Association between obesity and postoperative atrial fibrillation in patients undergoing cardiac surgery: a systematic review and meta-analysis

Running head: Obesity and postoperative atrial fibrillation

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Abstract

In a systematic review and random effects meta-analysis, we evaluated whether obesity is associated with postoperative atrial fibrillation (POAF) in patients undergoing cardiac surgery. Eighteen observational studies that excluded patients with preoperative AF were selected until December 2011 (n=36,147). Obese patients had a modest higher risk of POAF in comparison to non-obese (OR 1.12, 95%CI 1.04-1.21, p=0.002). The association between obesity and POAF did not vary substantially by type of cardiac surgery, study design or year of publication. POAF was significantly associated with higher risk of stroke, respiratory failure, and operative mortality.

Introduction

Obesity is an established independent risk factor for atrial fibrillation (AF) [1, 2]. The strongest evidence to date linking obesity to AF in adults comes from the Framingham study [1]. However, in the setting of cardiac surgery, the role of obesity in postoperative atrial fibrillation (POAF) remains uncertain and needs to be better defined. This is important for several reasons. First, more than 30% of patients undergoing coronary artery bypass grafting surgery (CABG) in the United States are obese (body mass index [BMI] ≥30 Kg/m^2) and despite significant advances, POAF remains the most common complication affecting 20-40% of patients after cardiac surgery [3]. Second, POAF incurs significant morbidity and increased risk of perioperative and long term mortality [4-8]. Finally, the increased length of hospital stay and frequent readmissions from POAF increase the cost burden.

Several studies have attempted to examine the association between BMI and POAF with inconsistent results. This is partly related to differences in inclusion/ exclusion criteria and study methodologies. For example, not all studies have excluded patients with preoperative AF. Additionally, some studies have used BMI as a continuous variable while others have used it as a categorical variable. A previous meta-analysis of 44,647 cardiac surgery patients from 11 studies concluded that obesity (defined as BMI $\geq$ 30 kg/m^2) does not pose an increased risk of POAF [9]. Of note, this meta-analysis included also patients with preoperative AF and only one study evaluated POAF as the main endpoint [2]. More recently, several more studies have been published and some have suggested a strong association between obesity and post cardiac surgery AF. Here we present a systematic review and meta-analysis of the association between obesity and POAF in patients without pre-existing atrial fibrillation undergoing cardiac surgery.

Material and Methods

Selection of studies

A literature search was conducted by three authors in Pubmed-MEDLINE, the Web of Science and Scopus until December 2011. The search used the MESH keywords “obesity”, “atrial fibrillation” and “cardiac surgery” as well as the text keywords “cardiac surgery” and “atrial fibrillation”. The search strategy of Pubmed is available in the Appendix. Our search was restricted to studies in adults (>18 years-old), with information about POAF among patients regardless of whether BMI was reported categorically (e.g. using a cut-off of 30 kg/m^2) or as a continuous distribution in patients with and without POAF, and published in any language. Only studies that excluded the presence of preoperative AF and that showed data for the subgroup without preoperative AF were eligible. Selection of abstracts was done independently by 3 reviewers (RK, VP, PV) and discrepancies resolved by consensus.

Data extraction

Two reviewers (VP and PB) independently extracted data from studies. The following information was extracted: age, gender, BMI, type of cardiac surgery, medical morbidities including: hypertension, diabetes, chronic obstructive pulmonary disease (COPD), asthma, peripheral vascular disease (PVD), coronary artery disease (CAD), cerebrovascular disease (CVD), postoperative complications including: CVD, myocardial infarction (MI), respiratory failure, and in-hospital/postoperative mortality. Information regarding intensive coronary unit (ICU) and hospital length of stay was also collected, whenever available. Two other authors (RK and AVH) reviewed the extractions for inconsistencies, and the four authors (RK, AVH, VP and PB) reached consensus.

Evaluation of Study Quality

The order of quality of studies was considered as follows, from higher to lower: (1) prospective cohort study; (2) retrospective cohort study; (3) case-control study and (4) cross-sectional study. We also systematically assessed other key points of study quality proposed by the MOOSE collaboration [10]. These key points were (1) clear identification of the study population; (2) clear definition of outcome and outcome assessment; (3) independent assessment of outcome parameters (i.e., ascertainment of outcomes done by researchers other than those involved in the study); (4) selective loss during follow-up and (5) important confounders and/or prognostic factors identified. Each point was rated as 'yes/no'. If the description was unclear, we considered this as 'no'.

Statistical Analysis

Our systematic review and meta-analysis follow the recommendations of the PRISMA collaboration [11]. Our primary objective was to evaluate the association between obesity and POAF. Due to the expected clinical heterogeneity among studies, the association between obesity and POAF was evaluated with random effects models [12], and associations are shown as odds ratios (OR) and 95% confidence intervals (CI). To be able to use the information from the subset of studies with continuous BMI information, we used the methodology reported by Chinn [13] to transform standardized mean differences (SMD) to the equivalent OR per study. This method works regardless of BMI values and the OR is assumed to be the same regardless of the chosen cut-off of BMI that is used to define obesity within a reasonable range. We then calculated the natural logarithm of the OR (logOR) and its standard error [SE(logOR)] per study for all studies in both sets, and these were meta-analyzed using the inverse variance (IV) method incorporating also the between-study variance estimator along with the within-study variance in the calculations.

Secondarily, we also evaluated, when possible, the association between obesity and secondary outcomes (stroke, respiratory failure and operative mortality), and the association between the presence of POAF and secondary outcomes. Given the scarcity of these major events, we used the fixed effects Mantel-Haenzel (M-H) method for the meta-analysis, since random effects estimates are unstable in the presence of many zero counts and small event counts. The associations were reported as OR and its 95% CI.

Statistical heterogeneity was tested with the Chi-square test and quantified with the I^2 metric (<25% low, 25-50% moderate, >50% high) and its 95% CIs [14]. We used a sequential approach to explore whether specific studies accounted primarily for the between-study heterogeneity [15]. To examine bias in the results of the meta-analysis, we used the Harbord test of asymmetry of the funnel plot [16]. The Harbord test is an unbiased test for evaluating small-study effects in funnel plot asymmetry. Funnel plot asymmetry should not be equated with publication bias, because it can have a number of other possible causes such as true heterogeneity between study results, poor methodological quality, reporting biases and chance [17].

To explore potential sources of heterogeneity among studies, we performed 3 sets of subgroup analyses: by type of cardiac surgery performed (CABG only vs. CABG plus valve surgery); by study design (prospective cohorts vs. retrospective cohorts); and by year of study publication (below median vs. above median). We also used cumulative meta-analysis to show the evolution of risks over time.

We performed sensitivity analysis by excluding studies where the association between obesity and POAF was opposite to the one from the majority of other studies. For all analyses, we used the *metafor* package of R (www.metafor-project.org) and the Review Manager (RevMan 5.1, Oxford, UK; The Cochrane Collaboration, 2011).

Results

Study Characteristics

Out of a total of 190 records, eighteen studies were included (n=36,147, 12910 [36%] POAF cases) for analysis. Among the main reasons for exclusion were presence of atrial fibrillation preoperatively, and unavailable BMI data by POAF group (Figure 1). There were six studies that did not provide mean BMI and their standard deviation (SD) in the POAF and non-POAF groups [18-23]; two studies evaluated the same population [19, 20]. We did not contact authors for providing missing information; these five studies included 13,688 patients and 3,847 (28%) POAF cases, which is 23% of all POAF cases including the eighteen selected studies and the five excluded studies.

One group of studies specifically addresses the question of obesity as a risk factor for POAF after cardiac surgery using BMI as a categorical variable (Table 1) [2, 24-26]. The second group reports POAF as one of the outcomes after cardiac surgery, while the information about BMI is provided as a continuous variable (Table 2) [2, 24, 25, 27-40].

Mean age ranged from 55.7 to 72.8 years, the proportion of male patients ranged between 41 and 100%, and the mean BMI ranged from 25.6 to 29.6 kg/m^2. The majority of patients underwent CABG only, four studies also underwent concomitant valve surgery [27, 35, 38-40], one study reported valve surgery alone [33] and one did not report the type of cardiac surgery [32]. The most commonly reported postoperative outcomes were stroke [24-26, 29-35, 40] and operative mortality [2, 24-26, 28-34, 37, 40]. Respiratory failure was reported less frequently [17, 24, 33, 34, 38].

Study Quality

Ten studies were prospective cohorts (Table 3). All studies clearly identified the study population and defined the outcome. According to the study reports, none of the studies lost patients during follow-up. All studies identified some important confounders and/or prognostic factors of the association between obesity/BMI and POAF, but these were not consistently the same or defined in the same way across studies. No adjusted estimates of the association between obesity and POAF were available, and therefore no comparison with the unadjusted association was possible.

Meta-analysis

Obese patients had a modest higher risk of POAF in comparison to non-obese (OR 1.12, 95%CI 1.04-1.21, p=0.002) (Figure 2). Heterogeneity among studies was nominally statistically significant (chi-square=27.79, p=0.05) and of moderate magnitude (I^2=39%, [95%CI 0% to 94%]). The heterogeneity was driven primarily by the study of Jideus et al.[28] : exclusion of this study yielded a similar OR (1.12, 95%CI 1.05-1.20) and lower heterogeneity (Chi-square=21.3, p=0.17, I^2=25% [95%CI 0% to 88%]) (Supplementary Figure a). The Jideus et al. study had a very selected population, with several exclusion criteria (including not only preoperative AF, but also several risk factors for AF –heart valve disease, diabetes, chronic renal disease, COPD, reduced ejection fraction, thyroid disorders, and use of anti-arrhythmia drugs) and a small sample size (n=80). There was no strong evidence of small-study effects (Harbord test p=0.26).

The association between obesity and POAF did not vary significantly by type of cardiac surgery (CABG: OR 1.14, 95%CI 1.02-1.28 vs. CABG+other surgery: OR 1.09, 95%CI 1.01-1.17; p=0.49 for subgroup differences), by study design (prospective: OR 1.06, 95%CI 0.96-1.17 vs. retrospective OR 1.19, 95%CI 1.08-1.31); p=0.09 for subgroup differences) or by year of publication (1999-2007: OR 1.21, 95%CI 1.03-1.43 vs. 2008-2011 OR 1.07, 95%CI 1.01-1.14; p=0.17 for subgroup differences). Details are provided in the Supplementary Figures b to d. Cumulative meta-analysis showed that a higher risk of POAF in obese patients was first observed in 2007 and has directed slightly towards the null afterwards (Supplementary Figure e).

In secondary analyses, we found that POAF was associated with higher incidence of stroke (OR 1.77, 95%CI 1.36-2.31, p<0.0001), respiratory failure (OR 2.11, 95%CI 1.29-3.45, p=0.003), and operative mortality (OR 2.76, CI 1.77- 4.32, p<0.0001) (Figure 3). Heterogeneity was high (p=0.008,

I^2=71% [95%CI 24% to 100%]) and moderate (p=0.06, I^2=46% [95%CI 12% to 96%]) for respiratory failure and operative mortality, respectively.

Comment

We found that obesity was associated with a nominally statistically significant, slightly higher risk of POAF, with evidence of moderate heterogeneity among studies. This association did not vary by type of cardiac surgery, by study design or by year of publication. Secondarily, POAF was associated with substantially higher risk of the major postoperative complications stroke, respiratory failure and operative mortality.

The magnitude of the association between obesity and POAF is small. In fact, the meta-analysis excludes with relatively high confidence the possibility that obesity is a strong risk factor for POAF, since the upper 95%CI extends only to 1.21. The true effect may even be very small or even tiny in magnitude [41]. However, even if very small, the effect cannot be dismissed, given the high prevalence of obesity in the community. The result of the meta-analysis corresponds to a Bayes factor of approximately 15-25 in support of a weak effect (in the range of an odds ratio of 1.05-1.20) according to a previously published nomogram translating p-values and effect sizes into Bayes factors [42]. Any causal inferences for this observed association have even more tenuous support than the magnitude of the association. Many previous studies investigating the preoperative predictors of POAF did not even evaluate BMI as a potential risk factor, while some others have reported postoperative atrial arrhythmia [43-45] as a complication after cardiac surgery as opposed to POAF. BMI was first shown to be an independent risk factor for new onset AF in the general population by Wang et al. [1] and in 2005 Zaccharias et al. [2] suggested it as an independent risk factor for POAF after cardiac surgery. Several other studies since then have also suggested this association [24-26, 29, 46]. The effect of BMI on POAF was reported to be more prominent after adjustment for age [2]. It remains unclear whether BMI or some other correlated risk factor is in the causal pathway to POAF. For example, subsequently Echahidi et al. [24] suggested that the relationship between obesity and POAF was dependent upon age, and among patients < 50 years in age POAF was associated primarily with metabolic syndrome (OR 2.36; 95%CI: 1.10-5.12; p=0.02) rather than BMI.

When Wang et al. [1] introduced left atrium (LA) size into their model the effect of BMI on POAF disappeared. Increased LA stretch, diastolic dysfunction [47] and elevated plasma volume [48] secondary to obesity have been proposed as mechanisms for vulnerability of the left atrium to the development of POAF. Inflammation, as measured by an increase in white blood cells, and patient waist circumference have also been reported to be better predictors of POAF than BMI [25].

We did not have enough information to evaluate adjusted associations between POAF and secondary outcomes. The most likely mechanism of stroke and postoperative mortality is the presence of cardioembolic events [34]; however, reduced cardiac output and impaired cerebral circulation predisposes to cerebrovascular thrombosis causing non-cardioembolic stroke [49]. Impaired hemodynamics from reduced ventricular filling may explain the higher risk of respiratory failure in POAF patients [34].

Little information about the effect of obesity on secondary outcomes in cardiac surgery patients is available. Habib et al. [3] in a propensity-matched analysis of 1032 patients undergoing coronary artery bypass surgery showed that permanent stroke rate in very obese patients was similar to the rate in normal patients (1.2% in BMI>36 kg/m^2 vs. 0.8% in BMI 22 to 32 kg/m^2). Also, the rate of prolonged ventilation was non-significantly higher in very obese (9.1% vs. 6.0%, respectively, $0.05 \leq p < 0.1$). However, very obese had a significant 1.44 times higher relative risk of 12-year long term mortality vs. normal patients ($p=0.02$); in particular, very obese patients showed a greater death hazard between 1 and 6 years [3]. Thus, given obesity does not seem to have a role in the risk of stroke and respiratory failure, POAF itself may explain these secondary outcomes.

There was heterogeneity of effects for these secondary outcomes, especially for respiratory failure and postoperative mortality. The heterogeneity may be partially explained by small sample sizes of most studies, by the scarcity of secondary outcomes, mainly for postoperative mortality, and by different definitions of outcomes among studies, mainly for respiratory failure and postoperative mortality. For example, some studies defined respiratory failure as the presence of prolonged intubation >24h [27], prolonged intubation >24h or re-intubation [33], and prolonged intubation >48h [24]. Also, mortality had different definitions: in-hospital mortality [30, 31, 34], 30-day mortality [24, 32, 36] and mortality without reference to time of follow-up [25, 28, 37, 40].

Limitations

We recognize several limitations in our analysis. First, we performed a univariable meta-analysis, as no access to individual patient data from individual studies was available. Second, this was a meta-analysis of observational studies and several sources of bias are present. Subgroup analyses for some potential confounders of the association between obesity and POAF were performed, and we did not find any strong subgroup effects. Modest differences may well have been missed however, and the magnitude of the overall association is quite weak to start with. In our analysis we have not been able to infer whether obesity is the primary cause of such increased AF rate or whether obesity is only a confounder between other risk factors (e.g. metabolic disorders) and postoperative AF. Third, none of the studies reported data for the association between obesity/BMI and secondary outcomes, and therefore we could not analyze this. Finally, there is variability on how BMI associations are modeled in POAF studies. BMI was used as a continuous or categorical variable in different studies. Previous studies evaluating morbidity and mortality among obese patients discourage categorization of obese patients for research purposes [19, 20]. This has been shown to bias study results and for continuous variables the use of smoothed functions has been encouraged in individual studies.

Conclusions

In patients without known history of AF and undergoing cardiac surgery, the presence of obesity seems to be associated with slightly higher risk POAF. Although their temporal relationship is not fully described in studies, POAF is significantly associated with higher risk of other postoperative complications such as stroke, respiratory failure and postoperative mortality.

Appendix

(("body mass index"[MeSH Terms] OR ("body"[All Fields] AND "mass"[All Fields] AND "index"[All Fields]) OR "body mass index"[All Fields]) OR BMI[All Fields] OR ("obesity"[MeSH Terms] OR "obesity"[All Fields])) AND ("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields]) AND ("thoracic surgery"[MeSH Terms] OR ("thoracic"[All Fields] AND "surgery"[All Fields]) OR "thoracic surgery"[All Fields] OR ("cardiac"[All Fields] AND "surgery"[All Fields]) OR "cardiac surgery"[All Fields] OR "cardiac surgical procedures"[MeSH Terms] OR ("cardiac"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "cardiac surgical procedures"[All Fields] OR ("cardiac"[All Fields] AND "surgery"[All Fields]))

References

1. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA 2004;292:2471-7.

2. Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah AS, Habib RH. Obesity and risk of new-onset atrialfibrillation after cardiac surgery. Circulation 2005;112:3247-55.

3. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A. Effects of obesity and small body size on operative and long term outcomes of coronary artery bypass surgery: a propensity matched analysis. Ann Thorac Surg 2005;79:1976-86.

4. Lauer MS, Eagle KA, Buckley MJ, Desanctis RW. Atrial fibrillation following coronary artery bypass surgery. Prog Cardiovasc Dis 1989;31:367-78.

5. Almassi GH, Schowalter T, Nicolosi AC, et al. Atrial fibrillation after cardiac surgery: a major morbid event? Ann Surg 1997;226:501-11.

6. Aranki SF, Shaw DP,Adams DH, et al. Predictors of atrial fibrillation after coronary artery surgery: current trends and impact on hospital resources. Circulation 1996;94:390-7.

7. Mathew JP, Parks R, Savino JS, et al. Atrial fibrillation in coronary artery bypass grafting surgery: predictors, outcomes and resource utilization. JAMA 1996;276:300-6.

8. Kaw R, Hernandez AV, Masood I, Gillinov AM, Saliba W, Blackstone EH. Short- and long-term mortality associated with new-onset atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis. J Thorac Cardiovasc Surg 2011;141:1305-12.

9. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity-results of a meta-analysis. Am Heart J 2008;55: 310-5.

10. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 2000;283:2008-12.

11. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: The PRISMA statement. PLoS Med 2009; 6: e1000097

12. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.

13. Chinn S. A simple method to convert an odds ratio to effect size for use in meta-analysis. Stat Med 2000;19:3127-31.

14. Ioannidis JP, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. BMJ. 2007;335:914-6.

15. Patsopoulos NA, Evangelou E, Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. Int J Epidemiol. 2008;37:1148-57.

16. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med 2006;25:3443-57.

17. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002 doi: 10.1136/bmj.d4002

18. Kuan P, Bernstein SB, Ellestad MH. Coronary artery bypass surgery morbidity. J Am Coll Cardiol 984;3:1391-7.

19. Filardo G, Hamilton C, Hebeler RF, Hamman B, Grayburn P. New-onset postoperative atrial fibrillation after isolated coronary artery bypass graft surgery and long-term survival. Circ Cardiovasc Qual Outcomes 2009;2:164-9.

20. Filardo G, Hamilton C, Hamman B, Hebeler RF, Grayburn PA. Relation of obesity to atrial fibrillation after isolated coronary artery bypass grafting. Am J Cardiol 2009;103:663-6.

21. Nazeri A, Razavi M, Elayda MA, Lee V-V, Massumi A, Wilson JM. Race/ethnicity and the incidence of new-onset atrial fibrillation after isolated coronary artery bypass surgery. Heart Rhythm 2010;7:1458-63.

22. Straus S, Kacila M, Omerbasic E, Mujicic E. Atrial fibrillation and coronary bypass surgery- what can be risk factors for its appearance? Bosnian J Basic Med Sciences 2010;10:78-82.

23. Lahiri MK, Fang K, Lamerato L, Khan AM, Schuger CD. Effect of race on the frequency of postoperative atrial fibrillation following coronary artery bypass grafting. Am J Cardiol 2011;107:383-6.

24. Echahidi N, Mohty D, Pibarot P, et al. Obesity and metabolic syndrome are independent risk factors for atrial fibrillation after coronary artery bypass graft surgery. Circulation 2007;116[Suppl I]:I213-I219.

25. Girerd N, Pibarot P, Fournier D, et al. Middle-aged men with increased waist circumference and elevated C-reactive protein at higher risk for postoperative atrial fibrillation following coronary artery bypass grafting surgery. Eur Heart J 2009;30: 1270-8.

26. Bramer S, van Straten AHM, Hamad MAS, Berreklouw E, van den Broek KC, Maessen JG. Body mass index predicts new onset atrial fibrillation after cardiac surgery. Eur J Cardiothorac Surg 2011;40:1185-90.

27. Duccheschi V, D'Andrea A, Liccardo B, et al. Perioperative clinical predictors of atrial fibrillation occurrence following coronary artery surgery. Eur J Cardiothorac Surg 1999;16:435-9.
28. Jideus L, Blomstrom P, Nilsson L, Stridsberg M, Hansell P, Blomstrom-Lundqvist C. Tacchyarrhythmias and triggering factors for atrial fibrillation after coronary artery bypass operations. Ann Thorac Surg 2000;69:1064-9.
29. Hakala T, Vanninen E, Hedman A, Hippelainen M. Analysis of heart rate variability does not identify the patients at risk for atrial fibrillation after coronary artery bypass grafting. Scand Cardiovasc J 2002;36:167-71.
30. Hravnak M, Hoffman L, Saul MI, Zulio TG, Whitman GR, Griffith BP. Predictors and impact of atrial fibrillation after isolated coronary artery bypass grafting. Crit Care Med 2002;30:330-7.
31. Auer J, Weber T, Berent R, Ng CK, Lamm G, Eber B. Risk factors of postoperative atrial fibrillation after cardiac surgery. J Card Surg 2005;20:425-31.
32. Kokkonen L, Majahalme S, Koobi T, et al. Atrial fibrillation in elderly patients after cardiac surgery: Postoperative hemodynamics and low postoperative serum triiodothyronine. J Cardiothorac Vasc Anesth 2005;19:182-7.
33. Banach M, Goch A, Misztal M, Rysz J, Jaszewski R, Goch JH. Predictors of paroxysmal atrial fibrillation in patients undergoing aortic valve replacement. J Thorac Cardiovasc Surg 2007;134:1569-76.
34. Mariscalco G, Klersy C, Zanobini M, et al. Atrial fibrillation after isolated coronarry surgery affects late survival. Circulation 2008;118:1612-8.
35. Ahlsson A, Bodin L, Fengsrud E, Englund A. Patients with postoperative atrila fibrillation have a doubled cardiovascular mortality. Scand Cardiovasc J 2009;43:330-6.
36. Bramer S, van Straten AHM, Hamad MAS, Berreklouw E, Martens EJ, Maessen JG. The impact of new-onset postoperative atrial fibrillation on mortality after coronary artery bypass grafting. Ann Thorac Surg 2010;90:443-50.
37. Golmohammadi M, Javid GE, Farajzadeh H. Incidence and risk factors for atrial fibrillation after first coronary artery grafting in urumiyeh imam khomeini hospital from 2006 to 2008. Iran Cardiovasc Res J 2010;4:86-90.
38. Mariscalco G, Braga SS, Banach M, et al. Preoperative n-3 polyunsaturated fatty acids are associated with a decrease in the incidence of early atrial fibrillation following cardiac surgery. Angiology 2010;61:643-50.

39. Mauermann WJ, Nuttall GA, Cook DJ, Hanson AC, Schroeder DR, Oliver WC. Hemofiltration during cardiopulmonary bypass does not decrease the incidence of atrial fibrillation after cardiac surgery. Anesth Analg 2010;110:329-34.

40. Melduni RM, Suri RM, Seward JB, et al. Diastolic dysfunction in patients undergoing cardiac surgery. A pathophysiological mechanism underlying the initiation of new-onset post-operative atrial fibrillation. J Am Coll Cardiol 2011;58:953-61.

41. Siontis GC, Ioannidis JP. Risk factors and interventions with statistically significant tiny effects. Int J Epidemiol 2011;40:1292-307.

42. Ioannidis JP. Effect of formal statistical significance on the credibility of observational associations. Am J Epidemiol 2008;168:374-83.

43. Prasad US, Walker WS, Sang CT, Campanella C, Cameron EW. Influence of obesity on the early and long term results of surgery for coronary artery disease. Eur J Cardiothorac Surg 1991;5:67-72.

44. Moulton MJ, Creswell LL, Mackey ME, Cox JL, Rosenbloom M. Obesity is not a risk factor for significant adverse outcomes after cardiac surgery. Circulation 1996;94(9 Suppl):II87-II92.

45. Prabhakar G, Haan CK,Peterson ED, Coombs LP, Cruzzaval JL,Murray GF. The risks of moderate and extreme obesity for coronary artery bypass grafting outcomes: a study from the Society of Thoracic Surgeron's database. Ann Thorac Surg 2002;74:1125-30.

46. Rader F, Constantini O, Jarrett C, Gorodeski EZ, Lauer MS, Blackstone EH. Quantitative electocardiography for predicting postoperative atrial fibrillation after cardiac surgery. J Electrocardiol 2011; 44:761-7.

47. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002;90:1284-9.

48. Iacobellis G, Ribaudo MC, Leto G, et al. Influece of excess fat on cardiac morphology and function: study in uncomplicated obesity. Obes Res 2002;10:767-73.

49. Petersen P, Kastrup J, Videbaek R, Boysen G. Cerebral blood flow before and after cardioversion of atrial fibrillation. J Cereb Blood Flow Metab 1989;9:422-5.

Tables

Table 1: Characteristics of studies evaluating the association of categorical BMI and POAF.

First Author / Year Published	Study design	BMI groups	n	Age (y), Mean (SD)	Male, n (%)	Surgery type, n (%)				Postoperative complications, n (%)		
						CABG	Valve surgery	CABG + Valve surgery	POAF	Stroke	RF	Operative mortality
Zacharias[2] /2005	RC	Non-obese	4887	NA	NA	6749 (84.0)			1068 (21.9)	NA	NA	NA
		Obese	3164						742 (23.5)			
Echahidi[24] / 2007	RC	Non-obese	3608	64.0 (10.0)	3900 (77.0)	3608 (100)			927 (25.7)	108 (2.1)	91 (1.8)	74 (1.5)*
		Obese	1478			1478 (100)			442 (29.9)			
Girerd[25] / 2009	RC	Non-obese	1475	56.2 (6.4)	1475 (100)	1475 (100)			266 (18.0)	23 (1.0)	NA	13 (0.6)
		Obese	739		739 (100)	739 (100)			167 (22.6)			
Bramer[26] / 2011	PC	Non-obese	7398	65.5	5524 (74.7)	7398 (100)			1974 (26.7)	NA	NA	NA
		Obese	1950	64	1264 (64.8)	1950 (100)			540 (27.7)			

*30-day mortality; RC = Retrospective cohort; PC = Prospective cohort; POAF = Post-operative atrial fibrillation; RF = Respiratory failure

Table 2: Characteristics of studies evaluating the association of POAF and continuous BMI.

First Author / Year Published	Study design	POAF groups	n	Age (y), Mean (SD)	Male, n (%)	BMI, Mean (SD)	Surgery type, n (%)			Postoperative complications, n (%)		
							CABG	Valve surgery	CABG + Valve surgery	Stroke	RF	Operative mortality
Ducceschi[27] / 1999	RC	POAF	24	65.4 (6.3)	23 (96.0)	27.4 (2.5)		24 (100)		NA	2 (8.0)	NA
		No POAF	126	58.4 (8.8)	103 (82.0)	26.1 (2.7)		126 (100)			8 (6.0)	
Jideus[28] / 2000	PC	POAF	29	65.7 (7.4)	23 (79.0)	25.6 (3.4)	29 (100)			NA	NA	0 (0)**
		No POAF	51	65.8 (7.8)	44 (86.0)	27.6 (3.8)	51 (100)					0 (0)**
Hakala[29] / 2002	PC	POAF	30	66.0 (9.0)	22 (73.3)	28.5 (3.7)	30 (100)			1 (1.1)	NA	0 (0)
		No POAF	62	59.7 (9.7)	48 (77.4)	27.0 (3.1)	62 (100)					0 (0)
Hravnak[30] / 2002	RC	POAF	260	69.6 (7.9)	183 (70.4)	29.1	260 (100)			NA	NA	2 (0.8)*
		No POAF	554	63.6 (10.6)	363 (65.5)	28.8	554 (100)					0 (0)*
Auer[31] / 2005	PC	POAF	99	67.5 (9.1)	55 (55.5)	27.7 (3.4)	62 (62.6)			2 (2.0)	NA	2 (2.0)*
		No POAF	154	63.7 (11.4)	97 (63.0)	27.7 (3.3)	112 (72.7)			0 (0)		0 (0)*
Kokkonen[32] / 2005	PC	POAF	19	72.8 (9.6)	14 (74.0)	28.8 (4.1)		NA		6 (31.6)	NA	3 (15.8)**
		No POAF	25	69.5 (7.4)	15 (60.0)	27.3 (3.5)				1 (4.0)		0 (0)**
Zacharias[2] / 2005	RC	POAF	1810	68 (10.0)	1199 (66.2)	29.6 (5.8)	1634 (90.3)			NA	NA	NA
		No POAF	6241	63 (11.0)	4173 (66.9)	29.3 (5.5)	5677 (91.0)					
Banach[33] / 2007	RC	POAF	131	64.1 (8.6)	79 (60.3)	26.7 (5.2)		131 (100)		10 (7.6)	7 (5.3)	12 (9.2)*
		No POAF	169	58.5 (9.4)	68 (40.2)	26.2 (3.6)		169 (100)		7 (4.1)	8 (4.7)	7 (4.1)*
Echahidi[24] / 2007	RC	POAF	1369	68.3 (8.8)	1056 (77.1)	28.3 (5.1)	1369 (100)			40 (2.9)	53 (3.9)	40 (2.9)**
		No POAF	3717	62.5 (10.1)	2834 (76.2)	27.8 (4.5)	3717 (100)			68 (1.8)	37 (1.0)	33 (0.9)**
Mariscalco[34] / 2008	PC	POAF	570	68.4 (7.9)	440 (77.2)	26.8 (3.7)	570 (100)			16 (2.8)	68 (12.0)	19 (3.3)*
		No POAF	1262	63.7 (9.1)	974 (77.2)	26.7 (4.1)	1262 (100)			11 (0.9)	63 (5.0)	6 (0.5)*
Ahlsson[35] / 2009	PC	POAF	419	69.2 (8.1)	326 (77.8)	26.8 (3.7)	419 (100)			7 (1.7)	NA	NA
		No POAF	1000	64.9 (9.5)	742 (74.2)	26.9 (3.9)	1000 (100)			6 (0.6)		
Girerd[25] / 2009	RC	POAF	433	58.4 (5.3)	433 (100)	29.3 (5.2)	433 (100)			7 (1.6)	NA	3 (0.7)
		No POAF	1781	55.7 (6.5)	1781 (100)	28.5 (4.5)	1781 (100)			16 (0.9)		10 (0.6)
Bramer[36] / 2010	PC	POAF	1122	68.5 (8.1)	884 (78.8)	27.4 (3.9)	1122 (100)			17 (1.5)	NA	35 (3.1)**
		No POAF	3976	64.0 (9.7)	3081 (77.5)	27.3 (3.8)	3976 (100)			32 (0.8)		64 (1.6)**

Golmohammadi[37] / 2010	PC	POAF	37	60.0 (9.0)	26 (70.0)	27.4 (4.0)	37 (100)			NA	NA	0 (0)
		No POAF	263	58.0 (10.0)	195 (74.0)	26.7 (4.0)	263 (100)					0 (0)
Mariscalco[38] / 2010	RC	POAF	237	69.6 (9.3)	150 (41.0)	25.9 (4.4)	111 (47.0)	62 (26.0)	43 (18.0)	10 (4.0)	43 (19.0)	NA
		No POAF	293	63.8 (11.5)	213 (71.0)	25.9 (3.9)	167 (57.0)	76 (26.0)	37 (13.0)	17 (6.0)	41 (14.0)	
Mauermann[39]/ 2010	RC	POAF	60	65.4 (10.1)	52 (87.0)	27.8 (4.4)	26 (43.3)	29 (48.3)	5 (8.3)	NA	NA	NA
		No POAF	125	61.4 (11.5)	104 (83.0)	27.7 (4.3)	66 (52.8)	56 (44.8)	3 (2.4)			
Melduni[40] / 2011	PC	POAF	135	72.5 (10.3)	87 (64.4)	29.3 (5.4)	52 (38.5)	41 (30.4)	42 (31.1)	4 (3.0)	NA	4 (3.0)
		No POAF	216	63.1 (14.1)	149 (69.0)	28.5 (5.0)	108 (50.0)	74 (34.3)	34 (15.7)	4 (1.9)		8 (3.7)

*Hospital mortality; **30-day mortality; RC = Retrospective cohort; PC = Prospective cohort; POAF = Post-operative atrial fibrillation; RF = Respiratory failure

Table 3: Quality of the included studies

Study	Study Design	Study population clearly identified?	Clear definition of outcome and outcome assessment?	Selective loss of patients during follow-up?	Important confounders and/or prognostic factors identified?
Zacharias[2] 2005	RC	Yes	Yes	No	Age, race, BMI, BSA, smoking status, hypertension, COPD, PVD, cerebrovascular disease, CHF, stable angina, triple-vessel disease, left main disease, LVEF, mean EF, digitalis, steroids, diuretics, surgery type, month-of-surgery, off-pump, perfusion time, cross-clamp time, and IABP
Echahidi[24] 2007	RC	Yes	Yes	No	Age, sex, hypertension, DM, COPD, previous stroke, previous MI, 3 vessel CAD, metabolic syndrome, beta-blocker medication, HDL cholesterol, triglycerides, BMI, and CPBT
Girerd[25] 2009	RC	Yes	Yes	No	Age, BMI, waist circumference, Parsonnet score, COPD, smoking status, DM, fasting glucose, LDL cholesterol, HDL cholesterol, triglycerides, hypertension, ACE inhibitors and/or ARBs, calcium channel blockers, and beta-blockers
Bramer[26] 2011	PC	Yes	Yes	No	Age, BMI, BSA, COPD, PVD, prior stroke, prior MI, LVEF, creatinine, type of procedure, ECC duration, transfusion of RBCs, FFP and platelets, and reop for bleeding
Ducceschi[27] 1999	RC	Yes	Yes	No	Age, BMI, preop paroxysmal AF, three-vessel CAD, and left atrial enlargement
Jideus[28] 2000	PC	Yes	Yes	No	BMI, total amount of cardioplegia, and SPB/min
Hakala[29] 2002	PC	Yes	Yes	No	Age, BMI, diabetes, hemoglobin, and heart rate variability measurements
Hravnak[30] 2002	RC	Yes	Yes	No	Age, gender, height, weight, BSA, MI, diabetes, COPD, CHF, type of surgery, number and location of vessels bypassed, and operating room time.
Auer[31] 2005	PC	Yes	Yes	No	Age, type of surgery, and preop beta-blockers usage
Kokkonen[32] 2005	PC	Yes	Yes	No	Age, and no. of grafts
Banach[33] 2007	RC	Yes	Yes	No	Age, BMI, preop and postop LVEF, mitral regurgitation, heart failure, preop ESIVST, preop EDIVST
Mariscalco[34] 2008	PC	Yes	Yes	No	Age, center, dyslipidemia, COPD, preop stroke, renal failure, LVEF, IABP, RF, stroke, infection, and warfarin use
Ahlsson[35] 2009	PC	Yes	Yes	No	Age, sex, CK-MB, DM, LVEF, and hypertension
Bramer[36] 2010	PC	Yes	Yes	No	Age, sex, BMI, DM, COPD, creatinine clearance, LVEF, preop stroke, preop Hb, redo procedure, emergency, IABP, no. of grafts, ECC time, re-op for bleeding, RBC transfusion, and periop infarction
Golmohammadi[37] 2010	PC	Yes	Yes	No	LVEF, and CHF
Mariscalco[38] 2010	RC	Yes	Yes	No	Age, left atrial area, IABP, PUFA, reoperation, pericardial effusion, operation type, valve replacement, combined surgery, and preop ACE inhibitors
Mauermann[39]	RC	Yes	Yes	No	Age, sex, smoking status, type of procedure, COPD, methylprednisone,

2010					hemofiltration, BMI, duration of anesthesia, aortic cross-clamp, CPB , intubation and surgery, CPB fluids, red cell transfusions and fluid balance
Melduni[40] 2011	PC	Yes	Yes	No	Age, BMI, hypertension, mitral regurgitation, diastolic function, type of surgery, and perfusion time

RC = Retrospective cohort; PC = Prospective cohort; BMI = body mass index; BSA = body surface area; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease; CHF = congestive heart failure, LVEF = left ventricular ejection fraction; EF = ejection fracttion; IABP = intra-aortic balloon pump; DM = diabetes mellitus; MI = myocardial infarction; CAD = coronary artery disease; HDL = high density lipoprotein; LDL = low density lipoprotein; CPBT = cardiopulmonary bypass time; ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; ECC = extracorporeal circulation; RBC = red blood cells; FFP = fresh frozen plasma; AF = atrial fibrillation; SPB = supraventricular premature beats; ESIVST = end-systolic intraventricular septum thickness; EDIVST = end-diastolic intraventricular septum thickness; RF = respiratory failure; CK-MB = creatinine kinase-mycocardial band; PUFA = polyunsaturated fatty acid

Figure Legends

Figure 1: Flow diagram of selected studies.

Figure 2: Association between Obesity and POAF

Figure 3: Association between POAF and postoperative outcomes (3a: Stroke; 3b: Respiratory failure; 3c: Postoperative mortality).

Abbreviations

AF: Atrial fibrillation

POAF: Postoperative atrial fibrillation

CABG: Coronary artery bypass graft

BMI: Body mass index

COPD: Chronic obstructive pulmonary disease

PVD: Peripheral vascular disease

CAD: Coronary artery disease

CVD: Cerebrovascular disease

MI: Myocardial infarction

ICU: Intensive care unit

MOOSE: Meta-analysis of Observational Studies in Epidemiology

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

OR: Odds ratio

SMD: Standardized mean difference

IV: Inverse variance

M-H: Mantel-Haenzel

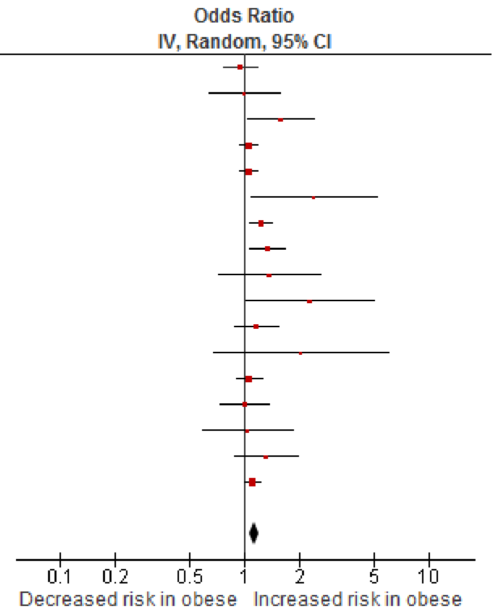
Supplementary material

Sensitivity analysis, Subgroup analyses, and cumulative meta-analysis of the association between obesity and POAF

a. Sensitivity analysis excluding Jideus 2000

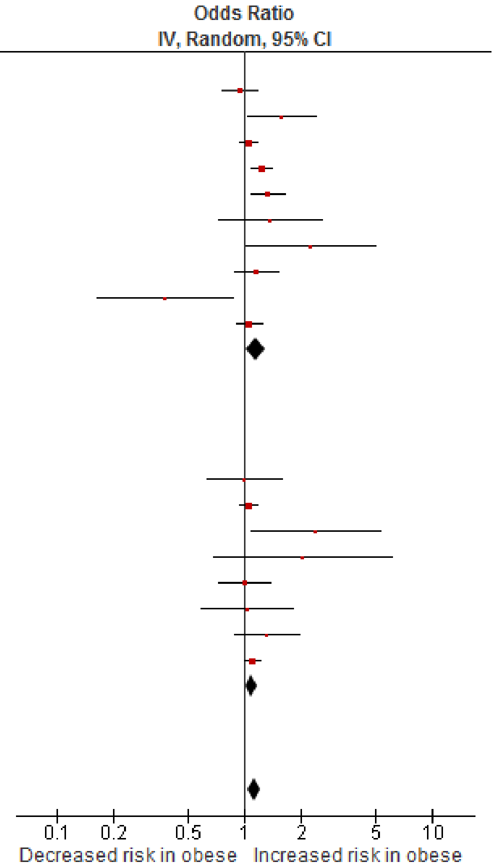
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Ahlsson 2009	-0.0543	0.110816	6.6%	0.95 [0.76, 1.18]
Auer 2005	0	0.230867	1.8%	1.00 [0.64, 1.57]
Banach 2007	0.4525	0.212398	2.2%	1.57 [1.04, 2.38]
Bramer 2010	0.0543	0.055408	15.5%	1.06 [0.95, 1.18]
Bramer 2011	0.04879	0.059553	14.5%	1.05 [0.93, 1.18]
Ducceschi 1999	0.8688	0.4063	0.6%	2.38 [1.08, 5.29]
Echahidi 2007	0.207014	0.069681	12.3%	1.23 [1.07, 1.41]
Girerd 2009	0.285179	0.109998	6.6%	1.33 [1.07, 1.65]
Golmohammadi 2010	0.3077	0.3232	1.0%	1.36 [0.72, 2.56]
Hakala 2002	0.8145	0.4063	0.6%	2.26 [1.02, 5.01]
Hravnak 2002	0.1448	0.13852	4.6%	1.16 [0.88, 1.52]
Kokkonen 2005	0.7059	0.554082	0.3%	2.03 [0.68, 6.00]
Mariscalco 2008	0.0543	0.083112	9.9%	1.06 [0.90, 1.24]
Mariscalco 2010	0	0.15699	3.7%	1.00 [0.74, 1.36]
Mauermann 2010	0.0362	0.286276	1.2%	1.04 [0.59, 1.82]
Melduni 2011	0.2715	0.2032	2.3%	1.31 [0.88, 1.95]
Zacharias 2005	0.09531	0.052827	16.2%	1.10 [0.99, 1.22]
Total (95% CI)			**100.0%**	**1.12 [1.05, 1.20]**

Heterogeneity: Tau² = 0.00; Chi² = 21.32, df = 16 (P = 0.17); I² = 25%
Test for overall effect: Z = 3.58 (P = 0.0003)



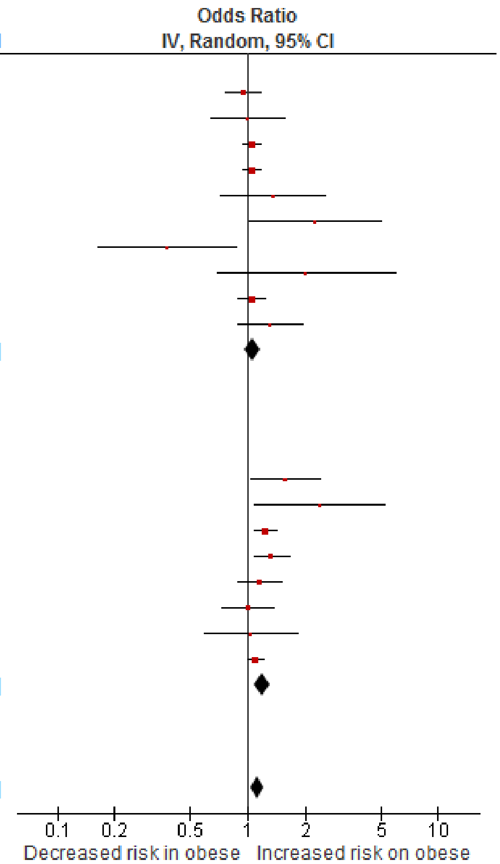
b. Subgroups by Type of surgery (CABG vs. CABG+other)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
33.1.1 CABG only				
Ahlsson 2009	-0.0543	0.110816	7.2%	0.95 [0.76, 1.18]
Banach 2007	0.4525	0.212398	2.7%	1.57 [1.04, 2.38]
Bramer 2010	0.0543	0.055408	13.5%	1.06 [0.95, 1.18]
Echahidi 2007	0.207014	0.069681	11.6%	1.23 [1.07, 1.41]
Girerd 2009	0.285179	0.109998	7.3%	1.33 [1.07, 1.65]
Golmohammadi 2010	0.3077	0.3232	1.3%	1.36 [0.72, 2.56]
Hakala 2002	0.8145	0.4063	0.8%	2.26 [1.02, 5.01]
Hravnak 2002	0.1448	0.13852	5.4%	1.16 [0.88, 1.52]
Jideus 2000	-0.9774	0.4248	0.8%	0.38 [0.16, 0.87]
Mariscalco 2008	0.0543	0.083112	9.9%	1.06 [0.90, 1.24]
Subtotal (95% CI)			**60.5%**	**1.14 [1.02, 1.28]**
Heterogeneity: Tau² = 0.02; Chi² = 20.71, df = 9 (P = 0.01); I² = 57%				
Test for overall effect: Z = 2.22 (P = 0.03)				
33.1.2 CABG+othersurgery				
Auer 2005	0	0.230867	2.3%	1.00 [0.64, 1.57]
Bramer 2011	0.04879	0.059553	13.0%	1.05 [0.93, 1.18]
Ducceschi 1999	0.8688	0.4063	0.8%	2.38 [1.08, 5.29]
Kokkonen 2005	0.7059	0.554082	0.5%	2.03 [0.68, 6.00]
Mariscalco 2010	0	0.15699	4.4%	1.00 [0.74, 1.36]
Mauermann 2010	0.0362	0.286276	1.6%	1.04 [0.59, 1.82]
Melduni 2011	0.2715	0.2032	2.9%	1.31 [0.88, 1.95]
Zacharias 2005	0.09531	0.052827	13.9%	1.10 [0.99, 1.22]
Subtotal (95% CI)			**39.5%**	**1.09 [1.01, 1.17]**
Heterogeneity: Tau² = 0.00; Chi² = 6.68, df = 7 (P = 0.46); I² = 0%				
Test for overall effect: Z = 2.29 (P = 0.02)				
Total (95% CI)			**100.0%**	**1.12 [1.04, 1.21]**
Heterogeneity: Tau² = 0.01; Chi² = 27.79, df = 17 (P = 0.05); I² = 39%				
Test for overall effect: Z = 3.05 (P = 0.002)				
Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49), I² = 0%				



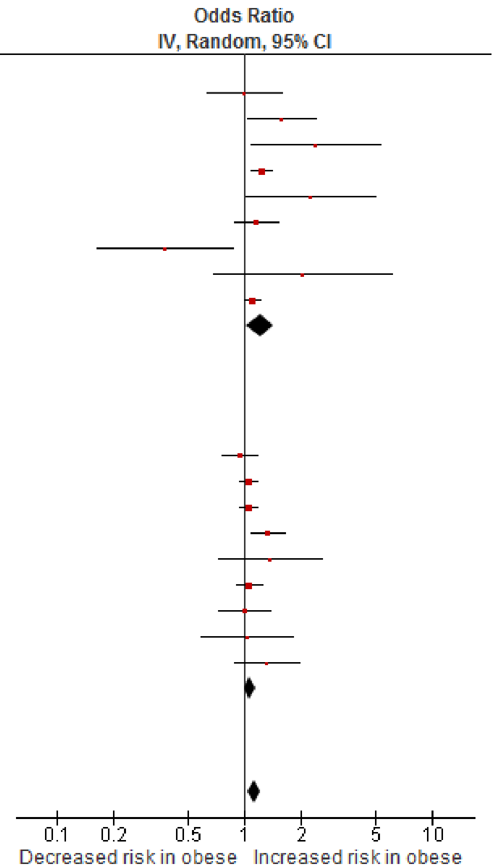
c. Subgroups by Study design (Prospective cohorts vs. retrospective cohorts)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
34.1.1 Prospective cohorts				
Ahlsson 2009	-0.0543	0.110816	7.2%	0.95 [0.76, 1.18]
Auer 2005	0	0.230867	2.3%	1.00 [0.64, 1.57]
Bramer 2010	0.0543	0.055408	13.5%	1.06 [0.95, 1.18]
Bramer 2011	0.04879	0.059553	13.0%	1.05 [0.93, 1.18]
Golmohammadi 2010	0.3077	0.3232	1.3%	1.36 [0.72, 2.56]
Hakala 2002	0.8145	0.4063	0.8%	2.26 [1.02, 5.01]
Jideus 2000	-0.9774	0.4248	0.8%	0.38 [0.16, 0.87]
Kokkonen 2005	0.7059	0.554082	0.5%	2.03 [0.68, 6.00]
Mariscalco 2008	0.0543	0.083112	9.9%	1.06 [0.90, 1.24]
Melduni 2011	0.2715	0.2032	2.9%	1.31 [0.88, 1.95]
Subtotal (95% CI)			**52.3%**	**1.06 [0.96, 1.17]**
Heterogeneity: Tau² = 0.01; Chi² = 13.56, df = 9 (P = 0.14); I² = 34%				
Test for overall effect: Z = 1.10 (P = 0.27)				
34.1.2 Retrospective cohorts				
Banach 2007	0.4525	0.212398	2.7%	1.57 [1.04, 2.38]
Ducceschi 1999	0.8688	0.4063	0.8%	2.38 [1.08, 5.29]
Echahidi 2007	0.207014	0.069681	11.6%	1.23 [1.07, 1.41]
Girerd 2009	0.285179	0.109998	7.3%	1.33 [1.07, 1.65]
Hravnak 2002	0.1448	0.13852	5.4%	1.16 [0.88, 1.52]
Mariscalco 2010	0	0.15699	4.4%	1.00 [0.74, 1.36]
Mauermann 2010	0.0362	0.286276	1.6%	1.04 [0.59, 1.82]
Zacharias 2005	0.09531	0.052827	13.9%	1.10 [0.99, 1.22]
Subtotal (95% CI)			**47.7%**	**1.19 [1.08, 1.31]**
Heterogeneity: Tau² = 0.00; Chi² = 9.43, df = 7 (P = 0.22); I² = 26%				
Test for overall effect: Z = 3.58 (P = 0.0003)				
Total (95% CI)			**100.0%**	**1.12 [1.04, 1.21]**
Heterogeneity: Tau² = 0.01; Chi² = 27.79, df = 17 (P = 0.05); I² = 39%				
Test for overall effect: Z = 3.05 (P = 0.002)				
Test for subgroup differences: Chi² = 2.82, df = 1 (P = 0.09), I² = 64.5%				



d. Subgroups by year of publication (1999-2007 vs. 2008-2011)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
35.1.1 Published until 2007				
Auer 2005	0	0.230867	2.3%	1.00 [0.64, 1.57]
Banach 2007	0.4525	0.212398	2.7%	1.57 [1.04, 2.38]
Ducceschi 1999	0.8688	0.4063	0.8%	2.38 [1.08, 5.29]
Echahidi 2007	0.207014	0.069681	11.6%	1.23 [1.07, 1.41]
Hakala 2002	0.8145	0.4063	0.8%	2.26 [1.02, 5.01]
Hravnak 2002	0.1448	0.13852	5.4%	1.16 [0.88, 1.52]
Jideus 2000	-0.9774	0.4248	0.8%	0.38 [0.16, 0.87]
Kokkonen 2005	0.7059	0.554082	0.5%	2.03 [0.68, 6.00]
Zacharias 2005	0.09531	0.052827	13.9%	1.10 [0.99, 1.22]
Subtotal (95% CI)			**38.8%**	**1.21 [1.03, 1.43]**
Heterogeneity: Tau² = 0.02; Chi² = 18.05, df = 8 (P = 0.02); I² = 56%				
Test for overall effect: Z = 2.27 (P = 0.02)				
35.1.2 Published 2008-2011				
Ahlsson 2009	-0.0543	0.110816	7.2%	0.95 [0.76, 1.18]
Bramer 2010	0.0543	0.055408	13.5%	1.06 [0.95, 1.18]
Bramer 2011	0.04879	0.059553	13.0%	1.05 [0.93, 1.18]
Girerd 2009	0.285179	0.109998	7.3%	1.33 [1.07, 1.65]
Golmohammadi 2010	0.3077	0.3232	1.3%	1.36 [0.72, 2.56]
Mariscalco 2008	0.0543	0.083112	9.9%	1.06 [0.90, 1.24]
Mariscalco 2010	0	0.15699	4.4%	1.00 [0.74, 1.36]
Mauermann 2010	0.0362	0.286276	1.6%	1.04 [0.59, 1.82]
Melduni 2011	0.2715	0.2032	2.9%	1.31 [0.88, 1.95]
Subtotal (95% CI)			**61.2%**	**1.07 [1.01, 1.14]**
Heterogeneity: Tau² = 0.00; Chi² = 7.06, df = 8 (P = 0.53); I² = 0%				
Test for overall effect: Z = 2.16 (P = 0.03)				
Total (95% CI)			**100.0%**	**1.12 [1.04, 1.21]**
Heterogeneity: Tau² = 0.01; Chi² = 27.79, df = 17 (P = 0.05); I² = 39%				
Test for overall effect: Z = 3.05 (P = 0.002)				
Test for subgroup differences: Chi² = 1.86, df = 1 (P = 0.17), I² = 46.1%				



e. Cumulative meta-analysis