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ORIGINAL CONTRIBUTIONS

Early Impact of Bariatric Surgery on Type II Diabetes, Hypertension, and Hyperlipidemia: A Systematic Review, Meta-Analysis and Meta-Regression on 6,587 Patients

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Abstract
Background This study aims to evaluate the 12–24-month impact of bariatric surgery on the foremost modifiable traditional risk factors of cardiovascular disease.
Methods A systematic review and meta-analysis of prospective interventional studies reporting the most commonly performed laparoscopic surgical procedures, i.e., Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB), and cardiovascular risk reduction after surgery.
Results The bibliographic research conducted independently by two authors yielded 18 records. When looking at RYGB and AGB separately, we observed a relevant heterogeneity (I^2 index ≥87 %) when BMI reduction was considered as the main outcome. When hypertension, type II diabetes, and hyperlipidemia risk reduction was estimated, a highly significant beneficial effect was found. The risk reduction was 0.33 [0.26; 0.42] for type II diabetes, 0.52 [0.42; 0.64] for hypertension, and 0.39[0.27; 0.56] for hyperlipidemia ($P<0.0001$ for all outcomes considered). When looking at surgical technique separately, a higher but not statistically significant risk reduction for all outcomes considered was found. Results from the meta-regression approach showed an inverse relation between cardiovascular risks and BMI reduction.
Conclusions The present study showed an overall reduction of cardiovascular risk after bariatric surgery. According to our analysis a BMI reduction of 5 after surgery corresponds to a type II diabetes reduction of 33 % (as reported by Peluso and Vanek (Nutr Clin Pract 22(1):22–28, 2007); SAS Institute Inc., (2000–2004)), a hypertension reduction of 27 % (as reported by Buchwald and Oien (Obes Surg 23(4):427–436, 2013); Valera-Mora et al. (Am J Clin Nutr 81(6):1292–1297, 2005)), and a hyperlipidemia reduction of 20 %(as reported by Adams et al. (JAMA 308(11):1122–31, 2012)); Alexandrides et al. (Obes Surg 17(2):176–184, 2007). In summary, our study showed that laparoscopic bariatric surgery is an effective therapeutic option to reduce the cardiovascular risk in severe obese patients.

Keywords Obesity · Laparoscopic Surgery · Meta-Analysis · Meta-Regression · Type II Diabetes · Hypertension · Hyperlipidemia

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Introduction

Excess bodyweight is the sixth most important risk factor contributing to the overall burden of disease worldwide [1]. Morbid obesity is a major problem in developed societies; it is responsible for a decreased expectancy and quality of life and leads to multiple comorbid conditions [2]. Recent studies also suggested that obesity is associated to esophageal adenocarcinoma arising from Barrett's esophagus [3].

In order to reduce the cardiovascular risk, even a moderate 5 to 10 % weight loss through diet and lifestyle interventions has been shown to be effective on overweight or mild obese patients [4]. Conversely, medical and behavioral therapy have limited short-term success in morbidly obese patients [5]. Bariatric surgery represents the only effective and durable treatment for these individuals [6–8]. These effects on mortality are largely due to the remarkable effect of surgical intervention on individual comorbid conditions such as type II diabetes, hypertension, and hyperlipidemia [9]. Functional and electrical cardiac investigations also documented positive changes in structural and electromechanical cardiac parameters after weight reduction [10, 11].

The volume of bariatric/metabolic surgery has increased dramatically in the past two decades owing to the evidence of decreased long-term mortality, disease burden, and cost-efficacy [12, 13]. A systematic review and meta-analysis targeting four common associated conditions (type II diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea) has shown that effective weight loss and resolution or improvement of comorbidities is achieved in morbidly obese patients after bariatric surgery [14].

We conducted a systematic review, meta-analysis, and meta-regression of published studies including three bariatric procedures, i.e., laparoscopic Roux-en Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (AGB), and biliopancreatic diversion (BPD). The aim of our study was to evaluate the 12–24 months impact of bariatric surgery on the foremost modifiable traditional risk factors of cardiovascular disease (type II diabetes, hypertension, and hyperlipidemia). A second aim of our study was to investigate the relation between cardiovascular risk after bariatric surgery and BMI reduction.

Data Source

Studies were identified by searching electronic databases and scanning reference lists of articles. This search was applied to MEDLINE, Embase, and CINAHL using bariatric surgery and laparoscopic as keywords. Additionally, hand searches of the reference lists of included studies, reviews, meta-analyses, and guidelines on bariatric surgery and cardiovascular disease were performed. To investigate to what extent bariatric surgery influenced cardiovascular risk, a second nested search having obesity, hypertension, and diabetes as supplementary keywords was performed.

Study Selection

The literature search was independently conducted and in duplicate by two investigators (MG and YM). The same authors independently selected potentially eligible studies for inclusion. Disagreements between reviewers were resolved by consensus; if no agreement could be reached, it was planned that a third senior author (LB) would decide.

Data Extraction

Studies screened according to the selection criteria quoted above were included if they (1) reported cardiovascular outcomes after bariatric surgery; (2) reported one or more of the following outcomes before and after surgery: weight reduction, number of subjects affected by, or rates of diabetes, hypertension, and hyperlipidemia; (3) were prospective interventional studies reporting selected outcomes after 12–24 months from surgery. The flow chart of paper selection was reported in Fig. 1.

Statistical Methods

A data extraction sheet was developed and pilot-tested on three randomly selected included studies. The following data were extracted from selected studies and entered in a data extraction form by one investigator (YM): author, study year, participants, outcomes, and country (Table 1). A second investigator (ER) ensured accurate reporting. Disagreements were resolved by discussion between the two investigators; if no agreement could be reached, it was planned that a third investigator would decide (CR). When body weight was reported as excessive body weight loss percentage, the BMI after surgery was imputed considering a BMI of 25 as ideal.

Between studies, heterogeneity was evaluated by the I^2 index, considering it as relevant if the I^2 index was greater

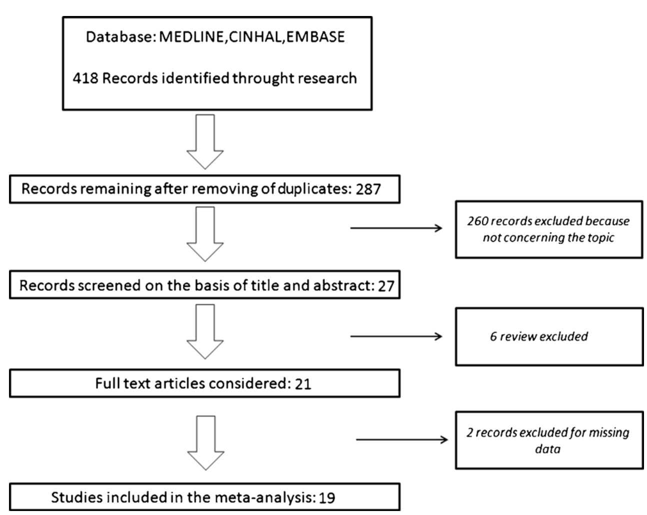


Fig. 1 Flowchart of paper selection

Table 1 General characteristics of included studies, BMI, and outcome rate reductions after bariatric surgery

Author	Year	Country	Patients	Surgical technique	BMI reduction	Type II diabetes (%)	Hypertension (%)	Hyperlipidemia (%)
Cowan et al. [26]	1998	USA	82	RYGB	14.1	16 vs. 2.4	32 vs. 1.2	40 vs. 6
Scopinaro et al. [27]	1998	Italy	2,241	BPD	16.6	7.9 vs. 0	39 vs. 7.4	55 vs. 0
Papasavas et al. [28]	2002	USA	116	RYGB	16.7	32.5 vs. 11.3	48.8 vs. 31.2	8.8 vs. 3.7
O'Brien et al. [29]	2002	Australia	709	AGB	10	3.9 vs. 1.8	20.7 vs. 9.4	34 vs. 9
Bacci et al. [30]	2002	Italy	130	AGB	8.0	15 vs. 6	37 vs. 25	36 vs. 25
Ponce et al. [31]	2004	USA	840	AGB	10.4	12.8 vs. 4.5	47 vs. 18.9	
Serra et al. [32]	2005	Spain	70	RYGB	19.7	17.4 vs. 0	54.3 vs. 20	44.9 vs.7.2
Valera-Mora et al. [20]	2005	USA	107	BPD	17.0	23 vs. 2.8	83 vs. 3.7	
Ahroni et al. [33]	2005	USA	193	AGB	13.5	15.4 vs. 4	43 vs. 18.8	27.5 vs. 18.8
Bowne et al. [34]	2006	USA	46	RYGB	26.5	17.4 vs. 0	56.5 vs. 21	37 vs.21
			60	AGB	9.8	18.3 vs. 11	40 vs. 29	18.3 vs. 11
Peluso et al. [19]	2007	USA	400	RYGB	14.5	30 vs. 9	60 vs.21	43 vs. 17
Torquati et al. [35]	2007	USA	500	RYGB	19.3	28 vs. 6		77.6 vs. 11.8
Yan et al. [36]	2007	USA	61	RYGB	13.7	41 vs. 15.8	68 vs.52	
Alexandrides et al. [21]	2007	Greece	111	BPD	15.4	100 vs. 2.7	46 vs. 18.9	55.9 vs. 0
			26	RYGB	25.4	100 vs. 25	50 vs. 25	76.9 vs. 41.7
Maher et al. [37]	2008	USA	450	RYGB	16.2	29.9 vs. 9.8	59.2 vs. 24.6	
Khalaileh et al. [38]	2008	Israel	50	RYGB	11.8	18 vs. 0	26 vs. 16	
Hinojosa et al. [39]	2008	USA	95	RYGB	15.8		100 vs. 64 %	
Ahmed et al. [40]	2008	USA	100	RYGB	16.0		58 vs. 32	
Campos et al. [41]	2011	USA	100	RYGB	16.0	34 vs. 8		
			100	AGB	9.0	34 vs. 17		

than 50 %. Type II diabetes, hypertension, and hyperlipidemia risk reduction after surgery was evaluated by a meta-analysis approach using the random effects model described by DerSimonian and Laird [15]. This analysis was subsequently stratified by surgical technique. Sensitivity analysis was performed dropping one study at a time and the publication bias was evaluated by funnel plot visual inspection and Begg's test [16]. The effect of BMI reduction on selected cardiovascular outcomes was investigated by two different approaches. First, a random-effect linear model having the logarithm of the relative risk as response variable was performed. Afterwards, if the relation between response and BMI did not result as linear, the nonlinear dose response meta-regression analysis described by Orsini et al. was applied [42].

An alpha value lower than 0.05 was considered statistically significant and all statistical tests were two-tailed. Meta-analysis, linear meta-regression, sensitivity analysis, Begg's test and funnel plots were obtained by STATA vers.11 [18] the nonlinear meta-regression analysis were performed by the SAS [17] software package vers. 9.2 using the percent metadose macro furnished by D. Spiegelmann (Harvard school of public health http://www.hsph.harvard.edu/spiegelman/metadose/metadose.sas).

Results

The bibliographic research conducted independently and in duplicate by two authors yielded 418 matches. After exclusion of duplicates, 287 records were retained; of these, 260 papers were excluded because they are not related to the topic or have not reported the requested outcomes. Six out of these 27 remaining records were excluded because of systematic reviews; and 2 more papers were excluded because of missing data. Among the 25 papers that remained, 6 were excluded because of literature review or meta-analysis. Finally, 19 papers were retained.

When gastric bypass procedures (RYGB or BPD) and gastric banding procedures (AGB) were compared considering BMI reduction after surgery a relevant heterogeneity between these two techniques was found. Moreover, while RYGB and BPD pooled random-effect estimate of BMI reduction could be approximated to 17.7 [15.7; 19.7] the same estimate for AGB was 10.3 [8.3; 12.3], this difference could be considered as statistically significant $P<0.0001$. This BMI reduction difference between surgical techniques could have been considered relevant and, according to our conjecture, could lead to a biased estimate of cardiovascular risk reduction if not considered. When looking at type II diabetes, hypertension, and hyperlipidemia risk reduction, a relevant heterogeneity was found ($I^2 \geq 70$ % for all outcomes considered). When type II diabetes, hypertension, and hyperlipidemia risk reduction was estimated by a random-effect model, a beneficial effect corresponding to risk reduction was found (Fig. 2). In particular, the risk reduction was 0.33 [0.26; 0.42] for type II diabetes, 0.52 [0.42; 0.64] for hypertension, and 0.39 [0.27; 0.56] for hyperlipidemia. All these risk reductions were highly significant from a statistical viewpoint ($P<0.0001$ for all outcomes considered). When looking at surgical techniques separately (Fig. 3), a higher risk reduction for all outcomes considered was found when RYGB and BPD were pooled. Type II diabetes risk reduction for RYGB and BPD was 0.26 [0.19; 0.37] whereas it was 0.44 [0.34; 0.55] for AGB; even if relevant, this risk difference could not be considered as statistically significant ($P=0.0841$). The same conclusions could be drawn when hypertension and hyperlipidemia were considered. In particular, for RYGB and BPD, the risk reductions were 0.49 [0.36; 0.65] and 0.28 [0.17; 0.48] for hypertension and hyperlipidemia, respectively ($P<0.0001$). The same risks for AGB were higher when compared to the ones reported for RYGB and BPD (0.55 [0.47; 0.65] $P<0.0001$ and 0.57 [0.34; 0.97] $P=0.0370$ for hypertension and hyperlipidemia respectively). When RYGB and BPD pooled risks reduction for hypertension and hyperlipidemia were compared to the ones for AGB no statistically significant differences were found ($P=0.2266$ and $P=0.1052$ for hypertension and hyperlipidemia, respectively). Results from the meta-regression approach showed an interesting inverse relation when cardiovascular risks were related to BMI reduction; these relations could not be considered as linear from a statistical viewpoint, on the other hand, nonlinear model fitting was statistically significant for all of the outcomes considered. When looking at Begg's test for publication bias, it could be noticed that none of the comparison performed was affected and visual inspection of funnel plots was consistent with Begg's test results. Sensitivity analysis did not identify any of the included studies as responsible for a statistically significant deviation from the estimates reported (Fig. 4).

Fig. 3 Meta-analysis and nonlinear meta-regression interpolation ▶ of type II diabetes, hypertension, and hyperlipidemia risk reduction versus BMI reduction after surgery. *Bubble diameter* represents study weight, *dotted lines* represent nonlinear model predicted value and its 95 % confidence intervals

Discussion

The present study showed an overall reduction of cardiovascular risk at 1–2 years after bariatric surgery. Both gastric bypass and gastric banding procedures were effective; nevertheless, the effect on BMI was more pronounced in patients undergoing RYGB and BPD. When comparing RYGB and BPD versus AGB, a higher but not statistically significant cardiovascular risk reduction was also found. By a first look, this higher risk reduction for RYGB and BPD could be due to a higher BMI reduction after surgery. We also evaluated the relation between cardiovascular risk reduction and weight loss considered as BMI reduction, this relation could not be considered statistically significant even if it could explain, at least qualitatively, cardiovascular risk reduction differences among surgical techniques. According to our nonlinear regression analysis, it could be estimated that after bariatric surgery, a BMI reduction of 5 corresponds to a type II diabetes reduction of 33 % [17, 19]. The same evaluation performed on hypertension and hyperlipidemia could be estimated as 27 [13, 20] and 20 % [12, 21], respectively. These rate reduction estimates could be considered consistent for a BMI reduction lower than 18–20. Previous studies have shown that cardiovascular risk reduction was comparable between laparoscopic and open approach on the short-term [22, 23]. On the long term, it is expected that these two approaches could have a similar effect too. Since the BMI is known to be of limited accuracy, recent studies have proposed some more alternative indicators of body fat, such as the body adiposity index, the waist/hip ratio, and the waist and hip circumferences [24, 25]. A potential pitfall of this meta-analysis was that we relied only on BMI because of the shortage of published papers that include other indicators. Therefore, further studies are needed to investigate

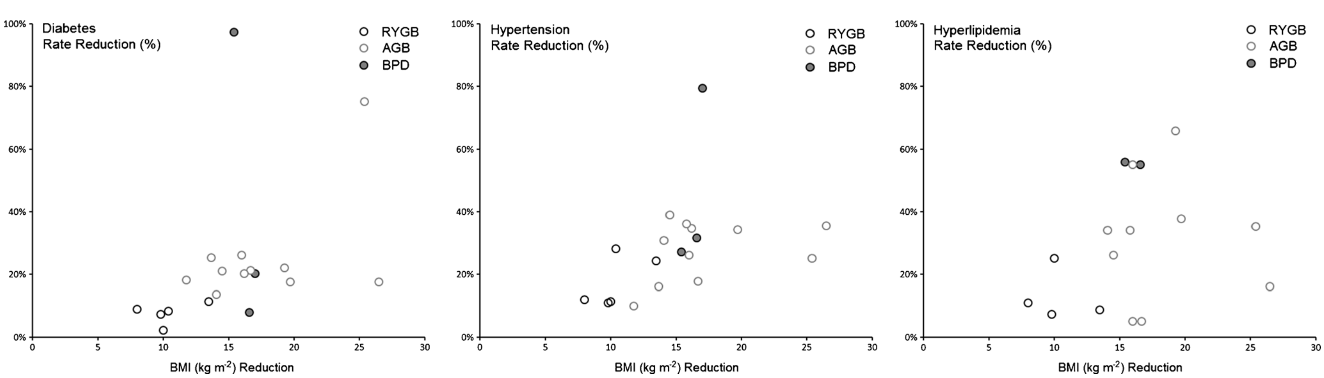
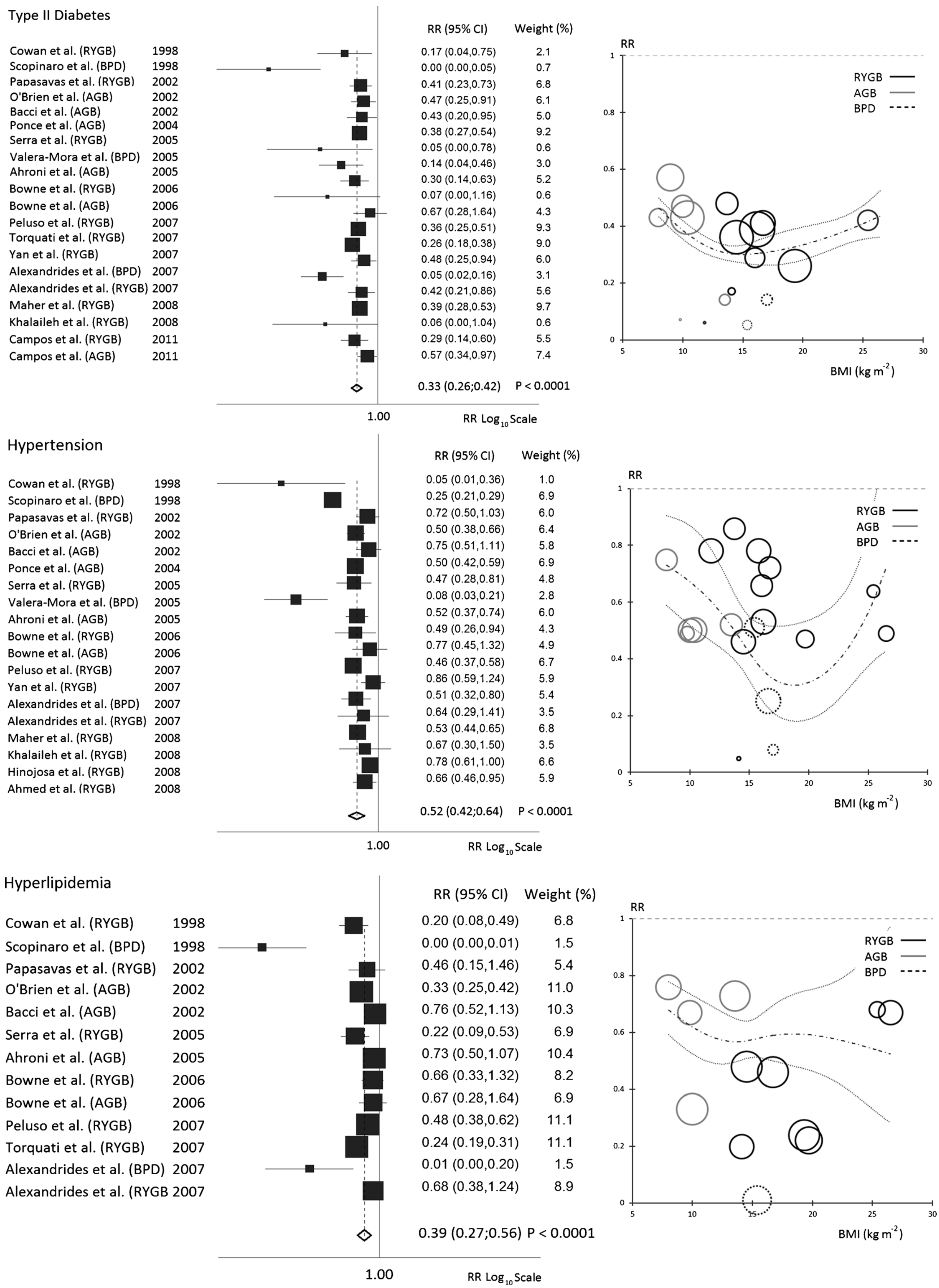


Fig. 2 Correlation between type II diabetes, hypertension and hyperlipidemia rate and BMI reduction


Type II Diabetes
RR (95% CI) Weight (%)
Cowan et al. (RYGB) 1998 0.17 (0.04,0.75) 2.1
Scopinaro et al. (BPD) 1998 0.00 (0.00,0.05) 0.7
Papasavas et al. (RYGB) 2002 0.41 (0.23,0.73) 6.8
O'Brien et al. (AGB) 2002 0.47 (0.25,0.91) 6.1
Bacci et al. (AGB) 2002 0.43 (0.20,0.95) 5.0
Ponce et al. (AGB) 2004 0.38 (0.27,0.54) 9.2
Serra et al. (RYGB) 2005 0.05 (0.00,0.78) 0.6
Valera-Mora et al. (BPD) 2005 0.14 (0.04,0.46) 3.0
Ahroni et al. (AGB) 2005 0.30 (0.14,0.63) 5.2
Bowne et al. (RYGB) 2006 0.07 (0.00,1.16) 0.6
Bowne et al. (AGB) 2006 0.67 (0.28,1.64) 4.3
Peluso et al. (RYGB) 2007 0.36 (0.25,0.51) 9.3
Torquati et al. (RYGB) 2007 0.26 (0.18,0.38) 9.0
Yan et al. (RYGB) 2007 0.48 (0.25,0.94) 6.0
Alexandrides et al. (BPD) 2007 0.05 (0.02,0.16) 3.1
Alexandrides et al. (RYGB) 2007 0.42 (0.21,0.86) 5.6
Maher et al. (RYGB) 2008 0.39 (0.28,0.53) 9.7
Khalaileh et al. (RYGB) 2008 0.06 (0.00,1.04) 0.6
Campos et al. (RYGB) 2011 0.29 (0.14,0.60) 5.5
Campos et al. (AGB) 2011 0.57 (0.34,0.97) 7.4
0.33 (0.26;0.42) P < 0.0001
1.00
RR Log10 Scale
RR
RYGB
AGB
BPD
BMI (kg m-2)
Hypertension
RR (95% CI) Weight (%)
Cowan et al. (RYGB) 1998 0.05 (0.01,0.36) 1.0
Scopinaro et al. (BPD) 1998 0.25 (0.21,0.29) 6.9
Papasavas et al. (RYGB) 2002 0.72 (0.50,1.03) 6.0
O'Brien et al. (AGB) 2002 0.50 (0.38,0.66) 6.4
Bacci et al. (AGB) 2002 0.75 (0.51,1.11) 5.8
Ponce et al. (AGB) 2004 0.50 (0.42,0.59) 6.9
Serra et al. (RYGB) 2005 0.47 (0.28,0.81) 4.8
Valera-Mora et al. (BPD) 2005 0.08 (0.03,0.21) 2.8
Ahroni et al. (AGB) 2005 0.52 (0.37,0.74) 6.0
Bowne et al. (RYGB) 2006 0.49 (0.26,0.94) 4.3
Bowne et al. (AGB) 2006 0.77 (0.45,1.32) 4.9
Peluso et al. (RYGB) 2007 0.46 (0.37,0.58) 6.7
Yan et al. (RYGB) 2007 0.86 (0.59,1.24) 5.9
Alexandrides et al. (BPD) 2007 0.51 (0.32,0.80) 5.4
Alexandrides et al. (RYGB) 2007 0.64 (0.29,1.41) 3.5
Maher et al. (RYGB) 2008 0.53 (0.44,0.65) 6.8
Khalaileh et al. (RYGB) 2008 0.67 (0.30,1.50) 3.5
Hinojosa et al. (RYGB) 2008 0.78 (0.61,1.00) 6.6
Ahmed et al. (RYGB) 2008 0.66 (0.46,0.95) 5.9
0.52 (0.42;0.64) P < 0.0001
1.00
RR Log10 Scale
RR
RYGB
AGB
BPD
BMI (kg m-2)
Hyperlipidemia
RR (95% CI) Weight (%)
Cowan et al. (RYGB) 1998 0.20 (0.08,0.49) 6.8
Scopinaro et al. (BPD) 1998 0.00 (0.00,0.01) 1.5
Papasavas et al. (RYGB) 2002 0.46 (0.15,1.46) 5.4
O'Brien et al. (AGB) 2002 0.33 (0.25,0.42) 11.0
Bacci et al. (AGB) 2002 0.76 (0.52,1.13) 10.3
Serra et al. (RYGB) 2005 0.22 (0.09,0.53) 6.9
Ahroni et al. (AGB) 2005 0.73 (0.50,1.07) 10.4
Bowne et al. (RYGB) 2006 0.66 (0.33,1.32) 8.2
Bowne et al. (AGB) 2006 0.67 (0.28,1.64) 6.9
Peluso et al. (RYGB) 2007 0.48 (0.38,0.62) 11.1
Torquati et al. (RYGB) 2007 0.24 (0.19,0.31) 11.1
Alexandrides et al. (BPD) 2007 0.01 (0.00,0.20) 1.5
Alexandrides et al. (RYGB 2007 0.68 (0.38,1.24) 8.9
0.39 (0.27;0.56) P < 0.0001
1.00
RR Log10 Scale
RR
RYGB
AGB
BPD
BMI (kg m-2)

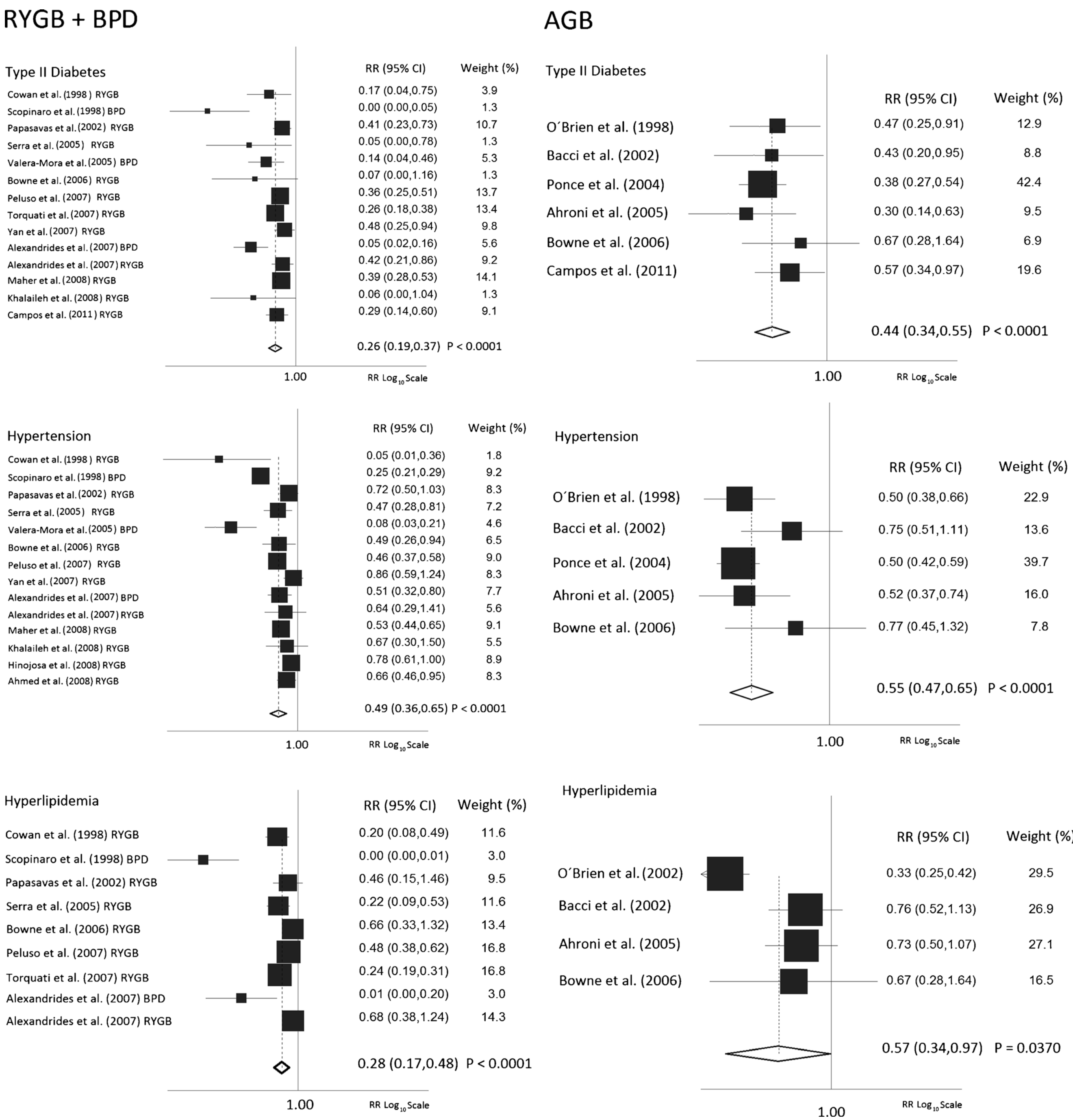


Fig. 4 Meta-analysis of type II diabetes, hypertension, and hyperlipidemia risk reduction by surgical technique

the outcomes of bariatric surgery which employ new surrogate indices of body fat. When more studies considering these alternative indicators of body fat will be available, a meta regression considering cardiovascular risks should be performed. Since that time, quantitative evaluations have to be considered carefully.

In summary, this study shows that RYGB, BPD, and AGB are effective surgical therapeutic options to reduce the cardiovascular risk in morbid obese patients at 1–2 years of follow-up. However, long-term evaluation of outcomes will be worthy of careful investigation as weight loss usually reaches a maximum of 12 months post-operatively and some weight regain is common thereafter.

Conflict of Interest Cristian Ricci, Maddalena Gaeta, Emanuele Rausa, Yuri Macchitella, and Luigi Bonavina have no conflict of interest to declare.

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