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REVIEW ARTICLE

Association Between Obesity and Wound Infection Following Colorectal Surgery: Systematic Review and Meta-Analysis

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Abstract

Background The aim of this meta-analysis is to comprehensively review and quantify the excess risk of surgical site infections (SSI) in obese patients following colorectal surgery.

Methods A systematic electronic search of the MEDLINE and EMBASE databases identified studies that investigated the association of obesity, defined by body mass index (BMI) with SSI among colorectal surgery patients.

Results Twelve studies were included in the final analysis. Patients with BMI ≥30 kg/m^2 were at 1.5 times (pooled OR 1.51, 95% CI: 1.39, 1.63, $p < 0.001$) higher odds of developing SSI after colorectal surgery when compared to BMI <30 kg/m^2. Subgroup analysis of the eight studies that investigated only elective procedures showed that the odds of developing SSI when BMI ≥30 kg/m^2 is 1.6 times that of those with BMI <30 kg/m^2 (pooled OR 1.60; 95% CI 1.34, 1.86; $p < 0.001$). The odds of having SSI when BMI is 25–29.9 kg/m^2 are 1.2 times than those with BMI <25 kg/m^2 (pooled OR 1.17; 95% CI 1.07, 1.28; $p < 0.001$).

Conclusion Overweight and obese patients carry at least 20% and 50% higher odds of developing SSI after colorectal surgery compared to normal weight patients, respectively.

Keywords Obesity · Surgical site infection · Colorectal surgery

Introduction

Colorectal surgery is associated with a high risk of surgical site infection (SSI) due to the increased likelihood of contamination.[1,2] Obesity is a significant risk factor for SSI in colorectal surgery.[1] It is considered to alter the immune function by reducing lymphocyte responsiveness.[3] Obesity also creates an imbalance between tissue oxygen demand and supply leading to decreased wound oxygen tension[4] as well as increases the technical difficulty of surgery resulting in longer operation times.[5]

The reported incidence rates of SSI in colorectal surgery are between 5 and 45%.[6] SSI can result in reoperations, prolonged hospital stay, and higher mortality,[7] thereby resulting in increased health care costs.[8,9] A preventable SSI can increase hospital stay by around 11 days with an increase in cost of approximately 27,000 USD per patient.[9] Identifying risk factors for SSI and the magnitude of their impact may enable targeted preventative measures and therefore more efficient perioperative SSI surveillance and control. However, there are not only discrepancies in literature about the estimated incidence of SSI but also uncertainty

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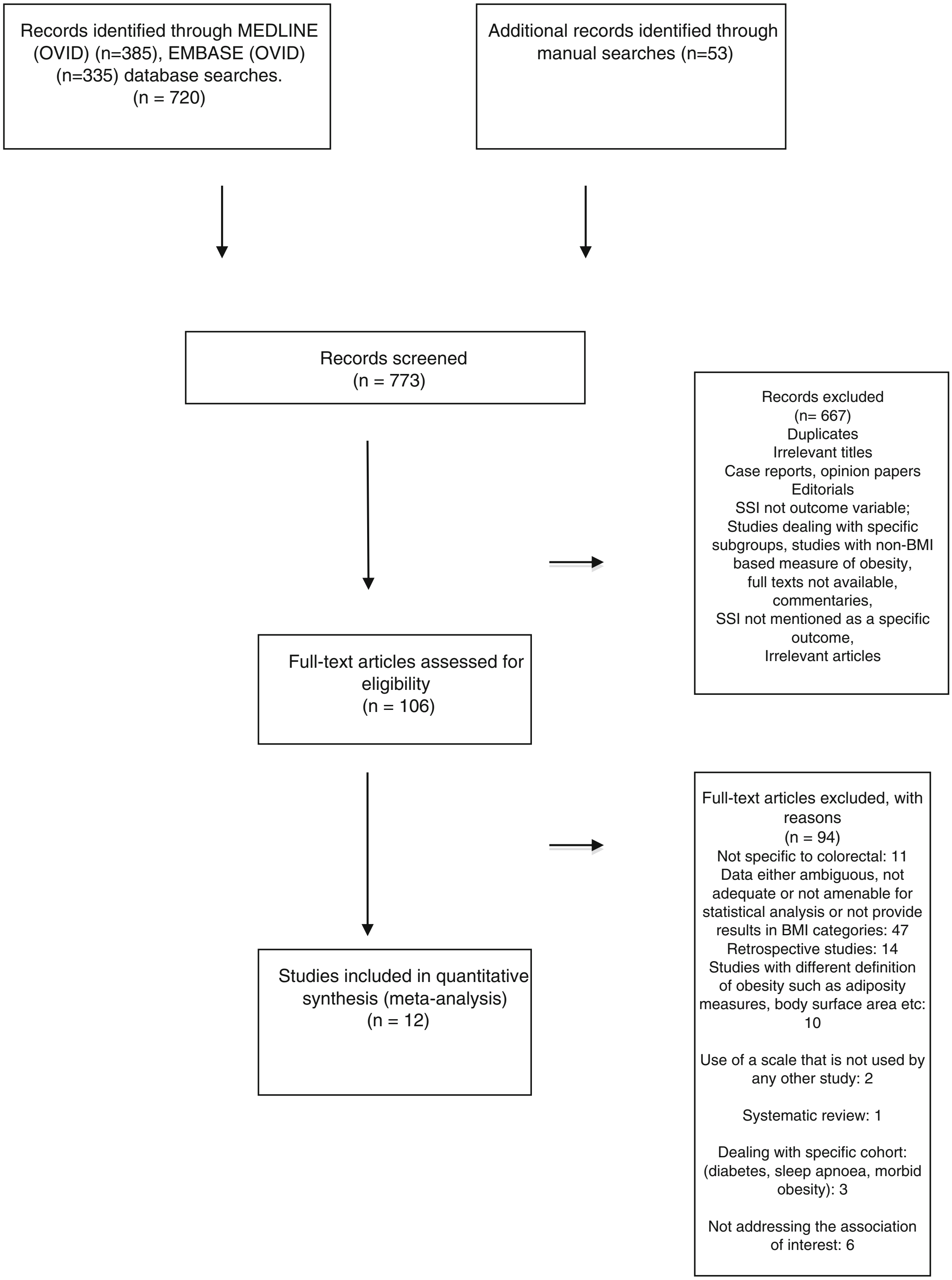


Fig. 1 Study flow diagram based on PRISMA recommendations. Seven hundred twenty articles through electronic search and 53 articles through manual searches were identified and final analysis included 12 studies

regarding the magnitude of risk from each predisposing factor.[10]

Obesity is a major risk factor for SSI, and the prevalence of severe obesity is expected to increase by 130%

by 2030.[11] Although large studies have shown that obesity per se is not a contraindication to elective surgery, [12,13] there are reports of increased anastomotic leakage,[14] higher conversion rate with laparoscopy,[5,14,15] higher incidence of morbidity including wound infections,[5,15] longer operating times, and longer hospital stay[15] following colorectal surgery in obese patients. Obesity has been shown to increase the cost of colectomy by approximately $17,000.[16]

While there are numerous studies investigating the risk of obesity following colorectal surgery, there is an urgent need to quantify the magnitude of this risk in the development of SSI given the alarming rise in the prevalence of obesity. Therefore, a systematic review and meta-analysis was undertaken to ascertain the risk of SSI in obese patients following colorectal surgery.

Methods

Search Strategy and Eligibility Criteria

A systematic electronic search of MEDLINE and EMBASE databases was performed by the investigators G.M. and U.G. Articles on human studies limited to adult population, published in English between 1990 and September 2016 were identified, with the following search terms: (1) obesity/body mass index, (2) open or laparoscopic colorectal surgeries/resections, and (3) SSI/wound infections. Search terms were modified appropriate to the search engine implemented. Both US Centers for Disease Control and Prevention's (CDC) definition[17] or wound infection as diagnosed by surgical team were acceptable. All the titles and abstracts were reviewed and the relevant articles were independently identified by the investigators U.G. and S.R.

Studies included were those that (1) investigated the association between obesity and surgical site infection/wound infection in colorectal surgery, (2) had prospective data collection or data collected from prospectively maintained database, (3) categorized obesity according to WHO classification, and (4) reported either quantitative risk estimates or raw data to calculate odds ratios and their 95% confidence intervals. The results of the search and the reasons for exclusion are shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Fig. 1). Full texts of the articles were obtained and the references manually searched for further relevant literature. Any discrepancy was resolved by discussion among the investigators. The search strategy is given in Appendix 1.

Data Abstraction and Quality Assessment

The following data were extracted on a standardized form by the investigators (S.R. and G.M.): first author, year of publication, study design, country and year of study, surgery, surgical outcomes, definition of obesity, definition of outcomes used by the investigators, duration of follow-up, total number of patients, number of patients with SSI/wound infection, and effect measure used and variables controlled if multivariate analyses were performed by the investigators. Studies finally selected for analysis were classified based on their definitions of obesity categories. Cochrane tool was used to assess the risk of bias in the studies selected for analysis.[18] This tool comprised eight questions (Table 1). The studies were scored on their likelihood of bias as definitely yes (high risk of bias), mostly yes, mostly no, and definitely no (low risk of bias) according to the Cochrane examples and topic-specific predetermined criteria agreed by the authors. Analysis and interpretation of results were carried out by M.W., L.W., U.G., and P.M. All the listed authors contributed in drafting this article and reviewing the final version of the manuscript.

Data Analysis

The analysis was based on the WHO classification of obesity which defines obesity as a BMI ≥30 kg/m^2 and overweight as body mass index (BMI) ≥25 kg/m.^{2} [19]

Table 1 Cochrane tool for assessment of risk of bias in observational studies [[18]]

1. Was selection of exposed and non-exposed cohorts drawn from the same population?
2. Can we be confident in the assessment exposure?
3. Can we be confident that the outcome of interest was not present at the start of the stud
4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?
5. Can we be confident in the assessment of the presence or absence of prognostic factors
6. Can we be confident in the assessment of outcome?
7. Was the follow-up of cohorts adequate?
8. Were co-interventions similar between groups?

Table 2 Characteristics of the included studies in the meta-analysis

Source	Country, year of study	Study design	Surgery	Obesity measure and classification	Outcome of interest (definition) and duration of follow-up	Total number of patients	Number of patients with outcome of interest	Covariates with multivariate analysis
Tuech et al. [49], 2001	France: 1995–2000	Prospective study	Laparoscopic colectomy, included laparotomy conversion	BMI (kg/m^2): < 25, 25–30, >30	Wound infection (N.R.); 6 weeks, 6 months, and 1 year	77	7	Regression analysis was not performed by authors
Itani et al. [26], 2008	USA: 2002–2005	Post hoc analysis of a randomized double blinded study	Elective open colorectal procedures; lap-assisted exclud-ed	BMI (kg/m^2): <18.5, 18.5–24.9, 25–29.9, 30–39.9, ≥40	SSI (CDC); 30 days	650	156	Regression analysis was not performed by authors
Merkow et al. [28], 2009	USA: 2007	Prospective cohort study (NSQIP database)	Elective colectomy	BMI (kg/m^2): 18.5–24.9, 25–29.9, 30–34.9, ≥35	SSI (CDC); 30 days	3202	380 (calculated from % data)	Surgical approach, gender, ASA class, functional status, intraoperative blood transfusion, white blood cells, diabetes, weight loss, dyspnea, wound class, creatinine, COPD
Bege et al. [50], 2009	France: 2002–2007	Retrospective review of prospective database	Laparoscopic rectal resection	BMI (kg/m^2): <30, ≥30	Wound infection (N.R.); N.R.	210	10	Not recorded
Singh et al. [51], 2011	UK: 2005–2008	Retrospective review from prospectively maintained database	Laparoscopic colorectal resections including laparotomy conversion	BMI (kg/m^2): <30, ≥30	Wound infection (N.R.); 30 days	234	13	Regression analysis was not performed by authors
Anannamchar-oen et al. [21], 2012	Thailand: 2008–2010	Prospective surveillance study	Elective and emergency laparoscopic and open colorectal resections	BMI (kg/m^2): <24, 25–29, ≥30	SSI (CDC); 30 days	229	54	Preoperative albumin, Hartman's procedure, postoperative hypotension, postoperative hypothermia
Gervaz et al. [22], 2012	Switzerland: 2008–2010	Prospective cohort study	Elective and emergency laparoscopic and open colorectal resections	BMI (kg/m^2): <30; ≥30	SSI (CDC); 30 days	534	114	Contamination class, open surgery, ASA grade
Lawson et al. [23], 2013	USA: 2011	Retrospective review from NSQIP database	Elective and emergency laparoscopic and open colectomy	BMI (kg/m^2): <18.5, 18.5–24.9, 25–29.9, 30–34.9. 35–39.9, ≥40	SSI (CDC); 30 days	27,011	2943	Procedure, postoperative diagnosis group, demographics, preoperative health status, risk factors, comorbidities
Hibbert et al. [25], 2015	Saudi Arabia: over a 6-year period	Prospective observational longitudinal study	Elective open colorectal resection; laparoscopic procedures were excluded	BMI (kg/m^2): <18.5, 18.5–24.9,25–-29.9, ≥30	SSI (CDC); 36 days	296	?89	Pre albumin, albumin, hemoglobin A1c, surgeon, difficulty caused by obesity, operation time, age, ASA, bowel preparation, blood loss
van Vugt et al. [52], 2015	Netherlands: variable time intervals between 2006 and 2014	Retrospective review from prospectively maintained database	Elective colorectal surgery	BMI (kg/m^2): <20, 20–25, 25–30, ≥30	SSI (Purulent drainage from the surgical site along with inflammatory signs); 30 days	1614	122	Age, gender, ASA, laparoscopic surgery
Pasam et al. [24], 2015	USA: 2006–2011	Retrospective cohort study from prospectively	Elective and emergency laparoscopic and	BMI (kg/m^2): <30, ≥30	SSI (CDC); 30 days	166,704	22,287	Surgical technique, age, smoking, diabetes, ASA, prior wound infection, resident involvement

Table 2 (continued)

Source	Country, year of study	Study design	Surgery	Obesity measure and classification	Outcome of interest (definition) and duration of follow-up	Total number of patients	Number of patients with outcome of interest	Covariates with multivariate analysis
		maintained database (NSQIP)	open colorectal resection					
Kiran et al. [27], 2015	USA: 2012	? Retrospective cohort from prospective database	Elective laparoscopic and open colorectal resection	BMI (kg/m^2): <30, ≥30	SSI (CDC); 30 days	8442	944	Operation time, site of surgery, laparoscopy, albumin, creatinine, WBC, hematocrit, prior infection or sepsis, transfusion, disseminated cancer, bleeding disorder, steroid use, ascites, dyspnea, hypertension, ASA, functional status, race, mechanical bowel preparation

BMI Body mass index, *SSI* surgical site infection, *N.R.* not recorded, *CDC* Centers for disease control and prevention, *ASA* American Society of Anesthesiologists, *NSQIP* National Surgical Quality Improvement Program

Only studies with equivalent BMI categories or data amenable to condensing BMI categories were combined. To substantiate the findings from our meta-analysis, in addition to the main meta-analysis, subgroup analyses were performed. Unadjusted odds ratios were combined using a random effects model. Variances were pooled using the inverse variance method. Meta-analysis was performed in STATA Version 13 (StataCorp. 2013, College Station, Texas). Heterogeneity among our studies was assessed using I^2 statistics [20] with I^2 values of 25, 50, and 75% corresponded to low, moderate, and high degrees of heterogeneity, respectively. Publication bias was assessed using funnel plots and bias coefficient was estimated using Egger (weighted regression) method. This study was registered with the PROSPERO database at the Centre for Reviews and Dissemination (CRD), University of York (No: CRD42016032642).

Results

The initial search identified 720 citations. The search strategy with MEDLINE and EMBASE is given in Appendix 1. Fifty-three further citations were retrieved through manual searches of references. After excluding 667 citations for the reasons given in the PRISMA diagram (Fig. 1), 106 full text articles were screened further for their eligibility. Of these, 12 suitable articles were included in the final analyses. Among these final 12 studies, 5 studies were from the USA and the rest were from Switzerland, Thailand, Saudi Arabia, UK, Netherlands, and France (Table 2).

Analysis of the 12 studies showed that there was a statistically significant increase in SSI among patients with BMI ≥30 kg/m^2 when compared to BMI <30 kg/m^2 (n = 209,196; pooled OR 1.51; 95% CI 1.39, 1.63; $p < 0.001$). The degree of heterogeneity was moderate, but not significant (I^2 = 41%, p = 0.07) (Fig. 2). The funnel plot of the meta-analysis investigating these 12 studies (Fig. 3) showed evidence of bias (bias coefficient = 1.1, standard error = 0.48; p = 0.04), thereby suggesting the possibility of small-study effects.

Of the 12 studies, four studies[21,24] had included elective and emergency procedures and hence subgroup analysis was performed on the rest of the eight studies that explored only elective procedures to identify the source of heterogeneity. This showed that the odds of developing SSI when BMI ≥30 kg/m^2 is 1.6 times that of those with BMI <30 kg/m^2 (n = 14,723; pooled OR 1.60 (1.34, 1.86), $p < 0.001$) and the heterogeneity between the included studies had reduced and was not significant (I^2 = 24%, p = 0.24*)* (Fig. 4). Their funnel

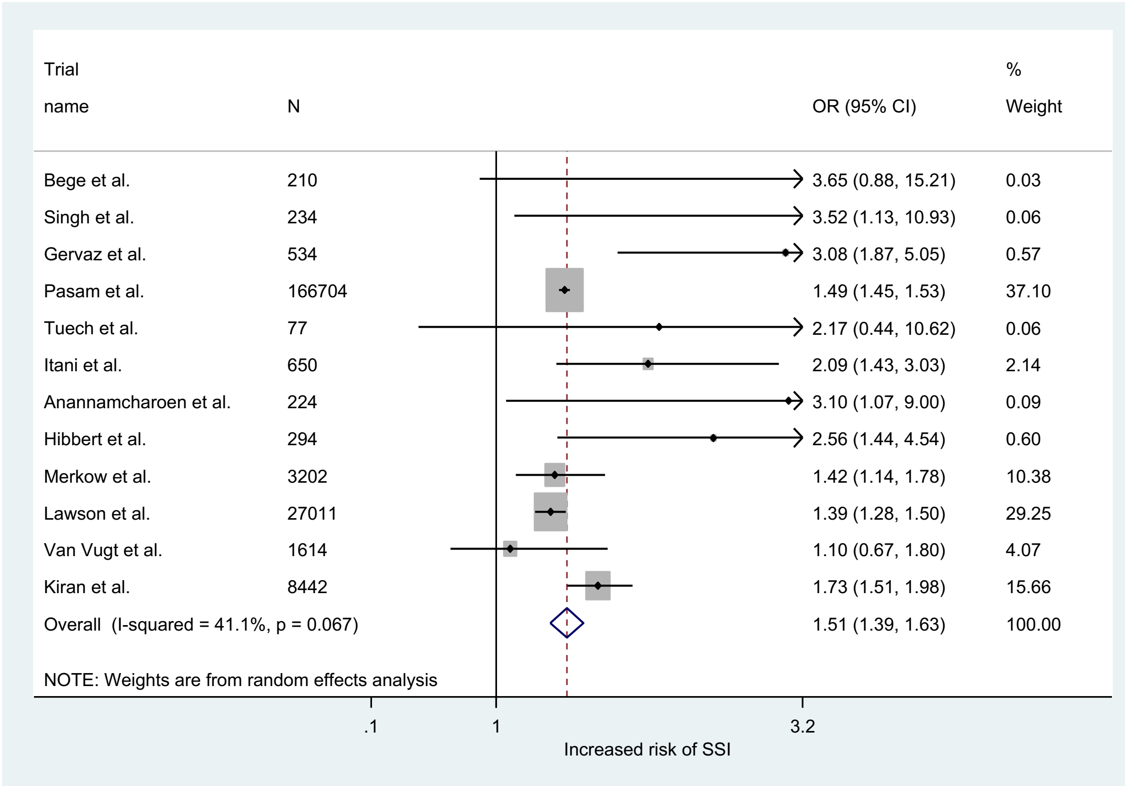
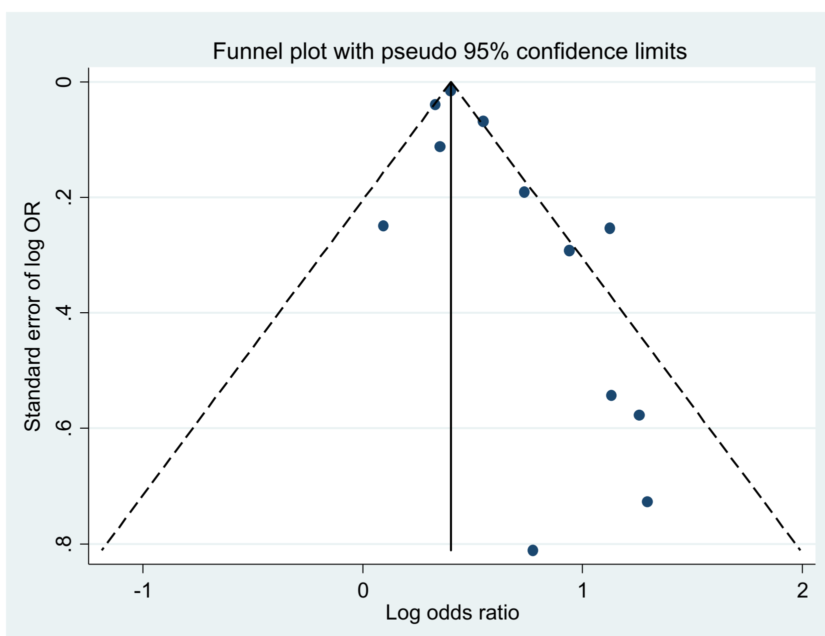


Fig. 2 Results from the main meta-analysis of the studies with BMI classification based on WHO guidelines. The figures show the result and the forest plot of the meta-analysis between BMI ≥ 30 kg/m^2 and BMI < 30 kg/m^2 in relation to the risk of developing surgical site infection following colorectal surgery

Fig. 3 Funnel plots for publication bias. The figure shows moderate publication bias in the analyses, namely comparison of BMI ≥ 30 kg/m^2 with BMI <30 kg/m^2



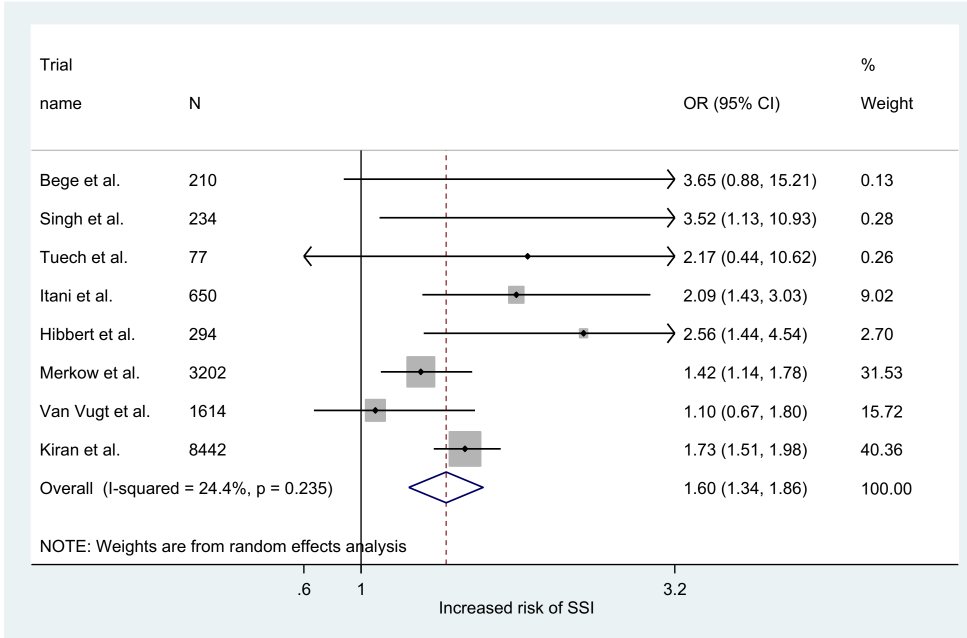


Fig. 4 Results from the meta-analysis of the studies that investigated only elective procedures. The figures show the result and the forest plot of the meta-analysis between BMI ≥ 30 kg/m^2 and BMI < 30 kg/m^2 in relation to the risk of developing surgical site infection following elective colorectal surgery

plots showed no evidence of bias (bias coefficient = 0.70, SE = 0.70, p = 0.36). Eight studies had used CDC definition for SSI.[21,28] Subgroup analysis of these eight studies showed that the odds of SSI with a BMI ≥30 kg/m^2 was found to be 1.5 times (n = 207, 061; pooled OR 1.53 (1.40, 1.66), p < 0.001) compared with a BMI of less than 30 kg/m^2.

Seven studies had reported the incidence of SSI comparing BMI less than 25 kg/m^2 with BMI between 25 and 29.9 kg/m^2. There was a statistically significant difference in SSI between the two groups. The odds of having SSI when BMI is 25–29.9 kg/m^2 is 1.2 times that of someone with BMI <25 kg/m^2 (n = 33,072; pooled OR 1.17 (1.07, 1.28), p < 0.001) (Table 3). The heterogeneity between the included studies was not significant (I^2 = 0%, p = 0.80) (Fig. 5). Their funnel plots showed no evidence of bias (bias coefficient = 0.18, standard error = 0.42, p = 0.7). Summary of all the results from the meta analysis is shown in Table 3.

Cochrane risk of bias tool for cohort studies was used to evaluate the quality of the included observational studies (Appendix 2). Clinical heterogeneity was present to a variable extent. Many studies reported data from major databases or tertiary hospitals receiving referrals from different centers. This also could have contributed to different co-interventions and management plan between the groups. A few studies had not controlled for confounders. Detection bias was minimal as many studies

Table 3 Summary of results from the meta-analysis

Definition (BMI in kg/m^2)	N	Pooled OR (95% CI)	p value
BMI < 25 vs BMI 25–29.9	33,072	1.17 (1.07, 1.28)	<0.001
BMI < 30 vs BMI ≥ 30	209,196	1.51 (1.39, 1.63)	<0.001
Subgroup analysis of BMI < 30 vs BMI ≥ 30 (only elective procedures)	14,723	1.60 (1.34, 1.86)	<0.001
Subgroup analysis of BMI < 30 vs ≥ 30 (only CDC definition)	207,061	1.53 (1.40, 1.66)	<0.001

OR odds ratio, *CI* confidence interval, *CDC* centers for disease control and prevention

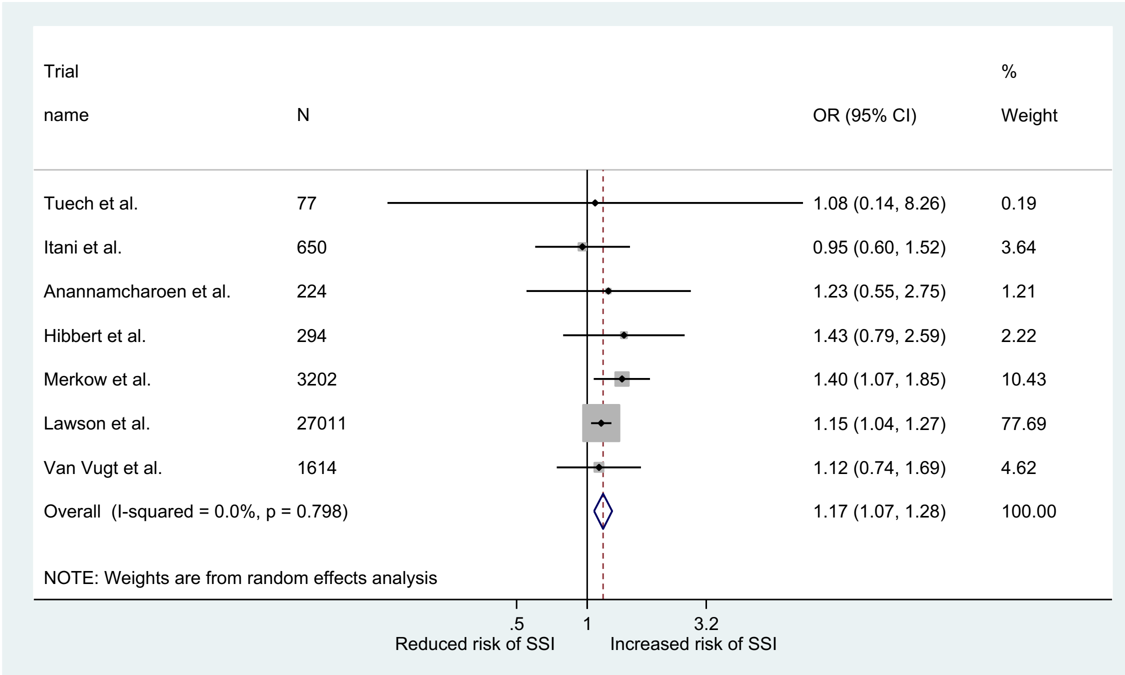


Fig. 5 Results from the meta-analysis of the studies that compared BMI < 25 kg/m^2 with BMI ≥ 25 kg/m^2. The figures show the result and the forest plot of the meta-analysis between BMI ≥ 25 kg/m^2 and BMI < 25 kg/m^2 in relation to the risk of developing surgical site infection following colorectal surgery

had defined the outcome and had also reported the duration of follow-up. Missing outcome data was, however, not reported.

Discussion

The results of this systematic review and meta-analysis show that the risk of developing SSI following colorectal surgery significantly increases with BMI. Overweight and obese patients have a 1.2- and 1.5-fold ($p < 0.001$) higher odds of developing SSI, compared to those with normal weight and non-obese patients, respectively.

Emergency surgery carries a higher risk of SSI compared to elective surgery with a potential higher risk of wound contamination.[29] Therefore, we performed a subgroup analysis of the 8 out of the 12 studies that only included elective surgery. We observed that the risk estimate was similar to the main meta-analysis; heterogeneity was reduced and funnel plots showed no bias. This confirmed the strength of our findings.

Several factors have been reported to contribute to wound infections in obese patients such as reduced vascularity of adipose tissue, reduced subcutaneous tissue oxygenation,[30,31] suppressed lymphocytic immunity,[3] and impaired collagen synthesis and prolonged operative time.[32] Although weight loss and dietary modification may be helpful in the perioperative setting, the malnourished state and sarcopenia in patients with cancers predispose them to wound infections.[33]

Another theory is based on the suboptimal tissue concentrations of antibiotics in obese patients either due to inadequate dosing or due to inadequate tissue penetration despite higher dosing and higher plasma concentration.[4,34] Maintenance of therapeutic drug concentration in the tissue during the entire surgery is also crucial to prevent SSI. Obesity leads to increased volume of distribution, altered plasma protein binding, reduction in tissue blood flow, changes in hepatic metabolism, and renal excretion, thereby requiring a higher or more frequent dosage of antibiotics compared to patients with a normal weight range.[35] Currently, there seems to be inadequate data on the exact dosing and pharmacodynamics for most of the antibacterial agents in obese population.[35]

To the best of our knowledge, this is the first systematic review and meta-analysis that has comprehensively summarized the effect of obesity on the risk of SSI after colorectal surgery. We had only included prospective studies or data collected from prospective databases to strengthen the validity of our findings given that retrospective studies are more prone to inaccurate or incomplete data or documentation.[10,36]

A few studies had measured obesity in terms of adiposity such as waist circumference,[37] visceral fat area,[38,40] and others. We only included clinical studies that used BMI, the most common obesity measurement tool, and used the WHO definition of obesity. This had excluded a few Asian studies[41,42] that defined obesity with a cut-off BMI of 25 kg/m^2[43] (as opposed to Western studies that had a cut-off of 30 kg/m^2) and those that considered BMI as continuous variable. Thus, we had to exclude several studies because of our strict inclusion criteria, with an intention to achieve a homogenous pool of studies.

The incidence of SSI with laparoscopic surgery is reported to be significantly lower compared to open general abdominal surgery.[44] The studies included in our final analysis had included either open colorectal procedures or open conversions from laparoscopic surgery, hence were comparable to each other with the risk of wound infection, in that regard.

There were several drawbacks to consider in this review. Since the included studies were observational, there were areas of inconsistency between them. It is possible that the results may have been influenced by the presence of a few large-scale studies. Among the studies that performed regression analysis, the confounders adjusted were not all uniform. Hence, we had used raw data and calculated odds ratios if not provided. Since our review investigated only SSI, our results may be an underestimate of the magnitude of the overall wound complications in high BMI patients.

Development of infectious complications following colorectal surgery can be influenced by the presence of malignancy.[45] The issue of *reverse causality* may confound the study findings when a cancerous lesion causes weight loss as well as make the patient susceptible to infection.[46] In our analyses, all the finally selected studies except one had included cancer patients.

Among some of the included studies, no predetermined follow-up period, during which postoperative infection was to be captured, was set. This may have exposed our pooled data to the possible underestimation from attrition bias. A sizeable proportion of SSI is reported to occur post-discharge in elective colorectal surgery[47] and the risk estimate may not have included all the late infections.

For this analysis, both the search terms SSI and wound infection were accepted as they are often used interchangeably in practice. Nevertheless, the results from the subgroup analyses of the studies strictly based on CDC definition showed similar result to that of the main meta-analysis. The incidence of SSI reported in the included studies was categorized as superficial, overall incisional or organ/space infection. Quite frequently, if infection existed at all levels, the studies had recorded as deep or organ/space infection.[23] However, incisional and organ/space SSI have different etiologies, different sets of risk factors and outcomes.[23,48] For our analysis, we accepted the incidence of any SSI as the individual results for superficial and organ/space infection were not clearly reported in all the papers.

In summary, our results demonstrate that obese patients carry atleast 50% increased likelihood of SSI compared to non-obese patients. Future well-designed prospective studies are needed with standardized definitions both for obesity and SSI, robust methods of SSI detection supported by in-hospital and extended post discharge surveillance systems, stratified according to nature and site of surgery, surgical approach, and type of SSI. Additionally, there is a clear need for further research on preventative measures such as weight reduction strategies and appropriate antibiotic use and dosing to prevent SSI in this high-risk population.

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Author Contributions All the authors have provided substantial contributions to the conception and the design of the study, or the acquisition, analysis, or interpretation of the data for the work and were involved in drafting of the work or revising it critically for important intellectual content. All the authors have provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with Ethical Standards

Conflict of Interest and Source of Funding None.

Appendix

Table 4 Search Strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to September 2016>

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1 exp Intestinal Diseases/su [Surgery]
2 Colorectal Surgery/
3 exp Intestine, Large/su [Surgery]
4 Colectomy/
5 or/1-4
6 exp Body Size/
7 exp Obesity/
8 exp "Body Weights and Measures"/
9 exp Overweight/
10 exp Body Weight/
11 or/6-10
12 exp Wound Infection/
13 Postoperative Complications/
14 infection*.ti,ab,hw.
15 13 and 14
16 12 or 15
17 5 and 11 and 16
18 (colorectal or colon* or rectal or rectum or anal or large intestin*).ti,ab.
19 (body adj1 (size or weight or mass or fat or surface area)).ti,ab.
20 (obese or obesity or overweight or adipos* or waist circumference* or "waist-hip ratio*").ti,ab.
21 19 or 20
22 infection*.ti,ab.
23 (surger* or surgical or operat* or postoperat* or "post-operat*" or postsurg* or "post-surg*").ti,ab.
24 18 and 21 and 22 and 23
25 17 or 24
26 limit 25 to english language

Database: Embase <1974 to September 2016>

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1 exp enteropathy/dm, su [Disease Management, Surgery]
2 exp intestine surgery
3 1 or 2
4 exp "weight, mass and size"/
5 exp obesity/
6 4 or 5
7 *surgical infection/
8 *postoperative infection/
9 exp *postoperative complication/
10 "infection*".ti,hw,ab,kw,tw.
11 9 and 10
12 7 or 8 or 11
13 3 and 6 and 12

Table 5 Quality assessment of the studies using risk of bias tool (Cochrane)

Study Details	1. Was selection of exposed and non-exposed cohorts drawn from the same population?	2. Can we be confident in the assessment exposure?	3. Can we be confident that the outcome of interest was not present at the start of the study?	4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?	5. Can we be confident in the assessment of the presence or absence of prognostic factors?	6. Can we be confident in the assessment of outcome?	7. Was the follow up of cohorts adequate?	8. Were co-interventions similar between groups?
Tuech et al	***	****	****	**	**	**	***	***
Itani et al	**	****	****	***	****	****	***	***
Merkow et al	*	***	****	***	****	****	***	***
Bege et al	****	****	****	***	****	*	*	***
Singh et al	***	****	****	*	***	*	***	***
Anannamchareon et al	****	****	**	***	***	****	****	****
Gervaz et al	**	****	**	**	****	****	***	***
Lawson et al	**	****	**	***	****	****	***	***
van Vogt et al	**	****	****	****	***	****	****	**
Hibbert et al	***	****	****	***	****	****	****	***
Pasam et al	**	****	**	****	****	****	***	***
Kiran et al	**	****	****	***	****	****	***	***

**** Definitely yes (low risk of bias), *** Probably yes, **Probably no, * Definitely no (high risk of bias)

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