Overweight, but not obesity, paradox on mortality following coronary artery bypass grafting

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ABSTRACT

Objectives: To determine whether an “obesity paradox” on post-coronary artery bypass grafting (CABG) mortality exists, we abstracted exclusively adjusted odds ratios (ORs) and/or hazard ratios (HRs) for mortality from each study, and then combined them in a meta-analysis.

Methods: MEDLINE and EMBASE were searched through April 2015 using PubMed and OVID, to identify comparative studies, of overweight or obese versus normal weight patients undergoing CABG, reporting adjusted relative risk estimates for short-term (30-day or in-hospital) and/or mid-to-long-term all-cause mortality.

Results: Our search identified 14 eligible studies. In total our meta-analysis included data on 79,140 patients undergoing CABG. Pooled analyses in short-term mortality demonstrated that overweight was associated with a statistically significant 15% reduction relative to normal weight (OR, 0.85; 95% confidence interval [CI], 0.74–0.98; p = 0.03) and no statistically significant differences between mild obesity, moderate/severe obesity, or overall obesity and normal weight. Pooled analyses in mid-to-long-term mortality demonstrated that overweight was associated with a statistically significant 10% reduction relative to normal weight (HR, 0.90; 95% CI, 0.84 to 0.96; p = 0.001); and no statistically significant differences between mild obesity, moderate/severe obesity, or overall obesity and normal weight.

Conclusions: Overweight, but not obesity, may be associated with better short-term and mid-to-long-term post-CABG survival relative to normal weight. An overweight, but not obesity, paradox on post-CABG mortality appears to exist.

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Introduction

Cardiovascular risk factors and left ventricular structure and function are adversely affected by obesity, which is associated with an increase in risk of most cardiovascular disease (CVD) [1]. There is, however, an “obesity paradox,” i.e., obese and overweight patients with CVD have a better prognosis than normal weight patients with CVD [1]. A recent study by Banack and Kaufman [2], using data from 17,636 participants in the US National and Nutrition Examination Survey, reported that the adjusted risk ratio (RR) relating obesity and all-cause mortality was 1.24 (95% confidence interval [CI], 1.11 to 1.39) in the general population.

The adjusted RR comparing the obese and the non-obese was 0.79 (95% CI, 0.68 to 0.91) among subjects with CVD and 1.30 (95% CI, 1.12 to 1.50) among subjects without CVD, indicating that obesity is protectively associated with mortality among patients with CVD (which, however, can be explained by a simple selection bias) [2]. In addition, the obesity paradox has been demonstrated in patients undergoing cardiac and non-cardiac surgery. Although the obesity paradox could be explained by hypotheses including increased lean body mass, protective peripheral body fat, reduced inflammatory response, genetics, and a decline in CVD risk factors, the paradox would be probably contributed to also by unknown factors [3]. In a previous (published in 2008) meta-analysis by Oreopoulos et al. [4] of 12 cohort publications reporting results in post-coronary artery bypass grafting (CABG) populations, obese patients had lower short-term [odds ratio (OR), 0.63; 95% CI, 0.56 to 0.71] and similar long-term (OR, 0.88; 95% CI, 0.60 to 1.29) mortality risk compared to normal weight patients, and results were similar in overweight patients. The authors [4] abstracted
“unadjusted” (not “adjusted”) relative risk estimates for post-CABG mortality from each individual study, and then combined them in the meta-analysis. In such analyses, however, it can never be determined whether obesity or overweight is an “independent” predictor of post-CABG survival. To find independent predictors, multivariable logistic regression (MLR) and/or multivariable Cox proportional hazards regression (MCPHR) are used, generating an adjusted OR and/or hazard ratio (HR). Thus, we herein extracted exclusively adjusted ORs/HRs for post-CABG mortality from each study in which MLR/MCPR was applied to find independent predictors of post-CABG survival, and then combined them in an updated meta-analysis.

Methods

All eligible studies were identified using a 2-level search strategy. First, databases including MEDLINE and EMBASE were searched through April 2015 using Web-based search engines (PubMed and OVID). Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles and a search of reviews and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analysis. Search terms included body mass size, obese, or obesity; and coronary artery bypass surgery.

Studies considered for inclusion met the following criteria: the design was a comparative study of overweight or obese patients versus normal weight patients; the study population was patients undergoing CABG; and main outcomes included adjusted relative risk estimates for short-term (30-day or in-hospital) and/or mid- to long-term all-cause mortality using MLR/MCPR. Not all studies used the traditional World Health Organization (WHO) body mass index (BMI) classification system of 18.5–24.9 kg/m² for normal weight, 25.0–29.9 kg/m² for overweight, and >30.0 kg/m² for obesity. Accordingly, to avoid eliminating studies with important information, BMI levels within 2 kg/m² of standard categories were considered to be acceptable [4]. On the other hand, we excluded studies comparing obese and non-obese patients (i.e. normal weight and overweight patients are grouped together) unless outcomes in normal weight patients could be abstracted [4].

Data regarding detailed inclusion criteria, duration of follow-up, and an adjusted OR/HR for post-CABG mortality (overweight or obesity versus normal weight) were abstracted (as available) from each individual study. In a number of studies, a statistically non-significant adjusted OR/HR was unavailable (in case of only statement, e.g. “The multivariable analysis demonstrated that overweight/obesity was not an independent predictor of post-CABG mortality,” with no quantitative OR/HR). If the unavailable and statistically non-significant adjusted ORs/HRs were ignored and not included in a meta-analysis, the pooled result would be biased in favor of overweight/obesity. Thus, in such a case, we extracted a statistically non-significant unadjusted OR/HR (as available), instead of the unavailable and statistically non-significant adjusted OR/HR.

We conducted a meta-analysis of summary statistics from the individual studies. Study-specific estimates were combined using inverse variance-weighted averages of logarithmic ORs/HRs in both fixed- and random-effects models. Between-study heterogeneity was analyzed by means of standard $\chi^2$ tests. Where no significant statistical heterogeneity was identified, the fixed-effect estimate was used preferentially as the summary measure. Publication bias was assessed graphically using a funnel plot and mathematically using an adjusted rank-correlation and linear regression test. All analyses were conducted using Review Manager version 5.3 (Nordic Cochrane Center, Copenhagen, Denmark) and Comprehensive Meta-Analysis version 3 (Biostat, Englewood, NJ, USA).

Results

Our search identified 14 eligible studies [5–18] (Table 1). In total, our meta-analysis included data on 79,140 patients undergoing CABG. Pooled analyses in short-term mortality demonstrated that overweight was associated with a statistically significant 15% reduction relative to normal weight (fixed-effects OR, 0.85; 95% CI, 0.74 to 0.98; for effect = 0.03; p for heterogeneity = 0.41); and no statistically significant differences between mild obesity and normal weight (fixed-effects OR, 1.03; 95% CI, 0.84 to 1.25; for effect = 0.79; p for heterogeneity = 0.21), between moderate/severe obesity and normal weight (fixed-effects OR, 1.25; 95% CI, 0.91 to 1.73; for effect = 0.17; p for heterogeneity = 0.69), and between overall (including mild and moderate/severe) obesity and normal weight (fixed-effects OR, 1.05; 95% CI, 0.90 to 1.23; for effect = 0.52; p for heterogeneity = 0.23) (Fig. 1). Pooled analyses in mid-to-long-term mortality demonstrated that overweight was associated with a statistically significant 10% reduction relative to normal weight (fixed-effects HR, 0.90; 95% CI, 0.84 to 0.96; for effect = 0.001; p for heterogeneity = 0.16 [not shown in Fig. 2]; random-effects HR, 0.90; 95% CI, 0.82 to 0.99; for effect = 0.04); and no statistically significant differences between mild obesity and normal weight (random-effects HR, 1.00; 95% CI, 0.84 to 1.19; for effect = 0.98; p for heterogeneity = 0.04), between moderate/severe obesity and normal weight (random-effects HR, 1.27; 95% CI, 0.91 to 1.78; for effect = 0.15; p for heterogeneity = 0.03), and between overall obesity and normal weight (random-effects HR, 1.08; 95% CI, 0.86 to 1.34; for effect = 0.51; p for heterogeneity = 0.002) (Fig. 2).

To assess the impact of qualitative heterogeneity in study design and patient selection on the pooled effect estimate, we performed several sensitivity analyses. In 3 studies [10,12,18], the reference group included not only normal weight patients but also underweight patients. Because it has been well known that the underweight have poor post-CABG prognosis, including the underweight in the reference group might generate results favoring the overweight/obesity. Thus, we first excluded these 3 studies [10,12,18] from the pooled analysis (including 11 studies) of overweight versus normal weight in short-term mortality; combining the remaining 8 studies generated a still statistically significant result favoring overweight (fixed-effects OR, 0.83; 95% CI, 0.71 to 0.96; for effect = 0.01; p for heterogeneity = 0.28). From 4 studies [13,14,16,18], we extracted (and then combined) statistically non-significant unadjusted ORs for short-term mortality by reason mentioned in the methods section. Including these non-significant ORs in a meta-analysis, however, could generate results unfavorable for overweight/obesity. Hence, we second excluded these 4 studies [13,14,16,18] from the pooled analysis (including 10 studies) of overall obesity versus normal weight in short-term mortality. Without them, there was still no statistically significant difference between overall obesity and normal weight in a pooled analysis of the remaining 6 studies (fixed-effects OR, 1.07; 95% CI, 0.91 to 1.26; p for effect = 0.43; p for heterogeneity = 0.06). In the other pooled analyses, we did not perform sensitivity analyses because of the small number (<6) of included studies.

To assess publication bias we generated a funnel plot of the logarithm of effect size versus the standard error for each trial (not shown). There was no evidence of significant publication bias for the comparison of overweight versus normal weight (2-tailed p = 0.64 and 0.44 by the adjusted rank-correlation and linear regression test, respectively) and the comparison of overall obesity versus normal weight (2-tailed p = 1.00 and 0.98, respectively) in
Table 1
Study design, patient characteristics and mortality.

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjustment</th>
<th>Inclusion criteria</th>
<th>Definition (BMI [kg/m²])</th>
<th>Non-obesity</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Underweight</td>
<td>Normal weight</td>
<td>Overweight</td>
</tr>
<tr>
<td>Ao 2014 [5]</td>
<td>MCPHR</td>
<td>Primary isolated CABG</td>
<td>&lt;18.5</td>
<td>18.5–23.9</td>
<td>24.0–27.9</td>
</tr>
<tr>
<td>APPROACH 2009 [6]</td>
<td>MCPHR</td>
<td>CABG</td>
<td>&lt;18.5</td>
<td>18.5–24.9</td>
<td>25.0–29.9</td>
</tr>
<tr>
<td>Atalan 2012 [7]</td>
<td>MLR</td>
<td>Isolated on-pump CABG</td>
<td>&lt;20.0</td>
<td>20.0–24.9</td>
<td>25.0–29.9</td>
</tr>
<tr>
<td>BARI 2002 [8]</td>
<td>MCPHR</td>
<td>CABG for severe angina or multivessel disease</td>
<td>&lt;20.0</td>
<td>20.0–24.9</td>
<td>25.0–29.9</td>
</tr>
<tr>
<td>Benedetto 2014 [9]</td>
<td>MLR</td>
<td>Primary isolated CABG</td>
<td>–</td>
<td>18.5–24.9</td>
<td>25.0–29.9</td>
</tr>
<tr>
<td>Cemerlíc-Adjic 2014 [10]</td>
<td>MLR</td>
<td>Isolated CABG</td>
<td>&lt;25.0 [under/normal]</td>
<td>25.0–29.9</td>
<td>30.0–34.9</td>
</tr>
<tr>
<td>Jin 2005 [11]</td>
<td>MLR</td>
<td>Isolated CABG</td>
<td>&lt;18.5</td>
<td>18.5–24.9</td>
<td>25.0–29.9</td>
</tr>
<tr>
<td>Kim 2003 [12]</td>
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<td>&lt;25.0 [under/normal]</td>
<td>25.0–29.9</td>
<td>30.0–34.9</td>
</tr>
<tr>
<td>Le-Bert 2011 [13]</td>
<td>MLR</td>
<td>Isolated on-pump CABG</td>
<td>–</td>
<td>18.0–24.9</td>
<td>25.0–29.9</td>
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<tr>
<td>Reeves 2003 [15]</td>
<td>Stratified logistic regression</td>
<td>On-pump and off-pump CABG</td>
<td>&lt;20.0</td>
<td>20.0–24.9</td>
<td>25.0–29.9</td>
</tr>
<tr>
<td>Shirzad 2009 [16]</td>
<td>MLR</td>
<td>Isolated CABG</td>
<td>&lt;18.5</td>
<td>18.5–24.9</td>
<td>25.0–29.9</td>
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<tr>
<td>van Straten 2010 [17]</td>
<td>MLR</td>
<td>Isolated CABG</td>
<td>&lt;25.0 [under/normal]</td>
<td>25.0–29.9</td>
<td>30.0–34.9</td>
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<tr>
<td>Wang 2013 [18]</td>
<td>MLR</td>
<td>Isolated CABG</td>
<td>&lt;25.0 [under/normal]</td>
<td>25.1–30.0</td>
<td>30.1–35.0</td>
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Study Sample size | Mean age (year) |
<table>
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<tbody>
<tr>
<td>Study</td>
<td>Women (%)</td>
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<td>Non-obesity</td>
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<tr>
<td></td>
<td>Underweight</td>
</tr>
<tr>
<td>Ao 2014 [5]</td>
<td>[31]</td>
</tr>
<tr>
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<td>[32]</td>
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<td>Atalan 2012 [7]</td>
<td>[15]</td>
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<tr>
<td>BARI 2002 [8]</td>
<td>[28]</td>
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<tr>
<td>Benedetto 2014 [9]</td>
<td>–</td>
</tr>
<tr>
<td>Cemerlik-Adjic 2014 [10]</td>
<td>[62]</td>
</tr>
<tr>
<td>Jin 2005 [11]</td>
<td>[67]</td>
</tr>
<tr>
<td>Le-Bert 2011 [13]</td>
<td>–</td>
</tr>
<tr>
<td>Orhan 2004 [14]</td>
<td>[133]</td>
</tr>
<tr>
<td>Reeves 2003 [15]</td>
<td>–</td>
</tr>
<tr>
<td>Shirzad 2009 [16]</td>
<td>[67]</td>
</tr>
<tr>
<td>van Straten 2010 [17]</td>
<td>[128]</td>
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<tr>
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<td>[181]</td>
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Table 1 (Continued)

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<th>Study</th>
<th>Follow-up</th>
<th>Relative risk estimate</th>
<th>Non-obes</th>
<th>obesity</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Le-Bert 2011 [13]</td>
<td>In-hospital</td>
<td>Unadjusted non-significant OR (unavailable adjusted non-significant OR)</td>
<td>37.8</td>
<td>29.3</td>
<td>36.2</td>
<td>In-hospital</td>
<td>Unadjusted non-significant OR (unavailable adjusted non-significant OR)</td>
</tr>
<tr>
<td>Orhan 2004 [14]</td>
<td>In-hospital</td>
<td>Unadjusted non-significant OR (unavailable adjusted non-significant OR)</td>
<td>15.62</td>
<td>17.4</td>
<td>20.47</td>
<td>In-hospital</td>
<td>Unadjusted non-significant OR (unavailable adjusted non-significant OR)</td>
</tr>
</tbody>
</table>
| APPROACH, Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease; BARI, Bypass Angioplasty Revascularization Investigation; BMI, body mass index; CABG, coronary artery bypass grafting; HR, hazard ratio; standard error. Stratified by consultant team and adjusting for the 5 propensity scores divided into quintiles. 

Discussion

The results of our meta-analysis of adjusted (not unadjusted) risk estimates suggest that overweight (neither mild, moderate, severe, nor overall obesity) may be associated with better short-term and mid-to-long-term post-CABG survival than normal weight. Whereas, the previous meta-analysis by Oreopoulos et al. [4] of unadjusted (not adjusted) risk estimates demonstrated that overweight (OR, 0.70; 95% CI, 0.63 to 0.77; p < 0.00001), overall obese (OR, 0.63; 95% CI, 0.56 to 0.71; p < 0.00001), and moderately/severely obese (OR 0.66; 95% CI, 0.51 to 0.86; p = 0.002) patients had significantly lower short-term post-CABG mortality compared to normal weight patients. Although overweight was also associated with lower mid-to-long-term mortality (OR, 0.78; 95% CI, 0.60 to 1.00), which was marginally significant (p = 0.05), both overall obesity (OR 0.88; 95% CI, 0.60 to 1.29; p = 0.51) and moderate/severe obesity (OR, 1.42; 95% CI, 0.76 to 2.65; p = 0.28) were associated with a neutral mortality risk [4]. Accordingly, adjustment for possible confounders made overall obesity and moderate/severe obesity unassociated with better short-term survival. The shifting of the relative risk estimates suggests that the risk associated with being obese is increased for a hypothetical population homogeneous with respect to all the other risk factors, which may be owing to the fact that the obese patients are younger and the majority of risk variables being adjusted appear to be more closely associated with being normal weight [19].

A number of authors investigating the present topic (association between overweight/obesity and post-CABG mortality) had entered BMI into MLR/MCPHR as a continuous numeric (not categorized) variable. In a study by Christakis et al. [20], BMI contributed poorly to the predictive value of 30-day mortality (OR, 0.97; 95% CI, 0.94 to 1.01). Also in a study by Harvey et al. [21], BMI was not a predictor of 30-day mortality (p = 0.34) or late (44 ± 34 months) death (OR, 0.96; p = 0.18). Additionally, in a study by Bhamidipati et al. [22], BMI did not independently reduce 30-day/in-hospital mortality (OR, 0.97; 95% CI, 0.93 to 1.02; p = 0.21). In another study by Bhamidipati et al. [23], using BMI as a continuous variable with a quadratic transformation adjustment, BMI was not an independent predictor of 30-day mortality. Furthermore, in a study by Sung et al. [24], BMI was independently correlated with 3.26 ± 1.6-year cardiovascular (not all-cause) death (HR, 0.912; 95% CI, 0.833 to 0.998; p = 0.044). In addition to the aforementioned non linear relationship between continuous BMI and post-CABG mortality, our meta-analysis of categorized BMI (Figs. 3 and 4) suggests that BMI shows a non-linear “U-shaped” or “J-shaped” effect on mortality, which may be strengthened by the results of the following studies. Schwann et al. [25] indicated that 30-day/in-hospital mortality was noticeably lower in patients with median BMI (~2%) compared with those with low BMI (~5% for the smallest patients), while only a small tendency for higher operative mortality was seen at the highest BMI. In a study by Wagner et al. [19], generalized additive models (GAM) were used in the logistic regression setting to estimate the non-linear relationship of BMI with 30-day mortality. Non-linear GAM curves, giving the estimated probability of death across the BMI range, revealed a U-shaped risk function with a minimum around BMI of 30 kg/m², indicating that patients classified as overweight have the lowest risk, and even those in the lower end of the obese range do not have seriously elevated risk [19]. Also in the relationship between BMI and the ORs for mortality in the multivariable model (using a referent value of BMI of 25 kg/m²), the minimum of the U-shaped curve of BMI remains in the overweight [19]. In addition, examining BMI as a continuous variable using fractional polynomial CPHR in the
study by Oreopoulos et al. [6] demonstrated a J-shaped association between BMI and adjusted median-46-month all-cause mortality, where the mortality decreased with increasing BMI until ~33 kg/m², and then began to increase again at a BMI of ~40 kg/m². Moreover, Benedetto et al. [9] demonstrated that BMI as a continuous variable showed a U-shaped effect on the adjusted risk of 30-day/in-hospital mortality with a significant risk reduction for BMI values of 26 to 32 kg/m². A significant protective effect on 7.6 ± 4.5-year mortality was shown only for a BMI of 27 to 29 kg/m² [9].

Several researchers have endeavored to overcome the unexpected survival benefit of the overweight and obese [3]. Based on the U-shaped association between BMI and mortality in a nationally representative sample of Canadian adults, Orpana et al. [26] raised an important question about which reference group to use for the calculation of excess deaths associated with excess weight, i.e. using the acceptable BMI category as defined by the WHO would include individuals with higher risk of death than those in the overweight category. This may have a significant impact on the RR used in the calculation of excess deaths attributable to excess body weight, e.g. the RR for obesity class II+ (BMI ≥ 35 kg/m²) was estimated to be 1.36 when acceptable BMI was used as the reference category versus 1.64 when the overweight BMI category (25–30 kg/m²) was used [26]. On the other hand, since BMI does not discriminate between fat mass and lean mass [27,28], it might not adequately reflect adiposity [3]. Consequently, overweight and mild obese subjects may not have more fat, but instead have a preserved or increased lean body mass, which could offer a explanation for the survival benefit in
Fig. 2. Forrest plot of hazard ratios for post-coronary artery bypass grafting mid-to-long-term mortality. APPROACH, Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease; BARI, Bypass Angioplasty Revascularization Investigation; CI, confidence interval; IV, inverse variance.

Fig. 3. Summary measures in short-term (30-day/in-hospital) mortality. Vertical bars denote standard errors.

Fig. 4. Summary measures in mid-to-long-term mortality. Vertical bars denote standard errors.
these subjects [3]. As an index of body fat, BMI might be omitted and replaced with more accurate indices [3] such as waist circumference [29–31], waist-to-hip ratio [29,31], waist-to-height ratio [29], and waist-to-stature ratio [31].

Other investigators have attempted to find explanations for the occurrence of the obesity paradox [3], which was first recognized in chronic disease populations and subsequently described also in the general population. In a study by Flegal et al. [32] examining the association of cause-specific mortality with different weight categories among US adults, overweight was associated with significantly decreased mortality from non-cancer, non-CVD causes but not associated with cancer or CVD mortality. On the other hand, obesity was associated with significantly increased mortality from CVD and obesity-related cancer (colon, breast, esophageal, uterine, ovarian, kidney, and pancreatic cancer) [32]. Wasting and increased inflammatory responses characterize chronic diseases including CVD and cancer, which would offer possible explanations for the obesity paradox [3].

In conclusion, overweight, but not obesity, may be associated with better short-term and mid-to-long-term post-CABG survival relative to normal weight. An overweight, but not obesity, paradox on post-CABG mortality appears to exist.

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Disclosures

The authors declare that there is no conflict of interest.

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