported in Supplemental Tables 8-10. Quality assessment process according to NOS identified 9 (35%) studies being of high quality (NOS = 9), 12 (46%) of good quality (NOS = 8), and 5 (19%) of sub-optimal quality (NOS ≤ 7) (Supplemental Table 12).

Group Comparison and Sub-group Analysis

Due to the different BMI definitions for the underweight patient group, we defined the included studies as standard (underweight definition level: < 18.5 kg/m^2) or modified WHO classification (underweight definition level: < 20 kg/m^2).[1,2] Other encountered definitions of the underweight group were solved by including those with a BMI < 18.5 kg/m^2 or BMI ≥ 18.5 and < 20 kg/m^2 into the standard or the modified WHO groups, respectively.[3-5] In addition, the studies were grouped according to NOS and type of operation received. Isolated coronary artery bypass graft (iCABG), isolated heart valve surgery (VALVE), CABG procedures with concomitant heart valve surgery (CABG+VALVE), ventricular assist device (VAD) implantation, and all cardiac operations (All) were considered. Summary of comparison data sets is shown in Supplemental Table 11.

Comparisons with obese groups resulted in significant effect size estimates and ranged from 0.65 to 0.83 in favour of obese patients as shown in Supplemental Table 13 and Figure 4. However, estimates of comparisons with obese class II and III should be taken with caution since the number of studies was limited to 4 and 5, respectively. Moreover, two studies and one study were identified as significantly influencing the fitted models in comparisons with obese class II and III, respectively (Supplemental Table 14). Removing these studies increased the model's estimate to 0.79 (NACSA registry in comparison with obese class II) and 0.76 (study by Jin et al.[6] with obese class II); or 0.81 NACSA registry in comparison with obese class III) rendering the estimates insignificant (Supplemental Table 14). Taken together, the estimates for comparisons with obese class II and III may not have been accurate. Subgroup analysis resulted in significant estimates for iCABG in overweight, class I and class II obese patients, while standard WHO subgroups in all comparisons. Significant estimates were noted for all type of operation (All) subgroup in comparison with overweight and obese class I and III patients, and for modified WHO subgroup in comparison with overweight patients only (Supplemental Table 13). In any case, RRs favoured obese patients over the normal weight patients (Figure 4). Cumulative analysis with increasing NOS generally indicated that lower quality studies (NOS ≤ 7) resulted in insignificant estimates, and only the addition of studies with a higher NOS (≥ 8) reduced estimate's *P* value below .05 (Supplemental Figures 8A and 8B). In addition, separate random-effects models were fitted for studies with NOS ≥ 8, and with the exception of obese class II patients, studies with a NOS = 9 resulted in a significant estimates (Supplemental Table 13 and Figures 3 and 4). Funnel plots and *regtest* analysis revealed no publication bias in any of the mortality comparisons with patients of normal weight (Supplemental Figure 4). In addition, cumulative analysis by year of publication indicated that the significant effect size estimates in favour of obese groups appears with the publication of Jin et al.[6] in 2005, with the exception of comparisons with obese class II and III patients where the results were variable (Supplemental Figure 9A). Cumulative analysis by cohort size resulted

in significant estimates in favour of overweight patients after combining of 9 out of 27 studies (cohort size: from 109 to 1313), while in the comparison with obese class I, 14 out of 17 studies (cohort size: from 77 to 7090) were required (Supplemental Figures 10A and 10B).

Finally, comparison with underweight group resulted in a significant estimate (RR, 1.77; 95% CI, 1.30-2.42) in favour of normal weight patients (Supplemental Table 13 and Figure 3). One study (Wagner et al.[9]) was found to significantly influence the model, and removing it from the analysis resulted in an increased estimate (RR, 2.00; 95%CI, 1.39-2.89). Comparisons within All and iCABG operation subgroups, in a similar way to obese groups, resulted in significant estimates (RR_{All} = 1.93, P<0.001, and RR_{iCABG} = 2.07, P=0.022, respectively). Interestingly, analysis within underweight definition subgroups, resulted in a significant and smaller effect size estimate only for studies with using a BMI definition for underweight group <20 kg/m^2 (mWHO; RR_{mWHO} = 2.00, P<0.001; Supplemental Table 13). This is in contrast to comparisons with obese groups where standard WHO classification estimates were significant and smaller, potentially indicating that patients of BMI between 18.5 and 20 substantially contribute in comparisons with normal BMI patients, although no differences in comorbidity profile was observed between standard and modified WHO definition groups (Supplemental Table 18). Cumulative analysis by NOS showed again that addition of higher quality studies resulted in significant model's estimate (Supplemental Figure 8B). Funnel plots and *regtest* analysis revealed no publication bias and cumulative analysis by year of publication indicated that the consistently significant effect size estimates in favour of the normal group would be reported since the publication of van Straten and colleagues[10] in 2010 (Supplemental Figures 4 and 9B). Estimates of cumulative analysis by cohort size became significant (in favour of normal weight patients) after combining two smallest studies (Cemerlić-Adjić et al.[11], size: n=162; and Atalan et al.[12], size: n=174), and later after combining 10 studies (size: n=162 to 1299) (Supplemental Figure 10B).

Heterogeneity analysis

Out of all comparisons only three indicated a significant level of heterogeneity in the random-effects models: normal weight *versus* overweight patients (I^2=62.27, Q=59.987, P<0.001), normal weight *versus* obese class I patients (I^2=62.06, Q=42.249, P<0.001), and underweight *versus* normal weight patients (I^2=77.73, Q=59.29, P<0.001). To explain the variability we used publication year, NOS and clinical demographics as moderators in mixed effects models (see above eMethods section). Since covariate data was missing for some studies, random-effect models were fitted without them ('*moderator-no Mods*' rows in Supplemental Table 15) and compared with the full models ('*All Studies in, no Mods*' rows in Supplemental Table 15). In most cases, models' overall effects were comparable. However, when a substantial amount of studies had missing data, the estimates occasionally deviated from those predicted by the full models ('*intercept.est*' column). Data for continuous covariate models is summarised in Supplemental Table 15 and for factorial covariates (operation type and underweight BMI range definition) in Supplemental Table 16. In comparisons with overweight and obese class I groups, several covariates reduced heterogeneity. However, only average age and underweight BMI definition had a significant effect on the fitted model, and solely in the comparison with obese class I (Age: R^2=82.35%, Intercept=1.99, P=0.016, Age= -0.037, P=0.005; underweight BMI definition: R^2=53.87%, Intercept=-0.387, P<0.001, modified WHO=0.241, P=0.026). In Supplemental Figure 5 the average age is plotted against studies' RR. Out of four potential confounders, underweight BMI definition range and study size significantly interacted with average patient age (P=0.019 and P=0.009, respectively). Interaction with study size was driven by inclusion of NACSA registry due to the large amount of enrolled patients. Therefore, mixed models were fitted for standard and modified WHO subgroups without NACSA registry study. As shown in Supplemental Table 16, age did not have any significant influence on the model's estimate when fitted in underweight different BMI definitions.

However, the results particularly in the standard WHO subgroup should be interpreted with caution due to low number of studies.

Comparison of underweight and normal patients identified 6 covariates partially explaining heterogeneity (Supplemental Table 15). However, only fraction of patients with prior MI (R^2=61.55%) and COPD (R^2=43.86%) had a significant influence on the models. Plotting these covariates against the RRs of the included studies indicated that the higher the fraction with previous MI the lower the mortality (Intercept=0.322, MI=-3.083, Supplemental Figure 5 mid panel), while fraction of patients with chronic pulmonary disease had an opposite effect (Intercept=-1.418, COPD=6.388, Supplemental Figure 5 low panel). Fraction with prior MI and COPD were further tested for interactions with potential confounders, and the latter was found to interact significantly with study size (P=0.025). This was driven by two largest studies that included more than 19,000 patients (Wagner et al.[9] and the NACSA registry). In a model fitted without these studies fraction of patients with COPD did not have any significant influence on the model estimate.

Supplemental Tables

Table 1. PICOS Criteria for Inclusion and Exclusion of Studies into Qualitative/Quantitative Meta-analysis

Parameter	Inclusion criteria	Exclusion criteria
Patients	Adult patients undergoing cardiac surgery	Patients affected by CAD undergoing PCI, ACS, heart failure
Intervention	Groups of BMI according WHO classification	Study without BMI groups defined by WHO classification
Comparator	Normal BMI group	-
Outcomes	Primary: in-hospital/30-day mortality (all cause) Secondary: Low cardiac output (IABP insertion); perioperative MI; stroke; renal replacement therapy; length of hospitalization	Late mortality
Study design	Clinical randomised trials Controlled before-and-after studies Prospective and retrospective cohort studies Cross-sectional studies Case-control studies	Repeat publications of the same analysis or dataset Conference abstracts Editorials & opinion pieces Books or grey literature

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; IABP, intra-aortic balloon pump; MI, myocardial infarction; PCI, percutaneous coronary intervention; PICOS, patients, intervention, comparator, outcomes, study design; WHO, World Health Organization.

Table 2. Distribution of Key Variables by Complete Dataset (No Missing in Any Key Variable)

Exposure	**Incomplete N (%)***	**Complete (analyzed) N (%)***
Female	13,899 (27.7)	94,997 (27.1)
Age, median (25^{th}-75^{th} percentiles)	67 (59-74)	67 (59-74)
BMI, median (25^{th}-75^{th} percentiles)	27.5 (24.7-30.8)	27.5 (24.8-30.7)
Previous MI	13,855 (31.3)	121,859 (34.7)
Diabetes	7,659 (17.4)	71,217 (20.3)
Poor (LVEF <30%)	2,995 (7.7)	21,866 (6.2)
Creat > 200 mmol/l	885 (3.2)	8,905 (2.5)
CPB use	43,157 (86.6)	308,757 (87.6)
CABG	33,078 (65.6)	244,954 (69.8)
Outcome		
In-Hospital death	2,245 (4.7)	11.511 (3.3)
Postoperative IABP	357 (0.8)	3,155 (1.01)
Re-exploration for bleeding/tamponade	1,712 (5.0)	14,509 (4.6)
Stroke	265 (0.9)	3,120 (1.0)
Dialysis	892 (3.0)	10,814 (3.6)
DSWI	108 (0.3)	681 (0.2)

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; Creat, creatinine; DSWI, deep sternal wound infection; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

*Unless otherwise specified.

Table 3. Distribution of Clinical Outcomes among Increasing BMI Groups and their Adjusted ORs and 95%CI (Multivariable Analysis)

Outcome*	**Underweight**	**Normal†**	**Overweight**	**Obese class I**	**Obese class II**	**Obese class III**	***P* value‡**
BMI class (Kg/m^2)	**<18.5**	**18.5-<25**	**25-<30**	**30-<35**	**35-<40**	**≥40**	
N.Pts	**3382**	**91378**	**150769**	**77614**	**21610**	**6047**	
In-hospital mortality	286 (8.5)	4014 (4.4)	4283 (2.8)	2092 (2.7)	613 (2.8)	223 (3.7)	<0.0001
Low cardiac output (postoperative IABP)	29 (1.0)	1040 (1.3)	1320 (1.0)	588 (0.9)	138 (0.7)	40 (0.7)	<0.0001
Re-exploration bleeding/tamponade	232 (7.7)	5096 (6.3)	6019 (4.5)	2398 (3.4)	597 (3.0)	167 (3.0)	<0.0001
Stroke	49 (1.7)	1030 (1.3)	1300 (1.0)	534 (0.8)	167 (0.9)	40 (0.8)	<0.0001
RRT	183 (6.4)	3159 (4.1)	4173 (3.2)	2264 (3.3)	786 (4.1)	249 (4.7)	<0.0001
DSWI	7 (0.3)	99 (0.1)	250 (0.2)	202 (0.3)	89 (0.5)	34 (0.6)	<0.0001
Estimate	**OR (95%CI)**	**OR**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	***P* value‡**
In-hospital mortality[§]	1.51 (1.41-1.62)	1	0.79 (0.76-0.83)	0.81 (0.76-0.86)	0.83 (0.74-0.94)	0.99 (0.80-1.22)	<0.0001
Low cardiac output (postoperative IABP)	0.58 (0.44-0.77)	1	0.86 (0.80-0.92)	0.77 (0.67-0.89)	0.71 (0.57-0.87)	0.52 (0.32-0.86)	<0.0001
Re-exploration bleeding/tamponade	1.13 (1.00-1.27)	1	0.75 (0.71-0.79)	0.61 (0.57-0.64)	0.55 (0.49-0.61)	0.53 (0.46-0.62)	<0.0001
Stroke	0.93 (0.50-1.72)	1	0.84 (0.73-0.97)	0.69 (0.55-0.88)	0.74 (0.61-0.91)	0.81 (0.54-1.21)	<0.0001
RRT	1.26 (1.06-1.50)	1	0.88 (0.85-0.92)	0.99 (0.91-1.08)	1.12 (0.97-1.29)	1.25 (1.10-1.42)	<0.0001
DSWI	1.13 (0.37-3.42)	1	1.35 (0.98-1.87)	2.11 (1.39-3.20)	3.65 (2.46-5.43)	4.70 (2.46-8.98)	<0.0001

Model discrimination (AUC ROC): in-hospital death, 0.82; postoperative IABP, 0.75; re-exploration for bleeding/tamponade 0.65; stroke, 0.74; RRT, 0.78; DSWI, 0.73.
Variables entered in the multivariable models: age, BMI class, IMD (index of Multiple Deprivation) score, gender (male/female), status (elective *vs* urgent *vs* emergent), reoperation, NYHA class, CCS class, CAD presence, left main stem disease, previous acute myocardial infarction, previous percutaneous coronary intervention, ejection fraction category (>50% *vs* 30-50% *vs* <30%), history of atrial fibrillation, preoperative iv nitrates, smoking status (never *vs* former *vs* current), hypertension, diabetes, chronic lung disease, extracardiac arteriopathy, history of cerebrovascular accident, creatinine > 200 µmol/l, cardiopulmonary bypass use, operation type (isolated CABG, isolated valve, valve+CABG, thoracic aorta, other).
Abbreviations: AUC, Model area under the ROC curve; BMI, body mass index; CI, confidence interval; DSWI, deep sternal wound infection; IABP, intra-aortic balloon pump; OR, odds ratio; ROC, receiver operating curve; RRT, renal replacement therapy.
*Outcomes are presented as number (percent). †Reference category. ‡*P* values from logistic model with clustered robust standard errors to account for region. [§]Primary endpoint.

Table 4. Predictors of Hospital Mortality at Multivariable Analysis (Logistic Regression)

Variable	OR	95% CI	*P* value
Demographics			
Age*	1.04	1.04-1.05	0.000
Gender (Female)	1.47	1.36-1.58	0.000
BMI groups (Kg/m^2)			
Underweight (<18.5)	1.51	1.41-1.62	0.000
Normal (18.5-<25)	1.00 (Ref)		
Overweight (25-<30)	0.79	0.76-0.83	0.000
Obese Class I (30-<35)	0.81	0.76-0.86	0.000
Obese Class II (35-<40	0.83	0.74-0.94	0.002
Obese Class III (≥40)	0.99	0.80-1.22	0.895
Presentation			
Urgent/Emergent	1.62	1.40-1.88	0.000
Reoperation	2.73	2.41-3.08	0.000
Nitrates IV	1.56	1.33-1.82	0.000
NYHA class			
Class I	1.00 (Ref)		
Class II	1.00	0.94-1.06	0.936
Class III	1.39	1.32-1.47	0.000
Class IV	2.10	1.89-2.34	0.000
CCS class III/IV	1.15	1.09-1.22	0.000
Cardiac status			
CAD	1.45	1.30-1.61	0.000
LMS	1.17	1.08-1.28	0.000
Previous MI	1.14	1.04-1.24	0.005
Previous PCI	1.20	1.08-1.32	0.000
History of AF	1.17	1.05-1.31	0.006
LVEF (%)	1.60	1.51-1.69	0.000
Comorbidities			
Hypertension	1.01	0.95-1.08	0.753
Diabetes	1.19	1.12-1.27	0.000
Lung disease	1.18	1.11-1.27	0.000
Extracardiac arteriopathy	1.43	1.36-1.51	0.000
History of CVA	1.10	1.02-1.19	0.014
Creat > 200 mmol/l	3.45	2.91-4.09	0.000
Smoking status			
Never smoked	1.00 (Ref)		
Formerly smoked	0.96	0.87-1.05	0.365
Currently smoking	1.12	0.96-1.31	0.148

Table 4 (Continued)			
Variable	**OR**	**95% CI**	***P* value**
IMD score†			
IMD group I	1.00 (Ref)		
IMD group II	0.98	0.89-1.08	0.735
IMD group III	1.04	0.95-1.13	0.431
Operative data			
CPB use	1.41	1.16-1.71	0.000
Type of operation			
Isolated CABG	1.00 (Ref)		
Isolated Valve(s)	2.20	2.03-2.38	0.000
CABG+valve	2.48	2.25-2.72	0.000
Major aortic surgery	7.75	7.32-8.21	0.000
Other procedures	3.94	3.52-4.40	0.000

AF indicates atrial fibrillation; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CI, confidence interval, CPB, cardiopulmonary bypass; Creat, creatinine; CVA, cerebrovascular accident; IMD, Index of Multiple Deprivation (score); IV, intravenous; NYHA, New York Heart Association; LMS, left main stem; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention.

*Considered as continuous (numeric) variables.

†The IMD score is a calculated deprivation score for geographical area inhabited by at least 1000 people, and is used for investigating social deprivation and cardiovascular disease outcomes. The IMD score is based on: 1) income deprivation; 2) employment deprivation; 3) health deprivation and disability; 4) education, skills and training deprivation; 5) barriers to housing and services; 6) crime and disorder; 7) living environment.

Table 5. Comparison of Hospital Mortality for Patients with different BMI Categories using Propensity Score: the Risk Difference from Normal Weight is Presented (95%CI) for the Univariable Setting and with the Use of the Propensity Score computed from a Multinomial Logit Model

Models	Underweight	Normal	Overweight	Obese Class I	Obese Class II	Obese Class III
BMI class (Kg/m^2)	**<18.5**	**18.5-<25**	**25-<30**	**30-<35**	**35-<40**	**≥40**
Univariable Binomial Model	0.041 (0.034 to 0.047)	0	-0.015 (-0.017 to -0.014)	-0.017 (-0.020 to -0.014)	-0.016 (-0.020 to -0.011)	-0.007 (-0.011 to -0.003)
***P* value**	<0.001	Reference	<0.001	<0.001	<0.001	<0.001
Multivariable PS adjusted (AIPW) Model	0.029 (0.013 to 0.045)	0	-0.007 (-0.009 to -0.005)	-0.007 (-0.009 to -0.005)	-0.005 (-0.010 to -0.001)	-0.004 (-0.012 to 0.005)
***P* value**	<0.001	Reference	<0.001	<0.001	0.010	0.393

Abbreviations: AIPW, augmented inverse-probability weighting; BMI, body mass index; PS, propensity score.

Table 6. Interactions and sub-Group Analysis for Adjusted Hospital Mortality by BMI class

BMI Class	OR	95% CI	*P* value	BMI Class	OR	95% CI	*P* value	Interaction (*P* value)
Male				**Female**				
Underweight	2.00	1.54-2.61	<0.001	Underweight	1.41	1.23-1.63	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.72	0.67-0.77	<0.001	Overweight	0.80	0.73-0.88	<0.001	0.001
Obese Class I	0.75	0.69-0.81	<0.001	Obese Class I	0.73	0.64-0.82	<0.001	
Obese Class II	0.73	0.59-0.89	0.003	Obese Class II	0.75	0.66-0.85	<0.001	
Obese Class III	1.04	0.85-1.29	0.694	Obese Class III	0.86	0.69-1.07	0.182	
CAD				**No CAD**				
Underweight	1.59	1.33-1.89	<0.001	Underweight	1.60	1.30-1.97	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.72	0.66-0.79	<0.001	Overweight	0.85	0.78-0.92	<0.001	0.002
Obese Class I	0.74	0.68-0.81	<0.001	Obese Class I	0.79	0.70-0.90	<0.001	
Obese Class II	0.76	0.65-0.87	<0.001	Obese Class II	0.75	0.62-0.90	0.003	
Obese Class III	0.97	0.77-1.22	0.776	Obese Class III	0.96	0.78-1.19	0.723	
CCS class III/IV				**CCS class I/II**				
Underweight	1.33	0.90-1.94	0.158	Underweight	1.64	1.47-1.82	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.74	0.65-0.85	<0.001	Overweight	0.76	0.70-0.82	<0.001	0.567
Obese Class I	0.75	0.66-0.85	<0.001	Obese Class I	0.75	0.69-0.82	<0.001	
Obese Class II	0.78	0.65-0.93	0.007	Obese Class II	0.73	0.60-0.88	0.001	
Obese Class III	0.98	0.78-1.23	0.869	Obese Class III	0.95	0.82-1.09	0.451	
NYHA class III/IV				**NYHA class I/II**				
Underweight	1.40	1.21-1.62	<0.001	Underweight	1.89	1.45-2.48	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.76	0.70-0.84	<0.001	Overweight	0.74	0.68-0.81	<0.001	0.007
Obese Class I	0.69	0.62-0.77	<0.001	Obese Class I	0.83	0.76-0.91	<0.001	
Obese Class II	0.73	0.63-0.86	<0.001	Obese Class II	0.76	0.62-0.92	0.006	
Obese Class III	0.99	0.82-1.18	0.888	Obese Class III	0.80	0.54-1.20	0.282	
EF < 30%				**EF ≥ 30%**				
Underweight	1.06	0.75-1.49	0.751	Underweight	1.69	1.50-1.91	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.78	0.68-0.89	<0.001	Overweight	0.75	0.70-0.79	<0.001	<0.001
Obese Class I	0.76	0.61-0.94	0.013	Obese Class I	0.74	0.69-0.79	<0.001	
Obese Class II	0.73	0.57-0.94	0.016	Obese Class II	0.74	0.64-0.86	<0.001	
Obese Class III	1.23	0.84-1.82	0.288	Obese Class III	0.91	0.78-1.06	0.216	

Table 6 (Continued)								
BMI Class	**OR**	**95% CI**	***P* value**	**BMI Class**	**OR**	**95% CI**	***P* value**	**Interaction (*P* value)**
History of AF				**No history of AF**				
Underweight	1.64	1.44-1.86	<0.001	Underweight	1.40	1.08-1.80	0.011	
Normal	Ref			Normal	Ref			
Overweight	0.73	0.67-0.80	<0.001	Overweight	0.82	0.75-0.89	<0.001	<0.001
Obese Class I	0.74	0.69-0.80	<0.001	Obese Class I	0.75	0.65-0.86	<0.001	
Obese Class II	0.77	0.67-0.88	<0.001	Obese Class II	0.60	0.47-0.76	<0.001	
Obese Class III	1.01	0.86-1.18	0.916	Obese Class III	0.62	0.41-0.95	0.027	
Chronic lung disease				**No chronic lung disease**				
Underweight	1.79	1.26-2.54	0.001	Underweight	1.50	1.26-1.78	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.83	0.35-0.95	0.021	Overweight	0.73	0.67-0.80	<0.001	<0.001
Obese Class I	0.77	0.66-0.90	0.003	Obese Class I	0.74	0.68-0.80	<0.001	
Obese Class II	0.90	0.72-1.13	0.546	Obese Class II	0.70	0.60-0.82	<0.001	
Obese Class III	0.98	0.80-1.20	0.961	Obese Class III	0.95	0.79-1.14	0.582	
Chronic kidney disease				**No chronic kidney disease**				
Underweight	0.90	0.70-1.15	0.392	Underweight	1.64	1.45-1.84	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.79	0.65-0.97	0.024	Overweight	0.75	0.70-0.80	<0.001	<0.001
Obese Class I	0.82	0.71-0.95	0.009	Obese Class I	0.74	0.69-0.80	<0.001	
Obese Class II	0.85	0.61-1.18	0.336	Obese Class II	0.74	0.65-0.84	<0.001	
Obese Class III	1.70	1.18-2.45	0.004	Obese Class III	0.88	0.73-1.07	0.202	
Extracardiac arteriopathy				**No extracardiac arteriopathy**				
Underweight	2.14	1.78-2.57	<0.001	Underweight	1.41	1.19-1.67	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.76	0.68-0.85	<0.001	Overweight	0.75	0.69-0.80	<0.001	<0.001
Obese Class I	0.70	0.61-0.81	<0.001	Obese Class I	0.75	0.69-0.82	<0.001	
Obese Class II	0.76	0.59-0.97	0.025	Obese Class II	0.74	0.65-0.84	<0.001	
Obese Class III	0.90	0.63-1.29	0.576	Obese Class III	0.95	0.81-1.12	0.578	
Diabetes				**No diabetes**				
Underweight	1.43	0.92-2.22	0.114	Underweight	1.58	1.44-1.73	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.75	0.67-0.84	<0.001	Overweight	0.75	0.69-0.81	<0.001	0.046
Obese Class I	0.75	0.71-0.84	<0.001	Obese Class I	0.74	0.68-0.81	<0.001	
Obese Class II	0.72	0.60-0.87	0.001	Obese Class II	0.76	0.67-0.86	<0.001	
Obese Class III	0.99	0.80-1.24	0.962	Obese Class III	0.89	0.74-1.06	0.196	

Table 6 (Continued)								
BMI Class	**OR**	**95% CI**	***P* value**	**BMI Class**	**OR**	**95% CI**	***P* value**	**Interaction (*P* value)**
Urgent/Emergent status				**Elective status**				<0.001
Underweight	1.26	1.08-1.48	0.003	Underweight	1.83	1.56-2.14	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.78	0.72-0.84	<0.001	Overweight	0.77	0.71-0.85	<0.001	
Obese Class I	0.78	0.72-0.85	<0.001	Obese Class I	0.79	0.71-0.87	<0.001	
Obese Class II	0.77	0.59-1.00	0.049	Obese Class II	0.81	0.71-0.92	0.001	
Obese Class III	0.94	0.79-1.12	0.521	Obese Class III	1.02	0.84-1.24	0.806	
CABG performed				**No CABG performed**				<0.001
Underweight	1.73	1.44-2.00	<0.001	Underweight	1.46	1.21-1.75	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.70	0.63-0.78	<0.001	Overweight	0.83	0.78-0.89	<0.001	
Obese Class I	0.75	0.68-0.83	<0.001	Obese Class I	0.77	0.70-0.84	<0.001	
Obese Class II	0.77	0.66-0.90	0.001	Obese Class II	0.75	0.63-0.88	0.001	
Obese Class III	0.98	0.77-1.24	0.849	Obese Class III	0.94	0.79-1.12	0.507	
Isolated CABG				**Isolated valve surgery**				
Underweight	1.76	1.42-2.18	<0.001	Underweight	1.73	1.34-2.25	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.77	0.68-0.86	<0.001	Overweight	0.86	0.79-0.94	0.001	
Obese Class I	0.81	0.71-0.92	0.001	Obese Class I	0.85	0.73-1.00	0.049	
Obese Class II	0.80	0.65-0.99	0.042	Obese Class II	0.83	0.61-1.12	0.225	
Obese Class III	1.13	0.88-1.47	0.339	Obese Class III	1.26	1.01-1.58	0.041	
CABG + valve surgery				**Thoracic Aorta surgery**				
Underweight	1.60	1.22-2.11	0.001	Underweight	1.14			
Normal	Ref			Normal	Ref			
Overweight	0.67	0.58-0.79	<0.001	Overweight	0.81			
Obese Class I	0.75	0.62-0.89	0.001	Obese Class I	0.67			
Obese Class II	0.80	0.69-0.93	0.003	Obese Class II	0.85			
Obese Class III	0.82	0.58-1.16	0.262	Obese Class III	0.65			
Other operations								
Underweight	1.27	0.79-2.03	0.332					
Normal	Ref							
Overweight	0.82	0.70-0.95	0.009					
Obese Class I	0.73	0.64-0.84	<0.001					
Obese Class II	0.66	0.48-0.90	0.008					
Obese Class III	0.77	0.47-1.24	0.278					

Table 6 (Continued)								
BMI Class	**OR**	**95% CI**	***P* value**	**BMI Class**	**OR**	**95% CI**	***P* value**	**Interaction (*P* value)**
Age ≤ 18				**Age 18-<60**				
Underweight	1.20	0.64-2.26	0.569	Underweight	1.09	0.37-3.22	0.873	
Normal	Ref	Normal	Ref	Normal				
Overweight	1.02	0.69-1.51	0.925	Overweight	0.85	0.73-0.99	0.037	
Obese Class I	1.19	0.84-1.68	0.328	Obese Class I	0.80	0.65-0.98	0.033	
Obese Class II	0.82	0.57-1.20	0.313	Obese Class II	0.87	0.69-1.10	0.259	
Obese Class III	1.94	1.31-2.88	0.001	Obese Class III	0.92	0.73-1.14	0.44	
Age 60-<70				**Age 70-<80**				
Underweight	1.24	0.85-1.81	0.266	Underweight	1.77	1.46-2.16	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.71	0.59-0.86	<0.001	Overweight	0.76	0.70-0.82	<0.001	<0.001
Obese Class I	0.81	0.67-0.97	0.023	Obese Class I	0.73	0.65-0.83	<0.001	
Obese Class II	0.79	0.66-0.95	0.013	Obese Class II	0.77	0.60-0.98	0.031	
Obese Class III	0.82	0.59-1.15	0.252	Obese Class III	1.05	0.84-1.31	0.679	
Age≥80								
Underweight	1.56	1.03-2.38	0.037					
Normal	Ref							
Overweight	0.81	0.71-0.93	0.003					
Obese Class I	0.83	0.72-0.94	0.005					
Obese Class II	0.86	0.56-1.30	0.469					
Obese Class III	1.98	1.02-3.84	0.043					
Never smoked				**Ex-smoker**				
Underweight	1.56	1.31-1.87	<0.001	Underweight	1.60	1.22-2.11	0.001	
Normal	Ref			Normal	Ref			
Overweight	0.77	0.71-0.84	<0.001	Overweight	0.74	0.67-0.80	<0.001	
Obese Class I	0.79	0.71-0.88	<0.001	Obese Class I	0.72	0.66-0.78	<0.001	
Obese Class II	0.70	0.56-0.88	0.002	Obese Class II	0.79	0.69-0.91	0.001	
Obese Class III	0.94	0.74-1.19	0.607	Obese Class III	0.98	0.81-1.18	0.815	<0.001
Current smoker								
Underweight	1.45	1.02-2.05	0.037					
Normal	Ref							
Obese Class I	0.77	0.65-0.90	0.001					
Obese Class II	0.78	0.66-0.93	0.004					
Obese Class III	0.65	0.44-0.96	0.031					
Obese Class III	0.84	0.47-1.50	0.558					

Table 6 (Continued)								
BMI Class	**OR**	**95% CI**	***P* value**	**BMI Class**	**OR**	**95% CI**	***P* value**	**Interaction (*P* value)**
IMD score 1 (Tertile 1)				**IMD score 2 (Tertile 2)**				
Underweight	1.17	0.85-1.60	0.341	Underweight	1.75	0.66-0.79	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.78	0.70-0.87	<0.001	Overweight	0.72	0.66-0.79	<0.001	
Obese Class I	0.66	0.59-0.73	<0.001	Obese Class I	0.74	0.67-0.82	<0.001	
Obese Class II	0.76	0.54-1.06	0.111	Obese Class II	0.73	0.62-0.84	<0.001	
Obese Class III	1.09	0.82-1.45	0.538	Obese Class III	0.80	0.51-1.23	0.307	<0.001
IMD score 3 (Tertile 3)								
Underweight	1.77	1.54-2.02	<0.001					
Normal	Ref							
Obese Class I	0.74	0.68-0.80	<0.001					
Obese Class II	0.75	0.66-0.86	<0.001					
Obese Class III	0.74	0.63-0.87	<0.001					
Obese Class III	0.87	0.75-1.01	0.062					
Years: 2002-2005				**Years 2006-2009**				
Underweight	1.72	1.33-2.21	<0.001	Underweight	1.49	1.21-1.84	<0.001	
Normal	Ref			Normal	Ref			
Overweight	0.78	0.68-0.89	<0.001	Overweight	0.74	0.66-0.82	<0.001	
Obese Class I	0.76	0.66-0.86	<0.001	Obese Class I	0.75	0.66-0.85	<0.001	
Obese Class II	0.89	0.73-1.09	0.262	Obese Class II	0.71	0.62-0.81	<0.001	
Obese Class III	1.04	0.83-1.32	0.714	Obese Class III	0.95	0.72-1.26	0.747	<0.001
Years: 2010-2013								
Underweight	1.41	0.96-2.07	0.084					
Normal	Ref							
Overweight	0.75	0.69-0.81	<0.001					
Obese Class I	0.75	0.67-0.85	<0.001					
Obese Class II	0.72	0.52-1.00	0.052					
Obese Class III	0.94	0.77-1.15	0.571					

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CABG, coronary artery bypass grafting; CI, confidence interval; CCS, Canadian Cardiovascular Society (class); IMD, Index of Multiple Deprivation (score); NYHA, New York Heart Association (class); OR, odds ratio.

Table 7. Characteristics of the Studies Included

Study (author, year)	Design	Country	Sample Size	Study period	Inclusion criteria	Exclusion criteria	Outcomes	Definition of underweight class (Kg/m2)	BMI classes*
Allama et al,[13] 2014	Retrospective Single-Center Study	UK	3370	2005-2012	Isolated CABG; Isolated valve; Combined CABG and valve	Patients < 18 yrs	In-hospital mortality; Reoperation for bleeding; Cardiac arrest; Arrhythmia; Complications: neurological, pulmonary, renal, GI; Wound complication; LOS; ICU stay; Total blood loss; Ventilation time	<18.5	4 (Obese≥30)
Atalan et al,[12] 2012	Retrospective Single-Center Study	Turkey	803	2008-2010	Isolated CABG	Emergency; OPCAB; Redo; COPD; EF < 30%; Dialysis	In-hospital mortality; Reoperation for bleeding; Inotropic support; Ventricular arrhythmia; AF; Complications: neurological (stroke), pulmonary (reintubation, ventilator-associated pneumonia), GI; Blood transfusion; LOS; ICU stay; Reintubation; Ventilation time; Postoperative SCr	<20	5 (Morbidly Obese ≥ 35)
Benedetto et al,[21] 2014	Retrospective Single-Center Study	UK	13963	1996-2012	Isolated CABG	Redo; Underweight	In-hospital/30-day mortality; Late mortality	<18.5	4 (Morbidly Obese ≥ 35)
Brát et al,[22] 2005	Retrospective Single-Center Study	Czech Republic	4266	1998-2002	All cardiac procedures	-	In-hospital mortality; Complications: pulmonary; renal; Wound infection; LOS; ICU stay; Total blood loss; Ventilation time	<20	5 (Morbidly Obese ≥ 35)
Caliskan et al,[23] 2014	Retrospective Single-Center Study	Switzerland	3714	1999-2008	Isolated CABG	(Other cardiac procedures)	In-hospital mortality; MACE; MnACE; LOS	<20	5 (Morbidly Obese ≥ 35)
Čemerlić-Adjić et al,[11] 2014	Prospective Single-Center Study	Serbia	791	2010	Isolated CABG	Other cardiac procedures	30-day mortality; LOS	<18.5	4 (Obese≥30)
Gurm et al,[2] 2002	Retrospective Multicenter Study (from BARI randomized study)	USA	1526†	1981-1998	Isolated CABG	(Other cardiac procedures)	30-day mortality; Late mortality (3 and 5 years); Major events (death, MI, stroke, coma); Cardiopulmonary event (congestive HF, pulmonary oedema, hypotension requiring treatment, nonfatal cardiac arrest, cardiogenic shock, respiratory failure, requiring reintubation or intubation > 72hrs); Local complications	<20	5 (Severely Obese ≥ 35)

Table 7 (Continued)

Study (author, year)	Design	Country	Sample Size	Study period	Inclusion criteria	Exclusion criteria	Outcomes	Definition of underweight class (Kg/m2)	BMI classes*
Jin et al,[6] 2005	Retrospective Multicenter Study	USA	16218	1997-2003	Isolated CABG	Incomplete data (n=14)	In-hospital mortality; Reoperation; MI; CVA, Renal failure; DSWI; Blood transfusion; LOS>14 d; ICU ventilation>24 h; coronary angiograph intervention	<18.5	6
Le-Bert et al,[24] 2011	Retrospective Single-Center Study	USA	396	2006-2009	Isolated CABG‡	Other cardiac procedures; Redo; Underweight	In-hospital mortality; Reoperation for bleeding; Perioperative MI; Atrial arrhythmias; Stroke, Acute renal failure; Pulmonary complications (reintubation, pneumonia, prolonged ventilation); Wound infection; Composite end-point; LOS; ICU stay;	<18.5	3 (Obese ≥ 30)
Lopez-Delgado et al,[25] 2015	Prospective Single-Center Study	Spain	2499	2004-2009	All cardiac procedures	Emergency; Redo; Underweight	In-hospital mortality; Reoperation for bleeding; LCO; Pericardial tamponade; Perioperative MI; AF; Stroke; AKI; Septicaemia; Transfusions; Total blood loss; LOS; ICU stay; Postoperative SCr	<18.5	4 (Morbidly Obese ≥ 35)
Musci et al,[20] 2008	Retrospective Single-Center Study	Germany	590	1996-2006	VAD	(Other cardiac procedures)	30-day mortality; Late mortality; Transplantation after VAD placement; Neurologic complications (TIA, stroke); Infections; Bleeding complications (> 5 U RBC or re-thoracotomy for bleeding); Pump change for thrombosis	<20	6
Orhan et al,[3] 2004	Retrospective Single-Center Study	Turkey	1206	2001-2002	Isolated CABG	OPCAB; Other procedures; Underweight (n=1); Morbid Obese (BMI>40, n=2)	In-hospital mortality; Inotropes; IABP; AF; Stroke; Infections (DSWI, mediastinitis, dehiscence); LOS; ICU stay; Total blood loss; Transfusions (RBC, FFP, eritrosit suspension); Ventilation time	<18	3 (Obese≥30)

Table 7 (Continued)

Study (author, year)	Design	Country	Sample Size	Study period	Inclusion criteria	Exclusion criteria	Outcomes	Definition of underweight class (Kg/m2)	BMI classes*
Pan et al,[7] 2006	Retrospective Single-Center Study	USA	9862	1995-2004	Isolated CABG	Emergency; Redo; Concomitant procedures; Underweight	30-day mortality; MI; IABP; AF/atrial flutter; VF/ventricular tachycardia; Stroke; Renal insufficiency; Respiratory failure; Sepsis; sternal wound infection; Leg wound infection; LOS	<20	5
Rahamanian et al,[14] 2007	Retrospective Single-Center Study	USA	5950	1998-2006	All cardiac procedures	Aortic surgery; Cardiac transplant; VAD	In-hospital mortality; Late mortality; Reoperation for bleeding; Renal complications; Respiratory failure; GI complications; Stroke; Sepsis; Sternal infection	<20	4 (Obese≥30)
Ranucci et al,[8] 2014	Retrospective Single-Center Study	Italy	5023	2000-2013	All cardiac procedures	OPCAB; Patient without PaO_2/FiO_2 ratio	In-hospital mortality; allogenic blood products[d]	<18.5	6
Reeves et al,[15] 2003	Retrospective Single-Center Study	UK	4372	1996-2001	Isolated CABG	(Other cardiac procedures)	In-hospital mortality; Reoperation for bleeding/tamponade; MI; Inotropes; IABP; MOF; Postoperative arrhythmia (VF/VT); Complications: neurological (TIA, stroke), pulmonary (chest infection), renal (dialysis); Infective complications (septicaemia); Sternal rewiring/mediastinitis; Blood transfusions (RBC, FFP, platelets); LOS; ICU/HDU stay; Total blood loss; Ventilation time; Postoperative Hb	<20	5 (Severely Obese ≥ 35)
Reser et al,[4] 2013	Retrospective Single-Center Study	Switzerland	225	2009-2010	Minimally mitral surgery (right thoracotomy)	(Other cardiac procedures); Underweight	30-day mortality; Reoperation for bleeding; Stroke (major, minor); Wound infection (thoracotomy, groin); PM implantation; LOS, ICU stay; Ventilation time	<18	3 (Obese≥30)
Shirzad et al,[16] 2008	Retrospective Single-Center Study	Iran	10427	2002-2006	Isolated CABG	Other cardiac procedures	In-hospital mortality; IABP; AF; Stroke; Renal failure; GI complications; Sternal wound infection; LOS; ICU stay	<18.5	4 (Obese≥30)

Table 7 (Continued)

Study (author, year)	Design	Country	Sample Size	Study period	Inclusion criteria	Exclusion criteria	Outcomes	Definition of underweight class (Kg/m2)	BMI classes*
Stamou et al,[26] 2011	Retrospective Single-Center Study	USA	2440	2004-2008	Isolated CABG; Isolated valve; Combined CABG and valve	Underweight (n=25)	In-hospital mortality; Late mortality; Reoperation for bleeding; Cardiac arrest; Pericardial tamponade; AF; Stroke; Renal complications: (acute renal failure, dialysis); Respiratory complications (reintubation; pneumonia; pulmonary embolism); Infective complications (septicaemia; DSWI); MOF; LOS; ICU stay; Readmission	<18.5	3 (Obese≥30)
Sun et al,[5] 2009	Retrospective Single-Center Study	USA	14449‖	2000-2007	All cardiac procedures	-	In-hospital mortality; Reoperation for bleeding; MI; AF; Stroke; Renal failure; Infection complications (DSWI, sternal superinfections); Units of RBC; LOS; ICU stay	<19	6 (Obese 30-39; Severely obese (40-49; Extremely obese (≥ 50)
Vaduganathan et al,[17] 2012	Retrospective Single-Center Study	USA	2640	2004-2011	Isolated valve; Combined CABG and valve	(Other cardiac procedures)	In-hospital/30-day mortality; Late mortality; Reopening for bleeding/cardiac/tamponade; MI; AF; Heart block; Cardiac arrest; Complications: neurological (stroke, TIA), renal (failure, dialysis), pulmonary (prolonged ventilation, pneumonia), GI; MOF Sepsis; Blood products; LOS; ICU stay; ICU readmission	<18.5	4 (Obese≥30)
van Straten et al,[10] 2010	Retrospective Single-Center Study	Netherlands	10268	1998-2007	Isolated CABG	(Other cardiac procedures)#	In-hospital mortality; Late mortality; Reopening for bleeding; MI; IABP	<20	5 (Morbidly Obese ≥ 35)
van Straten et al,[18] 2013	Retrospective Single-Center Study	Netherlands	1748	1998-2010	Isolated AVR	(Other cardiac procedures)**	In-hospital mortality; Late mortality; Reopening for bleeding; MI; Pulmonary complications; Wound complications (superficial and mediastinitis)	<20	5 (Morbidly Obese ≥ 35)

Table 7 (Continued)

Study (author, year)	Design	Country	Sample Size	Study period	Inclusion criteria	Exclusion criteria	Outcomes	Definition of underweight class (Kg/m2)	BMI classes*
Wagner et al,[9] 2007	Retrospective Multicenter Center Study	USA	80792	1991-2005	Isolated CABG	(Other cardiac procedures); BMI>58 Kg/m^2	30-day mortality; Reoperation for bleeding; Reoperation (repeat CPB); Cardiac arrest; Neurological complications (coma, stroke); Renal failure; Infective complications (mediastinitis, endocarditis); Ventilator	<18.5	5 (Morbidly Obese ≥ 35)
Zalewska-Adamiec et al,[27] 2012	Retrospective Single-Center Study	Poland	257	2006-2008	Isolated CABG; Combined CABG and valve; Left ventricular plasty††	(Other cardiac procedures); Underweight	In-hospital mortality; Reoperation for bleeding/LOS; MI; Tamponade; AF; Stroke (early/late); Infective complications (pulmonary, complications with wound healing, sternum dehiscence); Repeat revascularization; Re-hospitalization	<18.5	4 (Morbidly Obese ≥ 35)
Zitterman et al,[19] 2014	Retrospective Single-Center Study	Germany	9125	2009-2012	All cardiac procedures including TAVI	-	In-hospital mortality; Late mortality; Reoperation for bleeding; MACCE; MI; LCO; stroke; Infection; Blood product requirement; LOS; ICU stay; Ventilation;	<20	5 (Morbidly Obese ≥ 35)

Abbreviations: AKI, acute kidney injury; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); AF, atrial fibrillation; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVA, cerebrovascular accident; DSWI, deep sternal wound infection; EF, ejection fraction; FFP, fresh frozen plasma; GI, gastro-intestinal; Hb, hemoglobin; HDU, high-dependency unit; HF, heart failure; IABP, intra-aortic balloon pump; ICU, intensive care unit (hours/days); LCO, low cardiac output; LOS, length of hospital stay (days); MACE, major adverse cardiac events; MACCE, major adverse cardiac and cerebrovascular event; MnACE, major non-cardiac adverse event; MI, myocardial infraction; MOF, multiorgan failure; OPCAB, off-pump coronary artery bypass; PM, pace-maker; RBC, red blood cell; SCr, serum creatinine; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack; VAD, ventricular assist device; VF, ventricular fibrillation; VT, ventricular tachycardia; WHO, World Health Organization.

*Number of BMI classes analysed according to the standard or modified WHO classification[1,2] in parenthesis grouped classes with BMI threshold.

†Number of extrapolated patients from the overall study (total n. of subjects 3634); other 2108 patients undergoing percutaneous coronary intervention excluded.

‡Only elderly patients (>70 years) were enrolled.

§Allogenic blood product (any transfusion; RBC; FFP; platelets) evaluated for obese (BMI ≥ 30 Kg/m^2) *versus* non-obese (BMI < 30 Kg/m^2) patients only.

‖Analysis mainly focused on 57 patients with BMI ≥ 50 kg/m^2; data for entire cohort study of 14449 patients divided in 6 groups also provided.

#122 patients who were lost to follow-up and 236 with missing preoperative BMI were excluded.

**20 patients who were lost to follow-up and 30 with missing preoperative BMI were excluded.

††Only patients with (critical) left main coronary artery disease were evaluated.

Table 8A. Descriptive Summary of Demographics and Cardiac Status in Underweight, Normal BMI and Overweight Patients

		Underweight (<18.5 or <20 Kg/m²)						Normal BMI (18.5/20-<25 Kg/m²)						Overweight (25-<30 Kg/m²)					
Source	**N.Pts.**	**N. (%)**	**Age***	**Male**	**Prior MI**	**NYHA III/IV**	**EF***	**N. (%)**	**Age***	**Male**	**Prior MI**	**NYHA III/IV**	**EF***	**N. (%)**	**Age***	**Male**	**Prior MI**	**NYHA III/IV**	**EF***
Allama et al.[13]	3370	194 (5.8)	69.7 (9.2)	46.4	36.1	42.8		944 (28)	68.9 (10.5)	72.4	36.3	39	-	1261 (37.4)	68.4 (9.7)	28.9	35.1	14.1	-
Atalan et al.[12]	803	15 (1.9)	61.6 (9.6)	80	-	-	45.3 (6.39)	159 (19.8)	62.3 (10)	88.7	-	-	49.37 (6.81)	371 (46.2)	60.1 (9.8)	38.7	-	-	48.2 (6.89)
Benedetto et al.[21]	13963	Excluded						3269 (23.4)	68 (9)	99.8	-	-	-	6662 (47.7)	66 (9)	47.6	-	-	-
Brát et al.[22]	4266	54 (1.3)	57.5†	72.2	-	-	49.5†	987 (23.1)	63.8	70.4†	-	-	49.3†	2139 (50.1)	63.7	35	-	-	49.9
Caliskan et al.[23]	3714	57 (1.5)	63.5 (12.4)	61.4	38.6	-	-	991 (26.7)	64.3 (10.4)	79.7	61.3	-	-	1802 (48.5)	64.2 (10)	40.8	60.5	-	-
Čemerlić-Adjić et al.[10]	791	7 (0.9)	61 (7.09)	57.1	42.9	-	52.86 (12.95)	155 (19.6)	63.63 (8.22)	71.6	22.6	-	51.42 (10.4)	390 (49.3)	63 (7.88)	36.5	17.7	-	54.18 (8.7)
Gurm et al.[2]	1526	28 (1.8)	-	-	-	--	-	362 (23.7)	-	-	-	-	-	1526 (44.8)	-	-	-	-	-
Jin et al.[6]	16218	90 (0.6)	70 (12)	40	26.7	26.7	56 (18)	3475 (21.4)	69 (11)	73	19	20	55 (15)	6683 (41.2)	66 (10)	32.6	20.9	7.4	57 (15)
Le-Bert et al.[24]	396	Excluded						135 (34.1)	77.6 (5.6)	62.2	-	-	-	167 (42.2)	76.9 (4.5)	29.8	-	-	-
Lopez-Delgado et al.[25]	2499	-	-	-	-	-	-	523 (20.9)	63.8 (13.7)	65.8	26.6	-	59.7 (13)	1150 (46)	65.6 (11)	32	28.9	-	60.6 (11.6)
Musci et al.[20]	590	35 (5.9)	45.8 (17.6)	-	0	-	-	247 (41.9)	50.8 (12.6)	83.8	8.9	-	-	220 (37.3)	52.9 (11.2)	33.9	11.4	-	-
Orhan et al.[3]	1206	Excluded						320 (26.5)	61.95 (9.97)	84.4	25.6	-	-	632 (52.4)	60.37 (10.14)	9.1	30.1	-	-
Pan et al.[7]	9862	Excluded						2184 (22.1)	66 (10.7)	71.7	44.8	-	-	4257 (43.2)	63.3 (10.7)	79.9	43.6	-	-
Rahamanian et al.[14]	5950	328 (5.5)	62 (18)	44.2	26.2	-	56 (15)	2041 (34.3)	65 (15)	62.7	32.6	-	46 (14)	2289 (38.5)	64 (13)	26.2	32.7	-	47 (14)
Ranucci et al.[8]	5023	103 (2.1)	-	-	-	-	-	1968 (39.2)	-	-	-	-	-	2086 (41.5)	-	-	-	-	-
Reeves et al.[15]	4372	133 (3)	-	78.9	45.1	41.4	-	1166 (26.7)	-	84.4	44.4	32.2	-	2170 (49.6)	-	42.4	43.6	17.3	-
Reser et al.[4]	225	Excluded						108 (48)	60 (14)	63.9	0.9	23.1	-	90 (40)	61 (12)	28	4.4	12.4	-

Table 8A (Continued)

Source	N.Pts.	Underweight (<18.5 or <20 Kg/m²)						Normal BMI (18.5/20-<25 Kg/m²)						Overweight (25-<30 Kg/m²)					
		N. (%)	Age*	Male	Prior MI	NYHA III/IV	EF*	N. (%)	Age*	Male	Prior MI	NYHA III/IV	EF*	N. (%)	Age*	Male	Prior MI	NYHA III/IV	EF*
Shirzad et al.[16]	10427	67 (2)	60.9 (10.1)	83.6	47.8	-	50.7 (11.5)	3179 (30.5)	59.6 (9.6)	82.5	40.7	-	48.5 (10.5)	4809 (46.1)	58.4 (9.8)	35.4	37.3	-	49.4 (10.2)
Stamou et al.[26]	2440	Excluded						556 (22.8)	64 (11)	64.9	36.7	50.4	-	965 (39.5)	63 (11)	31.8	38.9	17.9	-
Sun et al.[5]	14449	214 (1.5)	66 (14)	45.3	46.3	-	-	3732 (28.5)	67 (12)	66.9	35.9	-	-	5551 (38.4)	65 (11)	28.7	37.5	-	-
Vaduganathan et al.[17]	2640	61 (2.3)	62 (17.2)	24.6	9.8	41	55 (40-60)	865 (32.8)	63.7 (15.9)	57	9.8	32.9	60 (50-65)	1020 (38.6)	63.2 (14.8)	26.9	9.8	12.9	60 (50-65)
van Straten et al.[10]	10268	128 (1.2)	63.8 (10.5)	47.7	-	-	-	2896 (28.2)	65.7 (9.7)	76.1	-	-	-	5234 (50.9)	64.6 (9.4)	41.3	-	-	-
van Straten et al.[18]	1748	46 (2.6)	64 (12)	41.3	-	-	-	484 (27.7)	64 (13)	60.7	-	-	-	829 (47.4)	66 (11)	29.6	-	-	-
Wagner et al.[9]	80792	887 (1.1)	64.9 (9)	98.9	9.2	-	-	18130 (22.4)	65 (9.4)	99	7.3	-	-	34063 (42.2)	64.1 (9.2)	41.9	7.1	-	-
Zalewska-Adamiec et al.[27]	257	Excluded						37 (14.4)	66.7 (11.2)	64.9	45.9	-	50.8 (10.5)	72 (28)	65.9 (9.8)	21.4	41.7	-	51.4 (11.4)
Zitterman et al.[19]	9125	273 (3)	71 (60-79)	38.5	12.8	-	71 (60-79)	2554 (28)	71 (62-78)	61.3	16.4	-	60 (50-60)	3937 (43.2)	71 (62-77)	31.5	18	-	60 (50-61)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); EF, ejection fraction; IQR, interquartile range; MI, myocardial infarction; NYHA, New York Heart Association; SD, standard deviation.

*For the variable Age and EF, values are expressed as mean (SD) or Median (range/IQR).

†Expressed as mean only, no SD provided.

Table 8B. Descriptive Summary of Demographics and Cardiac Status in the Obese Patients

Source	N.Pts.	Obese Class I (30-<35 Kg/m²)						Obese Class II (35-<40 Kg/m²)						Obese Class III (≥40 Kg/m²)					
		N. (%)	Age*	Male	Prior MI	NYHA III/IV	EF*	N. (%)	Age*	Male	Prior MI	NYHA III/IV	EF*	N. (%)	Age*	Male	Prior MI	NYHA III/IV	EF*
Allama et al.[13]	3370	971	66.1 (9.4)	70.1	34.6	41.5	-	Obese class I, II, III pts pooled						Obese class I, II, III pts pooled					
Atalan et al.[12]	803	199 (24.8)	60 (10.4)	78.4	-	-	48.2 (6.94)	59 (7.3)	60.1 (9.5)	42.4	-	-	46.9 (6.27)	Obese class II and III pts pooled					
Benedetto et al.[21]	13963	3821 (27.4)	64 (9)	99.8	-	-	-	211 (1.5)	60 (9)	63	-	-	-	Obese class II and III pts pooled					
Brát et al.[22]	4266	837 (22)	62.4†	71.7	-	-	50.2†	149 (3.5)	61.3†	69.1	-	-	52.2†	Obese class II and III pts pooled					
Caliskan et al.[23]	3714	708 (19.1)	63 (9.1)	79.9	58.6	-	-	61.6 (9.6)	61.6 (9.6)	63.1	57	-	-	Obese class II and III pts pooled					
Čemerlić-Adjić et al.[10]	791	239	60.46 (8.2)	69.6	20.5	-	53.09 (9.41)	Obese class I, II, III pts pooled						Obese class I, II, III pts pooled					
Gurm et al.[2]	1526	350 (22.9)	-	-	-	-	-	103 (6.8)	-	-	-	-	-	Obese class II and III pts pooled					
Jin et al.[6]	16218	3944 (24.3)	63 (10)	24.0	4.9	20	57 (14)	1396 (8.6)	61 (10)	68.0	21.0	23.0	57 (14)	630 (3.9)	60 (9)	53.9	22.1	23.0	57 (11)
Le-Bert et al.[24]	396	94 (23.7)	76.9 (4.6)	63.8	-	-	50 (39.5-60)	Obese class I, II, III pts pooled						Obese class I, II, III pts pooled					
Lopez-Delgado et al.[25]	2499	624 (25)	65.4 (10.2)	62.3	6.9	-	60.7 (11.5)	152 (6.2)	63.5 (10.2)	44.1	16.4	-	60.5 (10.7)	Obese class II and III pts pooled					
Musci et al.[20]	590	72 (12.2)	52.9 (10.5)	86.1	1.2	-	-	16 (2.7)	51.8 (13.2)	75	23.5	-	-	Obese class II and III pts pooled					
Orhan et al.[3]	1206	254 (21.1)	58.63 (8.89)	79.5	29.9	-	-	Obese class I, II, III pts pooled						Obese class I, II, III pts pooled					
Pan et al.[7]	9862	9862 (23.3)	60.8 (9.6)	75.5	10.0	-	-	785 (8.0)	60.5 (10.5)	67.1	43.6	-	-	338 (3.4)	57.9 (10.5)	61.5	41.4	-	-
Rahamanian et al.[14]	5950	1292 (22)	61 (12)	59	33	-	48 (13)	Obese class I, II, III pts pooled						Obese class I, II, III pts pooled					
Ranucci et al.[8]	5023	711 (14.2)	-	-	-	-	-	128 (2.6)	-	-	-	-	-	27 (0.5)	-	-	-	-	-
Reeves et al.[15]	4372	747 (17.1)	-	70.6	7.7	6.5	-	156 (3.6)	-	47.4	46.2	50.3	-	Obese class II and III pts pooled					
Reser et al.[4]	225	27 (12)	62 (10)	51.9	3.7	33.3	-	Obese class I, II, III pts pooled						Obese class I, II, III pts pooled					

Table 8B (Continued)

Source	N.Pts.	Obese Class I (30-<35 Kg/m²)						Obese Class II (35-<40 Kg/m²)						Obese Class III (≥40 Kg/m²)					
		N. (%)	Age*	Male	Prior MI	NYHA III/IV	EF*	N. (%)	Age*	Male	Prior MI	NYHA III/IV	EF*	N. (%)	Age*	Male	Prior MI	NYHA III/IV	EF*
Shirzad et al.[16]	10427	2136 (21)	57.8 (9.5)	58.3	33.7	-	50.3 (10)	Obese class I, II, III pts pooled						Obese class I, II, III pts pooled					
Stamou et al.[26]	2440	919 (38)	61 (10)	70.8	43	59.8	-	Obese class I, II, III pts pooled						Obese class I, II, III pts pooled					
Sun et al.[5]	14449	4340 (30)	62 (11)	65	39	-	-	Obese I and II pts pooled						612 (4.2)	58.9 (11)	45.6	39.9	-	-
Vaduganathan et al.[17]	2640	694 (	62.7 (12.9)	59	11	43	2	Obese class I, II, III pts pooled						Obese class I, II, III pts pooled					
van Straten et al.[10]	10268	1686 (16.4)	63.4 (9.4)	72.7	-	-	-	324 (3.2)	61.3 (9.9)	59.3	-	-	-	Obese class II and III pts pooled					
van Straten et al.[18]	1748	301 (17.2)	67 (11)	52.2	-	-	-	98 (5.6)	66 (10)	30.6	-	-	-	Obese class II and III pts pooled					
Wagner et al.[9]	80792	19391 (24)	62.3 (9)	99.1	1.6	-	-	8321 (10.3)	60.4 (8.8)	98.1	24.4	-	-	Obese class II and III pts pooled					
Zalewska-Adamiec et al.[27]	257	40 (15.6)	62.8 (10.4)	77.5	6.2	-	51 (10.4)	10 (6.4)	66.7 (7.8)	50	40	-	50.9 (8.84)	Obese class II and III pts pooled					
Zitterman et al.[19]	9125	1763 (19.3)	70 (62-76)	68.1	19.7	-	60 (50-60)	606 (6.6)	69 (60-74)	51.3	18.6	-	60 (50-74)	Obese class II and III pts pooled					

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); EF, ejection fraction; IQR, interquartile range; MI, myocardial infarction; NYHA, New York Heart Association; SD, standard deviation.

*For the variable Age and EF, values are expressed as mean (SD) or Median (range/IQR).

†Expressed as mean only, no SD provided.

Table 9A. Descriptive Summary of Comorbidities of Underweight, Normal BMI and Overweight Patients

Source	Underweight (<18.5 or <20 Kg/m²)								Normal BMI (18.5/20-<25 Kg/m²)								Overweight (25-<30 Kg/m²)							
	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	COPD (%)	Current smokers (%)	CVA/CVD (%)	PVD (%)	Dialysis (%)	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	COPD (%)	Current smokers (%)	CVA/CVD (%)	PVD (%)	Dialysis (%)	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	COPD (%)	Current smokers (%)	CVA/CVD (%)	PVD (%)	Dialysis (%)
Allama et al.[13]	56.7	11.9	60.8	7.2	12.4	1	11.3	-	70.4	23.3	62.5	13.5	11.1	1.6	15.7	-	77.4	24.9	69.0	14.7	8.2	3.0	12.7	-
Atalan et al.[12]	53.3	13.3	-	26.7	-	-	-	-	61.6	30.2	-	8.2	-	-	-	-	70.4	33.4	-	8.4	-	-	-	-
Benedetto et al.[21]	Excluded								-	12	-	10	-	1	10	-	-	14	-	9	-	1	10	-
Brát et al.[22]	Excluded								-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Caliskan et al.[23]	42.1	15.8	61.5	17.5	55.1	-	23.2	-	49.2	19.6	75.1	5.3	53.0	-	14.6	-	53.7	21.7	75.9	6.7	57.2	-	14.2	-
Čemerlić-Adjić et al.[10]	-	42.9	-	14.3	-	0*	57.1	-	-	35.5	-	5.2	-	1.9*	27.7	-	-	34.9	-	6.4	-	2.6*	23.3	-
Gurm et al.[2]	45	11	-	-	45	-	11	-	41	11	-	-	29	-	8	-	47	15	-	-	21	-	8	-
Jin et al.[6]	36	13	-	34	-	8	31	-	33	22	-	19	-	13	18	-	38	27	-	12	-	11	15	-
Le-Bert et al.[24]	Excluded								92.3	33.3	76.3	11.1	-	15.6	20.7	-	94.0	32.9	59.9	19.8	-	14.4	13.8	-
Lopez-Delgado et al.[25]	Excluded								46.1	13.6	39.2	10.1	26.4	5.2	9.8	1.3	65.6	17.8	54.5	10.7	22	5.8	9.4	0.9
Musci et al.[20]	32	22	21	-	-	-	-	-	27	19	19	-	-	-	-	-	40	27	28	-	-	-	-	-
Orhan et al.[3]	Excluded								46.3	15	-	13.7	-	-	-	-	44.3	25	-	11.2	-	-	-	-
Pan et al.[7]	Excluded								66.1	26.5	54	27	49.5	7.1	-	-	72.4	31.2	62.4	22	51.1	5.2	-	-
Rahamanian et al.[14]	31	13	-	10	-	8	12	-	44	24	-	5	-	7	10	-	49	26	-	6	-	8	9	-
Ranucci et al.[8]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 9A (Continued)

Source	Underweight (<18.5 or <20 Kg/m²)								Normal BMI (18.5/20-<25 Kg/m²)								Overweight (25-<30 Kg/m²)							
	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	COPD (%)	Current smokers (%)	CVA/CVD (%)	PVD (%)	Dialysis (%)	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	COPD (%)	Current smokers (%)	CVA/CVD (%)	PVD (%)	Dialysis (%)	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	COPD (%)	Current smokers (%)	CVA/CVD (%)	PVD (%)	Dialysis (%)
Reeves et al.[15]	62.4	20.3	62.6	11.3	8.3	10.5	12	-	55.9	14.6	69.7	4.6	12.4	9.4	9.1	-	55.3	14.6	73.5	4.6	12.2	7.7	9.5	-
Reser et al.[4]	Excluded								42.6	2.8	-	3.7	-	-	1.9	-	58.9	4.4	-	4.4	-	-	5.6	-
Shirzad et al.[16]	38.8	17.9	51.5	-	50	-	4.5	-	49.3	27.7	60.1	-	44.1	-	1.5	-	51.5	30.1	64.2	-	39.3	-	1.5	-
Stamou et al.[26]	Excluded								71.4	25.9	-	16.4	-	-	-	2.7	77.5	31.2	-	13.4	-	-	-	3.4
Sun et al.[5]	63	22	44	-	-	12*	-	-	65	24	59	-	-	8*	-	-	72	29	68	-	-	6*	-	-
Vaduganathan et al.[17]	39	10	30	26	5	13*	5	5	50	8	44	12	4	13*	6	2	60	13	54	11	3	10*	7	1
van Straten et al.[10]	39.1	10.2	-	16.4	-	-	18.8	-	36.2	14.2	-	12.4	-	-	11.9	-	41.5	20.5	-	11.8	-	-	11.5	-
van Straten et al.[18]	26.1	6.5	-	26.1	-	4.3	8.7	0.6	22.5	6	-	17.1	-	4.1	6.6	0	37.9	10.7	-	17.1	-	4.3	6.8	0.5
Wagner et al.[9]	-	23	-	37.5	45.4	25.9*	-	-	-	22.3	-	27.2	38.8	23.2*	-	-	-	30.5	-	21.5	29.6	20.4*	-	-
Zalewska-Adamiec et al.[27]	Excluded								62.2	10.8	59.5	-	51.4	-	-	-	75.0	16.7	70.8	-	60.0	-	-	-
Zitterman et al.[19]	58.6	13.6	-	15.4	26.4	4.0	9.9	-	70.2	16.7	-	7.8	29.9	2.8	8.6	-	78.6	24.8	-	8.7	34.8	3.0	10.0	-

Abbreviation: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA/CVD, cerebrovascular accident/cerebrovascular disease; PVD, peripheral vascular disease.
*Reported as history of stroke only.

Table 9B. Descriptive Summary of Comorbidities of Obese Patients

Source	Obese Class I (30-<35 Kg/m^2)								Obese Class II (35-<40 Kg/m^2)								Obese Class III (≥40 Kg/m^2)							
	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	COPD (%)	Current smokers (%)	CVA/CVD (%)	PVD (%)	Dialysis (%)	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	COPD (%)	Current smokers (%)	CVA/CVD (%)	PVD (%)	Dialysis (%)	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	COPD (%)	Current smokers (%)	CVA/CVD (%)	PVD (%)	Dialysis (%)
Allama et al.[13]	83	36.7	70.3	14.7	8.4	3.4	13.8	-	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Atalan et al.[12]	72.9	38.2	-	9.0	-	-	-	-	84.7	45.8	-	8.5	-	-	-	-	Obese class II and III pts pooled							
Benedetto et al.[21]	-	19	-	11	-	1	9	-	-	22	-	13	-	1	7	-	Obese class II and III pts pooled							
Brát et al.[22]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Obese class II and III pts pooled							
Caliskan et al.[23]	65.5	28.8	78.4	5.6	56.0	-	12.9	-	63.5	37.8	77.3	7.7	54.1	-	10.3	-	Obese class II and III pts pooled							
Čemerlić-Adjić et al.[10]	-	43.9	-	9.2	-	3.3*	16.3	-	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Gurm et al.[2]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Obese class II and III pts pooled							
Jin et al.[6]	43	38	-	13	-	11	13	-	50	48	-	13	-	11	13	-	50	61	-	18	-	10	12	-
Le-Bert et al.[24]	95.7	53.2	77.7	14.9	-	9.6	10.6	-	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Lopez-Delgado et al.[25]	76.3	20.2	58.5	15.4	21.6	4.2*	9.3	0.3	77	23.7	57.9	15.8	23.7	4.6*	7.9	0.7	Obese class II and III pts pooled							
Musci et al.[20]	45	27	37	-	-	-	-	-	45	37	37	-	-	-	-	-	Obese class II and III pts pooled							
Orhan et al.[3]	50.4	38.6	-	12.6	-	-	-	-	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Pan et al.[7]	79.1	38.9	63.8	23.2	51.4	5.6*	-	-	85.4	49.2	62.9	28.5	53.5	7.0*	-	-	86.4	54.7	64.8	23.7	49.1	4.7*	-	-
Rahamanian et al.[14]	51	37	-	8	-	8	10	-	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Ranucci et al.[8]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 9B (Continued)

Source	Obese Class I (30-<35 Kg/m²)								Obese Class II (35-<40 Kg/m²)								Obese Class III (≥40 Kg/m²)							
	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	COPD (%)	Current smokers (%)	CVA/CVD (%)	PVD (%)	Dialysis (%)	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	COPD (%)	Current smokers (%)	CVA/CVD (%)	PVD (%)	Dialysis (%)	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	COPD (%)	Current smokers (%)	CVA/CVD (%)	PVD (%)	Dialysis (%)
Reeves et al.[15]	61.4	18.5	78.2	4.8	14.6	7.8	8.2	-	64.1	28.2	82.7	3.9	12.2	5.6	5.8	-	Obese class II and III pts pooled							
Reser et al.[4]	85.2	22.2	-	11.1	-	-	7.4	-	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Shirzad et al.[16]	57.9	34.1	68.6	-	31.7	-	1.3	-	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Stamou et al.[26]	86.9	46.7	-	15.3	-	-	-	3.4	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Sun et al.[5]	79	45	71	-	-	7*	-	-	Obese class I and II pts pooled								84.3	57.5	70.8	-	-	6.4	-	-
Vaduganathan et al.[17]	73	28	62	15	4	11*	8	2	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
van Straten et al.[10]	49.5	31.4	-	13.6	-	-	11.3	-	61.7	43.8	-	17.0	-	-	11.4	-	Obese class II and III pts pooled							
van Straten et al.[18]	52.2	19.6	-	16.3	-	3.3	7.0	0.3	63.3	35.7	-	28.6	-	2.0	8.2	1.0	Obese class II and III pts pooled							
Wagner et al.[9]	-	41.4	-	22.7	26.0	18.5*	-	-	-	50.3	-	24.6	24.4	16.0*	-	-	Obese class II and III pts pooled							
Zalewska-Adamiec et al.[27]	92.5	40.0	67.5	-	53.8	-	-	-	100	80.0	60.0	-	40.0	-	-	-	Obese class II and III pts pooled							
Zitterman et al.[19]	83.9	34.7	-	9.1	35.2	3.5*	8.8	-	89.4	51.3	-	16.3	32.3	2.8*	7.3	-	Obese class II and III pts pooled							

Abbreviation: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA/CVD, cerebrovascular accident/cerebrovascular disease; PVD, peripheral vascular disease.

*Reported as history of stroke only.

Table 10A. Summary of Postoperative Outcomes of Included Underweight, Normal BMI and Overweight Patients

Source	Underweight (<18.5 or <20 Kg/m²)								Normal BMI (18.5/20-<25 Kg/m²)								Overweight (25-<30 Kg/m²)							
	Mortality (%)*	Reopening for Bleeding/Tamponade	Perioperative IABP	Perioperative MI	Stroke	RRT	DSWI	LOS (days)†	Mortality (%)*	Reopening for Bleeding/Tamponade	Perioperative IABP	Perioperative MI	Stroke	RRT	DSWI	LOS (days) †	Mortality (%)*	Reopening for Bleeding/Tamponade	Perioperative IABP	Perioperative MI	Stroke	RRT	DSWI	LOS (days) †
Allama et al.[13]	4.1	5.7	-	-	0[c]	-	-	18.8 (20.7)	3.5	4.3	-	-	1.0‡	-	-	19.4 (27)	1.7	2.7	-	-	1.0‡	-	-	18.3 (24.5)
Atalan et al.[12]	20	13.3	13.3	-	0	-	-	13.67 (12.09)	5.7	3.1	3.8	-	0.6	-	-	8.5 (3.38)	3.2	8.1	3.0	-	0.5	-	-	8.88 (6.15)
Benedetto et al.[21]	Excluded								3.81	-	-	-	-	-	-	-	1.99	-	-	-	-	-	-	-
Brát et al.[22]	1.9	-	-	-	-	-	-	9.5	2.9	-	-	-	-	-	-	8.6	2.4	-	-	-	-	-	-	9.7
Caliskan et al.[23]	1.8	-	-	-	-	-	-	7.6 (6.7-8.6)	1.5	-	-	-	-	-	-	7.9 (7.7-8.1)	2.2	-	-	-	-	-	-	7.9 (7.7-8.1)
Čemerlić-Adjić et al.[10]	0	-	-	-	-	-	-	8.29 (1.11)	1.93	-	-	-	-	-	-	9.41 (4.94)	2.05	-	-	-	-	-	-	10.03 (7.88)
Gurm et al.[2]	3.6	-	-	-	-	-	-	-	7.2	-	-	-	-	-	-	-	7.6	-	-	-	-	-	-	-
Jin et al.[6]	7.8	6.7	-	2.2	3.3‡	0	0	-	3.1	3.8	-	1.6	2.6‡	2.3	0.3	-	1.9	2.8	-	1.4	2.0‡	1.7	0.3	-
Le-Bert et al.[24]	Excluded								5.9	5.2	28.1	0	4.4	-	-	10 (7-16)	4.2	6.9	26.9	1.2	2.4	-	-	8 (7-12)
Lopez-Delgado et al.[25]	Excluded								5.2	3.8	6.8	11.8	2.1	-	-	24 (18)	4.4	4.2	7.7	11.1	1.3	-	-	6 (7.1)
Musci et al.[20]	42.3	20	-	-	11.4	-	-	-	40	14.9	-	-	12.9	-	-	-	34.5	11.1	-	-	-	-	-	-
Orhan et al.[3]	Excluded								1.9	-	2.5	-	1.6	-	0.6	7.6 (2.6)	1.9	-	2.2	-	1.9	-	0.6	8 (2.6)
Pan et al.[7]	Excluded								4.7	6.4	5.1	3.4	3.2	-	-	10.8 (8.3)	2.9	4.2	4.0	2.8	3.0	-	-	10.2 (9)
Rahamanian et al.[14]	4.6	4.6	-	-	2.4	-	1.8	-	3.1	2.0	-	-	1.7	-	1.1	-	3.3	2.4	-	-	2.1	-	1.4	-
Ranucci et al.[8]	6.8	-	-	-	-	-	-	-	3.0	-	-	-	-	-	-	-	3.1	-	-	-	-	-	-	-

Table 10A. (Continued)

Source	Underweight (<18.5 or <20 Kg/m²)								Normal BMI (18.5/20-<25 Kg/m²)								Overweight (25-<30 Kg/m²)							
	Mortality (%)*	Reopening for Bleeding/Tamponade	Perioperative IABP	Perioperative MI	Stroke	RRT	DSWI	LOS (days)†	Mortality (%)*	Reopening for Bleeding/Tamponade	Perioperative IABP	Perioperative MI	Stroke	RRT	DSWI	LOS (days)†	Mortality (%)*	Reopening for Bleeding/Tamponade	Perioperative IABP	Perioperative MI	Stroke	RRT	DSWI	LOS (days)†
Reeves et al.[15]	6.8	4.5	8.3	3.0	0	4.5	-	-	0.9	5.0	2.9	2.0	0.5	1.8	-	-	0.8	3.5	2.2	1.8	0.5	0.8	-	-
Reser et al.[4]	Excluded								0.9	14.8	-	-	2.8	-	-	8 (3-35)	0	8.9	-	-	1.1	-	-	8 (3-30)
Shirzad et al.[16]	3.0	-	3.0	-	0	-	0	7.4 (2.5)	0.9	-	2.7	-	0.4	-	0.1	7.6 (5.2)	0.7	-	2.0	-	0.3	-	0.2	7.6 (4.8)
Stamou et al.[26]	Excluded								4.7	8.3	-	-	1.8	2.3	0.4	9 (1-134)	1.8	3.7	-	-	1.9	1.1	0.8	8 (6-12)
Sun et al.[5]	13	8	-	4	5	-	0.5	4 (1-9)	6	5	-	2	3	-	0.6	3 (1-6)	4	3	-	2	2	-	0.6	3 (1-6)
Vaduganathan et al.[17]	7	7	-	2	3	7	-	7 (5-11)	4	5	-	1	3	4	-	6 (5-8)	2	5	-	1	1	2	-	6 (5-8)
van Straten et al.[10]	7.8	10.2	3.9	3.9	-	-	-	-	2.5	6.5	2.9	3.3	-	-	-	-	2.0	5.1	1.9	2.8	-	-	-	-
van Straten et al.[18]	8.7	7.3	-	0.8	-	-	-	-	4.1	10.6	-	0	-	-	-	-	2.8	7.0	-	0.7	-	-	-	-
Wagner et al.[9]	7.1	4.5	-	-	2.0	-	1.4	1.1	4.0	3.8	-	-	1.9	-	1.1	1.2	3.2	2.6	-	-	1.8	-	1.2	1.0
Zalewska-Adamiec et al.[27]	Excluded								18.9	11.1	-	0	0	-	-	-	9.7	5.6	-	2.5	2.8	-	-	-
Zitterman et al.[19]	4.8	11.9	-	0.4	3.3	-	-	14 (11-17)	3.2	9.8	-	0.9	2.4	-	-	13 (11-16)	2.7	7.8	-	0.5	2.7	-	-	13 (11-16)

Abbreviations: BMI, body mass index; DSWI, deep sternal wound infection; IQR, interquartile range; LOS, length of hospital stay; RRT, renal replacement therapy; SD, standard deviation.

*Intended as in-hospital or 30-day mortality (all cause).

†Expressed as mean (SD) or median (range/IQR).

‡Intended as neurological complication or cerebrovascular accident (stroke and TIA).

Table 10B. Summary of Postoperative Outcomes of Included Obese Patients

Source	Obese Class I (30-<35 Kg/m²)								Obese Class II (35-<40 Kg/m²)								Obese Class III (≥40 Kg/m²)							
	Mortality (%)*	Reopening for Bleeding/Tamponade	Perioperative IABP	Perioperative MI	Stroke	RRT	DSWI	LOS (days) †	Mortality (%)*	Reopening for Bleeding/Tamponade	Perioperative IABP	Perioperative MI	Stroke	RRT	DSWI	LOS (days) †	Mortality (%)*	Reopening for Bleeding/Tamponade	Perioperative IABP	Perioperative MI	Stroke	RRT	DSWI	LOS (days) †
Allama et al.[13]	1.2	2.9	-	-	0.5	-	-	17.1 (22.2)	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Atalan et al.[12]	3.0	3.5	2.5	-	1.0‡	-	-	8.0 (12.57)	3.4	5.1	1.7	-	3.4‡	-	-	8.51 (3.68)	Obese class II and III pts pooled							
Benedetto et al.[21]	2.23	-	-	-	-	-	-	-	1.43	-	-	-	-	-	-	-	Obese class II and III pts pooled							
Brát et al.[22]	1.7	-	-	-	-	-	-	8.7§	2.0	-	-	-	-	-	-	11.1§	Obese class II and III pts pooled							
Caliskan et al.[23]	2.0	-	-	-	-	-	-	8.0 (7.7-8.3)	2.6	-	-	-	-	-	-	8.0 (7.5-8.7)	Obese class II and III pts pooled							
Čemerlić-Adjić et al.[10]	2.51	-	-	-	-	-	-	10.43 (7.03)	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Gurm et al.[2]	1.7	-	-	-	-	-	-	-	0.97	-	-	-	-	-	-	-	Obese class II and III pts pooled							
Jin et al.[6]	2.0	1.9	-	1.2	1.5‡	2.1	0.6	-	1.8	1.8	-	1.1	1.5‡	1.9	1.1	-	1.9	1.7	-	1.1	1.7‡	-	1.4	-
Le-Bert et al.[24]	4.3	0	28.7	0	1.1	-	-	10 (7-13)	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Lopez-Delgado et al.[25]	5.4	2.1	7.7	13.5	1.3	-	-	23 (18)	3.9	1.3	7.9	13.2	1.3	-	-	24 (14)	Obese class II and III pts pooled							
Musci et al.[20]	40.8	10.8	-	-	14.7	-	-	-	64.7	11.8	-	-	5.9	-	-	-	Obese class II and III pts pooled							
Orhan et al.[3]	2.8	-	1.6	-	2.1	-	1.6	8.5 (3.4)	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Pan et al.[7]	3.2	3.1	4.5	3.2	1.9	-	-	10.4 (7.1)	3.6	4.1	4.3	3.3	3.2	-	-	11.5 (9.4)	3.8	3.0	5.6	3.8	1.5	-	-	12.5 (9.3)
Rahamanian et al.[14]	3.8	1.8	-	-	2.1	-	2.4	-	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Ranucci et al.[8]	2.6	-	-	-	-	-	-	-	4.7	-	-	-	-	-	-	-	0	-	-	-	-	-	-	-

Table 10B (Continued)

Source	Obese Class I (30-<35 Kg/m²)								Obese Class II (35-<40 Kg/m²)								Obese Class III (≥40 Kg/m²)							
	Mortality (%)*	Reopening for Bleeding/Tamponade	Perioperative IABP	Perioperative MI	Stroke	RRT	DSWI	LOS (days)†	Mortality (%)*	Reopening for Bleeding/Tamponade	Perioperative IABP	Perioperative MI	Stroke	RRT	DSWI	LOS (days) †	Mortality (%)*	Reopening for Bleeding/Tamponade	Perioperative IABP	Perioperative MI	Stroke	RRT	DSWI	LOS (days) †
Reeves et al.[15]	0.8	2.0	1.9	1.6	0.7	0.8	0.8	-	0.6	3.2	1.3	1.3	0.7	0.7	0	-	Obese class II and III pts pooled							
Reser et al.[4]	0	22.2	-	-	7.4	-	-	9 (6-61)	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Shirzad et al.[16]	0.8	-	1.7	-	0.2	-	0.2	7.9 (4.1)	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Stamou et al.[26]	3.7	5.1	-	-	2.2	1.3	1.2	9 (6-14)	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
Sun et al.[5]	4	2	-	2	2	-	0.9	3 (1-6)	Obese class I and II pts pooled								5.2	2.8	-	1.5	3.8	-	1.5	2 (1-4)
Vaduganathan et al.[17]	2	5	-	0	1	-	0	6.5 (5-9)	Obese class I, II, III pts pooled								Obese class I, II, III pts pooled							
van Straten et al.[10]	2.4	4.6	-	2.7	-	-	-	-	2.5	5.2	-	5.2	-	-	-	-	Obese class II and III pts pooled							
van Straten et al.[18]	3.7	7.6	-	1.7	-	-	-	-	3.1	6.0	-	1.0	-	-	-	-	Obese class II and III pts pooled							
Wagner et al.[9]	3.0	2.6	-	-	1.7	1.7	1.1	-	3.6	2.0	-	-	1.3	2.6	1.4	-	Obese class II and III pts pooled							
Zalewska-Adamiec et al.[27]	2.5	7.7	-	2.5	0	-	-	-	20	0	-	10	0	-	-	-	Obese class II and III pts pooled							
Zitterman et al.[19]	2.9	9.1	-	0.8	2.9	-	-	13 (11-16)	2.7	6.7	-	0.8	2.5	-	-	13 (11-16)	Obese class II and III pts pooled							

Abbreviations: BMI, body mass index; DSWI, deep sternal wound infection; IQR, interquartile range; LOS, length of hospital stay; RRT, renal replacement therapy; SD, standard deviation.

*Intended as in-hospital or 30-day mortality (all cause).

†Expressed as mean (SD) or median (range/IQR).

‡Intended as neurological complication or cerebrovascular accident (stroke and TIA).

§Expressed as mean only, no SD provided.

Table 11. Summary of the Comparison Dataset

Comparison*	Subgroup	Studies (n)	Normal Event	Normal Total	Event	Total
Normal *vs* Overweight	All	6	4428	101142	4785	165632
	CABG+VALVE	2	90	2597	92	3254
	iCABG	15	1261	37402	1751	69256
	VAD	1	99	247	77	220
	VALVE	3	61	1457	48	1939
	modified WHO classification	12	728	17803	870	29482
	standard WHO classification	15	5211	125042	5883	210819
	NOS #6	3	51	2015	98	4013
	NOS #7	2	107	382	84	387
	NOS #8	12	652	19968	758	31835
	NOS #9	10	5129	120480	5813	204066
	Total	*27*	*5939*	*142845*	*6753*	*240301*
Normal *vs* Obese class I	All	5	4210	97410	2213	81649
	iCABG	10	1182	32669	894	33184
	VAD	1	99	247	30	72
	VALVE	1	20	484	11	301
	modified WHO classification	10	446	12030	256	9061
	standard WHO classification	7	5065	118780	2892	106145
	NOS #6	3	51	2015	31	1685
	NOS #7	1	99	247	30	72
	NOS #8	5	291	9568	189	7893
	NOS #9	8	5070	118980	2898	105556
	Total	*17*	*5511*	*130810*	*3148*	*115206*
Normal *vs* Obese class II	All	2	4073	93346	619	21738
	iCABG	2	211	5659	53	2181
	modified WHO classification	1	103	2184	28	785
	standard WHO classification	3	4181	96821	644	23134
	NOS #8	1	108	3475	25	1396
	NOS #9	3	4176	95530	647	22523
	Total	*4*	*4284*	*99005*	*672*	*23919*
Normal *vs* Obese class III	All	3	4291	97078	255	6686
	iCABG	2	211	5659	25	968
	modified WHO classification	2	321	5916	45	950
	standard WHO classification	3	4181	96821	235	6704
	NOS #8	2	326	7207	44	1242
	NOS #9	3	4176	95530	236	6412
	Total	*5*	*4502*	*102737*	*280*	*7654*
Normal *vs* Underweight	All	5	4401	100619	334	4026
	CABG+VALVE	1	64	2041	15	328
	iCABG	10	1012	31457	56	1606
	VAD	1	99	247	15	35

Table 11 (Continued)						
Comparison*	**Subgroup**	**Studies (n)**	**Normal Event**	**Normal Total**	**Event**	**Total**
Normal *vs* Underweight	VALVE	2	60	1349	8	107
	modified WHO classification	11	625	15619	99	1311
	standard WHO classification	8	5011	120094	329	4791
	NOS #6	2	44	1978	2	111
	NOS #7	1	99	247	15	35
	NOS #8	10	645	19540	85	1229
	NOS #9	6	4848	113948	326	4727
	Total	*19*	*5636*	*135713*	*428*	*6102*

Abbreviations: CABG, coronary artery bypass grafting; iCABG, isolated CABG; Na, not applicable; NOS, New-Ottawa scale (number, score); VAD, ventricular assist device; WHO, World Health Organization.

*Comparison performed among BMI groups defined by standard or modified WHO classification:[1,2] underweight (BMI<18.5 or 20 Kg/m^2), normal weight (BMI 18.5/20-<25), overweight (BMI 25-<30), obese class I (BMI 30-<35), obese class II (BMI 35-<40), and obese class III (BMI ≥ 40): modified WHO classification: cut-off for underweight/normal weight groups set at BMI of 20 kg/m^2; standard WHO classification: cut-off for underweight/normal weight groups set at BMI of 18 kg/m^2.

Table 12. Quality Assessment of Observational Studies According the New-Ottawa Scale

Study (author)	Selection	Comparability	Outcome	Exposure	*Total*
Allama et al.[13]	4	2	3	-	*9*
Atalan et al.[12]	4	2	2	-	*8*
Benedetto et al.[21]	4	2	3	-	*9*
Brát et al.[22]	4	1	1	-	*6*
Caliskan et al.[23]	4	2	2	-	*6*
Čemerlić-Adjić et al.[10]	4	2	2	-	*8*
Gurm et al.[2]	4	2	3	-	*9*
Jin et al.[6]	4	2	2	-	*8*
Le-Bert et al.[24]	3	2	2	-	*7*
Lopez-Delgado et al.[25]	4	2	3	-	*9*
Musci et al.[20]	3	2	2	-	*7*
Orhan et al.[3]	4	2	2	-	*8*
Pan et al.[7]	4	2	3	-	*9*
Rahamanian et al.[14]	4	2	2	-	*8*
Ranucci et al.[8]	4	2	3	-	*9*
Reeves et al.[15]	4	2	3	-	*9*
Reser et al.[4]	3	2	3	-	*8*
Shirzad et al.[16]	4	2	2	-	*8*
Stamou et al.[26]	4	2	3	-	*9*
Sun et al.[5]	4	1	3	-	*8*
Vaduganathan et al.[17]	4	2	2	-	*8*
van Straten et al.[10]	4	2	2	-	*8*
van Straten et al.[18]	4	2	2	-	*8*
Wagner et al.[9]	4	2	3	-	*9*
Zalewska-Adamiec et al.[27]	2	2	2	-	*6*
Zitterman et al.[19]	4	2	2	-	*8*

A study can be awarded a maximum of 4 points for the Selection category, 2 points for the comparability category and 3 points for the Outcome/Exposure categories. Therefore the maximum points a study can obtain is 9 which indicates a high quality study.[38]

Table 13. Models Summary of Comparison and Sub-group Analysis

Comparison	Subgroup	Studies (n)	Estimate			I^2	H^2	τ^2	Q	Q *P* value
			RR	95%CI	*P* value					
Normal *vs* Overweight	*All Studies*	*27*	*0.73*	*0.66-0.81*	*<0.001*	*62.27*	*2.65*	*0.02*	*59.99*	*<0.001*
	All procedures	6	0.76	0.65-0.89	0.001	63.48	2.74	0.02	13.28	0.021
	CABG+VALVE	2	0.65	0.24-1.76	0.394	88.23	8.50	0.46	8.50	0.004
	iCABG	15	0.70	0.61-0.81	<0.001	44.03	1.79	0.02	23.83	0.048
	VAD	1	0.87	0.69-1.11	0.260	Na	Na	0.00	0.00	1.000
	VALVE	3	0.58	0.40-0.85	0.005	0.00	1.00	0.00	0.42	0.811
	mod WHO†	12	0.80	0.71-0.90	<0.001	26.29	1.36	0.01	13.91	0.238
	stand WHO‡	15	0.67	0.58-0.77	<0.001	71.05	3.45	0.03	36.16	0.001
	NOS #8	12	0.75	0.66-0.85	<0.001	18.24	1.22	0.01	10.76	0.463
	NOS #9	10	0.68	0.57-0.80	<0.001	81.89	5.52	0.04	33.98	<0.001
Normal *vs* Obese class I	*All Studies*	*17*	*0.76*	*0.67-0.86*	*<0.001*	*62.06*	*2.64*	*0.03*	*42.25*	*<0.001*
	All procedures	5	0.77	0.60-0.98	0.036	60.87	2.56	0.04	11.92	0.018
	iCABG	10	0.72	0.65-0.81	<0.001	9.53	1.11	0.00	11.97	0.215
	VAD	1	1.04	0.76-1.42	0.808	Na	Na	0.00	0.00	1.000
	VALVE	1	0.88	0.43-1.82	0.739	Na	Na	0.00	0.00	1.000
	mod WHO†	10	0.86	0.73-1.02	0.084	13.40	1.15	0.01	8.23	0.512
	stand WHO‡	7	0.68	0.60-0.77	<0.001	61.10	2.57	0.01	19.37	0.004
	NOS #8	5	0.80	0.64-1.01	0.057	26.64	1.36	0.02	4.56	0.336
	NOS #9	8	0.70	0.61-0.79	<0.001	58.94	2.44	0.01	18.27	0.011
Normal *vs* Obese class II	*All Studies*	*4*	*0.65*	*0.60-0.71*	*<0.001*	*0.00*	*1.00*	*0.00*	*5.24*	*0.155*
	All procedures	2	0.91	0.39-2.12	0.829	77.35	4.41	0.30	4.41	0.036
	iCABG	2	0.66	0.49-0.89	0.007	0.00	1.00	0.00	0.80	0.370
	mod WHO†	1	0.76	0.50-1.14	0.181	Na	Na	0.00	0.00	1.000
	stand WHO‡	3	0.65	0.60-0.70	<0.001	0.00	1.00	0.00	4.72	0.095
	NOS #9	3	0.76	0.54-1.08	0.126	59.79	2.49	0.05	4.90	0.086

Table 13 (Continued)

Comparison	Subgroup	Studies (n)	Estimate			I^2	H^2	τ^2	Q	Q *P* value
			RR	95%CI	*P* value					
Normal *vs* Obese class III	*All Studies*	*5*	*0.83*	*0.74-0.94*	*0.003*	*0.00*	*1.00*	*0.00*	*1.27*	*0.867*
	All procedures	3	0.85	0.75-0.96	0.008	0.00	1.00	0.00	0.17	0.918
	iCABG	2	0.71	0.47-1.07	0.102	0.00	1.00	0.00	0.47	0.493
	mod WHO†	2	0.87	0.64-1.18	0.375	0.00	1.00	0.00	0.07	0.786
	stand WHO‡	3	0.82	0.71-0.96	0.011	2.08	1.02	0.00	1.10	0.578
	NOS #8	2	0.80	0.57-1.12	0.195	13.13	1.15	0.01	1.15	0.283
	NOS #9	3	0.84	0.74-0.95	0.007	0.00	1.00	0.00	0.07	0.965
Normal *vs* Underweight	*All Studies*	*19*	*1.77*	*1.30-2.42*	*<0.001*	*77.73*	*4.49*	*0.27*	*59.29*	*<0.001*
	All procedures	5	1.93	1.73-2.14	<0.001	0.01	1.00	0.00	2.49	0.646
	CABG+VALVE	1	1.46	0.84-2.53	0.179	Na	Na	0.00	0.00	1.000
	iCABG	10	2.07	1.11-3.87	0.022	74.53	3.93	0.64	47.27	<0.001
	VAD	1	1.07	0.71-1.61	0.750	Na	Na	0.00	0.00	1.000
	VALVE	2	1.72	0.84-3.51	0.139	0.00	1.00	0.00	0.29	0.589
	mod WHO†	11	2.00	1.39-2.90	<0.001	60.73	2.55	0.19	23.25	0.010
	stand WHO‡	8	1.51	0.90-2.54	0.118	79.76	4.94	0.36	36.01	<0.001
	NOS #8	10	2.05	1.65-2.55	<0.001	0.00	1.00	0.00	6.38	0.701
	NOS #9	6	1.71	0.77-3.80	0.187	91.09	11.22	0.80	44.10	<0.001

Abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; mod, modified; iCABG, isolated CABG; Na, not applicable; NOS, New-Ottawa scale (number,score); RR, risk ratio; stand, standard; VAD, ventricular assist device; WHO, World Health Organization.

*Comparison performed among BMI groups defined by standard or modified WHO classification:[1,2] underweight (BMI<18.5 or 20 Kg/m^2), normal weight (BMI 18.5/20-<25), overweight (BMI 25-<30), obese class I (BMI 30-<35), obese class II (BMI 35-<40), and obese class III (BMI ≥ 40).

†modified WHO classification: cut-off for underweight/normal weight groups set at BMI of 20 kg/m^2.

‡standard WHO classification: cut-off for underweight/normal weight groups set at BMI of 18.5 kg/m^2.

Table 14. Influence Analysis – Numerical Data

Comparison *,†	Author	Year	OP Type	BMI class	NOS	rstudent	dffits	cook.d	cov.r	dfbτ	hat	weight	Est (RR)	95%CI	Z value	*P* value	Q	Q *P* value	τ^2	I^2	H^2	Influential
Normal *vs* Overweight	Allama et al.[13]	2014	iCABG	mWHO	9	-1.24	-0.20	0.04	1.02	-0.20	0.03	2.53	0.74	0.67-0.82	-6.03	<0.001	58.66	<0.001	0.02	62.52	2.67	
	Atalan et al.[12]	2012	iCABG	sWHO	8	-0.54	-0.06	0.00	1.03	-0.06	0.01	1.18	0.73	0.67-0.81	-6.13	<0.001	59.82	<0.001	0.02	63.66	2.75	
	Benedetto et al.[21]	2014	iCABG	mWHO	9	-1.96	-0.47	0.18	0.87	-0.46	0.06	6.34	0.75	0.68-0.82	-6.26	<0.001	55.12	<0.001	0.02	52.65	2.11	
	Brát et al.[22]	2005	All	sWHO	6	0.37	0.06	0.00	1.07	0.06	0.03	3.23	0.73	0.66-0.81	-6.11	<0.001	59.41	<0.001	0.03	64.39	2.81	
	Caliskan et al.[23]	2014	iCABG	sWHO	6	2.12	0.32	0.10	0.93	0.33	0.02	2.17	0.72	0.66-0.79	-6.83	<0.001	53.47	0.001	0.02	58.77	2.43	
	Čemerlić-Adjić et al.[10]	2014	iCABG	mWHO	8	0.54	0.04	0.00	1.01	0.04	0.01	0.52	0.73	0.66-0.81	-6.28	<0.001	59.56	<0.001	0.02	63.33	2.73	
	Gurm et al.[2]	2002	iCABG	sWHO	9	0.15	0.01	0.00	1.02	0.01	0.01	0.83	0.73	0.66-0.81	-6.22	<0.001	59.90	<0.001	0.02	63.59	2.75	
	Jin et al.[6]	2005	iCABG	mWHO	8	-0.83	-0.22	0.05	1.10	-0.22	0.06	6.10	0.74	0.67-0.82	-5.78	<0.001	59.44	<0.001	0.03	63.29	2.72	
	Le-Bert et al.[24]	2011	iCABG	mWHO	7	-0.07	-0.01	0.00	1.02	-0.01	0.01	0.89	0.73	0.66-0.81	-6.19	<0.001	59.98	<0.001	0.02	63.65	2.75	
	Lopez-Delgado et al.[25]	2015	All	mWHO	9	0.58	0.10	0.01	1.06	0.10	0.03	3.18	0.73	0.66-0.81	-6.18	<0.001	59.00	<0.001	0.03	63.99	2.78	
	Musci et al.[20]	2008	VAD	sWHO	7	0.93	0.24	0.06	1.07	0.24	0.06	6.43	0.72	0.65-0.80	-6.29	<0.001	55.71	<0.001	0.02	62.03	2.63	
	Orhan et al.[3]	2004	iCABG	mWHO	9	0.63	0.06	0.00	1.02	-0.27	0.01	0.92	0.73	0.66-0.81	-6.28	<0.001	59.35	<0.001	0.02	63.39	2.73	
	Pan et al.[7]	2006	iCABG	sWHO	8	-0.81	-0.21	0.05	1.10	0.06	0.06	6.04	0.74	0.67-0.82	-5.78	<0.001	59.48	<0.001	0.03	63.40	2.73	
	Rahamanian et al.[14]	2007	CABG+VALVE	sWHO	9	1.68	0.39	0.14	0.93	-0.21	0.05	4.76	0.72	0.65-0.79	-6.88	<0.001	53.44	0.001	0.02	57.26	2.34	
	Ranucci et al.[8]	2014	All	mWHO	8	1.58	0.35	0.12	0.95	0.40	0.04	4.47	0.72	0.65-0.79	-6.77	<0.001	54.29	0.001	0.02	58.49	2.41	
	Reeves et al.[15]	2003	iCABG	sWHO	9	0.45	0.05	0.00	1.03	0.36	0.01	1.46	0.73	0.66-0.81	-6.23	<0.001	59.54	<0.001	0.02	63.70	2.75	
	Reser et al.[4]	2013	VALVE	mWHO	9	-0.37	-0.01	0.00	1.00	0.05	0.00	0.09	0.73	0.66-0.81	-6.25	<0.001	59.88	<0.001	0.02	63.24	2.72	
	Shirzad et al.[16]	2009	iCABG	mWHO	8	0.19	0.03	0.00	1.07	-0.01	0.03	2.83	0.73	0.66-0.81	-6.09	<0.001	59.73	<0.001	0.03	64.46	2.81	
	Stamou et al.[26]	2011	CABG+VALVE	mWHO	8	-1.97	-0.26	0.07	0.96	0.03	0.02	2.09	0.74	0.67-0.82	-6.13	<0.001	56.24	<0.001	0.02	60.35	2.52	
	Sun et al.[5]	2009	All	sWHO	9	-0.22	-0.08	0.01	1.19	-0.27	0.08	7.62	0.74	0.66-0.82	-5.68	<0.001	59.88	<0.001	0.03	64.84	2.84	
	Vaduganathan et al.[17]	2012	VALVE	mWHO	8	-1.11	-0.19	0.04	1.03	-0.08	0.03	2.85	0.74	0.67-0.82	-6.00	<0.001	58.97	<0.001	0.02	62.84	2.69	
	van Straten et al.[10]	2010	iCABG	sWHO	8	0.38	0.08	0.01	1.12	-0.19	0.05	5.30	0.73	0.66-0.81	-6.00	<0.001	58.93	<0.001	0.03	64.82	2.84	
	van Straten et al.[18]	2013	VALVE	sWHO	8	-0.26	-0.04	0.00	1.05	0.08	0.02	2.16	0.73	0.66-0.81	-6.07	<0.001	59.98	<0.001	0.03	64.22	2.79	
	Wagner et al.[9]	2007	iCABG	mWHO	8	0.54	0.15	0.03	1.19	-0.04	0.09	9.46	0.73	0.65-0.81	-5.90	<0.001	46.71	0.005	0.03	56.41	2.29	
	Zalewska-Adamiec. et al.[27]	2012	iCABG	mWHO	9	-0.69	-0.07	0.00	1.02	0.16	0.01	0.92	0.73	0.67-0.81	-6.14	<0.001	59.66	<0.001	0.02	63.50	2.74	
	Zitterman et al.[19]	2014	All	sWHO	6	0.75	0.18	0.03	1.09	-0.07	0.05	5.50	0.73	0.66-0.80	-6.18	<0.001	57.49	<0.001	0.03	63.44	2.73	
	NACSA registry	2015	All	mWHO	8	-0.81	-0.27	0.08	1.16	0.18	0.10	10.14	0.74	0.67-0.82	-5.57	<0.001	41.87	0.019	0.03	48.52	1.94	

Table 14 (Continued)

Comparison *,†	Author	Year	OP Type	BMI class	NOS	rstudent	dffits	cook.d	cov.r	dfbt	hat	weight	Est (RR)	95%CI	Z value	*P* value	Q	Q *P* value	τ^2	I^2	H^2	Influential
Normal *vs* Obese class I	Atalan et al.[12]	2012	iCABG	sWHO	8	-0.66	-0.10	0.01	1.04	-0.09	0.01	1.40	0.76	0.67-0.87	-4.18	<0.001	42.08	<0.001	0.03	64.31	2.80	
	Benedetto et al.[21]	2014	iCABG	mWHO	9	-1.32	-0.41	0.17	1.09	-0.41	0.09	9.14	0.78	0.68-0.89	-3.78	<0.001	41.46	<0.001	0.02	61.28	2.58	
	Brat et al.[22]	2005	All	sWHO	6	-0.78	-0.18	0.03	1.08	-0.17	0.03	3.39	0.77	0.67-0.87	-4.02	<0.001	42.09	<0.001	0.03	64.76	2.84	
	Caliskan et al.	2014	iCABG	sWHO	6	1.39	0.25	0.06	0.97	0.26	0.03	2.53	0.75	0.66-0.84	-4.66	<0.001	38.75	0.001	0.02	61.14	2.57	
	Gurm et al.[2]	2002	iCABG	sWHO	9	0.53	0.06	0.00	1.01	0.06	0.01	1.16	0.75	0.67-0.86	-4.37	<0.001	41.62	<0.001	0.03	63.56	2.74	
	Jin et al.[6]	2005	iCABG	mWHO	8	-0.77	-0.29	0.09	1.18	-0.29	0.09	8.72	0.77	0.67-0.88	-3.74	<0.001	42.23	<0.001	0.03	64.79	2.84	
	Lopez-Delgado et al.[25]	2015	All	mWHO	9	1.16	0.29	0.08	1.00	0.29	0.05	4.62	0.74	0.66-0.84	-4.64	<0.001	38.65	0.001	0.02	60.95	2.56	
	Musci et al.[20]	2008	VAD	sWHO	7	1.64	0.65	0.35	0.88	0.66	0.08	8.01	0.73	0.65-0.82	-5.27	<0.001	33.82	0.004	0.02	53.01	2.13	
	Pan et al.[7]	2006	iCABG	sWHO	9	-0.49	-0.21	0.05	1.20	-0.59	0.09	8.54	0.77	0.67-0.88	-3.77	<0.001	42.18	<0.001	0.03	65.70	2.92	
	Ranucci et al.[8]	2014	All	mWHO	9	0.54	0.10	0.01	1.07	-0.21	0.04	4.38	0.75	0.66-0.86	-4.30	<0.001	40.86	<0.001	0.03	63.92	2.77	
	Reeves et al.[15]	2003	iCABG	sWHO	9	0.22	0.02	0.00	1.03	0.10	0.01	1.45	0.76	0.67-0.86	-4.31	<0.001	41.98	<0.001	0.03	63.95	2.77	
	van Straten et al.[10]	2010	iCABG	sWHO	9	1.02	0.30	0.08	1.03	0.02	0.07	6.52	0.74	0.65-0.84	-4.58	<0.001	38.22	0.001	0.02	61.02	2.57	
	van Straten et al.[18]	2013	VALVE	sWHO	8	0.39	0.05	0.00	1.04	0.30	0.03	2.54	0.75	0.66-0.86	-4.31	<0.001	41.59	<0.001	0.03	64.01	2.78	
	Wagner et al.[9]	2007	iCABG	mWHO	8	-0.09	-0.12	0.02	1.34	0.05	0.14	14.35	0.76	0.66-0.88	-3.64	<0.001	35.16	0.002	0.03	54.99	2.22	
	Zalewska-Adamiec et al.[27]	2012	iCABG	mWHO	9	-1.66	-0.11	0.01	1.01	-0.13	0.00	0.37	0.76	0.67-0.87	-4.21	<0.001	39.89	<0.001	0.03	63.89	2.77	
	Zitterman et al.[19]	2014	All	sWHO	6	0.91	0.27	0.07	1.06	-0.11	0.07	7.28	0.74	0.65-0.85	-4.49	<0.001	38.24	0.001	0.02	61.55	2.60	
	NACSA registry	2015	All	mWHO	8	-1.67	-0.64	0.28	0.98	0.27	0.16	15.61	0.78	0.69-0.89	-3.87	<0.001	21.05	0.135	0.02	33.67	1.51	
Normal *vs* Obese class II	Jin et al.[6]	2005	iCABG	mWHO	8	-0.77	-2.65	14.95	18.45	-1.03	0.03	3.47	0.76	0.54-1.08	-1.53	0.126	4.90	0.086	0.05	59.79	2.49	*
	Pan et al.[7]	2006	iCABG	sWHO	9	0.72	0.14	0.02	1.04	-1.02	0.04	3.83	0.65	0.60-0.70	-10.37	<0.001	4.72	0.095	0.00	0.00	1.00	
	Ranucci et al.[8]	2014	All	mWHO	9	2.10	0.21	0.04	1.01	0.14	0.01	0.95	0.65	0.60-0.70	-10.59	<0.001	0.84	0.658	0.00	0.00	1.00	
	NACSA registry	2015	All	mWHO	9	-0.52	-0.65	21.51	32.58	0.21	0.92	91.75	0.79	0.50-1.25	-1.02	0.310	4.50	0.106	0.09	57.19	2.34	*
Normal *vs* Obese class III	Jin et al.[6]	2005	iCABG	mWHO	8	-1.04	-0.21	0.05	1.04	-0.21	0.04	4.05	0.84	0.75-0.95	-2.74	0.006	0.19	0.980	0.00	0.00	1.00	
	Pan et al.[7]	2006	iCABG	sWHO	9	-0.08	-0.02	0.00	1.05	0.53	0.04	4.41	0.83	0.74-0.94	-2.93	0.003	1.26	0.738	0.00	0.00	1.00	
	Ranucci et al.[8]	2014	All	mWHO	9	-0.24	-0.01	0.00	1.00	-0.02	0.00	0.19	0.83	0.74-0.94	-3.00	0.003	1.21	0.751	0.00	0.00	1.00	
	Sun et al.[5]	2009	All	sWHO	9	0.41	0.14	0.02	1.12	-0.01	0.11	10.82	0.83	0.73-0.94	-2.98	0.003	1.10	0.778	0.00	0.00	1.00	
	NACSA registry	2015	All	mWHO	8	0.26	0.53	0.28	5.14	0.14	0.81	80.54	0.81	0.62-1.06	-1.56	0.118	1.20	0.753	0.00	0.00	1.00	*

Table 14 (Continued)

Comparison *,†	Author	Year	OP Type	BMI class	NOS	rstudent	dffits	cook.d	cov.r	dfbτ	hat	weight	Est (RR)	95%CI	Z value	*P* value	Q	Q *P* value	τ^2	I^2	H^2	Influential
Normal *vs* Underweight	Allama et al.[13]	2014	iCABG	mWHO	9	-0.63	-0.17	0.03	1.11	-0.17	0.06	5.97	1.82	1.31-2.53	3.58	<0.001	58.06	<0.001	0.29	78.97	4.76	
	Atalan et al.[12]	2012	iCABG	sWHO	8	0.88	0.18	0.03	1.05	0.18	0.04	3.91	1.72	1.25-2.37	3.35	0.001	58.06	<0.001	0.28	78.54	4.66	
	Brat et al.[22]	2005	All	sWHO	6	-0.92	-0.13	0.02	1.03	-0.13	0.02	1.96	1.81	1.32-2.48	3.68	<0.001	58.19	<0.001	0.28	78.81	4.72	
	Caliskan et al.[23]	2014	iCABG	sWHO	6	-0.37	-0.06	0.00	1.04	-0.06	0.02	1.91	1.79	1.30-2.46	3.59	<0.001	59.10	<0.001	0.28	79.07	4.78	
	Cemrmelic-Adjic et al.[11]	2014	iCABG	mWHO	8	0.29	0.03	0.00	1.02	0.03	0.01	1.04	1.76	1.29-2.42	3.54	<0.001	59.20	<0.001	0.28	78.88	4.73	
	Gurm et al.[2]	2002	iCABG	sWHO	9	0.17	0.02	0.00	1.04	0.02	0.02	1.80	1.77	1.29-2.43	3.52	<0.001	59.26	<0.001	0.28	79.04	4.77	
	Jin et al.[5]	2005	iCABG	mWHO	8	0.54	0.13	0.02	1.11	0.13	0.06	6.09	1.73	1.25-2.41	3.29	0.001	58.51	<0.001	0.29	78.89	4.74	
	Musci et al.[20]	2008	VAD	sWHO	7	-0.92	-0.27	0.08	1.10	-0.27	0.08	7.94	1.85	1.33-2.57	3.69	<0.001	52.74	<0.001	0.28	76.48	4.25	
	Rahmanian et al.	2007	CABG+VALVE	sWHO	9	-0.33	-0.11	0.01	1.15	0.03	0.07	7.16	1.80	1.29-2.52	3.46	0.001	58.69	<0.001	0.30	78.92	4.74	
	Ranucci et al.	2014	All	mWHO	8	0.38	0.08	0.01	1.12	-0.11	0.06	5.96	1.75	1.26-2.43	3.32	0.001	58.93	<0.001	0.29	79.17	4.80	
	Reeves et al.[15]	2003	iCABG	sWHO	9	2.31	0.60	0.30	0.85	0.08	0.05	5.40	1.62	1.22-2.16	3.31	0.001	49.33	<0.001	0.20	72.01	3.57	
	Shirzad et al.[16]	2009	iCABG	mWHO	9	0.70	0.12	0.02	1.05	0.61	0.03	3.18	1.74	1.26-2.39	3.39	0.001	58.60	<0.001	0.28	78.84	4.73	
	Sun et al.[6]	2009	All	sWHO	8	0.35	0.09	0.01	1.16	0.12	0.08	8.13	1.75	1.25-2.44	3.25	0.001	58.35	<0.001	0.30	77.17	4.38	
	Vaduganathan et al.[17]	2012	VALVE	mWHO	8	-0.31	-0.08	0.01	1.10	0.09	0.05	4.75	1.79	1.29-2.49	3.51	<0.001	59.06	<0.001	0.29	79.42	4.86	
	van Straten et al.[10]	2010	iCABG	sWHO	8	0.94	0.25	0.06	1.07	-0.08	0.07	6.65	1.70	1.23-2.35	3.23	0.001	56.45	<0.001	0.27	77.63	4.47	
	van Straten et al.[18]	2013	VALVE	sWHO	8	0.23	0.04	0.00	1.10	0.25	0.05	4.59	1.76	1.27-2.44	3.40	0.001	59.20	<0.001	0.29	79.37	4.85	
	Wagner et al.[9]	2007	iCABG	mWHO	8	-3.79	-0.86	0.32	0.52	0.04	0.07	7.41	1.94	1.55-2.43	5.75	<0.001	26.67	0.063	0.08	49.76	1.99	*
	Zitterman et al.[19]	2014	All	sWHO	9	-0.28	-0.09	0.01	1.15	-0.82	0.07	7.03	1.80	1.29-2.51	3.44	0.001	58.88	<0.001	0.30	79.05	4.77	
	NACSA registry	2015	All	mWHO	8	0.15	0.03	0.00	1.19	-0.09	0.09	9.11	1.76	1.25-2.48	3.27	0.001	55.55	<0.001	0.31	69.47	3.28	

Abbreviations: All, all type of cardiac surgical operations; BMI, body mass index; iCABG, isolated coronary artery bypass grafting; MI, myocardial infarction; mWHO, modified (classification of obesity, underweight cut-off at 20 Kg/m^2) World Health Organization; sWHO, standard (classification of obesity, underweight cut-off at 18.5 Kg/m^2) World Health Organization; VAD, ventricular assist device; WHO, World Health Organization.

*Comparison performed among BMI classes defined by standard or modified WHO classification:[1,2] underweight (BMI<18.5 or 20 Kg/m^2), normal weight (BMI 18.5/20-<25), overweight (BMI 25-<30), obese class I (BMI 30-<35), obese class II (BMI 35-<40), and obese class III (BMI ≥ 40).

†**rstudent**, externally standardised residuals; **dffits**, indicates how many standard deviations the predicted (average) effect for the ith study changes after excluding the ith study from the model fitting; **cook.d,** cook distances; **cov.r,** covariance ratios; **dfb,** DFBETAS = (regression coefficient for whole data-set) – (regression coefficient with the specific study deleted); **Hat,** hat values; **Weight,** study weight; **Est,** estimate - model estimate without the specific study; ***Z* Value,** z values without the specific study; ***P*** Value, ***P*** value for the estimate; ***Q,*** Q test value; **Q *P* Value,** Q-test *P* value; τ^2 – Tau^2 for a model without the specific study; ***I*^{2},** I^2 for a model without the specific study; ***H*^{2}**, H^2 for a model without the specific study; **Influential** - Asterisks indicate an influential study for which DFFITS value is larger than 3*sqrt(p/(k-p)), (p = number of model Coefficients, k = number of studies), or lower tail area of a chi-square distribution with p degrees of freedom cut off by the Cook's distance is larger than 50%, or hat > 3(p/k) or DFBETAS > 1, as described in the metaphor package manual.[38,39]

Table 15. Meta-regression Analysis (Continuous Moderators) – Numerical Data

Comparison*	Correction	Missing data	τ^2	I^2	H^2	R^2	Q	Q *P* Value	QM	QM *P* value	intercept. est	intercept. *P* value	moderator. est	moderator0. *P* value
Normal *vs* Overweight	*All Studies in, no Mods*	*0*	*0.024*	*62.27*	*2.65*	*NA*	*59.99*	*<0.001*	*NA*	*NA*	*-0.312*	*<0.001*	*NA*	*NA*
	Cohort Size	0	0.03	50.29	2.01	0.00	43.51	0.012	0.56	0.456	-0.294	0.000	0.000	0.456
	Quality	0	0.02	53.32	2.14	23.29	49.10	0.003	3.63	0.057	0.56	0.224	-0.105	0.057
	Year	0	0.025	51.26	2.05	0.00	43.01	0.014	0.38	0.540	16.487	0.547	-0.008	0.540
	Age-no Mods	4	0.022	62.20	2.65	NA	51.13	<0.001	NA	NA	-0.343	<0.001	NA	NA
	Age	4	0.013	46.96	1.89	40.22	37.24	0.016	3.53	0.060	0.996	0.164	-0.021	0.060
	EF-no Mods	19	0.021	27.11	1.37	NA	7.75	0.355	NA	NA	-0.256	0.012	NA	NA
	EF	19	0.011	13.98	1.16	48.99	5.46	0.487	1.21	0.271	0.858	0.400	-0.021	0.271
	Male-no Mods	2	0.021	59.89	2.49	NA	54.20	<0.001	NA	NA	-0.329	<0.001	NA	NA
	Male	2	0.022	61.52	2.60	0.00	53.74	<0.001	0.57	0.450	-0.319	<0.001	0.000	0.450
	NYHA-no Mods	20	0.000	0.78	1.01	NA	5.39	0.495	NA	NA	-0.444	<0.001	NA	NA
	NYHA	20	0.010	22.07	1.28	0.00	4.84	0.436	1.01	0.315	-0.175	0.595	-1.063	0.315
	MI-no Mods	8	0.019	61.86	2.62	NA	47.70	<0.001	NA	NA	-0.309	<0.001	NA	NA
	MI	8	0.022	54.53	2.20	0.00	32.94	0.011	0.06	0.811	-0.282	0.022	-0.097	0.811
	Hypertension-no Mods	6	0.017	45.56	1.84	NA	35.11	0.020	NA	NA	-0.325	<0.001	NA	NA
	Hypertension	6	0.015	41.33	1.70	10.44	29.23	0.062	2.41	0.121	-0.025	0.899	-0.532	0.121
	Diabetes-no Mods	3	0.022	62.13	2.64	NA	53.60	<0.001	NA	NA	-0.333	<0.001	NA	NA
	Diabetes	3	0.014	44.19	1.79	35.59	35.18	0.037	2.26	0.132	-0.516	<0.001	0.854	0.132
	Dyslipidemia-no Mods	16	0.014	26.67	1.36	NA	14.15	0.166	NA	NA	-0.312	<0.001	NA	NA
	Dyslipidemia	16	0.015	25.39	1.34	0.00	12.82	0.171	0.29	0.587	-0.175	0.502	-0.249	0.587
	Smoker-no Mods	16	0.016	63.15	2.71	NA	31.14	0.001	NA	NA	-0.321	<0.001	NA	NA
	Smoker	16	0.012	37.16	1.59	26.41	14.66	0.101	2.44	0.118	-0.482	<0.001	0.586	0.118
	COPD-no Mods	7	0.030	69.10	3.24	NA	48.31	<0.001	NA	NA	-0.346	<0.001	NA	NA
	COPD	7	0.040	68.61	3.19	0.00	40.29	0.002	0.18	0.673	-0.293	0.039	-0.420	0.673
	CVA-no Mods	11	0.021	67.54	3.08	NA	39.62	0.001	NA	NA	-0.378	<0.001	NA	NA
	CVA	11	0.018	54.24	2.19	15.17	24.26	0.043	0.94	0.332	-0.451	<0.001	0.850	0.332
	PVD-no Mods	11	0.034	59.49	2.47	NA	28.78	0.017	NA	NA	-0.321	<0.001	NA	NA
	PVD	11	0.035	58.00	2.38	0.00	27.94	0.014	1.05	0.305	-0.466	0.003	1.504	0.305

Table 15 (Continued)

Comparison*	Correction	Missing data	τ^2	I^2	H^2	R^2	Q	Q *P* Value	QM	QM *P* value	intercept. est	intercept0. *P* value	moderator. est	moderator0. *P* value
Normal *vs* Overweight	CKD-no Mods	11	0.017	39.95	1.67	NA	24.26	0.061	NA	NA	-0.301	<0.001	NA	NA
	CKD	11	0.023	44.21	1.79	0.00	22.90	0.062	0.11	0.745	-0.325	0.001	0.249	0.745
Normal *vs* Obese class I	*All Studies in, no Mods*	*0*	*0.025*	*62.06*	*2.64*	*NA*	*42.25*	*<0.001*	*NA*	*NA*	*-0.278*	*<0.001*	*NA*	*NA*
	Cohort Size	0	0.014	32.19	1.48	43.42	20.50	0.154	3.49	0.062	-0.227	0.001	0.000	0.062
	Quality	0	0.02	49.41	1.98	37.92	31.97	0.006	1.95	0.163	0.493	0.383	-0.093	0.163
	Year	0	0.031	51.90	2.08	0.00	29.60	0.013	0.01	0.911	-4.018	0.904	0.002	0.911
	Age-no Mods	4	0.026	67.32	3.06	NA	35.87	<0.001	NA	NA	-0.309	<0.001	NA	NA
	Age	4	0.005	24.02	1.32	82.35	17.83	0.086	8.01	0.005	1.989	0.016	-0.037	0.005
	Age in modified WHO classes	7 included	0.019	21.551	1.275	9.960	6.189	0.288	0.821	0.365	0.944	0.443	-0.018	0.365
	Age in standard WHO classes	5 included	0.000	0.008	1.000	99.970	5.517	0.138	2.951	0.086	5.031	0.107	-0.083	0.086
	EF-no Mods	12	0.025	21.88	1.28	NA	6.15	0.188	NA	NA	-0.381	0.010	NA	NA
	EF	12	0.000	0.01	1.00	99.97	2.89	0.409	3.26	0.071	-3.728	0.045	0.060	0.071
	Male-no Mods	2	0.027	65.52	2.90	NA	40.23	<0.001	NA	NA	-0.288	<0.001	NA	NA
	Male	2	0.033	60.99	2.56	0.00	34.53	0.001	0.03	0.872	-0.228	0.516	-0.073	0.872
	NYHA-no Mods	14	0.000	0.00	1.00	NA	0.52	0.769	NA	NA	-0.486	<0.001	NA	NA
	NYHA	14	0.000	0.00	1.00	NA	0.42	0.515	0.10	0.751	-0.372	0.300	-0.340	0.751
	MI-no Mods	7	0.030	74.05	3.85	NA	34.47	<0.001	NA	NA	-0.261	0.001	NA	NA
	MI	7	0.033	60.99	2.56	0.00	21.24	0.007	0.18	0.674	-0.201	0.209	-0.234	0.674
	Hypertension-no Mods	5	0.037	58.69	2.42	NA	32.27	0.001	NA	NA	-0.231	0.008	NA	NA
	Hypertension	5	0.038	55.72	2.26	0.00	24.53	0.006	0.93	0.336	0.057	0.855	-0.520	0.336
	Diabetes-no Mods	3	0.029	68.41	3.17	NA	40.07	<0.001	NA	NA	-0.277	<0.001	NA	NA
	Diabetes	3	0.034	65.64	2.91	0.00	32.77	0.001	0.04	0.841	-0.306	0.097	0.153	0.841
	Dyslipidemia-no Mods	11	0.032	33.14	1.50	NA	8.94	0.111	NA	NA	-0.116	0.384	NA	NA
	Dyslipidemia	11	0.042	32.13	1.47	0.00	7.54	0.110	0.27	0.605	0.078	0.844	-0.387	0.605
	Smoker-no Mods	9	0.026	72.57	3.65	NA	25.85	0.001	NA	NA	-0.284	0.001	NA	NA
	Smoker	9	0.023	49.54	1.98	12.03	11.98	0.062	0.68	0.408	-0.425	0.021	0.475	0.408
	COPD-no Mods	5	0.020	62.43	2.66	NA	29.24	0.002	NA	NA	-0.311	<0.001	NA	NA
	COPD	5	0.026	61.48	2.60	0.00	23.88	0.008	0.00	0.985	-0.304	0.040	0.017	0.985

Table 15 (Continued)

Comparison*	Correction	Missing data	τ^2	I^2	H^2	R^2	Q	Q *P* Value	QM	QM *P* value	intercept. est	intercept0. *P* value	moderator. est	moderator0. *P* value
Normal *vs* Obese class I	CVA-no Mods	8	0.013	58.84	2.43	NA	21.19	0.007	NA	NA	-0.356	<0.001	NA	NA
	CVA	8	0.018	53.89	2.17	0.00	14.06	0.050	0.06	0.805	-0.371	0.001	0.241	0.805
	PVD-no Mods	8	0.041	64.93	2.85	NA	20.54	0.008	NA	NA	-0.264	0.006	NA	NA
	PVD	8	0.053	67.29	3.06	0.00	20.51	0.005	0.34	0.560	-0.378	0.114	1.299	0.560
	CKD-no Mods	8	0.000	0.00	1.00	NA	7.94	0.440	NA	NA	-0.276	<0.001	NA	NA
	CKD	8	0.000	0.00	1.00	NA	7.52	0.377	0.42	0.517	-0.343	0.002	0.452	0.517
Normal *vs* Underweight	*All Studies in, no Mods*	*0*	*0.274*	*77.73*	*4.49*	*NA*	*59.29*	*<0.001*	*NA*	*NA*	*0.572*	*<0.001*	*NA*	*NA*
	Cohort Size	0	0.311	69.63	3.29	0.00	56.76	0.000	0.06	0.815	0.592	0.001	0.000	0.815
	Quality	0	0.3	73.95	3.84	0.00	57.15	0	0.34	0.563	-0.467	0.796	0.127	0.563
	Year	0	0.299	72.70	3.66	0.00	56.27	<0.001	0.07	0.787	24.261	0.782	-0.012	0.787
	Age-no Mods	4	0.241	76.88	4.33	NA	48.57	<0.001	NA	NA	0.466	0.006	NA	NA
	Age	4	0.258	76.56	4.27	0.00	42.82	<0.001	0.40	0.526	-0.795	0.691	0.020	0.526
	EF-no Mods	13	0.024	7.53	1.08	NA	4.29	0.508	NA	NA	0.678	0.002	NA	NA
	EF	13	0.000	0.00	1.00	100.00	3.29	0.510	1.00	0.317	-1.734	0.469	0.049	0.317
	Male-no Mods	2	0.303	80.51	5.13	NA	58.91	<0.001	NA	NA	0.555	0.001	NA	NA
	Male	2	0.301	79.22	4.81	0.48	43.53	<0.001	0.43	0.510	1.227	0.236	-0.929	0.510
	NYHA-no Mods	14	0.263	74.14	3.87	NA	11.34	0.023	NA	NA	0.792	0.005	NA	NA
	NYHA	14	0.365	80.82	5.21	0.00	9.86	0.020	0.33	0.564	1.717	0.291	-2.871	0.564
	MI-no Mods	6	0.335	84.38	6.40	NA	53.59	<0.001	NA	NA	0.485	0.014	NA	NA
	MI	6	0.129	65.36	2.89	61.55	23.50	0.015	8.33	0.004	-0.322	0.291	3.083	0.004
	Hypertension-no Mods	5	0.100	60.01	2.50	NA	25.18	0.022	NA	NA	0.669	<0.001	NA	NA
	Hypertension	5	0.120	62.74	2.68	0.00	23.61	0.023	0.10	0.754	0.533	0.256	0.285	0.754
	Diabetes-no Mods	3	0.307	81.63	5.44	NA	57.82	<0.001	NA	NA	0.578	0.001	NA	NA
	Diabetes	3	0.324	77.39	4.42	0.00	52.56	<0.001	0.09	0.766	0.743	0.196	-0.871	0.766
	Dyslipidemia-no Mods	12	0.322	72.40	3.62	NA	19.10	0.004	NA	NA	0.652	0.018	NA	NA
	Dyslipidemia	12	0.188	52.46	2.10	41.70	9.48	0.091	2.67	0.103	-0.386	0.563	2.027	0.103
	Smoker-no Mods	11	0.578	87.29	7.87	NA	45.24	<0.001	NA	NA	0.469	0.134	NA	NA
	Smoker	11	0.539	82.77	5.80	6.66	24.50	<0.001	0.84	0.360	0.889	0.108	-1.826	0.360

Table 15 (Continued)

Comparison*	Correction	Missing data	τ^2	I^2	H^2	R^2	Q	Q *P* Value	QM	QM *P* value	intercept. est	intercept0. *P* value	moderator. est	moderator0. *P* value
Normal *vs* Underweight	COPD-no Mods	6	0.374	81.34	5.36	NA	49.98	<0.001	NA	NA	0.591	0.005	NA	NA
	COPD	6	0.210	70.82	3.43	43.86	28.26	0.003	5.74	0.017	1.418	<0.001	-6.388	0.017
	COPD w/o large size	11 included	0.182	49.393	1.976	0.000	16.324	0.060	0.046	0.829	0.858	0.085	-0.893	0.829
	CVA-no Mods	8	0.361	85.31	6.81	NA	46.73	<0.001	NA	NA	0.528	0.014	NA	NA
	CVA	8	0.274	81.24	5.33	24.20	27.51	0.001	2.53	0.111	0.982	0.005	-5.142	0.111
	PVD-no Mods	7	0.000	0.00	1.00	NA	16.10	0.138	NA	NA	0.664	<0.001	NA	NA
	PVD	7	0.094	50.40	2.02	NA	16.10	0.097	0.02	0.902	0.768	0.071	-0.441	0.902
	CKD-no Mods	8	0.471	77.53	4.45	NA	47.95	<0.001	NA	NA	0.679	0.008	NA	NA
	CKD	8	0.542	79.14	4.79	0.00	47.80	<0.001	0.03	0.865	0.717	0.034	-0.344	0.865

Abbreviations: BMI, body mass index; CKD, chronic kidney disease (dialysis); COPD, chronic obstructive pulmonary disease; EF, ejection fraction; CVA, cerebrovascular accident; MI, myocardial infarction; NA, not applicable; NYHA, New York Heart Association; PVD, peripheral vascular disease; WHO, World Health Organization.

*Comparison performed among BMI groups defined by standard or modified WHO classification:[1,2] underweight (BMI<18.5 or 20 Kg/m^2), normal weight (BMI 18.5/20-<25), overweight (BMI 25-<30), and obese class I (BMI 30-<35).

Table 16. Meta-regression Analysis (Factorial Moderators) – Numerical Data

Comparison*	Correction	Missing data	τ^2	I^2	H^2	R^2	Q	Q *P* value	QM	QM *P* value	Model	Estimate (RR)	Estimate *P* Value
Normal *vs* Overweight	Operation type	0	0.030	56.23	2.28	<0.001	46.02	0.002	2.37	0.667	Intercept	-0.351	<0.001
		0									All	0.097	0.418
		0									VALVE	-0.188	0.433
		0									CABG+VALVE	0.070	0.744
		0									VAD	0.216	0.339
	Underweight BMI definition	0	0.021	55.63	2.25	13.500	50.07	0.002	3.51	0.061	Intercept	-0.395	<0.001
		0									mWHO	0.179	0.061
Normal *vs* Obese Class I	Operation type	0	0.024	44.98	1.82	4.830	23.89	0.032	2.48	0.479	Intercept	-0.324	<0.001
		0									All	0.031	0.820
		0									VALVE	0.201	0.623
		0									VAD	0.363	0.129
	Underweight BMI definition	0	0.012	41.37	1.71	53.870	27.59	0.024	4.98	0.026	Intercept	-0.387	<0.001
		0									mWHO	0.241	0.026
Normal *vs* Underweight	Operation type	0	0.379	77.79	4.50	<0.001	50.05	<0.001	0.94	0.919	Intercept	0.706	0.008
		0									All	-0.128	0.758
		0									VALVE	-0.163	0.796
		0									CABG+VALVE	-0.329	0.651
		0									VAD	-0.639	0.363
	Underweight BMI definition	0	0.272	71.62	3.52	0.760	59.26	<0.001	0.87	0.350	Intercept	0.702	0.001
		0									sWHO	-0.299	0.350

Abbreviations: CABG, coronary artery bypass grafting; mWHO, modified (classification of obesity, underweight cut-off at 20 Kg/m^2) World Health Organization; VAD, ventricular assist device; WHO, World Health Organization.

*Comparison performed among BMI groups defined by standard or modified WHO classification:[1,2] underweight (BMI<18.5 or 20 Kg/m^2), normal weight (BMI 18.5/20-<25), overweight (BMI 25-<30), and obese class I (BMI 30-<35).

Table 17. Misclassification and Inconsistent Data Definition: Rolling Epoch and Association of BMI with In-Hospital Mortality (Multivariable Analysis) – NACSA Registry

In-Hospital Mortality	Number Patients	Underweight	Normal*	Overweight	Obese Class I	Obese Class II	Obese Class III	*P* value	Model discrimination (AUC ROC)
BMI		**<18.5**	**18.5-<25**	**25-<30**	**30-<35**	**35-<40**	**≥40**		
Estimate		**OR (95%CI)**	**OR**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**		
2002 - 2007	184,608	1.54 (1.40-1.71)	1	0.80 (0.73-0.88)	0.80 (0.71-0.91)	0.92 (0.83-1.02)	1.09 (0.80-1.49)	<0.001	0.824
2008 - 2013	165,678	1.44 (1.26-1.64)	1	0.79 (0.75-0.85)	0.84 (0.77-0.91)	0.78 (0.65-0.95)	0.98 (0.78-1.22)	<0.001	0.82

Abbreviations: AUC ROC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; NACSA, National Adult Cardiac Surgery Audit; OR, odds ratio.
*Normal weight patients: reference group for comparisons.

Table 18. Comparison of Clinical Characteristic Distribution among BMI Defined Groups (cut-off) and Classes

Comparison*	Variable	sWHO mean	mWHO mean	*P* value
Normal *vs* Overweight	Age	65.15	61.89	0.114
	EF	55.70	49.27	0.135
	Male	0.75	0.74	0.898
	MI	0.26	0.35	0.449
	Hypertension	0.61	0.55	0.571
	Diabetes	0.21	0.23	0.722
	Dyslipidemia	0.57	0.58	0.935
	Smoker	0.30	0.37	0.587
	COPD	0.13	0.12	0.726
	CVA	0.09	0.05	0.397
	PVD	0.09	0.10	0.842
	CKD	0.09	0.09	0.990
Normal *vs* Obese Class I	Age	65.25	62.93	0.233
	EF	53.79	48.30	0.048
	Male	0.74	121.72	0.341
	MI	0.25	0.35	0.230
	Hypertension	0.61	0.54	0.328
	Diabetes	0.21	0.22	0.667
	Dyslipidemia	0.60	0.59	0.891
	Smoker	0.25	0.38	0.348
	COPD	0.12	0.11	0.784
	CVA	0.09	0.06	0.235
	PVD	0.10	0.10	0.937
	CKD	0.05	0.07	0.540
Normal *vs* Underweight	Age	64.85	61.69	0.214
	EF	52.41	47.58	0.086
	Male	0.73	0.72	0.854
	MI	0.24	0.33	0.366
	Hypertension	0.51	0.48	0.669
	Diabetes	0.21	0.18	0.458
	Dyslipidemia	0.55	0.55	0.999
	Smoker	0.22	0.32	0.556
	COPD	0.15	0.09	0.140
	CVA	0.10	0.06	0.401
	PVD	0.14	0.10	0.476
	CKD	0.07	0.09	0.762

Abbreviations: COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease (dialysis); COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; EF, ejection fraction; MI, myocardial infarction; mWHO, modified (classification of obesity, underweight cut-off at 20 Kg/m^2) World Health Organization; PVD, peripheral vascular disease; sWHO, standard (classification of obesity, underweight cut-off at 18.5 Kg/m^2) World Health Organization; PVD, peripheral vascular disease; WHO, World Health Organization.

*Comparison performed among BMI groups defined by standard or modified WHO classification:[1,2] underweight (BMI<18.5 or 20 Kg/m^2), normal weight (BMI 18.5/20-<25), overweight (BMI 25-<30), and obese class I (BMI 30-<35).

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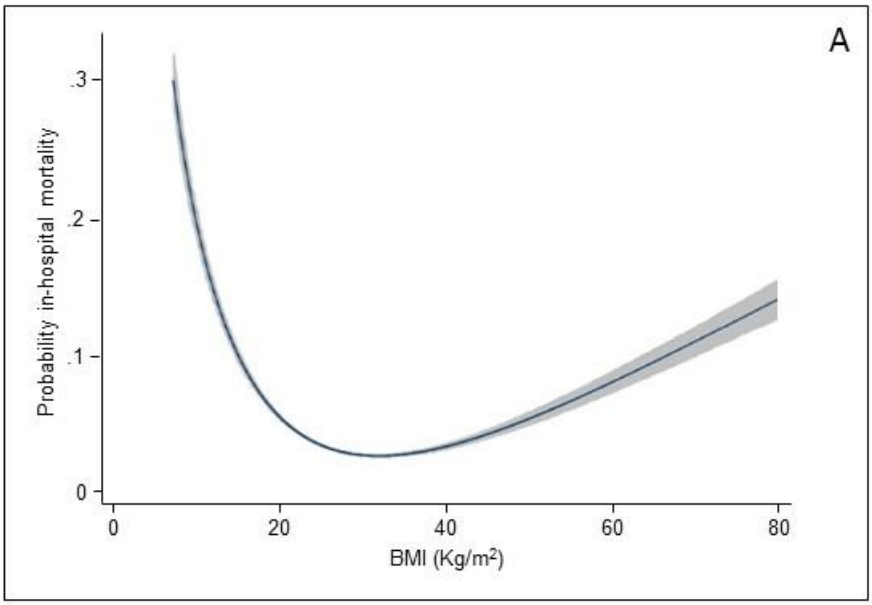
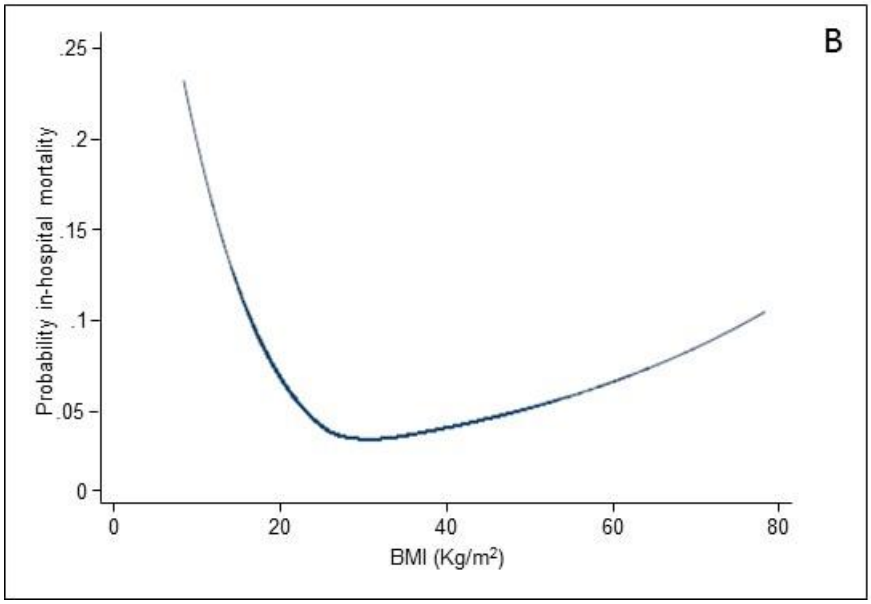
FIGURES

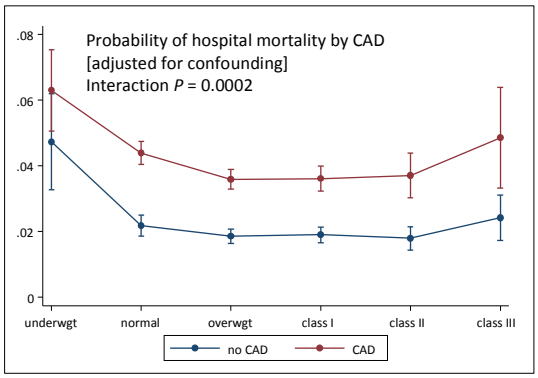
Figure 1. Hospital Mortality (Probability) Expressed by Mean of Fractional Polynomials (A) and Restricted Cubic Spline (B).

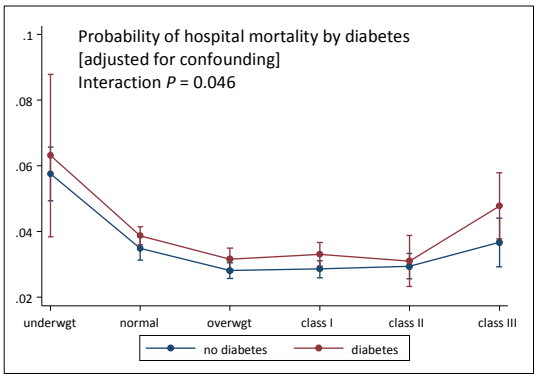


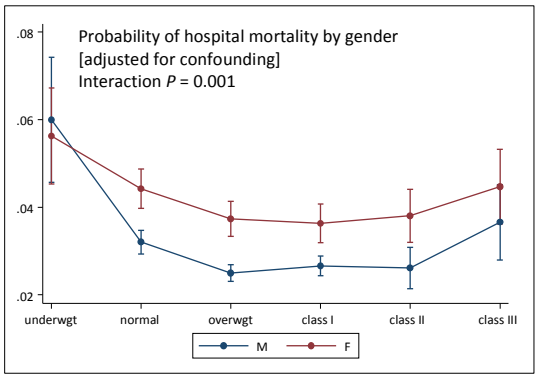


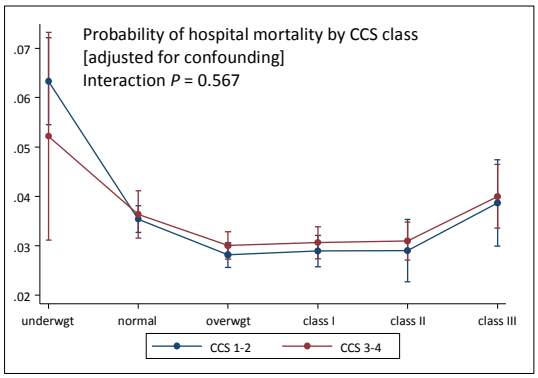
Abbreviations: BMI, body mass index.

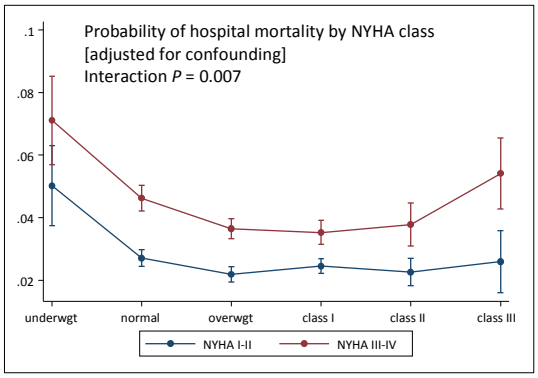
Figure 2A. Probability of Hospital Death by Risk Factor (Adjusted for Confounding) and their Interaction.

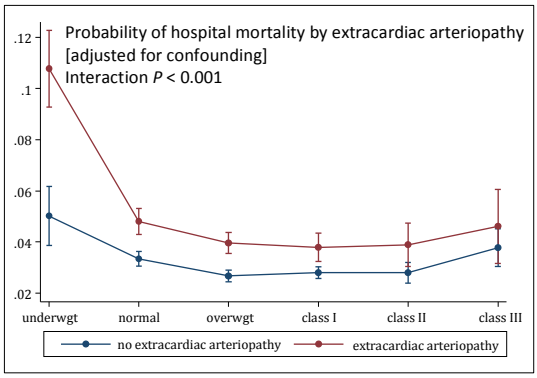






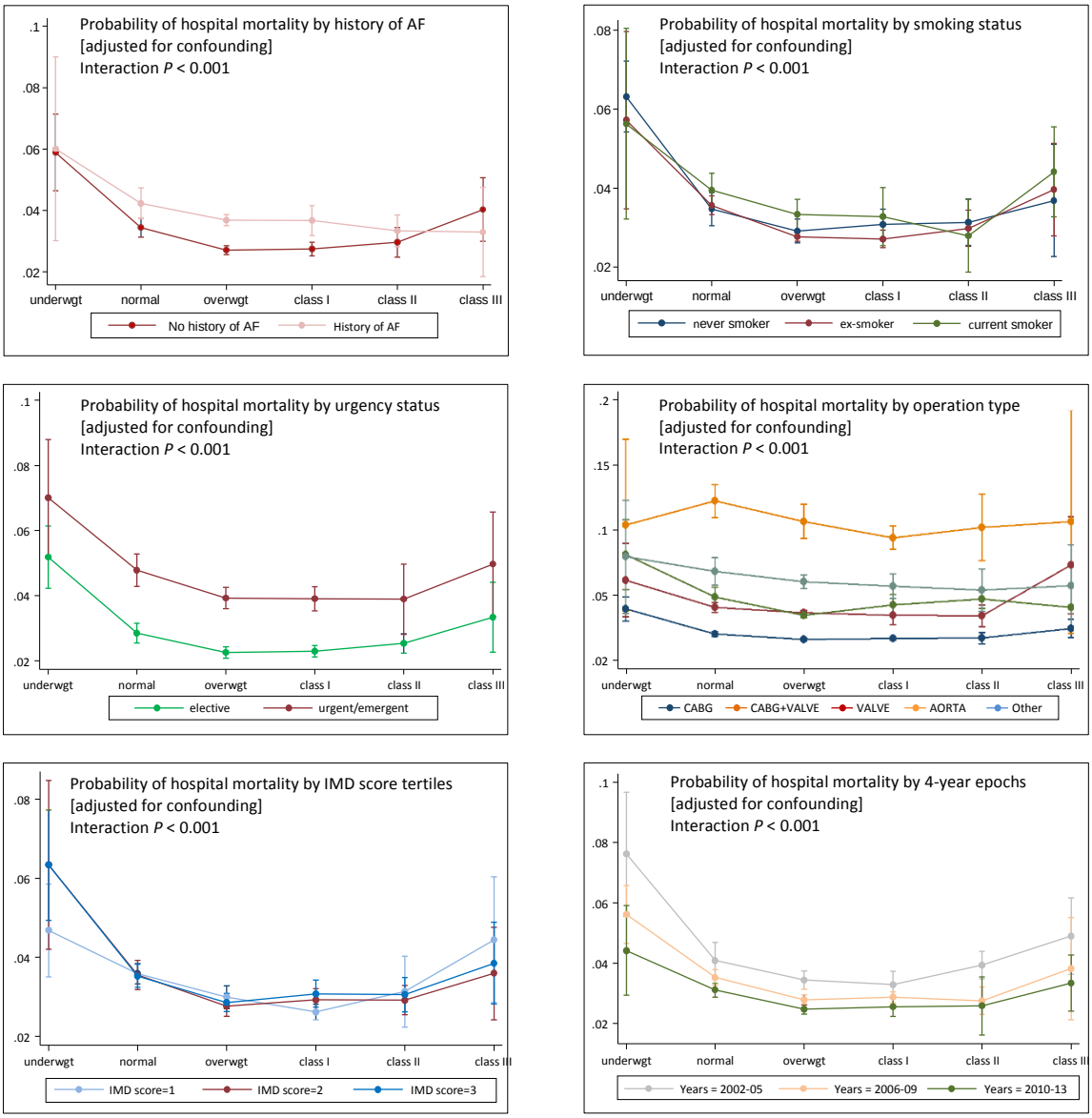






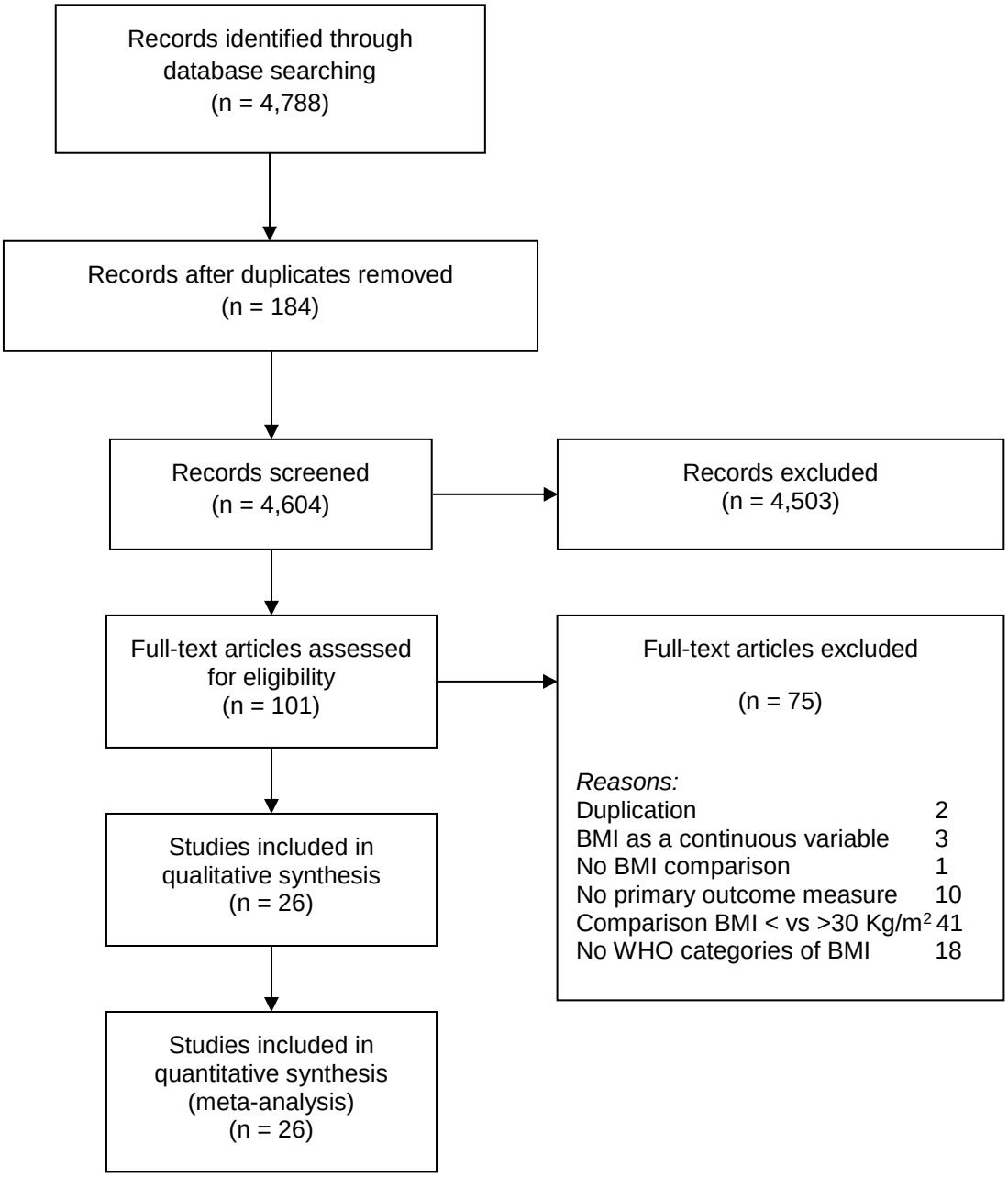
Bars represent probability effect estimates (95% Confidence intervals). Abbreviations: CAD, coronary artery disease; CCS, Canadian Cardiovascular Society (classification); NYHA, New York Heart Association.

Figure 2B. Probability of Hospital Death by Risk Factor (Adjusted for Confounding) and their Interaction.



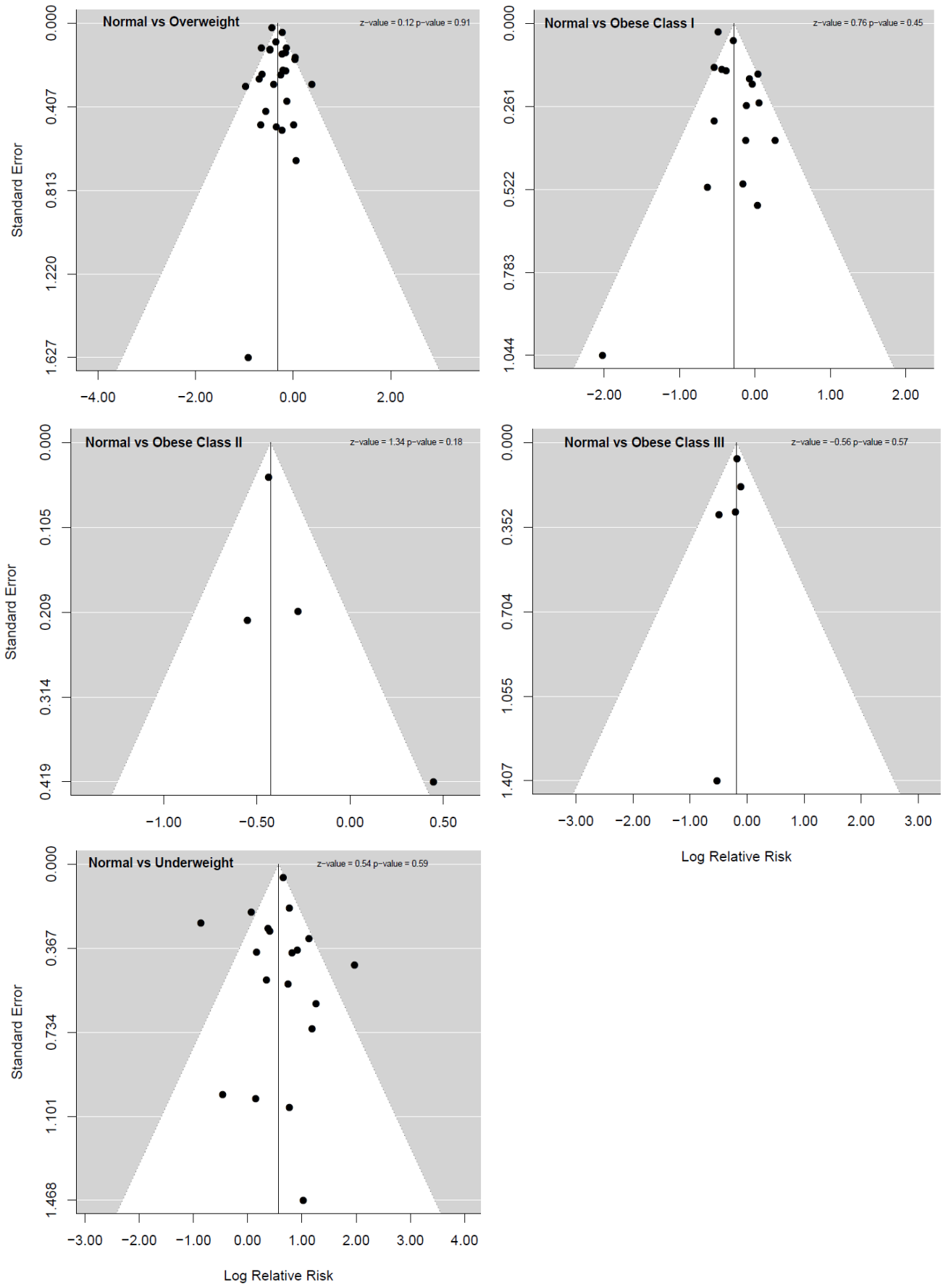
Bars represent probability effect estimates (95% Confidence intervals). Abbreviations: AF, Atrial Fibrillation; IMD, Index of Multiple Deprivation.

Figure 3. PRISMA Flow Chart of Search Strategy



Abbreviations: BMI, body mass index; WHO, World Health Organization.

Figure 4. Funnel Plots with Effect Size for All Group Comparisons



All panels show symmetrical plot in the absence of bias.

Figure 5. Meta-regression Plots

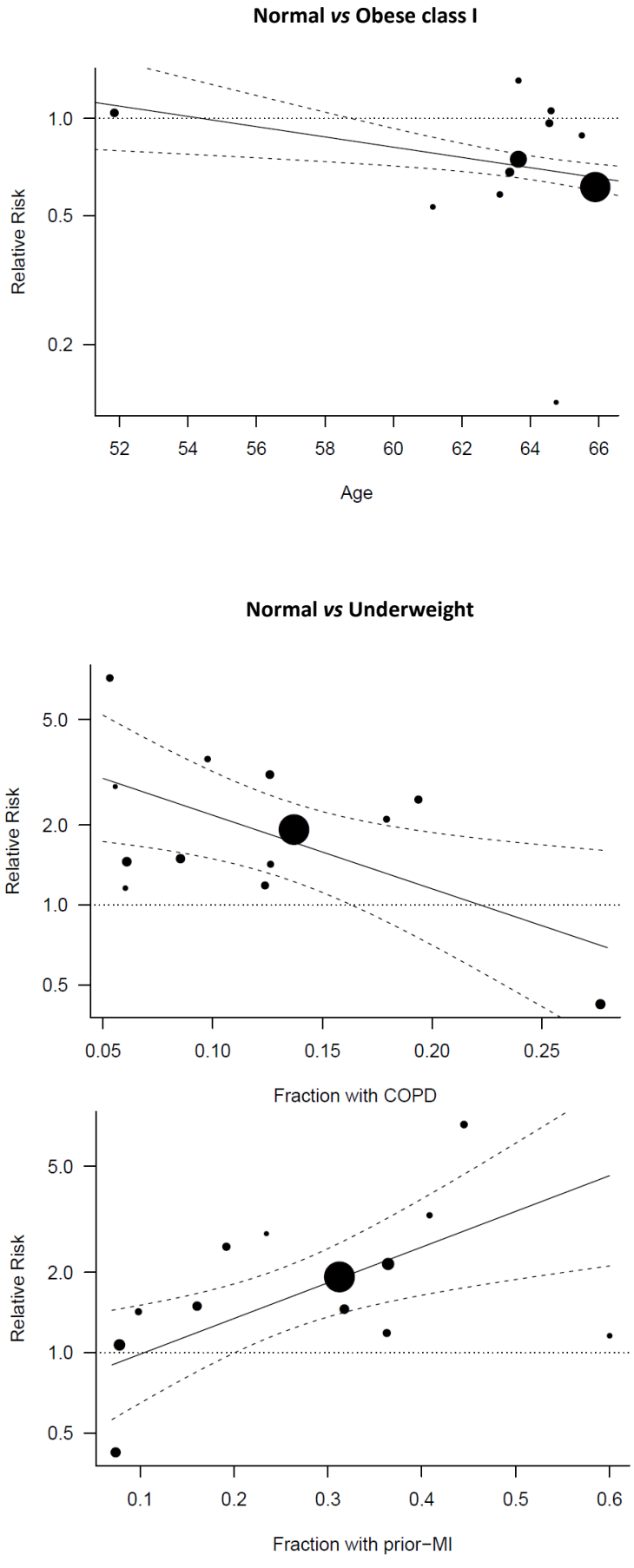
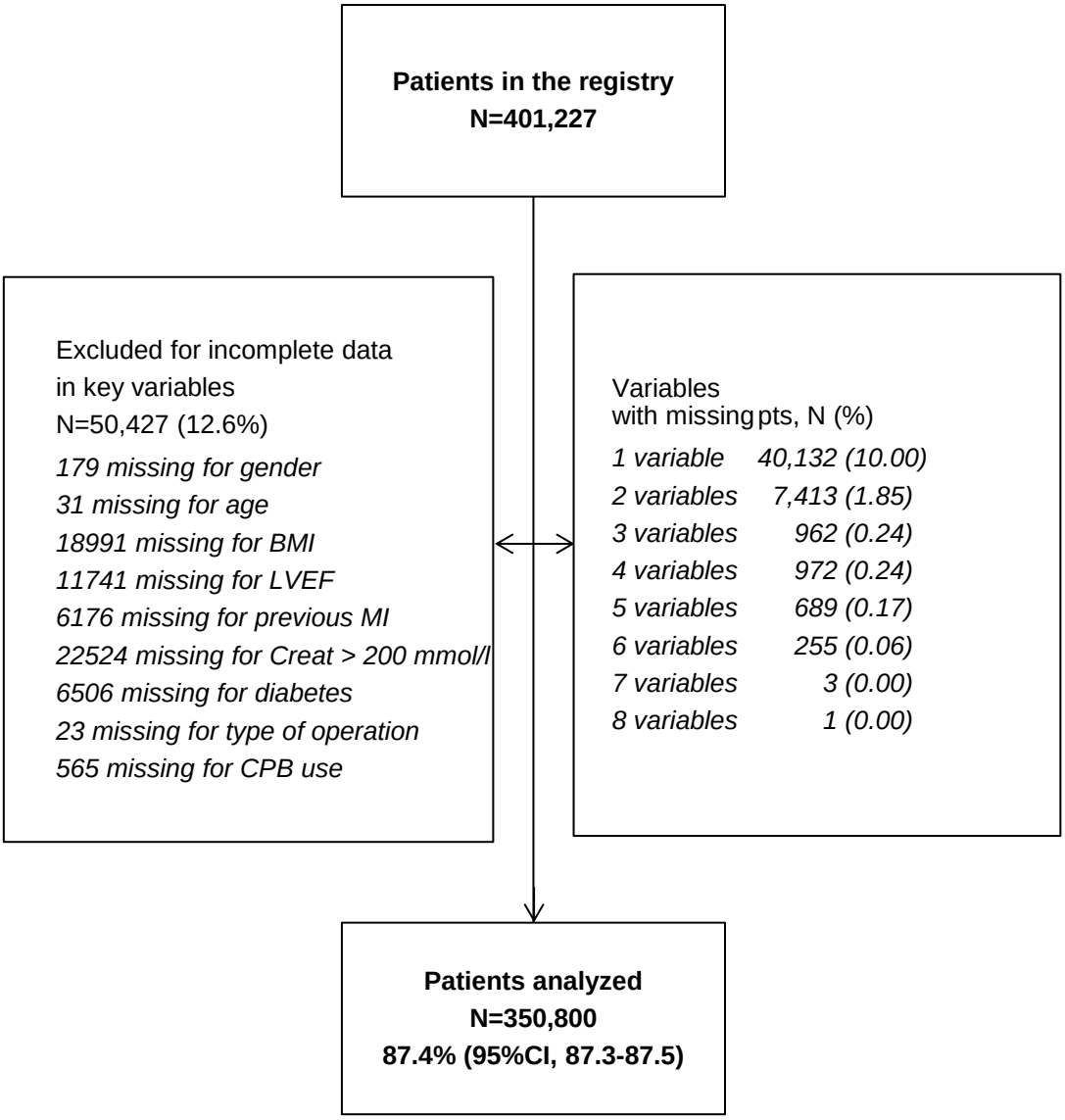
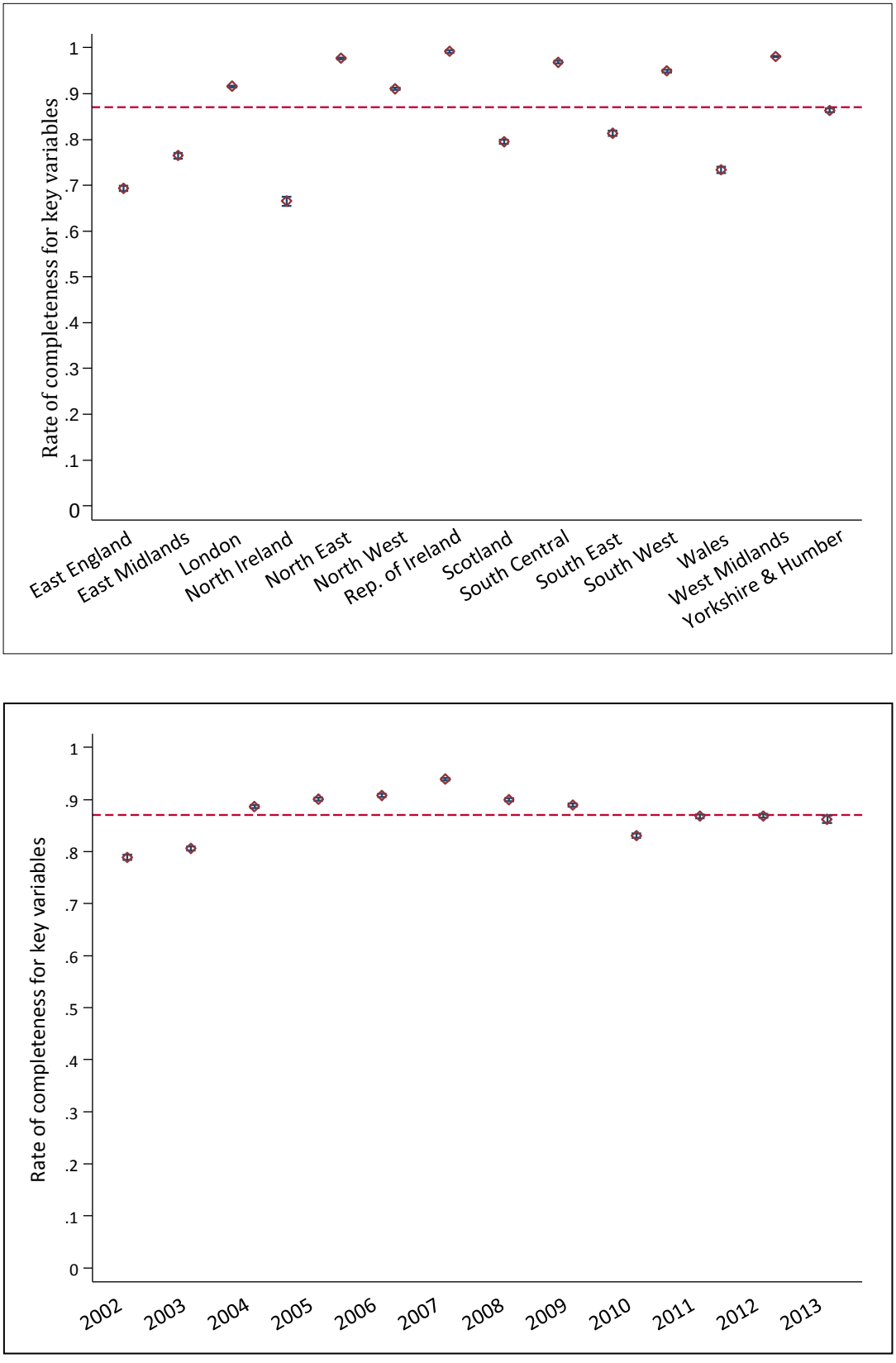


Figure 6. Patient Disposition Flow Chart



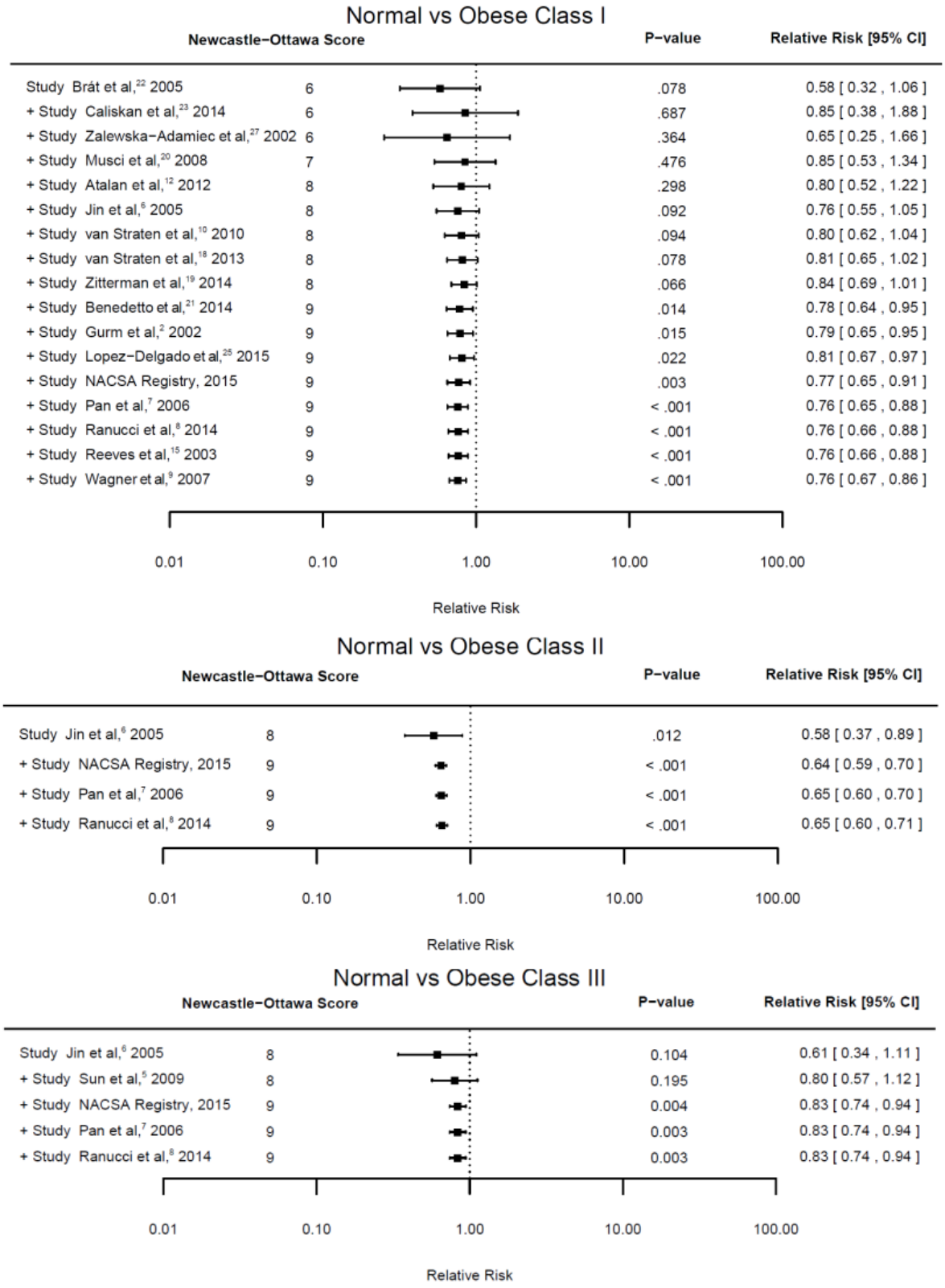
Abbreviations: BMI, body mass index; CPB, cardiopulmonary bypass; Creat, creatinine; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

Figure 7. Rate of Missingness (95%CI) According to Region (upper panel) and Year of Surgery (lower panel)



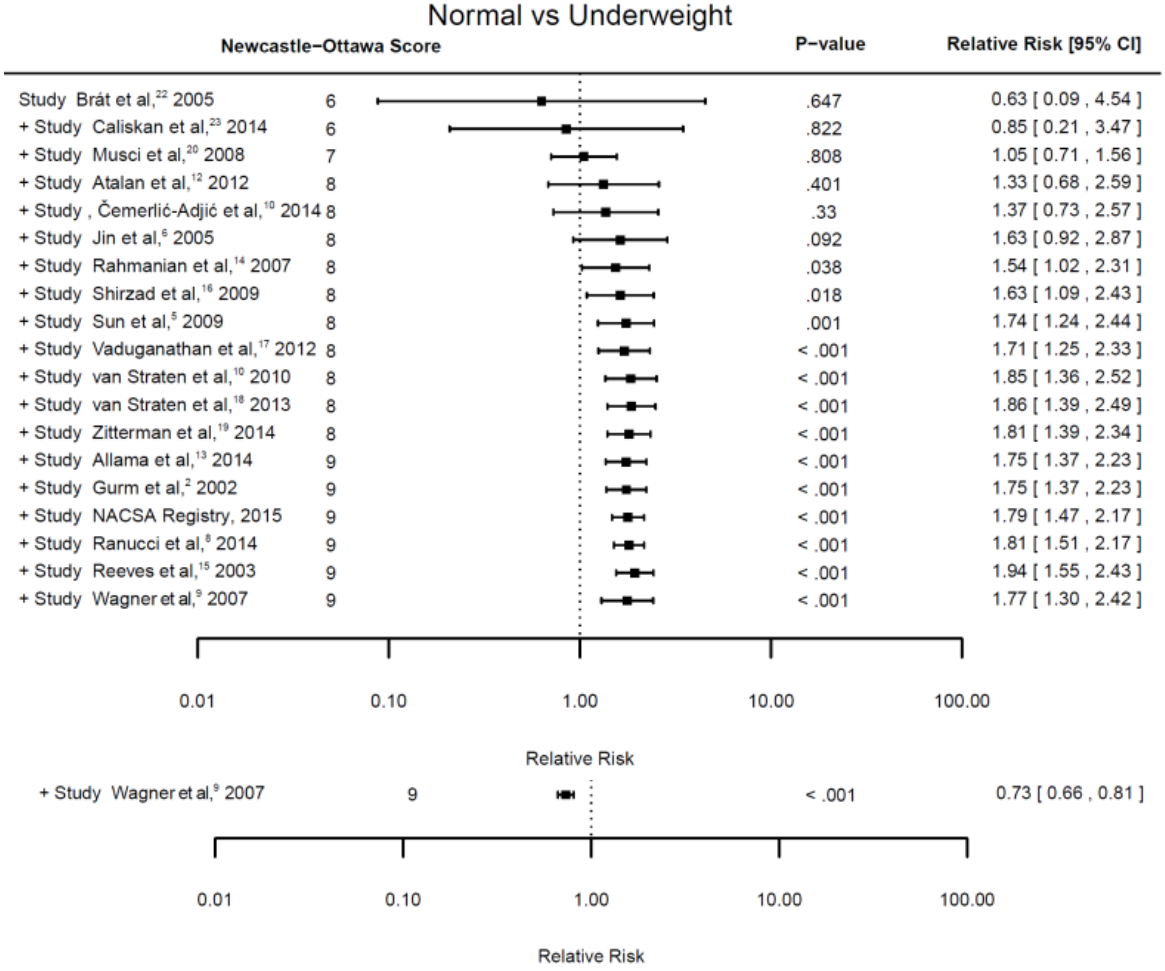
The Red Line corresponds to the overall rate of missingness (87.4%).

Figure 8A. Cumulative Forest Plots by NOS
(Groups: Obese Class I, Obese Class II, and Obese Class III Patients)



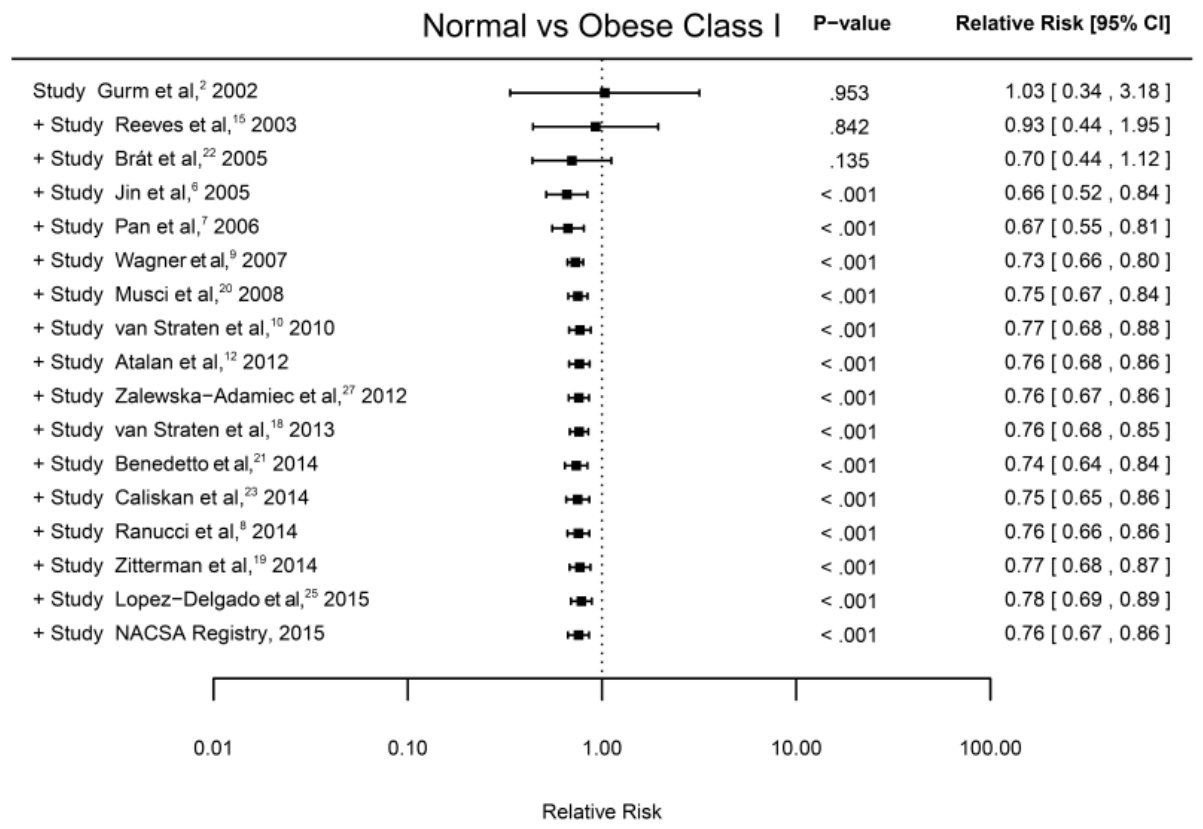
Data markers indicate relative risk, and error bars indicate 95% confidence intervals
Abbreviations: CI, confidence interval; NOS, New-Ottawa Scale.

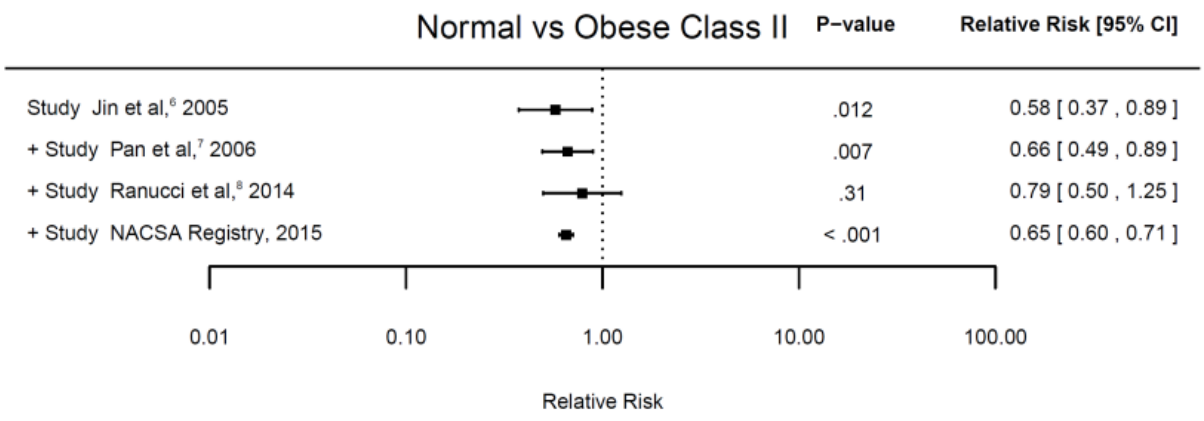
Figure 8B. Cumulative Forest Plots by NOS
(Groups: Overweight and Underweight patients)

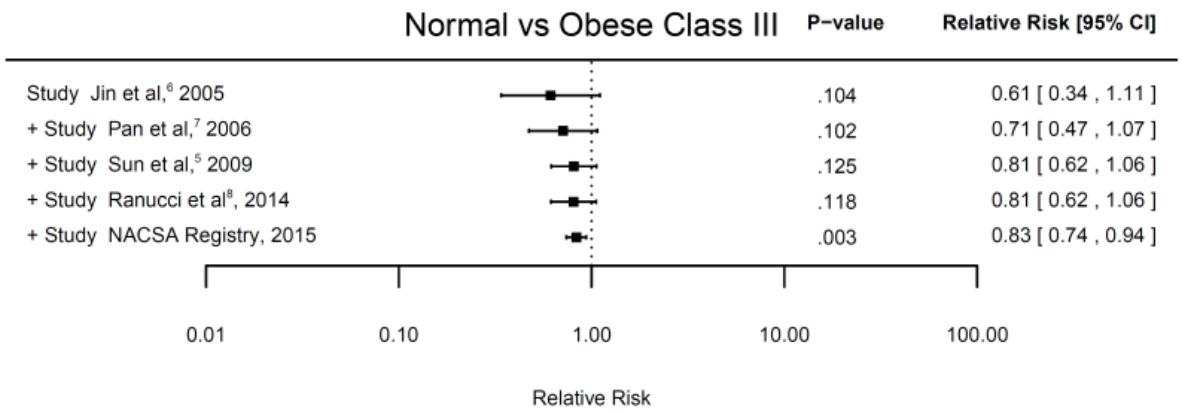


Data markers indicate relative risk, and error bars indicate 95% confidence intervals
Abbreviations: CI, confidence interval; NOS, New-Ottawa Scale.

Figure 9A. Cumulative Forest Plots by Year of Study Publication
(Groups: Obese Class I, Obese Class II, and Obese Class III Patients)

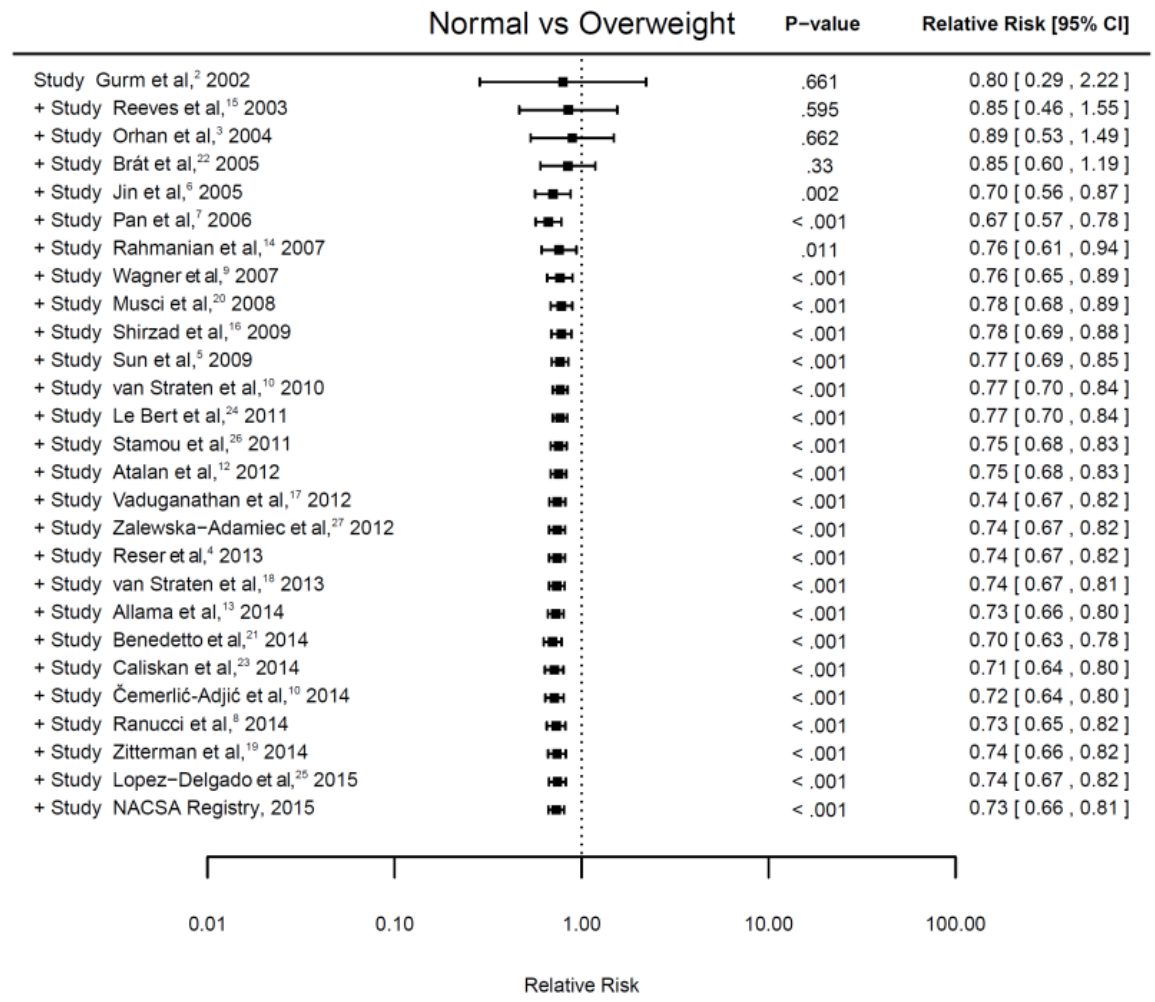






Data markers indicate relative risk, and error bars indicate 95% confidence intervals
Abbreviations: CI, confidence interval.

Figure 9B. Cumulative Forest Plots by Year of Study Publication
(Groups: Overweight and Underweight patients)



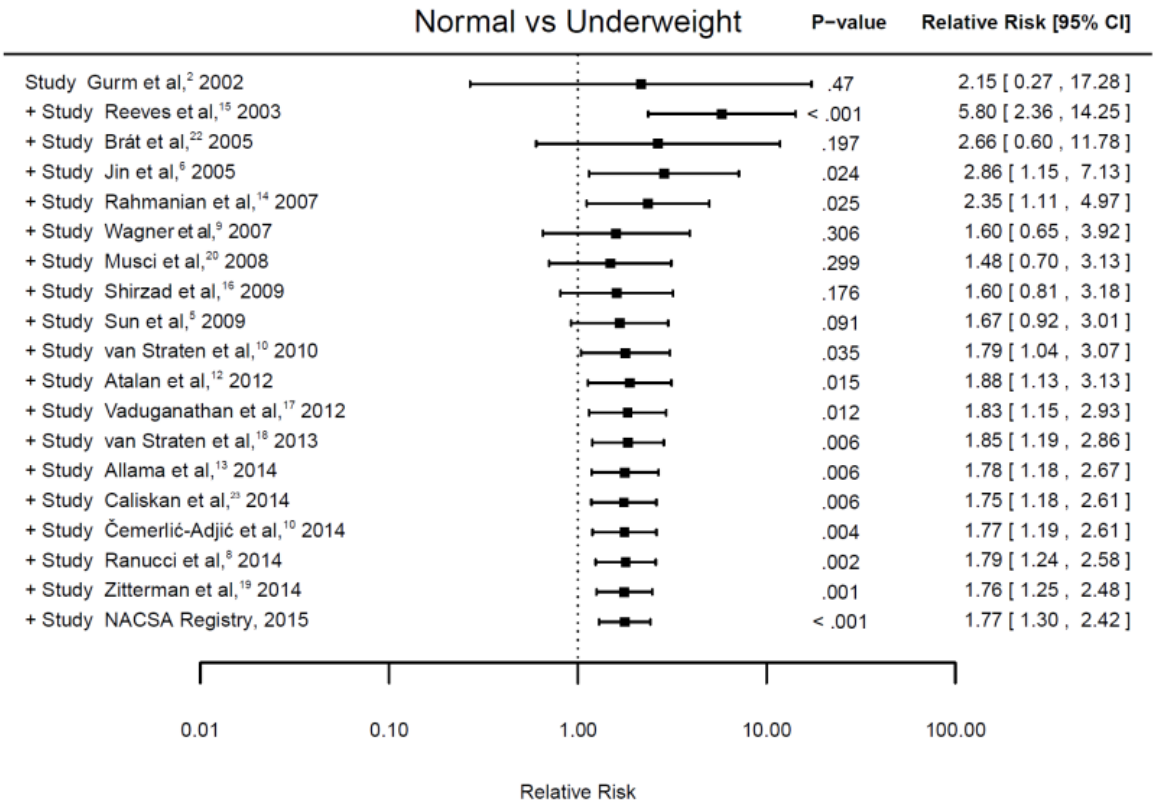
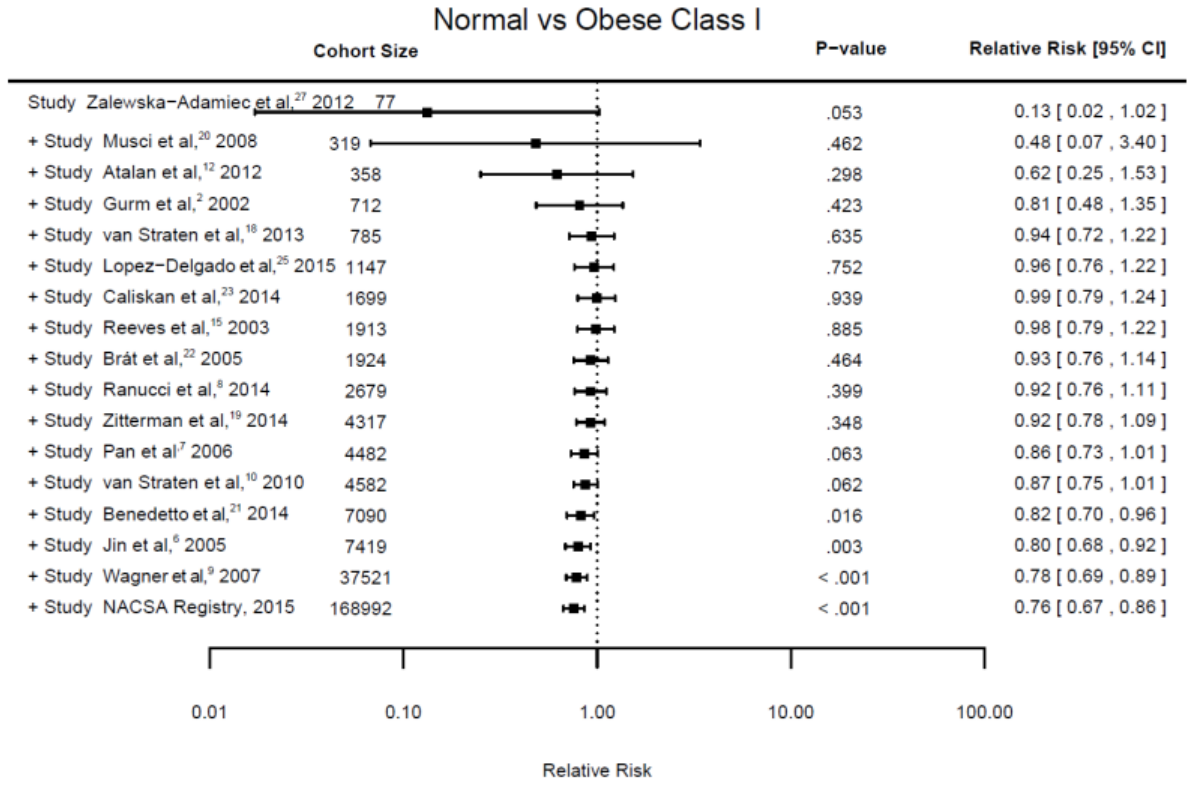
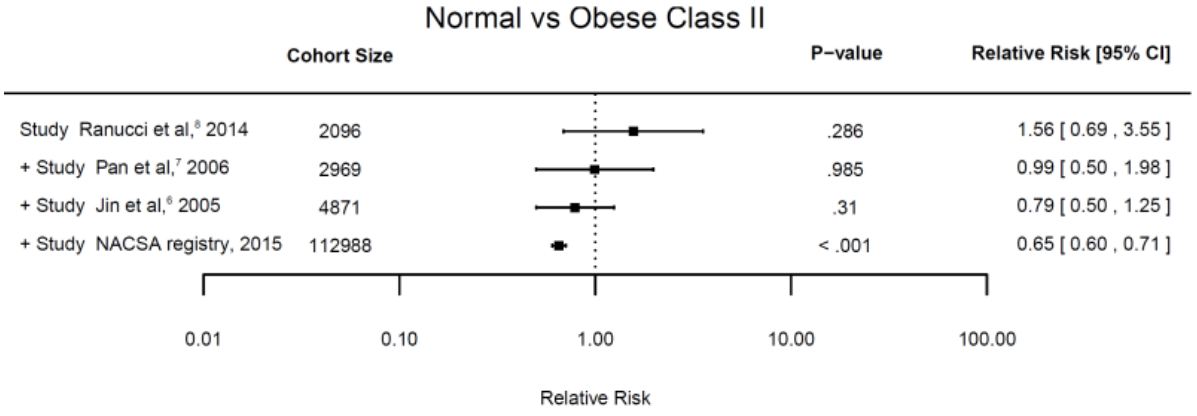
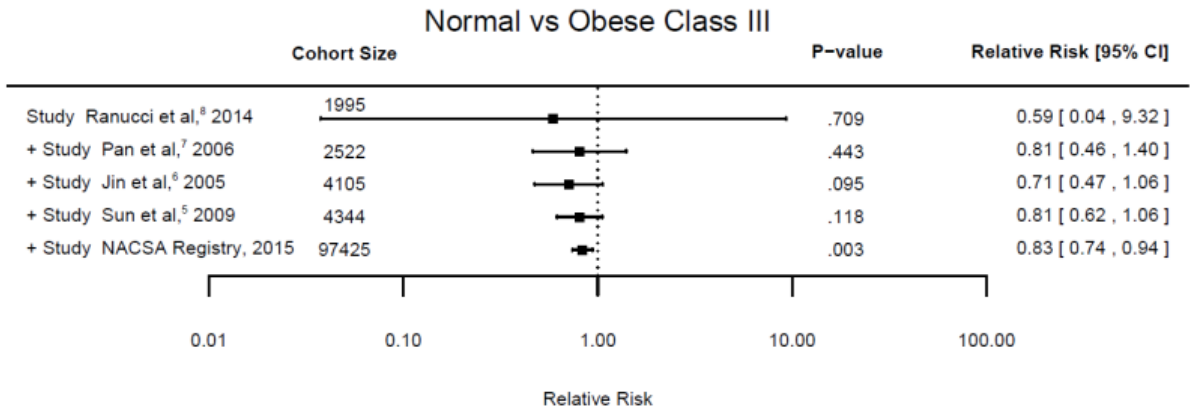


Figure 10A. Cumulative Forest Plots by Cohort Size
(Groups: Obese Class I, Obese Class II, and Obese Class III Patients)

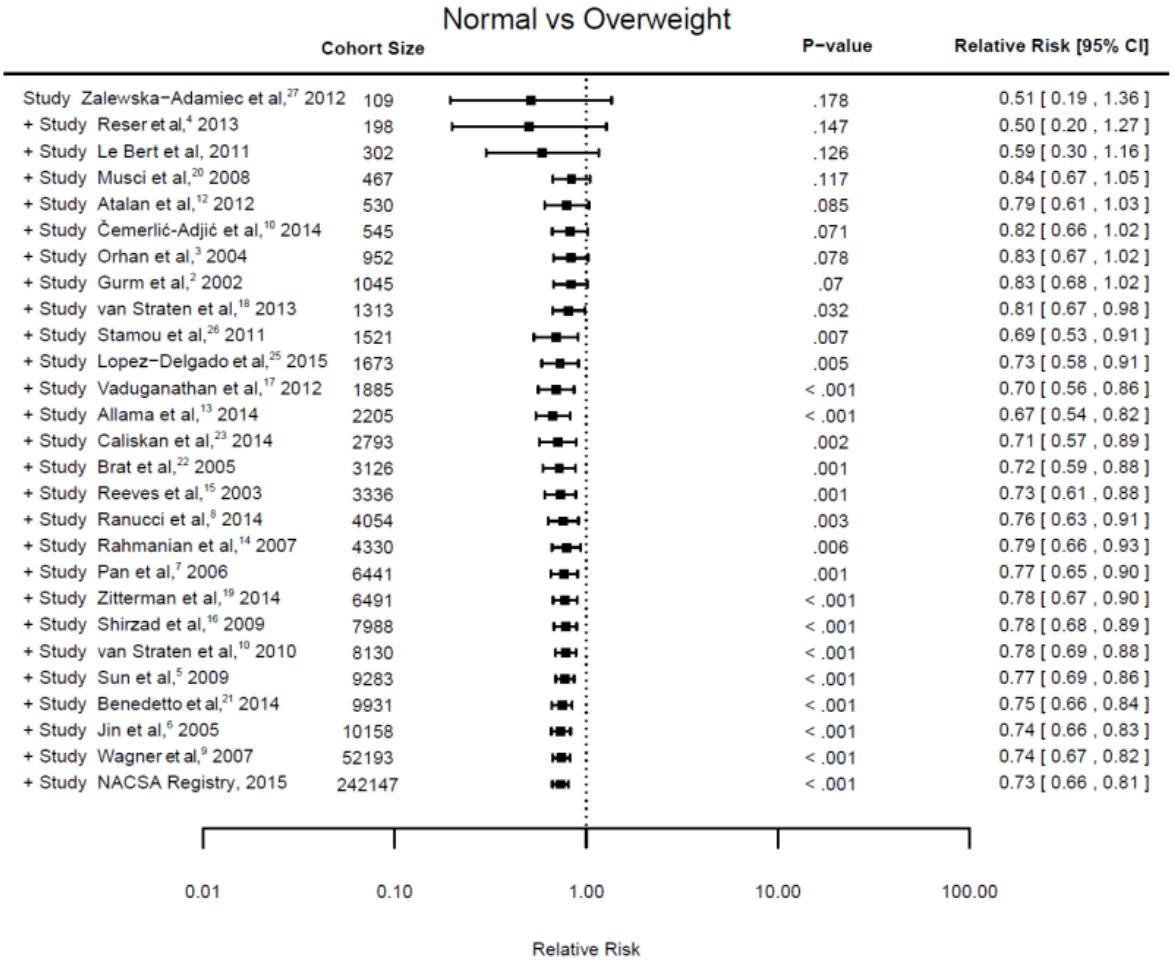


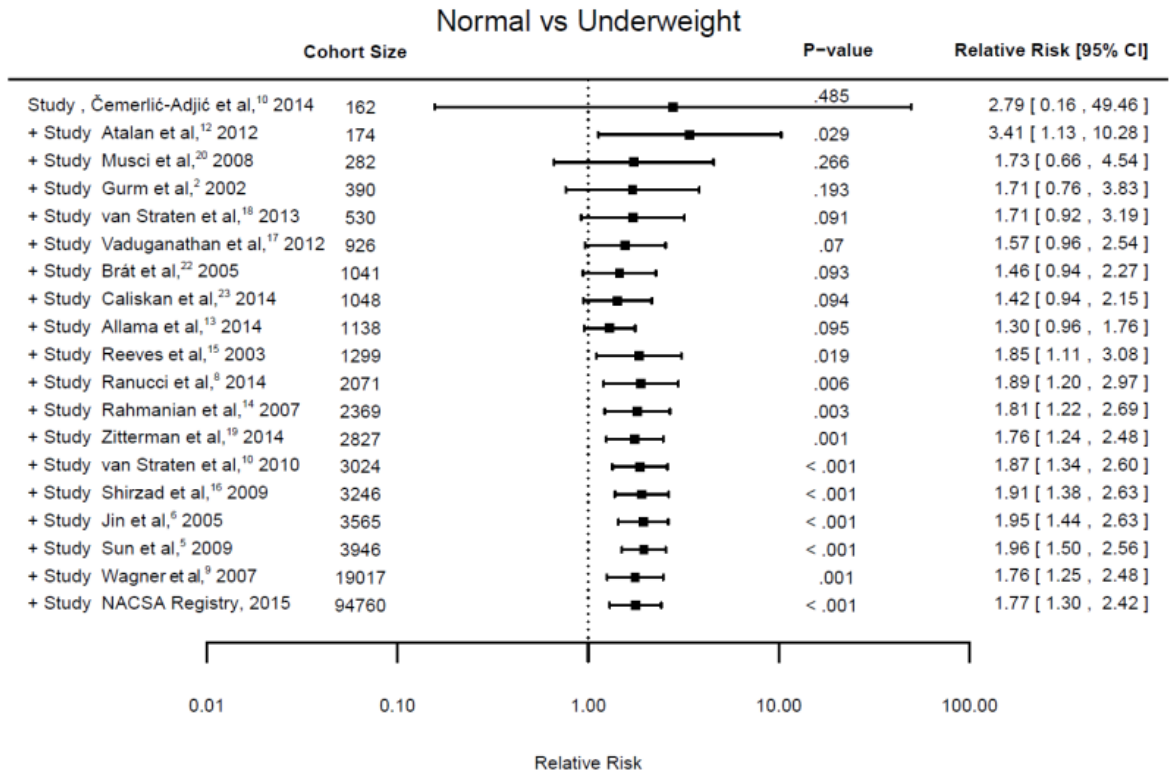




Data markers indicate relative risk and error bars indicate 95% confidence intervals
Abbreviations: CI, confidence interval.

Figure 10B. Cumulative Forest Plots by Cohort Size
(Groups: Overweight and Underweight patients)





APPENDIX

Appendix 1. STROBE Statement for Observational Studies

	Item No	Recommendation	Reported on Page N.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5,6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 Appendix V
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6 Appendix V
Bias	9	Describe any efforts to address potential sources of bias	6, and s3, s4
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6 Appendix V
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8, and s2
		(*b*) Describe any methods used to examine subgroups and interactions	7,8, and s2
		(*c*) Explain how missing data were addressed	s2
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7,8, and s2
		(*e*) Describe any sensitivity analyses	7,8, and s2
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9, and s3, Figure VI
		(b) Give reasons for non-participation at each stage	9, and s3
		(c) Consider use of a flow diagram	Figure VI

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	9, and s3, s4 Figure VI
Outcome data	15*	Report numbers of outcome events or summary measures	9, 10, and s3, s4 Table III
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, and s3, s4 Table III-IV
		(*b*) Report category boundaries when continuous variables were categorized	Na
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, and s3-4
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13, 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15,16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

Appendix 2. MOOSE Checklist for Meta-analyses of Observational Studies

Item N.	Recommendation	Reported on Page N.
Reporting of background should include		
1	Problem definition	4 Appendix VI
2	Hypothesis statement	4 Appendix VI
3	Description of study outcome(s)	5,6 Appendix VI
4	Type of exposure or intervention used	5,6 Appendix VI
5	Type of study designs used	5,6 Appendix VI
6	Study population	5,6 Appendix VI
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	6 Appendix VI
8	Search strategy, including time period included in the synthesis and key words	6 Appendix VI
9	Effort to include all available studies, including contact with authors	6 Appendix VI
10	Databases and registries searched	6 Appendix VI
11	Search software used, name and version, including special features used (eg, explosion)	Appendix VI
12	Use of hand searching (eg, reference lists of obtained articles)	Appendix VI
13	List of citations located and those excluded, including justification	6, Figure III
14	Method of addressing articles published in languages other than English	6 Appendix VI
15	Method of handling abstracts and unpublished studies	Appendix VI
16	Description of any contact with authors	Appendix VI
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6, and s2,s3 Appendix VI
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6, and s2,s3 Appendix VI
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6, and s2,s3 Appendix VI
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	6, and s2,s3 Appendix VI
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6, and s2,s3 Appendix VI
22	Assessment of heterogeneity	7, and s2,s3 Appendix VI
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7, and s2,s3 Appendix VI

24	Provision of appropriate tables and graphics	Appendix VI
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures 3,4
26	Table giving descriptive information for each study included	Tables VII-X
27	Results of sensitivity testing (eg, subgroup analysis)	Tables XI-XV, XVII
28	Indication of statistical uncertainty of findings	s4,s5,s6
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	13, s5, s6
30	Justification for exclusion (eg, exclusion of non-English language citations)	13, and s5
31	Assessment of quality of included studies	12, Table XI, Appendix VI
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	13,14
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	14,15
34	Guidelines for future research	15,16
35	Disclosure of funding source	17

Appendix 3. Checklist of Items to Include when Reporting a Systematic Review or Meta-analysis According to PRISMA Statement

Section/topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4, Table I
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5, Appendix VI
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6, Appendix VI
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6, Appendix VI
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix VI
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, Appendix VI
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Appendix VI
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5,6, Table VI, Appendix VI
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7, Appendix VI

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7, and s2, s3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7, and s2, s3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7, and s2, s3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	s2, s3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Figure III
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables VI-IX
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, and Tables XI, XII
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 3 and 4, Table XII
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table XII
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10,11, and e4,e5,e6 and Tables X-XV
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10,11, and e4,e5,e6 and Tables X-XVI
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14,15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15,16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

Appendix 4. Abbreviations

AKI	Acute Kidney Injury
AF	Atrial Fibrillation
AUC	Area Under the Curve
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPB	Cardiopulmonary Bypass
CVA	Cerebrovascular Accident
DSWI	Deep Sternal Wound Infection
FFP	Fresh Frozen Plasma
GI	Gastro-Intestinal
HDU	High Dependency Unit
HF	Heart Failure
IABP	Intra-Aortic Balloon Pump
IQR	Interquartile Range
ICU	Intensive Care Unit
LCO	Low Cardiac Output
LOS	Length of Stay
LVEF	Left Ventricular Ejection Fraction
MACCE	Major Adverse Cardiac Cerebrovascular Event
MOF	Multi-Organ Failure
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
NACSA	National Adult Cardiac Surgery Audit
NICOR	National Institute for Cardiovascular Outcomes Research
NYHA	New York Heart Association
NOS	New-Ottawa Scale
OPCAB	Off-Pump Coronary Artery Bypass
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVD	Peripheral Vascular Disease
RBC	Red Lood Cell
ROC	Receiver Operating Characteristic
RR	Relative Risk
RRT	Renal Replacement Therapy
SCr	Serum Creatinine
SD	Standard Deviation
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TAVI	Transcatheter Aortic Valve Implantation
TIA	Transient Ischemic Attack
VAD	Ventricular Assist Device
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WHO	World Health Organization

Appendix 5. Protocol – Observational Cohort Study (NACSA Registry)

Insights into the Obesity Paradox in Cardiac Surgery

Version No: Version 1.1
Date: 14 September 2014
Sponsor: University of Leicester
Funder: British Heart Foundation
Type of study: **Cross-sectional observational study**

Authors

Prof Gavin J. Murphy British Heart Foundation Professor of Cardiac Surgery University of Leicester • Glenfield Hospital Clinical Sciences Wing Leicester, LE3 9QP Tel: 0116 258 3054 Email: gjm19@le.ac.uk	**Dr Giovanni Mariscalco** Senior Lecturer in Cardiac Surgery University of Leicester • Glenfield Hospital Clinical Sciences Wing Leicester, LE3 9QP Tel: 0116 258 3019 Fax: Email: gm247@leicester.ac.uk
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1. STUDY SYNOPSIS

Title of Study	**Insights into the Obesity paradox**
Name of Sponsor	University of Leicester
Study Hypothesis	Primary hypothesis: The primary hypothesis is that there is no independent association between BMI and the primary outcome once important covariates are considered. Secondary hypotheses: 1. The associations between obesity and outcome will be different in patients with or without systemic inflammatory diseases including ischaemic heart disease, diabetes, heart failure, chronic kidney disease, systemic atherosclerosis or old age. 2. The associations between obesity and outcome will be different in patients with unstable symptoms; severe or unstable angina, recent myocardial infarction, urgent surgery.
Study Objectives	Objectives: 1. To establish whether patients who are overweight or are obese have a lower risk of death, low cardiac output, acute kidney injury or prolonged ICU stay relative to normal or underweight weight patients. 2. To establish whether the obesity paradox is evident in patients who have pre-existing and severe systemic inflammatory diseases. 3. To establish whether the effects of obesity on outcome are influenced by recent myocardial ischaemia or cardiac decompensation
Study Design	Retrospective multi-centre observational cohort study using prospectively collected data from 44 cardiac surgery units in the UK and Ireland. The study will consider the associations between body mass and clinical outcomes in cardiac surgery.
Planned Sample Size	This study will use data from the NICOR Cardiac Surgery Audit dataset which contains data from 44 UK and Irish hospitals collected between April 2002 and March 2013. It is anticipated that this database contains clinical details for over 250,000 patients.
Subject Selection Criteria	Inclusion Criteria: Adult cardiac surgery patients undergoing surgery with or without cardiopulmonary bypass. Exclusion criteria: salvage patients, patients with critical preoperative state (balloon pump, ventilated, cardiogenic chock, inotropic support); Stage 5 Chronic Kidney Disease (dialysis).
Intervention	This is a non-interventional study.
Outcomes	• Primary Exposure of Interest: The primary exposure of interest is Body Mass Index. BMI is will be determined using the equation BMI=body mass (kg)/ hieght^2 (m). BMI will be further categorized as Underweight BMI<18.5, Normal weight BMI 18.5-25, Overweight BMI 25-30, Obese CLASS I BMI 30-35, Obese CLASS II BMI 35-40 and Morbidly obese BMI≥40. • Primary Outcome: In-hospital death. • Secondary Outcomes: low cardiac output defined as the use of a postoperative intra-aortic balloon pump that was not placed pre-operatively, stroke, severe acute kidney injury (renal replacement therapy), and sternal wound infection.
Statistical Considerations	A statistical analysis plan will be drafted prior to analysis. The principal analysis will be performed in the complete case data using regression analyses. A set of candidate models will be developed incorporating a main effects model plus potential interactions and/or quadratic terms. The best model will be selected and tested by fitting the final complete case model in the multiply imputed data. Sensitivity analyses will establish whether using accepted definitions of obesity, as described above, will have influenced our results, for example by considering BMI as a continuous variable or excluding patients with very low (BMI<18) or very high (BMI>40). In addition we will determine the sensitivity of our results to alternative models and to simulated unobserved confounders. Sub group analysis will assess the interactions between obesity and other risk factors for adverse outcome.

2. GLOSSARY/ABBREVIATIONS

CABG	Coronary Artery Bypass Grafting
CCS	Canadian Cardiovascular Society (class)
CKD (Stage)	International Classification of Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CPB	Cardiopulmonary bypass
CSCTT	Cardiac Surgery Clinical Trials Team
CTU	Clinical Trials Unit
CVA	Cerebrovascular Accident
IMD	Index of Multiple Deprivations
LVEF	Left Ventricular Ejection Fraction
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
NACSA	National Adult Cardiac Surgery Audit (NACSA)
NICOR	National Institute for Cardiovascular Outcomes Research
NYHA	New York Heart Association (class)
PTCA	Percutaneous Transluminal Coronary Angioplasty
PVD	Peripheral Vascular Disease
REC	Research Ethics Committee
RIND	Reversible Ischaemic Neurological Deficit
RRT	Renal Replacement Therapy
TIA	Transient Ischemic Accident

3. BACKGROUND AND RATIONALE

3.1. Trial Summary

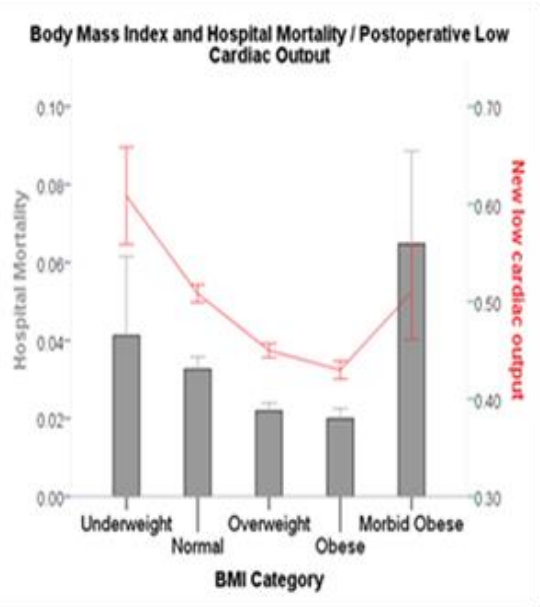
Low cardiac output is a key determinant of outcome following cardiac surgery. In a single centre cohort we have demonstrated that obesity confers protection against low cardiac output and death. This phenomenon, referred to as the 'obesity paradox' has been shown in other clinical settings characterised by acute metabolic stress including trauma and major surgery. In addition, our experimental work has identified a plausible hypothesis to explain the obesity paradox, and we suggest that inflammatory preconditioning may be responsible. The validity of these observations has been questioned however; they are at odds with large epidemiological analyses in non-surgical populations and may be attributable to confounding and bias, or reverse epidemiology. To address this uncertainty we wish to determine the effects of obesity on clinical outcomes in a large multicentre cohort using the National Adult Cardiac Surgery Audit dataset. Importantly we also wish to study the interaction between obesity and other important risk factors. This will assist with the design of future studies intended to explore the mechanisms that underlie our clinical observations.

3.2. Background

Low cardiac output is a key determinant of outcome following cardiac surgery. Aortic cross clamping, myocardial ischaemia and reperfusion, followed by the systemic inflammatory response to surgery can result in myocardial injury and dysfunction, which when severe contributes to oxygen supply dependency, multiple organ failure and death. Effective protection against myocardial injury is therefore an important consideration if good clinical outcomes are to be achieved [1]. Myocardial protection is facilitated by operative strategies including cardioplegic technique, or the avoidance of cardiopulmonary bypass. Despite these developments low cardiac output affects as many as 5%-40% of patients, depending on its definition, where it contributes significantly to morbidity, mortality and the increased use of healthcare resources [1-4].

In an observational cohort study we have shown increased body mass index (BMI) is associated with a reduced risk of developing low cardiac output (defined as the use of at least 1 major inotrope or an intra-aortic balloon pump) and death following cardiac surgery (Figure 1).

Figure 1. Graph demonstrating a significant reduction in risk of perioperative low cardiac output or death in overweight (BMI 25-30) and obese (BMI 30-40) patients. Logistic regression demonstrated significantly risk of death in these groups after adjustment for other risk factor (Unpublished observations from n=10898 patients at a single UK centre).



	Odds Ratio	P value	95% Confidence intervals
Obesity/Overweight vs other	0.70	0.020	0.52 - 0.95
Female sex	1.45	0.024	1.05 – 2.01
Age	1.05	< 0.001	1.03 – 1.07
Ejection Fraction <30%	1.72	0.030	1.05 – 2.80
IV heparin or nitrates pre-op	1.17	0.652	0.60 – 2.27
Chronic Dialysis	2.47	0.198	0.62 – 9.80
COPD	1.70	0.030	1.05 – 2.75
Previous neurological accident	1.47	0.081	0.95 – 2.30
Diabetes mellitus	1.70	0.003	1.20 – 2.41
Serum Creatinine	1.01	< 0.001	1.00 – 1.01
Elective	0.54	< 0.001	0.39 – 0.74
Major aortic	2.66	< 0.001	1.64 – 4.33
Statin	0.93	0.691	0.66 – 1.32
Pre-op Haemoglobin	0.87	0.003	0.79 – 0.95

This observation, referred to as the obesity paradox [5], has been reported by others in cardiac surgery [6, 7], and in other settings where patients are subjected to severe metabolic stress including intensive care [8], major surgery [9], and myocardial infarction [10]. To explore the basis of the obesity paradox we evaluated the effects of a high fat diet on inflammatory organ injury following cardiopulmonary bypass (CPB) in swine [11]. In this study, high fat feeding resulted in obesity and hyperlipidaemia, and protected swine against post CPB myocardial and kidney injury. This organ protection was associated with a paradoxical increase in renal and myocardial inflammatory signalling. In the kidney increased NF-kB signalling, epithelial cell proliferation and monocyte infiltration in obese pigs conferred protection against post CPB acute kidney injury (AKI). In the myocardium high fat feeding also resulted in changes in inflammatory gene expression and pro-inflammatory signalling and HF swine had reduced troponin release following CPB relative to controls fed a normal diet (unpublished data, available on request). These are not isolated findings; pigs fed a high fat diet are protected against myocardial ischaemia reperfusion injury following coronary vessel occlusion [12], as are Langendorff perfused hearts from rabbits or ApoE -/- mice fed a high fat diet [13, 14].

Our observations have led us to hypothesise that attributes of the metabolic syndrome promote tissue inflammation that protects organs against ischemic reperfusion injury. This may represent a novel form of preconditioning against ischaemic injury that has therapeutic potential. However, ours is not the only hypothesis that has been put forth to explain the obesity paradox; some authors have suggested that this may represent the anti-inflammatory effects of increased adipokine levels in the obese [15, 16]. Others have suggested that these findings are a consequence of reverse epidemiology [17], or are attributable to bias and confounding from unmeasured variables [18]. These suggestions are supported by the results of multiple large epidemiological studies in non-surgical populations that show an increased risk of cardiovascular death in patients with obesity [19-21].

A limitation of our existing analysis is that it includes patients from a single UK cardiac centre. A second is that the 95% confidence intervals for the effect estimate of overweight/ obesity are wide, suggesting that the effect may be heterogeneous; and may differ when present with other important risk factors such as for example diabetes, or in specific patient subgroups. To address this uncertainty we propose to undertake an observational study in a large multicentre cohort. This will allow better precision, in terms of the effect estimate for obesity on outcome, well as the statistical power to assess interactions with other important risk factors for death and low cardiac output.

3.3. Aims and Objectives

Primary hypothesis:
The primary hypothesis is that there is no independent association between BMI and the primary outcome once important covariates are considered.

Secondary hypotheses:
The associations between obesity and outcome will be different in patients with or without systemic inflammatory diseases including ischaemic heart disease, diabetes, heart failure, chronic kidney disease, systemic atherosclerosis or old age. Therefore, the associations between obesity and outcome will be different in patients with unstable symptoms; severe or unstable angina, recent myocardial infarction, urgent surgery.

Objectives:

A. To establish whether patients who are overweight or are obese have a lower risk of death, low cardiac output, acute kidney injury or prolonged ICU stay relative to normal or underweight weight patients.

B. To establish whether the obesity paradox is evident in patients who have pre-existing and severe systemic inflammatory diseases.

C. To establish whether the effects of obesity on outcome are influenced by recent myocardial ischaemia or cardiac decompensation.

4. PLAN OF INVESTIGATION

4.1. Study design

This study is a cross-sectional observational cohort study using prospectively collected data from all cardiac surgery units in the UK and Ireland. The study will consider the associations between body mass and clinical outcomes in cardiac surgery.

4.2. Study population

This study will use prospectively collected data from the National Institute for Cardiovascular Outcomes Research (NICOR) National Adult Cardiac Surgery Audit (NACSA) registry (version 4.1.2). This dataset contains data from 44 UK and Irish hospitals collected between 1 April 2002 and 31 March 2013. This is extracted from data routinely submitted as part of the UK National Audit for Adult Cardiac Surgery [22]. This undergoes internal and external quality control procedures and is considered to be of high quality.

• *Inclusion Criteria:* Adult cardiac surgery patients undergoing surgery with or without cardiopulmonary bypass.

• *Exclusion criteria:* emergency or salvage patients, patients with critical preoperative state (balloon pump, ventilated, cardiogenic chock, inotropic support), Stage 5 Chronic Kidney Disease (dialysis).

4.3. Definitions of Exposures of Interest and Potential Confounding Factors

The primary exposure of interest is BMI, which will be determined using the equation BMI=body mass (kg)/ hieght^2 (m). According to the World Health Organization [23], BMI (Kg/m^2) will be further categorised in 6 classes: underweight (BMI<18.5 kg/m^2), normal weight (BMI 18.5-25), overweight (BMI 25-30), obese class I (BMI 30-35), obese class II (35-40), and obese class III (BMI≥40).

The frequency and outcomes in specific high-risk subgroups will be analysed namely decades of age, left ventricular ejection fraction (LVEF), diabetes, pulmonary disease, gender, renal impairment, coronary artery bypass graft (CABG) performed, angina class (according to the Canadian Cardiovascular Society classification), coronary artery disease (CAD), peripheral vascular disease (PVD) and New York Heart Association (NYHA) classification.

4.4 Outcomes of Interest

• *Primary Outcome:* In hospital death.

• *Secondary Outcomes:*

1. Low cardiac output
2. Re-exploration for bleeding/tamponade
3. Stroke
4. Severe acute kidney injury (renal replacement therapy)
5. Sternal wound infection

4.5. Definitions

The UK Society for Cardiothoracic Surgery in Great Britain and Ireland National Cardiac Surgery Audit definitions for perioperative variables will be used [24].

• *Outcomes:* Death will be defined as death in hospital, as per the national audit. Low cardiac output will be defined by the new use of an intra-aortic balloon pump postoperatively. Severe postoperative acute kidney injury will be defined as new postoperative renal replacement therapy. In addition, postoperative stroke occurrence, re-exploration for bleeding/tamponade and deep sternal wound infection will be evaluated.

• *Administrative data:* date of admission; date of operation; date of discharge; region; discharge site.

• *Preoperative Variables:* Gender (female/male). Operative priority will be defined as elective (admission from home), urgent (surgery within current hospital admission), emergency (cardiac compromise – no delay in surgery), and salvage (cardio pulmonary resuscitation pre-anaesthetic induction). Cardiac related indicators will include: cardiogenic shock; ejection fraction (categorised as good (≥50%), moderate (30-49%) and poor (<30%)); previous cardiac surgery; left main stem disease, and an indicator for whether the patient had a myocardial infarction (MI) <30 days prior to operation; NYHA class; CCS angina class; history of atrial fibrillation. Preoperative cardiac-related interventions will include: failed percutaneous transluminal coronary angioplasty (PTCA); and the administration of intravenous heparin or nitrates until operation.

• *Comorbidities* will include: hypertension; chronic obstructive pulmonary disease (COPD), including emphysema; previous neurological disease (Transient Ischaemic Attack [TIA], Reversible Ischaemic Neurological Deficit [RIND], Cerebrovascular Accident [CVA] or other significant neurological disease); peripheral vascular disease; smoking status; renal failure (creatinine > 200 mmol/l); chronic dialysis (onset more than 6 weeks prior to cardiac surgery); and diabetic on medication (oral therapy or insulin). Age and sex will also be extracted. Height and weight measurements will be used to calculate the BMI. Except for BMI continuous variables will be mean centred. The index of multiple deprivation (IMD) score will be adopted as index of deprivation status.

• *Operations* will be classified by procedure(s): namely coronary artery bypass grafting (CABG), Valve, or 'Other cardiac procedures', or any combination of the three. A subgroup of the 'Other' cardiac procedures category: all procedures involving the aorta will be additionally categorised as 'major aortic procedures'. Operative variables will also include use of cardiopulmonary bypass (CPB), CPB-time, aortic cross-clamp time, and number of performed grafts.

4.6. Sample size

The size of the study cohort is limited by the data available. Formal methods for estimating sample sizes in regression based studies are complex and require specification of the expected relationship between risk factors and outcome, which is often unknown and difficult to predict. However, it is generally accepted that the number of factors examined, when using multiple regression analysis, should not exceed $^{1}/_{10}$ of the sample size. Initial exploration of the data suggests that the cohort analyses will include over 250,000 patients of whom approximately 69% will be obese or overweight, 2.5% will have died and around 3% required the insertion of an intra-aortic balloon pump. The sample size should therefore be more than adequate to address the questions posed.

5. STUDY METHODS

5.1. Study treatment, randomisation and code breaking

This is a non-interventional retrospective study. Randomisation to study treatment and unblinding procedures are not applicable.

5.2. Trial specific tests and procedures

No study specific tests or procedures will be performed.

5.3. End of the trial

The end of the study is defined as the completion of the statistical analysis.

5.4. Data collection

The data source to be used is the National Adult Cardiac Surgery Audit (NACSA) database held by the National Institute for Comparative Outcomes Research (NICOR). This prospectively collects data on risk factors, operation details and outcome (in-hospital and longer-term, including post-discharge mortality) on all patients undergoing cardiac surgery in the UK, as well as from some units in Ireland.

Table 1 **Key data collection points**

The study timeline is as follows:

Months	Activity
0-3	Research approvals/set-up
4-9	Study subject recruitment and data collection
9-12	Data analysis
12-15	Dissemination of findings

5.5. Screening and eligibility assessment

This study will include data on all patients who underwent cardiac surgery in the cardiac surgery centres that contribute to the NACSA within the specified time-frame and for whom a complete data set is available.

6. STUDY ANALYSIS

6.6. Plan of analysis

Data Considerations: The data will be cleaned to remove implausible entries and duplicate observations [25]. Patients aged 18 years or over undergoing elective or urgent cardiac surgery will be included.

Patients undergoing emergency or salvage procedures, or for whom it was not possible to calculate BMI, or where the sex of the patient or type of cardiac operation was missing, will be excluded. A "complete-case" dataset will be obtained by including all cases with complete data on a set of key preoperative, intraoperative and post-operative variables as follows: female, age, BMI, ejection fraction category, myocardial infarction status, renal impairment, and diabetic on medication, previous cardiac surgery, operation type and cardiopulmonary bypass.

Analysis: A statistical analysis plan will be drafted prior to analysis. The principal analysis will be performed in the complete case data using regression analyses. A set of candidate models will be developed incorporating a main effects model plus potential interactions and/or quadratic terms. The robustness of the model will be also tested by fitting the final complete case model in the multiply imputed data. Sensitivity analyses will establish whether using accepted definitions of obesity, as described above, will have influenced our results, for example by considering BMI as a continuous variable or excluding patients with very low (BMI<18.5) or very high (BMI>40). In addition we will possibly determine the sensitivity of our results to alternative models and to simulated unobserved confounders using the methods proposed by Ichino et al. [26]. To best reflect contemporaneous surgical practice, the final models will also be fitted to data over the last 5 years of the dataset.

Subgroup Analyses: effect estimates will be determined in the following subgroups: decades (age); male *versus* female; patients with CAD vs patients without; CCS class I/II *versus* CCS class III/IV; NYHA class I/II *versus* NYHA class III/IV; poor LV (EF<30%) *versus* moderate/good LV (EF >30%), diabetics versus non diabetics, COPD *versus* non COPD; peripheral vascular disease *versus* no peripheral vascular disease; renal impairment *versus* no renal impairment; patients with metabolic syndrome *versus* patients without; CABG *versus* non CABG operation.

7. TRIAL MANAGEMENT

The study will be managed by the Cardiac Surgery Clinical Trials Team (CSCTT) at the University of Leicester, supported by the Leicester Clinical Trials Unit (CTU), a UK Clinical Research Collaboration registered Clinical Trials Unit. The CSCTT will prepare trial documentation and data collection forms, register patients and carry out trial procedures; the CTU will develop and maintain the study database, check data quality as the trial progresses, and carry out trial analyses in collaboration with the principal investigator.

7.1. Day-to-day management

The trial will be managed by a Clinical Trials Manager, supported by a Clinical Trial Coordinator from the Cardiac Surgery Clinical Trials Team at the University of Leicester.

7.2. Trial steering committee and data monitoring and safety committee

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the Research Governance Framework and the Medicines for Human Use (Clinical Trials) Regulations 2004. All study related documents will be made available on request for monitoring and audit by the sponsor, the REC or any other regulating body. The trial will be monitored by the Cardiovascular Surgery Research Group Steering Committee (CSRGSC). As this is an observational study no Data Safety and Monitoring Board (DSMB) will be convened. The CSRGSC will provide overall supervision of the trial and ensure that the local, national and international research framework is adhered to, will agree trial amendments, as necessary, and provide relevant guidance on study design and conduct to participating investigators. Membership includes members of the Trial executive, principal investigators, independent experts, a service user representative and a representative of the study Sponsor.

8. SAFETY REPORTING

Not required as this is a retrospective study.

9. ETHICAL CONSIDERATIONS

9.1. Review by a NHS Research Ethics Committee

This study will not consider any patient identifiable data and will therefore be exempt REC approval. The study will however be submitted to the local R&D department for approval and to the University of Leicester for sponsorship.

9.2. Risks and anticipated benefits

As this is a retrospective observational study there are no immediate risks to patients.

9.3. Obtaining informed consent from participants

As this is a retrospective study of prospectively collected, anonymised data we will ask for informed consent to be waived.

10. RESEARCH GOVERNANCE

This study will be conducted in accordance with

- The Medicine for Human Use (Clinical Trial) Regulations 2004;
- International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines;
- Declaration of Helsinki (World Medical Association 2000)
- Research Governance Framework for Health and Social Care.
- European Union Directive 2001/20/EC on clinical trials

10.1. Sponsor approval

Any amendments to the trial documents must be approved by the sponsor prior to implementation.

10.2. NHS approval

Approval from University Hospitals Leicester NHS Trust will be obtained prior to the start of the trial.
Any amendments to the trial documents will be submitted to the Trust for information or approval as required.

10.3. Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements have been signed off by all parties before initiating the research at their institution.
Investigators accept the responsibility for compliance to the protocol and accuracy of the submitted data sets. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor, CTEU or any regulatory authorities. Investigators will be required to read, acknowledge and inform their local team of any amendments to the trial documents and ensure that the changes are complied with.

10.4. Monitoring by sponsor

The study will be monitored and audited in accordance with the University of Leicester policy which is consistent with the Research Governance Framework and the Medicines for Human Use (Clinical Trials) Regulations 2004.

All trial related documents will be made available on request for monitoring and audit by University of Leicester, CTU ort other regulatory bodies as required.

10.5. Indemnity

This is a University of Leicester sponsored research study.

10.6. Clinical Trial Authorisation

A Clinical Trial Authorisation from the MHRA is not required.

11. DATA PROTECTION AND PATIENT CONFIDENTIALITY

11.1. Data protection

Data will be collected and retained in accordance with the Data Protection Act 1998.
All personal identifiers have been removed from the data prior to transfer to the University of Leicester. All research staff involved in this process will have at least an honorary contract with the University of Leicester or the Institution the data is originating from. The anonymised data sets to the coordinating centre where they will be stored, processed and analysed by a designated researcher or statistician.

11.2. Data handling, storage and sharing

Data will be stored in a secure server and analysis will only take place on University networked computers or encrypted laptops. Access will be restricted to named individuals. Data validation and cleaning will be carried out according to standard operating procedures (SOPs) for database use, data validation and data cleaning.
All trial documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study.

12. DISSEMINATION FINDINGS

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications and through patient organisations and newsletters to patients, where available.

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14. APPENDIX – Collected Variables

Variable	Unit/Reference	Type	Definition	Range
Demographic				
Age	Years	Numerical	Median/IQR	
Height	m	Numerical	Median/IQR	
Weight	Kg	Numerical	Median/IQR	
BMI	Kg/m^2	Numerical	Median/IQR	
Gender	Female	Categorical	N (%)	Male/Female
Clinical				
Presentation	Emergent	Categorical	N (%)	Elective/Urgent/Emergent
Reoperation	Yes	Categorical	N (%)	Yes/no
CCS class	IV	Ordinal	N (%)	I to IV
NYHA class	III/IV	Ordinal	N (%)	I to IV
Preop rhythm	AF	Categorical	N (%)	SR-AF-PM-Other
CAD	Yes	Categorical	N (%)	Yes/no
LMS	Yes	Categorical	N (%)	Yes/no
Prior AMI	90 days	Categorical	N (%)	No-≤90 days->90 days
Prior PCI	Yes	Categorical	N (%)	Yes/no
EF	Poor (<30%)	Ordinal	N (%)	<30%/30-50%/>50%
Comorbidities				
Hypertension	Yes	Categorical	N (%)	Yes/no
Diabetes	Insulin dependent	Categorical	N (%)	No/diet/oral /insulin
Pulmonary disease	Yes	Categorical	N (%)	Yes/no
Smoking status	Current smoker	Categorical	N (%)	Never/ex smoker/current
Extracardiac arteriopathy	Yes	Categorical	N (%)	Yes/no
CVA	Yes	Categorical	N (%)	Yes/no
Creat > 200 mmol/l	Yes	Categorical	N (%)	Yes/no
Dialysis	Yes	Categorical	N (%)	Yes/no
IMD	score	Numerical	Median/IQR	
Intraoperative				
Type of operation	Isolated CABG	Categorical	N (%)	Isolated CABG/isolated Valve/CABG+Valve/ Aorta surgery/Other procedures
CPB use	Yes	Categorical	N (%)	Yes/no
CPB time	min	Numerical	Median/IQR	
ACC time	min	Numerical	Median/IQR	
N.graft	n.	Numerical	Median/IQR	
Postoperative				
IABP use	Yes	Categorical	N (%)	Yes/no
Re-exploration bleeding	Yes	Categorical	N (%)	Yes/no
Stroke	Yes	Categorical	N (%)	Yes/no
Dialysis	Yes	Categorical	N (%)	Yes/no
DSWI	Yes	Categorical	N (%)	Yes/no
Hospital mortality	Yes	Categorical	N (%)	Yes/no
Other				
Region	-	Categorical	N (%)	-
OP date	Year	Categorical	Year (%)	From 2002 to 2013

A Systematic Review of the Effects of Obesity on Outcomes in Patients with Heart Disease

Version No: Version 0.4
Date: 01 January 2016
Sponsor: University of Leicester
Funder: N/A
Type of study: **Systematic Review/Meta-analysis**

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1. PROTOCOL INFORMATION

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1.2. Conflict of interest

None

1.3. Founding Sources/Sponsor

University of Leicester

1.4. Dates

- Start date: 10 July 2015
- Anticipated completion date: 31 January 2016

1.5. Type of review

Epidemiologic; Intervention

1.6. Language

English

1.7. Country

United Kingdom

1.8. Keywords

Systematic review; body mass index; obesity; obesity paradox; heart failure; cardiovascular disease; acute coronary syndrome; myocardial infarction; percutaneous coronary intervention; angioplasty; coronary artery bypass grafting, cardiac surgery; mortality.

2. GLOSSARY/ABBREVIATIONS

ACS	Acute Coronary Intervention
AHA	American Heart Association
BMI	Body Mass Index
CABG	Coronary artery Bypass Grafting
CPB	Cardiopulmonary Bypass
HF	Heart Failure
IABP	Intra-Aortic Balloon Pump
MI	Myocardial Infraction
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention

PICOS	Patients, Intervention, Comparator, Outcomes, Study design
VAD	Ventricular Assist Device
WHO	World Health Organisations

3. BACKGROUND AND RATIONALE

3.1. The clinical problem

Over the last decades, improvement in socioeconomic conditions has led to an increase of the overweight population worldwide, and studies in diverse patient groups have demonstrated strong associations between increased body mass index (BMI) and improved clinical outcomes. This phenomenon termed the "obesity paradox" is at odds with the well-recognised causal association between obesity and cardiovascular disease. The clinical importance of these observations is unclear; recent studies have attempted to establish whether the obesity paradox can be simply explained by bias and unmeasured confounding, or whether there are important underlying mechanisms that may be harnessed to improved prognosis in patients with cardiovascular disease. This systematic review will summarise recent developments to identify areas of uncertainty or gaps in knowledge that need to be addressed by future studies.

3.2. The "Obesity Paradox"

Cardiovascular disease remains the leading cause of death in the UK (73,000 deaths per year, 200 deaths per day). The total cost of premature death, lost productivity, treatment and prescriptions for cardiovascular disease in the UK is £19 billion per year (www.bhf.org). Multiple clinical studies have demonstrated that patients with heart disease who are overweight, or obese have improved long-term survival when compared to normal weight, underweight or severely obese patients [1,2]. This is a controversial finding; diabetes, pre-diabetes, hyperlipidaemia and obesity, all manifestations of the metabolic syndrome, are key risk factors for the development of cardiovascular disease, and multiple observational analyses have demonstrated an increase in premature cardiovascular death in these patients [3,4]. Furthermore, these conditions are rapidly increasing in prevalence and are predicted to consume a significant and increasing proportion of all healthcare expenditure in the coming years [5]. However, if obesity or being overweight is associated with improved outcomes in specific clinical settings this may have important implications for a number of reasons: i) It may help tailor strategies or the use of interventions in underweight and very obese patients that may improve outcome; ii) it may challenge current assumptions that patients with these conditions should lose weight acutely, particularly prior to surgery; iii) it may deliver new treatments that can target specific processes underlying these observations; iv) it may provide new insights into the pathogenesis of diabetes and the metabolic syndrome that will lead to better outcomes and reduced healthcare expenditure in general.

3.3. Study bias

There are significant limitations in the existing evidence for the obesity paradox. Firstly, these observations have been made in non-randomised studies that included relatively small cohorts of selected patients, typically suffering from multiple sources of bias that relate either to the limitations of the study design, or the effects of unmeasured confounders [6,7]. Specific sources of bias include:

1. Selection bias: observational analyses are normally conducted in retrospective cohorts of patients who have already been selected for specific interventions or diagnostic groups by clinicians. Obese or overweight patients may be preferentially selected because they are younger. Similarly, 'fitter' obese or overweight patients may have been selected for these interventions (percutaneous coronary intervention [PCI], cardiac surgery), excluding the less fit obese or overweight patients from analyses [8]. Alternatively, "survival bias" may lead to more obese patients dying from cardiovascular disease before they present for treatment, interventions or the diagnosis of heart failure [8].

2. Treatment bias: overweight and obese patients may be considered more suitable for aggressive or multiple interventions than other patient groups, particularly those with low body weight, increasing the likelihood that they will have better clinical outcomes.
3. Study Power: the assumptions that must be met to ensure the accuracy of regression analyses, the most common type of analyses in these studies, are not necessarily met in smaller samples where multiple covariates are considered alongside the effects of obesity. Conversely, large analyses may detect very small effects that are highly statistically significant, leading to an over-interpretation of their importance.
4. Reverse epidemiology: this is a limitation of all epidemiologic studies, which by design can never demonstrate causality. Rather than demonstrating that increased body mass index (BMI) improves survival these studies may instead demonstrate that factors that lead to low BMI also lead to poor survival. For example smoking, poverty and malnutrition, or cachexia attributable to other diseases is likely to lead to low BMI and also to high mortality [9, 10].
5. Definitions of Obesity: there is a large variety in defining obesity categories across studies. The most recognized classification system for BMI is the one defined by the World Health Organization [11]. According to the WHO system, six major BMI (Kg/m^2) groups are recognized: underweight (BMI<18.5 Kg/m^2), normal weight (BMI 18.5-<25), overweight (BMI 25-<30), obese class I (BMI 30-<35), obese class II (BMI 35-<40), and obese class III (BMI ≥ 40) [Appendix]. However, although the great majority of studies adopt the above WHO classification for obesity, slightly different cut-offs have been also introduced [12,13]: the American Heart Association (AHA) previously identified underweight patients group as those having a BMI < 20 kg/m^2. Other studies defined the cut-off for the underweight at < 18 kg/m^2 or < 19 kg/m^2 [14-17] (Table 1). Therefore the inclusion of underweight patients in the normal group, therefore creating a source of bias, could explain controversial results among study comparison (Table 1). Other differences involve the obese patients (BMI ≥ 30 kg/m^2). This definition includes patients that are overweight alongside those that are normal and underweight and potentially confounds analyses.

Table 1. Examples of different classification of obesity defined by Body Mass Index (BMI) used in clinical studies

Classification/Author							
WHO,[11] 1995							
Class	Underweight	Normal range	Overweight	Obese class II	Obese class II	Obese class III	
BMI cut-off	18.5	18.5-24.99	25-29.99	30-34.99	35-39.99	≥ 40	
AHA,[12] 1993 – Gurm et al,[13] 2002							
Class	Underweight	Normal range	Overweight	Obese	Severely Obese	-	
BMI cut-off	< 20	20-24.99	25-29.99	30-34.99	≥ 35	-	
Orhan et al,[14] 2004 – Reser et al,[15] 2013							
Class	Underweight	Normal range	Overweight	Obese	-	-	
BMI cut-off	< 18	18-24.99	25-29.99	≥ 30	-	-	
Sun et al,[16] 2009							
Class	Underweight	Normal range	Overweight	Obese	Severely Obese	Extremely obese	
BMI cut-off	< 19	19-24.99	25-29.99	30-39.99	40-49.99	≥ 50	
Tobias et al,[17] 2011							
Class	Underweight	Normal I	Normal II	Overweight I	Overweight II	Obese I	Obese II
BMI cut-off	< 18.5	18.5-22.4	22.5-24.9	25.0-27.4	27.5-29.9	30.0-34.9	≥ 35

3.4. Unmeasured Confounders

1. Body mass index: BMI is the main exposure of interest in many of these studies, not necessarily delineating a homogeneous group of patient who for example have or do not have obesity or the metabolic syndrome.

BMI may be elevated by visceral adiposity that is thought to promote insulin resistance and the metabolic syndrome, or by subcutaneous adiposity or increased muscle mass, that may counter the pathological effects of the metabolic syndrome [18,19].

2. Race and geographical setting: for example the relationship between BMI and the metabolic syndrome are different between ethnic groups [20].

3. Association between obesity (measured as BMI) and outcome: this association may be spurious. The result may be attributable to other key covariates including the presence or absence of atherosclerosis, smoking, socioeconomic group, dietary fat or sugar content, serum lipid levels, glucose levels or insulin levels, all of which have different exposures in obese and non-obese patients [21-23].

3.5. The knowledge gap

Although obesity has been implicated as one of the major risk factors for hypertension, heart failure, and coronary artery disease, evidence from clinical cohorts of patients with cardiovascular diseases indicates that obesity is associated with favourable survival in patients affected by heart disease (defined as patients with heart failure, heart valve disease or symptomatic coronary artery disease). More recent evidence has suggested that these findings may be attributed to bias attributable to study design or to confounding factors. In this review we will assess the contribution of methodological bias, or unmeasured covariates such as lean body mass, visceral adiposity, impaired glucose tolerance, smoking or exercise tolerance on the obesity paradox. Better understanding of this phenomenon may assist with the risk stratification and management of existing patients and also help develop new treatment strategies for patients with cardiovascular disease.

3.6. Why it is important to do this review

Obesity, diabetes and the metabolic syndrome are currently reaching epidemic proportions and have significant implications for health services and national economies [5]. These are important risk factors for most cardiovascular diseases, the most common cause of death in the UK and elsewhere. Improved understanding of how the metabolic syndrome affects clinical outcomes, or how these patients may be better risk stratified or treated, may ultimately improve clinical outcomes. This review will define the knowledge gap in our understanding of the “obesity paradox”, identify areas of uncertainty and identify areas for further research.

4. OBJECTIVES

The overarching aim of the review is to assess the interaction between obesity and hospital clinical outcomes in patients affected by heart diseases.

4.1. Hypothesis

It is our hypothesis that the association between obesity, currently defined by the WHO as an elevated BMI [11], and improved survival in patients affected by cardiac diseases is likely to represent the effects of methodological bias or residual confounding.

4.2. Aims

The aims of the present review will be:

1. To summarise published studies that have considered the associations between obesity and mortality in patients with heart disease;
2. To estimate the associations between obesity and mortality in patients with heart disease;
3. To assess the potential effects of study quality, potential sources of bias, and unmeasured confounders on our estimates in these studies;

5. METHODS

5.1. Criteria for Selecting Studies

5.1.1. Types of studies

We will consider clinical studies that have evaluated the effect of the primary exposure of interest (BMI) on mortality in patients with heart disease. The following types of studies will be analysed:

1. Clinical randomised trials;
2. Controlled before-and-after studies;
3. Prospective and retrospective cohort studies;
4. Cross-sectional studies;
5. Case-control studies.

Study design features will be assessed according to established criteria from the Cochrane Handbook [24]. In addition, inclusion and exclusion criteria for qualitative and quantitative analyses will be presented according to PICOS criteria.

5.1.2. Study exclusion criteria

Exclusion criteria will include:

1. Studies where BMI is expressed only as a continuous variable;
2. Repeat publications of the same analysis or dataset;
3. Conference abstracts;
4. Editorials & opinion pieces;
5. Books or grey literature.

5.1.3. Types of participants

Adult patients with heart failure (HF), acute coronary syndrome (ACS) including patients with acute myocardial infarction (MI), those undergoing percutaneous coronary interventions (PCI), and cardiac surgery (all type of operation will be considered).

5.1.4. Exposures of Interest

The primary exposure of interest will be obesity, stratified according to the WHO classification [11]. Therefore, six BMI (Kg/m^2) groups will be considered: underweight (BMI<18.5 Kg/m^2), normal weight (BMI 18.5-25), overweight (BMI 25-30), obese class I (BMI 30-35), obese class II (BMI 35-40), and obese class III (BMI ≥ 40). Alternate definitions of obesity, as described in Table 1 will also be considered.

Subgroup analyses will include the following clinical settings: HF, ACS (including MI), PCI, CABG surgery and non-CABG surgery.

5.1.5. Types of outcome measures

- Primary outcome measure will be in-hospital/30-day mortality (all cause).
- Secondary Outcome will include:
    a. Long-term mortality
    b. Low cardiac output (defined by the need of IABP)
    c. Perioperative MI
    d. Reopening for bleeding/tamponade
    e. Stroke
    f. Renal replacement therapy
    g. Deep sternal wound infection
    h. Length of hospitalization

5.2. Search Methods for Identification of Studies

5.2.1. Search strategy

We will search the following databases (from inception to 30 June 2015):

1. Cochrane Central Register of Controlled Trials
2. MEDLINE (OvidSP, 1946 to 30 June 2015);
3. Embase (OvidSP, 1974 to October 2015);
4. PubMed (e-publications only: searched 30 June 2015);
5. SCOPUS (1960 to 30 June 2015);

No language restriction will be applied. We also anticipate that articles not in English will be translated using Google Translate® which is a free, Web-based program with a reputation for accurate, natural translation [25,26].

5.2.2. Searching other resources

We will check references of all identified trials, relevant review articles, and current treatment guidelines for further literature. These searches will be limited to the 'first generation' reference lists.

5.2.3. Search terms

The following search terms will be used in multiple queries: (obesity OR body mass index OR adiposity OR body weight) AND (mortality OR death OR morbidity OR survival OR patient outcomes) AND (adult) AND (heart failure OR acute coronary syndrome OR myocardial infarction OR percutaneous coronary intervention OR angioplasty OR stent OR percutaneous coronary intervention OR cardiac surgery OR coronary artery bypass OR heart valve surgery OR cardiac transplant OR ventricular assist device)

5.2.4. Results of the scoping search

A preliminary electronic search (PUBMED) using the above search terms has specifically identified more than 10000 titles with reference to individual category of study:

- Acute coronary syndrome (ACS): 3554;
- Cardiac surgery: 1500;
- Heart failure (HF): 2528;
- Percutaneous coronary intervention (PCI): 3848.

5.3. Data collection

5.3.1. Selection of studies (screening-eligibility-inclusion)

Three authors (A.D., F.S. and S.P.) will screen all titles and abstracts of papers identified for relevance to the review aims (electronic search). An independent search with the review of all articles will be conducted by a third review (G.M.). Studies clearly not meeting the eligibility criteria will be excluded at this stage. Remaining studies will be assessed on the basis of their full text for inclusion or exclusion using the criteria indicated above. At this stage, three reviewers (A.D., F.S., and G.M.) will independently assess eligibility. Disagreements will be resolved by consensus in discussion with a fourth reviewer (G.J.M.). Numbers of studies assessed, included and excluded will be recorded. Duplicate reporting of studies will be carefully assessed and indicated.

5.3.2. Qualitative analysis

A qualitative analysis will help to explore questions such as how patient selection, treatment and type of study may have influenced the primary effect estimate. The following questions will be considered for a qualitative analysis:

1. Was the study population well described?
2. Were the outcomes of interest clearly defined?
3. Was the study sample size adequate?
4. Were the exposures of interest (primary and secondary) well defined?

5. Does the article state both inclusion and exclusion criteria?
6. Were the analysed variables clearly defined?
7. How was missing data managed?
8. Was the duration of follow-up sufficient?
9. Was the follow-up for following variables of interest well stated?
10. Were important confounders and prognostic factors identified?

5.3.3. Data extraction and management

Two authors (A.D. and F.S.) will extract selected data from eligible studies, which will be subsequently checked by a third author (G.M.). The following data will be collected and tabulated with Microsoft Excel (Microsoft Corporation, Redmond, WA):

1. Study characteristics:

Author/authors; date of publication; country of origin; study design; recruitment period (range, years); inclusion/exclusion criteria.

2. Population characteristics:

Patient number [sample size]; demographic (age [expressed as mean ± standard deviation or median with range/interquartile range], sex); cardiac status (proportion of patients in NYHA class III/IV, previous myocardial infarction, and left ventricular ejection fraction [expressed as mean ± standard deviation]); comorbidities (hypertension, diabetes, dyslipidaemia, smoking status [proportion of current smokers], chronic obstructive pulmonary disease, cerebrovascular accident, peripheral vascular disease, and renal failure defined as dialysis); type of operation.

3. Exposures:

Number of BMI groups according the WHO classification.

4. Outcomes:

Outcome definition; outcome measures;

5. Results:

Number of participants allocated to each BMI group; summary data.

6. Miscellaneous:

Conclusions; comments; specific BMI group definition/cut-offs (underweight/obese), exploratory analyses of confounders or sources of bias.

Two authors (A.D., and G.M.) will perform data extraction independently. Data will be extracted onto study specific data extraction form. Disagreements will be resolved by consensus between the authors or by discussion with a third author where necessary (G.J.M.). Another reviewer (F.S.) will assess all data entry for discrepancies. Missing data will be requested from study authors. If data are unclear, missing, or presented in a form that is unable to be reliably extracted, authors will be contacted to assist in the process. The corresponding author will be initially contacted by email, with the first author (if not the corresponding author) copied into all correspondence. If email addresses are not available, authors will be contacted by phone. Authors will be given seven days to respond to emails, after which they will be followed up with a phone call and an additional email. If no responses are received after an additional seven days, another phone call will be made to contact the author. Attempts to reach authors will occur for an additional seven days and if authors are unable to be contacted, the authors will be classified as uncontactable.

5.4. Risk of bias assessment

Two authors (A.D., and G.M.) will independently assess the risk of study bias by considering the following:

- Randomised trials will be assessed using the Cochrane Collaboration's Risk of Bias tool [27], assessing randomization, sequence generation, concealment of allocation, blinding of patients, health care providers, data collectors, and outcome assessors; incomplete outcome data, selective reporting of outcomes, and reporting of adherence to study protocol.
- Observational studies will be assessed using the Newcastle-Ottawa Scales (NOS) for cohort and case-control studies, which consist of 3 parameters for: selection (maximum 4 points), comparability (2 points), and exposure/outcome assessment (3 points). A maximum score of 9 points thus reflects the lowest risk of bias (highest quality) [28]. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author if necessary (G.J.M.).

5.5. Measures of treatment effect and data analysis

5.5.1. Measures and data representation

The review will adhere to MOOSE and PRISMA guidelines [29,30]. A narrative synthesis of the included studies will be provided, focusing on the impact of obesity on early and late outcomes. Detailed tables of the findings from the included studies will be provided, with reference to the type of study (i.e. randomized, cohort studies, case control studies...), origin (country), the study period (year), the inclusion/exclusion criteria, type of analysed outcomes, and BMI categories. In addition, additional tables will be provided listing relevant characteristics of each study, with reference to population age, gender proportions (male vs. female), cardiac status (ejection fraction, prior history of PCI/MI, NYHA class), comorbidity proportions (i.e. hypertension, diabetes, dyslipidaemia, chronic obstructive pulmonary disease, peripheral vascular disease, cerebrovascular accident, smoking status, renal dysfunction), number of treatment or control subjects, proportions of periprocedural/postoperative complications (i.e. stroke, renal dysfunction, perioperative myocardial infarction, infections…). Additional tables will summarize the obtained study (randomized or observational) points obtained by the Cochrane Collaboration's Risk of Bias tool, the Newcastle-Ottawa Scales for cohort and case-control studies, and the checklist proposed by MOOSE [28,30].

5.5.2. Data analysis

All extracted data will be tabulated with Microsoft with Microsoft Excel (Microsoft Corporation, Redmond, WA); and the analysis will be performed with R version 3.2.2 (R Core Team, 2015) and *metafor package* version 1.9-8 [31,32]. Both fixed and random/mixed-effects models may be adopted to summarize the overall results and within subgroups [33,34]. Sub-group analyses will specifically consider whether the obesity paradox is observed in the above-mentioned populations (ACS, PCI, HF and cardiac surgery). Sensitivity analyses will consider the influence of i) sample size; ii) year of publication; iii) study quality; iv) obesity definition on the effect estimates. Meta-regression will consider the effects of subgroup, demographic or baseline clinical differences on effect estimates where heterogeneity is considered statistically significant ($P < .05$). Between studies heterogeneity will be assessed with Cochran's Q-test [35] in random models without moderators. For mixed models with moderators QE test for residual heterogeneity may be employed. Heterogeneity will be estimated as Q with *P*-value (Q-test), τ^2 (estimated mount of residual heterogeneity), I^2 (percentage of total variability due to heterogeneity between true effects) or H^2 (percentage of total variability and sampling variability) [36,37]. Meta-regression results will be presented as plots (R, graphics package) of relative risks (RR) as a function of the moderator with fitted mixed model estimates and 95% confidence intervals [32,38,39]. The influence of individual studies on the fitted random-effects model will be tested [32]. Finally, any publication bias will be visualised in funnel plots and analysed Egger's test [40]. Where publication bias is significant, the missing studies will be estimated with *trimfill* function, and visualised with a funnel plot. Statistical tests will be 2-sided and will use a significance threshold of $P < .05$ [41,42].

5.3.4. Data publication

The scale of this review is such that we envisage the results will be published in more than one publication.

6. COMPETING INTERESTS

The authors declare that they have no competing interests.

7. REVISED VERSION

The following revisions have been undertaken (version 0.4):

1. Section 3.3., and Sub-section 5.1.4. Alternate definitions of BMI have been specified. Table 1 added.
2. Section 4.2. The aims of the review have been clarified.
3. Sub-section 5.1.5 Secondary outcomes have been better listed.
4. Sub-section 5.2.2. has been implemented.
5. Sub-section 5.2.3 and 5.2.4. Search terms for individual databases have been specified.
6. Sub-section 5.3.1. Authors included in data collection have been amended.
7. Sub-section 5.3.3. Patient data has been amended, and details of qualitative data collection included.
8. Section 5.5.2. The data analysis section has been expanded to describe sub-group and sensitivity analyses. In addition, meta-regression analyses have been introduced.
9. Section 5.3.4. Publication plan has been specified to include potentially multiple publications.

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APPENDIX – WHO classification of BMI groups[11]

Table 2.1
Classification of adults according to BMI[a]

Classification	BMI	Risk of comorbidities
Underweight	<18.50	Low (but risk of other clinical problems increased)
Normal range	18.50–24.99	Average
Overweight:	≥25.00	
Preobese	25.00–29.99	Increased
Obese class I	30.00–34.99	Moderate
Obese class II	35.00–39.99	Severe
Obese class III	≥40.00	Very severe

[a] These BMI values are age-independent and the same for both sexes. However, BMI may not correspond to the same degree of fatness in different populations due, in part, to differences in body proportions (see section 2.3.2). The table shows a simplistic relationship between BMI and the risk of comorbidity, which can be affected by a range of factors, including the nature of the diet, ethnic group and activity level. The risks associated with increasing BMI are continuous and graded and begin at a BMI above 25. The interpretation of BMI gradings in relation to risk may differ for different populations. Both BMI and a measure of fat distribution (waist circumference or waist : hip ratio (WHR)) are important in calculating the risk of obesity comorbidities.