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Feinkohl, I., Winterer, G., and Pischon, T. (2016) Obesity and post-operative cognitive dysfunction: a systematic review and meta-analysis. Diabetes Metab Res Rev, 32: 643–651. doi: 10.1002/dmrr.2786.

which has been published in final form in:

Diabetes/Metabolism Research and Reviews
2016 SEP; 32(6): 643-651
2016 APR 06 (first published online)
doi: 10.1002/dmrr.2786

Publisher: Wiley-Blackwell

Obesity and post-operative cognitive dysfunction: a systematic review and meta-analysis

Short title: Obesity and post-operative cognition

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Abstract

Background

Post-operative cognitive dysfunction (POCD) occurs frequently after surgery, and is related to dementia and premature death. Obesity increases the risk of late-life cognitive impairment, but little is known about its role in POCD. We conducted a systematic review and meta-analysis of studies on the association between obesity and risk of POCD.

Methods

PubMed and the Cochrane Library were systematically searched. Studies were included if they had prospective designs, reported on human adults undergoing surgery, if cognitive function was measured pre- and post-surgery, if obesity, body mass index (BMI) and/or body weight were ascertained, and if associations with POCD were reported as relative risks or odds ratios. Underweight, weight loss, and post-operative delirium were not considered.

Results

Inclusion criteria were met by six articles. Samples totaled 1432 older patients (mean age ≥62 years) who were followed up for 24 hours to twelve months after surgery. Analysis of studies with obesity defined as a categorical measure found a non-significantly higher risk of POCD among persons with BMI>30 kg/m^2 versus ≤30 kg/m^2 (RR 1.27; 95% CI 0.95, 1.70; p=0.10). No such associations were found for studies that analyzed BMI or body weight continuously as predictors of POCD (RR 0.98 per kg/m^2; 95% CI 0.93, 1.03, p=0.45; RR 0.99 per kg; 95% CI 0.89, 1.09; p=0.83, respectively).

Conclusions

Few studies have addressed the topic, and the results of these studies provide only limited support for an increased risk of POCD in patients who are obese. Further large-scale, prospective investigations are necessary for clarification.

Keywords: obesity, body weight, adiposity, post-operative cognitive dysfunction, POCD.

Word count (excluding Table): 3129

Introduction

Post-operative cognitive dysfunction (POCD) is a frequent condition that may occur after any type of surgery. POCD broadly refers to a "deterioration in cognition temporally associated with surgery" [1]. In contrast to post-operative delirium (POD), POCD is characterized by intact consciousness and a more subtle onset [2], and it is thought to be caused by distinct pathology. POCD is considered as a transient condition [3], but disease progression and resulting cognitive trajectories of POCD vary substantially between individuals [4] and depend on the time since surgery. Overall incidence rates in older age groups range between 10-38% [5-8] within the first 2 to 3 months and 3-24% at 6 to 12 months after surgery [7, 9, 10]. Further, POCD appears to increase the risk of subsequent dementia diagnosis as well as premature death [3, 6, 11, 12]. The etiology and pathophysiology of POCD are relatively unclear, and only a few risk factors have been identified to date, including higher age and pre-existing cognitive impairment [7, 13, 14]. In view of the high rate at which surgical procedures are performed in older adults [15], the identification of risk factors for POCD urgently warrants detailed investigation. Firm knowledge of its risk factors will enable identification of at-risk patients with the potential for tailoring of post-operative support and care according to individual risk. Further, a clear definition of its risk factors could guide the designs of studies including clinical trials that will ultimately shed light on the causal mechanisms underlying POCD.

Obesity is an established risk factor for a number of chronic diseases, most notably type 2 diabetes, cardiovascular disease, and certain types of cancer [16, 17]. Obesity has also been linked to cognitive impairment in the general population. For instance, a recent systematic review found that obesity at midlife increases dementia risk by 64% [18]. Obesity also increases the risk of hospitalization [19]; however, it is unclear whether obesity is a risk factor for POCD. Obesity is a major public health problem today in most countries of the world [20-22]. In the EU, approximately 40-50% of men and 25-35% of women are overweight (defined as a body mass index, BMI, between 25.0 and 29.9 kg/m^2) and an additional 15–25% of men and 15–25% of women are obese (BMI≥30 kg/m^2) [23]. Given the high prevalence of obesity, even weak associations with POCD could result in high attributable risks, which would be of substantial public health importance. We are not aware of any review that has assessed the evidence for an association of obesity with risk of POCD. We therefore aimed to systematically review the research literature on studies that have investigated the association of obesity with risk of cognitive dysfunction following surgery. For brevity, the term 'obesity' is used throughout this article to denote obesity, a higher BMI or a higher body weight.

Materials and Methods

Systematic search strategy

A literature search for relevant articles was performed in accordance with MOOSE and STROBE guidelines [24, 25] by one investigator (IF). The titles, abstracts and keywords of the PubMed database and Cochrane Database of Systematic Reviews were searched from their respective inception onwards for the following terms: ("obes*" OR "BMI" OR "body mass index" OR "waist*" OR "body weight" OR "overweight" OR "body size") AND (("post-operative cognit*" OR "postoperative cognit*" OR "POCD") OR (("surgery" OR "operation") AND ("cognit" OR "intelligence" OR "MMSE" OR "Mini Mental" OR "dementia" OR "Alzheim*" OR "mild cognitive impairment" OR "MCI"))). No language

restrictions or other search filters were applied. All abstracts of articles identified in the search were screened. If articles were deemed potentially relevant on the basis of their abstracts due to possibly matching inclusion criteria (e.g., reporting data both on BMI and POCD), full texts were accessed to formally compare against these criteria. Reference lists of articles that matched inclusion criteria and of review articles were additionally hand-searched. The final search was performed on 24th September 2015.

Study selection

Articles were included in the review if full-text assessment determined that the following criteria were met: i) original article reporting on humans aged ≥18 years, ii) prospective study of patients undergoing surgery, iii) cognitive function determined at least once pre-surgery and once post-surgery using performance-based cognitive assessment tools, iv) measurement of any anthropometric parameter (AP) prior to surgery, v) and reporting of their association with cognitive change in standardized form either as odds ratios or relative risks (both termed RR for the purpose of the present review). Studies on underweight were not considered as these exceeded the interest of the present article. Review articles and studies on diagnosed delirium were excluded. The use of the label 'POCD' was not required: As definition and measurement of POCD vary between studies [26], any operationalization of change in cognitive function between pre-surgery and post-surgery assessments qualified for inclusion.

Data extraction

Data on study design, location, number of patients included in the analysis, proportion of males, age, type of surgery and anesthesia, assessment methods for AP and cognitive function, prevalence of obesity, incidence of POCD, RR statistics, reference categories, and adjustment variables (if available) were extracted. We extracted fully adjusted analyses unless no adjustment was applied. If any essential information was unreported in an article, the first author of the article was contacted by email. That way, unreported information on the definition of 'obesity' was obtained for one article [27]. If a number of articles reported on a single study [28], articles with data on the longest follow-up period were selected to avoid duplicate inclusion of samples. Where several waves of follow-up were reported in a single article, the longest follow-up period was selected. Author contact to obtain information on 'non-significant' findings at 3-month follow-up was unsuccessful for one article, and so data for 7-day follow-up were used [29]. For another article, risk estimates did not appear to match the reported 95% CI [27]. The issue was not resolved in personal correspondence, and so we opted to take the reported 95% CI at face value to allow meta-analysis.

Quality assessment

Quality of reporting was assessed by one investigator (IF) using the STROBE statement checklist for cohort studies, a 22-item list addressing the reporting of objectives, methods, interpretation and potential biases [30]. Each positively evaluated item of the checklist was assigned a score of 1 (maximum score 22). As the checklist does not address methodological study quality [31], no exclusion based on these scores was applied.

Data synthesis and analysis

Extracted data were tabulated and were entered into Review Manager 5.3 (Cochrane, 2014) to calculate summary estimates of RR (95% CI) using inverse variance fixed effect models, and to derive standard I^2 as an index of statistical heterogeneity among studies [32].

Results

Study characteristics

The search resulted in 286 articles in PubMed and 1 article in the Cochrane Library (see Figure 1). All titles and abstracts were screened. Exclusion at this stage resulted from articles clearly failing inclusion criteria (and therefore being not deemed potentially relevant). This was most commonly due to articles reporting on animal studies or on unrelated topics such as 'cognitive restraint' or 'cognitive behavioral therapy' for weight loss. For 48 articles that passed the stage of abstract screening, full texts were accessed. Hand-searching of reference lists of relevant articles and review articles, and an independent online search resulted in 10 further potentially relevant original articles for which full texts were also accessed [29, 33-41]. The full texts of a total of N=58 original articles were therefore compared against inclusion criteria. All were in English language except 2 articles in Chinese, which were considered with help from a native speaker. Forty-seven of the 58 articles did not meet inclusion criteria due to failing to associate AP with POCD (including studies of bariatric surgery) (n=32), or due to cross-sectional study designs or analyses (n=5), lack of cognitive data (n=3), lack of reporting of RR (n=3), focus on underweight or weight gain surgery (n=2), case study (n=1) or due to describing the methodology and design of a future study (n=1). Within 5 [35-39] and within 2 articles [40, 42], we found that these articles appeared to report on identical patient samples. We therefore selected one article for each patient sample for inclusion [36, 42]. Thus, a total of N=6 articles remained for analysis.

Across studies, a total of 1432 patients were included (see Table 1). In one study, the reporting quality was limited because it was published as a three-page brief report [27]. The remaining five studies were exploratory in nature. Sample size ranged from 36 [27, 36, 42] to 585 [29, 41]. Studies stemmed from China, Japan, USA, Australia, and Spain, with follow-up periods of between 1 day and 12 months (median follow-up 7 days, interquartile range 7 days – 6 months). Publication dates spanned 2005 to 2015. Patients underwent heart surgery, carotid endarterectomy, or total hip replacement. Mean sample age ranged from 62 to 75 years (where reported). All studies except one study [36] included males and females at approximately equivalent proportions and none stratified the analyses by sex. All except one study [27] excluded patients with diagnosed or suspected dementia, or neurological/psychiatric disorders at baseline. Five studies applied detailed batteries of cognitive tests [27, 29, 36, 41, 42] of which four compared cognitive changes in the patient group to reference or control groups to define POCD [27, 29, 41, 42]. One study used raw change on the Mini Mental State Examination [43], a brief cognitive screening instrument [44]. In all studies, POCD was a dichotomous outcome.

Findings of included studies and meta-analysis

Three of the six studies compared obese (BMI>30 kg/m^2) with non-obese patients (BMI≤30 kg/m^2) [27, 41, 42], two studies used body weight as a continuous predictor [36, 44] and one study used BMI as a continuous predictor [29]. Individual effect sizes for all studies and

pooled effect sizes for the two groups with ≥2 studies (allowing subgroup analysis) are shown in Figure 2. The funnel plot including all studies is shown in Figure 3.

The study on BMI as a continuous predictor reported no association with risk of POCD at 7 days after surgery with statistically significant, independent contributions by age and type of surgery controlled for (RR per kg/m^2 increase 0.98; 95% CI 0.93, 1.03; p=0.45; see Figure 2) [29]. When the results of two studies that assessed body weight as a continuous predictor of POCD at 7-day and 6-month follow-up, respectively, were pooled [36, 44], we also found no significant association with risk of POCD (RR per kg increase 0.99; 95% CI 0.89, 1.09; p=0.83; see Figure 2). Both of these studies had adjusted for a range of sociodemographic and clinical covariates. Of the three studies that categorized patients according to obesity, two found that BMI>30 kg/m^2 at baseline was statistically significantly associated with an increased risk of POCD compared to BMI<30 kg/m^2 [27, 42]. In the larger of these studies, with a sample size of 75, analyses were controlled for age, diabetes and APOEe4 status. Here, BMI>30 kg/m^2 was associated with a 24-fold increased risk of POCD at 1 month after carotid endarterectomy surgery compared to BMI<30 kg/m^2 [42]. A smaller study of 36 patients that did not apply adjustment revealed a 2.14-fold increased risk of POCD at 12 months following cardiac surgery for patients with BMI>30 kg/m^2 versus ≤30 kg/m^2 [27]. One relatively large investigation with 1-day follow-up, in contrast, reported no such findings even in unadjusted analyses [41]. When we pooled the relative risks across these three studies, the association of obesity (BMI>30 kg/m^2) with risk of POCD was statistically not significant at the 5% level (RR 1.27; 95% CI 0.95, 1.70; p=0.10). Statistical heterogeneity between the three studies was moderate (Chi^2 (2) = 8.84; I^2=77%; p=0.01; see Figure 2).

Discussion

Here, we set out to combine the existing evidence on obesity and risk of post-operative cognitive dysfunction (POCD) but were restricted in our endeavour by the small number of studies conducted on the topic, by heterogeneity between studies and by overall poor study quality. Though further research is urgently needed, our findings at present offer only limited support for a role of obesity as increasing the risk of POCD.

Obesity is well-established as a risk factor for later cognitive impairment in the general population [18], and an extension of the relationship to impairment occurring after the 'insult' of surgery appears plausible. It would also be consistent with investigations in humans and animal models that have identified the metabolic syndrome, of which obesity is a key component, as increasing the risk for post-operative cognitive deficits [45-48]. Though the present marginal association of obesity with POCD across studies may indicate that the association is weak but global in nature, a masking of effects by the substantial degree of heterogeneity between studies is also possible. Any specific study characteristics that do not lead to associations of obesity with POCD may have rendered findings statistically non-significant when effects were pooled across all studies included here. Further, as body weight has a U-shaped relationship with cognitive impairment [18], we speculate whether the failure to detect statistically significant associations in the present analysis were caused partly by the fact that the non-obese groups may have included underweight patients. Their inclusion may have led to an underestimation of the effect sizes for the association of obesity and POCD. None of the studies reviewed here reported the prevalence of underweight in their total

samples or mean BMI in non-obese groups (which would provide some indication of the weight characteristics of these groups), and so potential confounding by this factor leaves scope for future re-analysis of their data. However, a role of obesity in POCD finds support in one additional study that strictly failed to meet inclusion criteria of the present analysis due to a lack of reporting of findings as relative risks: In that study, which did not apply any statistical adjustment, a group with POCD 7 days after surgery had a 0.7 standard deviation higher mean body weight compared with a cognitively unimpaired group [33].

The overall evidence is therefore inconclusive at present and warrants resolution in further investigations. Any future confirmation of links between obesity and an increased risk of cognitive dysfunction following surgery would have far-reaching implications. For instance, ascertainment of obesity, which is easy, cheap and quick even when precise measurements are unavailable, could prove useful for risk prediction in clinical management of older adults. In cases where surgery is essential, risk stratification could allow early introduction of support systems for at-risk patients. Obesity is also relatively unique as a risk factor in that although it is not modifiable at the time when patients present for surgery, it is modifiable in the long term, so that – should any observational evidence of associations with POCD prove causal – it could become a viable target for intervention. Briefly, potential underlying mechanisms, some of which could be targeted, include effects of circulating correlates of adipose tissue such as cortisol [49] or inflammatory markers [50], which have both been identified as risk factors for cognitive impairment in epidemiological research [51, 52]. Blood-brain barrier function also appears to be compromised in obesity [53] which may affect susceptibility to cognitive impairment [54] and so potentially to POCD. Causality is by no means certain, however, as confounding of obesity relationships with POCD by other factors, such as dyslipidemia, glycemia or pre-morbid ability, may be possible [55]. For instance, a lower pre-morbid ability is well-established as a risk factor for the metabolic syndrome [56] and is also a candidate risk factor for POCD [6]. The selection of adjustment variables to control for potential confounding was inconsistent across the studies included in the present analysis, and was typically based on univariable associations with POCD or a ‘throw in everything’ approach, rather than plausible underlying mechanisms or previous research. The role of confounders in the present pooled analysis of obesity and POCD risk is therefore entirely uncertain.
Strengths of the present review include wide inclusion criteria that allowed any definition of obesity and POCD. Generalizability of our findings was limited by the small number of articles, by overall poor study quality that often included small sample sizes, and by heterogeneity in study designs and in characteristics of patient samples. This complicated pooling of effects as well as assessment of contributions of any between-study differences in terms of surgery type, sample age or cognitive domain tested to the present findings. For instance, surgery type may itself influence the risk of POCD, though the evidence is not entirely clear as yet [6, 29, 57], and so could also play a role in associations of obesity with POCD.

Clearly, larger observational studies are needed to address the role of obesity on risk of POCD across diverse, well-characterized patient groups and to strategically assess the independence versus dependence of the relationship from other candidate risk factors. We further cannot rule out influences of delirium on cognitive status in studies with brief follow-up periods (e.g.,

[41]) on our findings. . A majority of investigations that we included in our analysis were exploratory, which hindered identification of articles, and our search strategy did not include any domain-specific terms. Therefore, readers should be aware that we may not have been successful in the identification of all relevant articles.
All of the included investigations used body weight or BMI to assess obesity. Studies conducted over the past years have shown that waist circumference as a marker of abdominal body fat distribution may be more closely related to risk of many chronic diseases and to mortality than BMI [17, 58]. Future studies on the role of obesity for risk of POCD should therefore additionally include the measurement of waist circumference to define the "obesity" phenotype [59]. Also, the potential effect of obesity at different times of the life-span on risk of POCD deserves investigation [18].

The definition of POCD as a dichotomous outcome based on underlying test batteries is somewhat arbitrary and may lead to loss of statistical power as compared to continuous outcomes in individual studies [60]. Future studies should therefore consider to also operationalize surgery-associated cognitive decline as a continuous outcome. Finally, it may be useful to assess potential associations of obesity with selective impairment on individual cognitive domains under careful consideration of the issue of multiple statistical testing.

In conclusion, in this systematic review we found limited evidence for an association of obesity and risk of POCD. We identified only six studies that have addressed this topic of which most had small sample sizes. The overall limited evidence of an increased risk of POCD in patients who are obese is tentative and preliminary at present, and may be affected by the inclusion of underweight patients. Large prospective studies are necessary to clarify whether POCD may or may not be added to the long list of health risks associated with obesity.

Acknowledgement: IF was supported by funding from the European Union, Seventh Framework Programme [FP7/2007-2013], under grant agreement No. HEALTH-F2-2014-602461: BioCog, Biomarker Development for Postoperative Cognitive Impairment in the Elderly): www.biocog.eu.

Conflicts of interest.
None declared.

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Tables

Table 1: Summary of included studies.

Authors, year, location	N in analysis	% male	Type of surgery, anesthesia	Mean age ± SD in years	Follow -up	Cognitive Assessment	Definition/ frequency of POCD	AP exposure variable	Adjustment variables	AP exposure and risk of POCD	Reporting quality score*
Heyer et al. (2005) [42] USA	75	61	Carotid endarterectomy. General anesthesia.	69 ± 9	30 days	Five detailed neuropsychological tests (Boston Naming Test; Halstead-Reitan Trails A; Halstead-Reitan Trails B; Controlled Oral Word Association Test; Rey Complex Figure Test). For each test, calculation of z scores: (Change score – mean change score of controls)/SD of change score of controls. Control group n=46. Z-scores used to derive 'total deficit score' (range 0-6 for each test) for each patient. Total deficit score	POCD defined as summed total deficit score of ≥7. POCD in n=8/75 (10.7%) of patients.	BMI >30 kg/m^2 (n=12/75; 16%) versus BMI≤30 kg/m^2 (n=63/75; 84%).	Age, diabetes, APOEe4,	RR 24.43 (95% CI 1.41, 422.9).	17/22

						summed across tests.					
Kadoi & Goto (2006) [36] Japan	88	80	CABG. General anesthesia.	62 ± 11	6 months	Five detailed neuropsychological tests (Rey Learning Test; Trail-Making Test A; Trail-Making Test B; Digit Span Forward; Grooved Pegboard); MMSE.	Definition of POCD unclear. POCD in n=24/88 (27.3%) of patients.	Body weight as continuous per kg (mean 56.9 ± 11** kg).	Total of 18 clinical and sociodemographic covariates.	RR 1.0 (95% CI 0.9, 1.1).	11/22
Evered et al. (2011) [29] Australia	443	63	Coronary angiography, CABG, total hip replacement surgery. Local, spinal or general anesthesia.	68 ± 8	7 days	Seven detailed neuropsychological tests (Auditory Verbal Learning Test; Digit Symbol Substitution Test; Trail-Making Test A; Trail-Making Test B; Controlled Oral Word Association Test; Verbal Fluency; Grooved Pegboard). For each test, calculation of RCI: (Change score − mean change score of controls)/SD of change score of controls. To obtain combined z-score, scores summed for each test and divided by SD of	POCD defined as RCI <1.96 on ≥2 tests and/or combined z-score < -1.96. POCD in n=150/443 (33.9%) of patients.	BMI as continuous per kg/m^2 (mean 28.5 ± 5 kg/m^2).	Age, diabetes, hypercholesterolemia, beta blockers, statins, PAD, MI, type of surgery.	RR 0.98 (95% CI 0.93, 1.03).	16/22

						summed score of control group. Control group n=34.					
Zhu et al. (2014) [44] China	205	51	Total hip replacement surgery. Spinal or general anesthesia.	75 ± 6	7 days	MMSE.	POCD defined as ≥1 SD decline on MMSE. POCD in n=56/205 (27.3%) of patients.	Body weight as continuous per kg (mean 61.1 ± 11 kg).	Age, education, blood loss, hydroxyethyl starch infusion, hemoglobin levels, red blood cell transfusion.	RR 0.43 (95% CI 0.12, 1.37).	15/22
Heyer et al. (2015) [41] USA	585	65	Carotid endarterectomy. General anesthesia.	34.4 % ≥75	1 day	Unclear number of neuropsychological tests of four cognitive domains. For each test, calculation of z-scores: (Change score – mean change score of controls)/SD of change score of controls. Control group n=156.	POCD defined as ≤2 SD worse performance in 2 or more cognitive domains and/or ≥1.5 SD worse performance in all 4 cognitive domains. POCD in n=145/585 (24.8%) of patients.	BMI >30 kg/m^2 (n=127/585; 22%) versus BMI≤30 kg/m^2 (n=458/585; 78%).	None.	RR 1.02 (95% CI 0.73, 1.43).	17/22
Perez-Belmonte et al. (2015) [27] Spain	36	69	CABG. Anesthesia unreported.	66 ± 1	12 months	Six detailed neuropsychological tests (Trail-Making Test; Stroop Test; Selective Reminding Test; Verbal Fluency Tests (semantic, phonological); Judgement of Line	POCD defined as 'MCI' (percentile rank ≤10%) or 'inferior normal function' (percentile rank 11% to 18%). POCD in mean 31% of patients	BMI >30 kg/m^2 (n=14/36; 39%) versus BMI≤30 kg/m^2 (n=22/36; 61%).	None.	Original reporting of RR 1.6 (95% CI 1.3, 3.8). RR 2.14 (95% CI 1.3, 3.8) for the purpose of the present analysis.	11/22

						Orientation Test. Scores for each patient converted to norm-compared reference scores (adjusted for age, education).	(n=11/36) across cognitive tests.				

APOEe4, apolipoprotein e4 allele; BMI, body mass index; CABG, coronary artery bypass grafting; MCI, mild cognitive impairment; MI, myocardial infarction; MMSE, Mini Mental State Examination; PAD, peripheral arterial disease; POCD, post-operative cognitive dysfunction; RCI, Reliable Change Index; RR, risk ratio; SD, standard deviation; RCT, randomized controlled trial.

*based on checklist for cohort studies by STROBE Initiative (2007); maximum score 22.

**original publication reports SD = 110 kg (assumed to be due to typographical error).

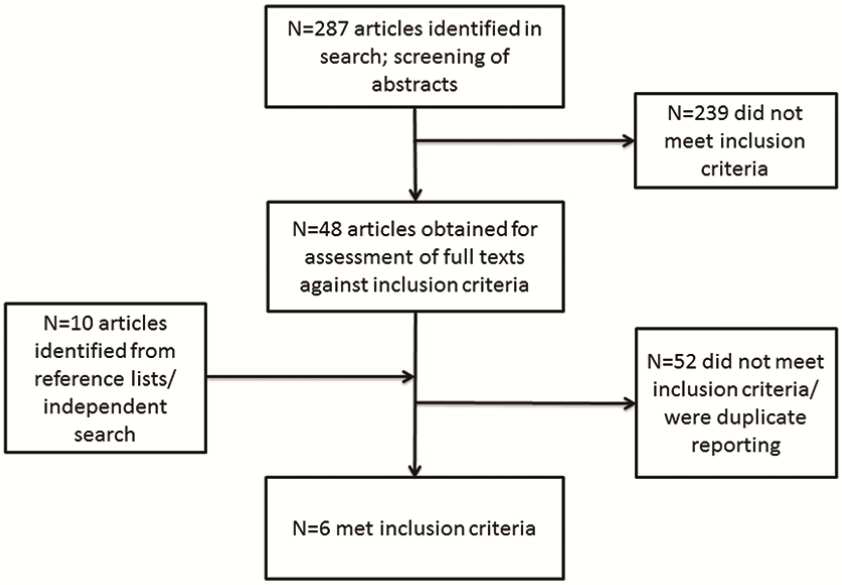

Figure 1: Flow chart for search on obesity and post-operative cognitive dysfunction

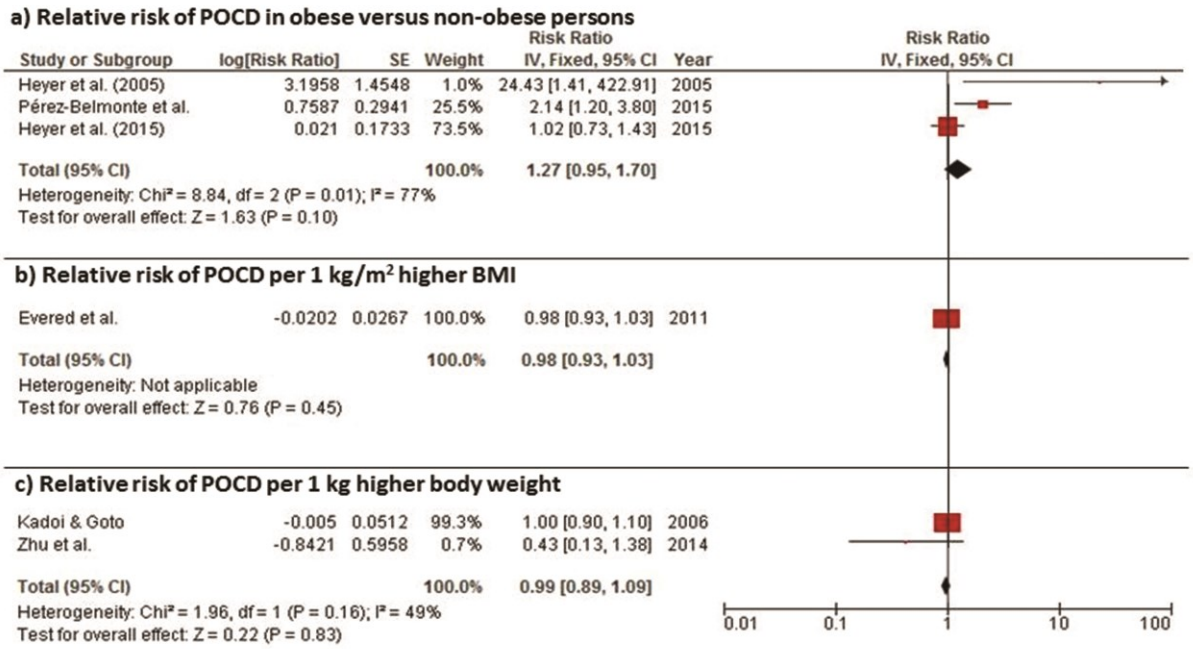

Figure 2: Summary of studies on obesity and post-operative cognitive dysfunction. Top Panel (a): Analysis of studies on body mass index >30 kg/m^2 versus ≤30 kg/m2. Middle Panel (b): Study on body mass index (kg/m^2). Bottom Panel (c): Analysis of studies on body weight (kg)

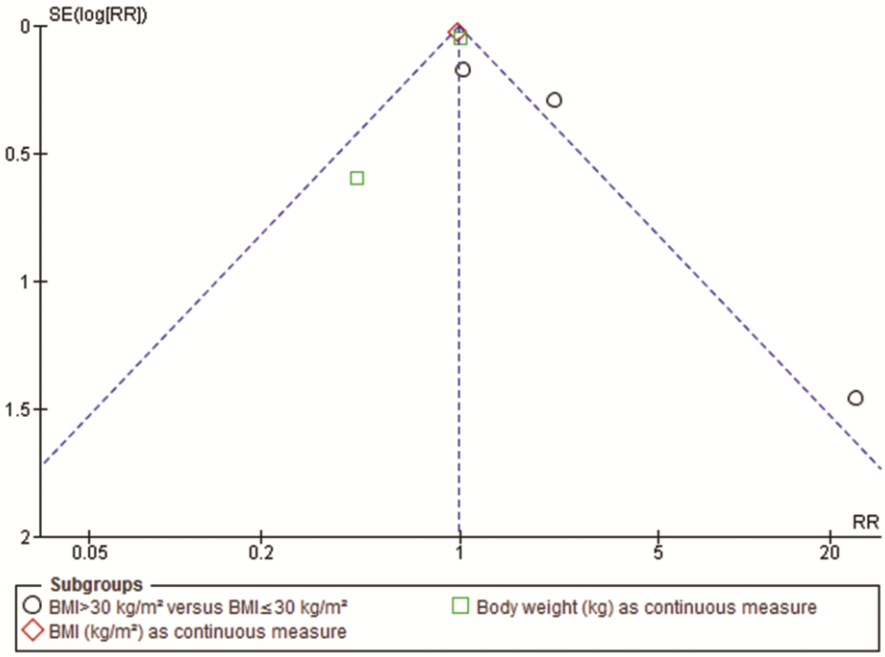

Figure 3: Funnel plot of studies on obesity and risk of post-operative cognitive dysfunction