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Original article

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.

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

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"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/MCPHR 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*.

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/MCPHR. Not all studies used the traditional World Health Organization (WHO) body mass index (BMI) classification system of 18.5–24.9 kg/m^2 for normal weight, 25.0–29.9 kg/m^2 for overweight, and $\geq$30.0 kg/m^2 for obesity. Accordingly, to avoid eliminating studies with important information, BMI levels within 2 kg/m^2 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 χ^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; p 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; p 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; p 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; p 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; p 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; p 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; p 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; p 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; p 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; p 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 ($\leq$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