Title: The relationship between body mass index and short term postoperative outcomes in patients undergoing potentially curative surgery for colorectal cancer: A systematic review and meta-analysis

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Abstract

Background

The prevalence of obesity has increased worldwide over the last few decades, and is a well-recognized risk factor for colorectal cancer. Surgical site infection is the most frequent complication following surgery for colorectal cancer, and the main cause of postoperative morbidity. The aim of the present systematic review and meta-analysis was to examine the relationship between increasing BMI and postoperative surgical site infection following surgery for colorectal cancer.

Methods

A systemic literature search was conducted using Medline, PubMed, Embase (Ovid) and Web of Science databases from inception to the end of August 2016. Studies examining the relationship between obesity and surgical site infection following surgery for colorectal cancer were included. Analysis of the data was performed using Review Manager version 5.3(The Nordic Cochrane Centre, The Cochrane Collaboration, Copen-hagen, Denmark,)

Results

In this meta-analysis, a total of 9535 patients from 16 studies were included. BMI <30 vs ≥ 30 kg/m^2 was used to examine the association of obesity and surgical site infection in patients from Western countries. The estimated pooled OR demonstrated that obesity increased the risk of surgical site infection by approximately 100% (OR=2.13; 95% CI 1.66-2.72, $p<0.001$).BMI < 25 vs ≥ 25 kg/m^2 was used to examine the association of obesity and surgical site infection from Asian countries. The estimated pooled OR demonstrated that obesity increased the risk of surgical site infection by approximately 60% (OR=1.63; 95% CI 1.29-2.06, p<0.001). There was little evidence of publication bias in the meta-analysis.

Conclusion

From this systematic review and meta-analysis there was good evidence that obesity was associated with a significantly higher risk of developing surgical site infection following surgery for colorectal cancer in both ethnic groups. The magnitude of the effect warrants further investigation.

Keywords: colorectal cancer, surgery, body mass index, obesity, surgical site infection and morbidity.

Introduction

The global prevalence of obesity has increased steadily over recent decades and continues to rise [1]. In the United Kingdom, the prevalence of obesity increased from 15% in 1993 to 26% in 2014 [2]. The WHO defines overweight, as a body mass index (BMI) of 25–29·9 kg/m², while BMI of 30.00 - 34.99 kg/m² is defined as obese grade I, with obese grade II as BMI 35.00 - 39.99 kg/m² and obesity grade III as BMI ≥40.00 kg/m². However, the prevalence of obesity by using the WHO definition is variable across different populations. For example: the prevalence of obesity using BMI ≥30 kg/m² is less than 10 % in East Asian populations [3]. In addition, the incidence of obesity related disorder such as dyslipidemia, hyperglycemia and hypertension was higher at BMI > 25.0 kg/m². Therefore, the International Obesity Task Force (IOTF) has recommended a BMI threshold of 25.0 kg/m² for obesity in these populations.

Nevertheless, obesity is a well-established risk factor for the development of several chronic diseases, such as diabetes, heart disease, and certain cancers, such as colorectal cancer. Indeed, a large scale study in the UK with 5.24 million subjects [4] found statistically significant associations between increased BMI and 17 of the 22 most frequent cancers including colorectal cancer. Each 5 kg/m² increase in BMI was associated with a higher risk of cancer of the colon and rectum of approximately 10% and 5 % respectively [4]. There is also good evidence that obesity is an important risk factor of death from colorectal cancer. A recent meta-analysis by Doleman and coworkers [5] showed that, compared with normal weight patients, obese patients with colorectal cancer (BMI>30 kg/m²) had an increased relative risk of all-cause mortality and cancer specific mortality of approximately 15 %.

In colorectal cancer, surgical resection remains the primary treatment, and resection may be associated with appreciable morbidity and mortality. Surgical site infection (SSI) is the most frequent group of complications amongst colorectal surgery patients with an incidence of up to 38% [6]. It is associated with increased cost of treatment, longer hospital stay and occasionally leads to mortality [7].

Despite considerable attention to both the increasing prevalence of obesity and the frequent occurrence of surgical site infection after colorectal surgery, the data regarding the impact of increased BMI on surgical site infection after colorectal surgery is conflicting. For example, some researchers have reported an increased risk of surgical site infection in obese patients [8], while others have reported no such association [9]. Such discrepancies in the literature may well reflect lack of statistical power. Therefore, the aim of the present systematic review and meta-analysis was to examine the relationship between increasing BMI and surgical site infection following surgery for colorectal cancer.

Methods

Literature search and data extraction:

A systematic search of the scientific literature was made using Medline, PubMed, Embase (Ovid) and Web of Science databases from inception to the end of August 2016.

Search and Data extraction:

The following search terms were used in free text and medical subject heading (MeSH) "body mass index OR obesity" AND "postoperative complications OR surgical site infection OR wound infections" AND colorectal "cancer OR neoplasms". A search of the bibliographies of selected papers was carried out to identify any relevant articles missed during the primary search. The literature search and data extraction was carried out by a single author (AA), any uncertainty regarding the inclusion, or otherwise, of a paper was discussed with the senior author (DM). Data on study characteristics (including year of publication, country of origin, design, sample size, cancer site, surgical approach), BMI threshold and surgical site infections were extracted to preconstructed tables for each individual study.

Study eligibility criteria:

Studies in humans, published in English with documented BMI and patients having undergone surgery for colorectal cancer were included in the review. The primary outcome was surgical site infection, including wound infection, deep/organ space infection including anastomotic leak and abdominopelvic abscess. There were no restrictions in terms of age, ethnicity, and stage of colorectal cancer or surgical approach.

Statistical analysis:

Unadjusted odds ratios (ORs) for risk of surgical site infection based on BMI were used where presented in the included studies. Raw data was used to calculate ORs if they were not presented in the original study. Analysis of the data was performed using Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark,). ORs with a 95 % confidence interval (CI) from each study were combined using a random effects model to account for variability in methodology. The Z test was used to assess the overall impact of BMI on surgical site infection. Heterogeneity was assessed by the I^2 test and two-tailed p-values <0.05 were considered to be statistically significant. The review methodology and reporting was designed and completed in keeping with the PRISMA statement.

Results

Study selection process:

The study selection process is summarized in Figure 1. A total of 447 articles were initially identified. The title and abstracts of all studies returned by the search were examined by two authors (ASA and CAE). Of the 447 studies, 379 studies were excluded after screening of the title and abstract. Sixty eight studies were selected for full text reading. Of these 68 studies, 54 were excluded; eight were reviews, and five included only a small number of cases (n<100), four studies had full text unavailable in English, 12 studies included cases with colorectal surgery not due to carcinoma, 11 used varying BMI thresholds, six included a variety of GI cancers, and in eight studies there was insufficient data to reconstruct odd ratios. The reference lists for the remaining articles were hand searched and a further two relevant studies were found giving a total of 16 articles which were included in the review.

The characteristics of the 16 studies included are shown in Table 1. A total of 9535 patients from all studies were included. The sample size of each study varied from 133 to 1980 patients. Of the included studies, eight were conducted in Asia, seven in Europe and one in Australia. All of the studies used BMI as a measure of obesity and non- obesity; studies conducted in Asian countries defined obese as BMI $\geq$ 25 kg/m^2 and studies conducted in Western countries defined obese as BMI $\geq$ 30 kg/m^2 .

The relationship between varying BMI thresholds and SSI:

The meta-analysis of studies using BMI <25 vs ≥25 kg/m^2 to examine the association of obesity and surgical site infection is shown in Figure 2. The estimated pooled OR showed that obesity increased the risk of surgical site infection by approximately 60% (OR=1.63; 95% CI 1.29-2.06, p<0.001). There was minimal degree of heterogeneity (I^2 = 11%).

The meta-analysis of studies using BMI <30 vs. ≥30 kg/m^2 and its association with surgical site infection is shown in Figure 3. The estimated pooled OR of the eight studies showed that obesity increased the risk of surgical site infection by approximately 100% (OR=2.13; 95% CI 1.66-2.72, p<0.001). There was minimal heterogeneity (I^2 = 0%).

The relationship between obesity, wound infection, and deep/organ space infection:

Meta-analysis stratified by type of surgical site infection; wound infection (Figure 4), and deep/organ space infection (Figure 5), was performed to examine whether one or both had a stronger relationship with obesity, including all 16 studies (i.e. obesity defined as either ≥25 kg/m^2 or ≥30 kg/m^2). There was a significant association between obesity and both wound infection (OR 2.32, 95% CI 1.84-2.92, p<0.001), and deep/organ space infection (OR 1.50, 95% CI 1.08-2.07, p=0.01), with minimal heterogeneity in either comparison (I^2=0%).

Assessment of publication bias:

Funnel plots were constructed to assess the presence of publication bias. BMI <25 vs. ≥25 kg/m^2 and association with surgical site infection (Figure 6). BMI <30 vs. >30 kg/m^2 and association with surgical site infection (Figure 7). The funnel plots analysis showed that there was little publication bias in the meta-analysis.

Discussion

The results of the present systematic review and meta-analysis showed that obesity, defined appropriately for each population, was associated with an increased risk of postoperative infective complications, in particular surgical site infections, in patients undergoing surgery for colorectal cancer. The higher risk associated with obesity appeared to be independent of geographic location. Therefore, there is good evidence that patients with a high BMI will have poorer short term outcomes following surgery for colorectal cancer.

There have been several systematic review and meta-analysis in this area [8, 10, 11]. However, the association of obesity and type of surgical site infection has not been addressed and whether superficial wound infection or deep organ infection risk is increased in patients with a high BMI was not clear. In the present systematic review the relationship between BMI and the types of infection in patient undergoing surgery for colorectal cancer has been defined.

Moreover, obesity has been defined appropriately for each population and sub-analyses has been conducted for and Western population. This is of importance since Asian population tend to have higher amount of abdominal fat and the present analysis concludes that obesity has an association with infection irrespective of ethnicity.

These results are of considerable importance as postsurgical site infection leads to increased length of postoperative hospital stay, higher rates of hospital readmission, and increased health care costs [12]. In particular, deep surgical site infections tend to be more difficult to treat.

Finally, the development of post-operative infective complications, in particular deep or organ space infection, is not only associated with increased cost but also associated with increased recurrence and poorer long term survival [13, 14]. Therefore, obese patients should undergo regular monitoring during the post-operative course. There is a need to better understand the basis of the above relationship so that the effect of obesity on post-operative outcomes may be mitigated. Therefore, the present review suggests that it is fat either inside or outside the abdominal wall that is associated with poor operative outcome. It may be technical demands of operating an obese patients and the need for long operative time. As a result obese patients are at risk of poor perfusion and decreased oxygen supply at the surgical site, this may lead to increased susceptibility to infections and impaired wound healing [8]. An implication of the present review is that since men and women have different fat distribution, with men more likely to have excess visceral fat in BMI defined obesity, there may be a sex difference in the surgical site infection rate in the obese. However, to our knowledge this relationship has not been examined and worthy of further study.

It is of interest that a prior meta-analysis reported that laparoscopic abdominal surgery was associated with a lower risk of surgical site infection than similar open surgery in obese patients [31]. This may be due, in part, to the longer and deeper wounds, with associated greater dead space, required for open surgery on obese patients. However, in the present study, although the risk of superficial/wound infection was greater, there was still a significant association between obesity and deep/organ space infection. This may suggest that obesity does not purely lead to surgical site infection by the nature and morphology of the wounds alone. It may be that other factors such as patient selection, comorbidity, or the lower postoperative stress and systemic inflammatory response following laparoscopic surgery may have a role to play.

The main limitation of the present systematic review was that it was based on observational studies, leading to several potential biases. Firstly, there are significant issues with the currently available studies examining post-operative surgical site infection in the obese patient. The most basic problem is the definition of obesity. Some published studies have not used standard BMI in Western countries (BMI>30 kg/m^2) and Asian countries (BMI >25 kg/m^2). As a result, papers were excluded because of variable definitions of obesity. A standardized definition of obesity is necessary to provide data that is valid and conveys an accurate risk assessment. In particular, with increasing number of patients who are obese, it will be important to define the risk associated with different degrees of obesity. In addition, although the Centers for Disease Control (CDC) have published definitions for surgical site infection, with the aim of allowing more accurate recording and comparison [30], the majority of included studies used more traditional descriptive methods of recording surgical site infection e.g. "wound infection", "pelvic abscess" and so on. Again, this lack of standardization in the definitions used may introduce error into the meta-analysis. Furthermore, the overall rate of surgical site infection in the included observational studies was perhaps lower than expected following colorectal surgery suggesting an element of selection bias.

In conclusion, the results of the present review indicate that obesity is associated with increased risk of surgical site infection in both Western and Asian populations. Further studies are needed to define the magnitude of this risk with increasing obesity, and to define which subcategories of surgical site infection are most common, in patients undergoing surgery for colorectal cancer.

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Figures and legends

Figure1: Flow chart of studies selection process

Figure 2: Forest plot of studies that compared BMI <25 vs. ≥ 25 kg/m^2 and association with surgical site infection in Asian countries following colorectal surgery

Figure 3: Forest plot of studies that compared BMI <30 vs. ≥ 30 kg/m^2 and association with surgical site infection in Western countries following colorectal surgery

Figure 4: Forest plot of studies that compared obese vs. non-obese patients in relation to postoperative wound infection after colorectal surgery

Figure 5: Forest plot of studies that compared obese vs. non-obese patients in relation to postoperative deep/organ space infection after colorectal surgery

Figure 6: Funnel plot of studies that compared BMI <25 vs. ≥ 25 kg/m^2 and association with surgical site infection in Asian countries following colorectal surgery

Figure 7: Funnel plot of studies that compared BMI <30 vs. ≥ 30 kg/m^2 and association with surgical site infection in Western countries following colorectal surgery

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Table1. Studies characteristic and the impact of BMI on surgical site infection

Study/year	Country	Design	n	Cancer site	Surgical approach	BMI groups Compared (kg/m^2)	OR (95% CI)
Nakamura et al 2008 [15].	Japan	Retrospective	144	Colorectal	Open /laparoscopic	≤25 vs >25	1.55 [0.53, 4.53]
Tsujinaka et al 2008 [16].	Japan	Retrospective	133	Colon	laparoscopic	<25 vs ≥ 25	1.78 [0.57, 5.58]
Park et al 2010[3].	Korea	Retrospective	984	Colorectal	Laparoscopic	<25 vs ≥ 25	1.50[0.55,4.06]
Akiyoshi et al 2011 [17].	Japan	Prospective	926	Colorectal	laparoscopic	<25 vs ≥ 25	1.89[1.06,3.35]
Itatsu et al 2014[18].	Japan	Prospective	1980	Colorectal	Open/ laparoscopic	<25 vs. ≥ 25	1.40 [1.02, 1.93]
Miyamoto et al 2014 [19].	Japan	Retrospective	561	Colorectal	Laparoscopic	<25 vs. ≥ 25	2.60 [1.50, 4.51]
Watanabe et al 2014 [20].	Japan	Prospective	338	Colon	Open /laparoscopic	<25 vs ≥ 25	2.06 [1.088,3.92]
Xia et al 2014 [21].	China	Retrospective	527	Colorectal	Laparoscopic	<25 vs ≥ 25	0.81[0.38,1.70]
Bege et al 2009[22].	France	Retrospective	210	Rectal	Open /laparoscopic	<30 vs ≥ 30	3.65 [0.88, 15.21]
Healy et al 2010[23].	Ireland	Retrospective	414	Colorectal	NR	<30 vs ≥ 30	1.46 [0.66, 3.22]

Singh et al 2011[24].	U.K	Retrospective	234	Colorectal	Laparoscopic	≤30 vs. >30	3.17 [1.49, 6.77]
Poulsen et al 2012 [25].	Denmark	Prospective	425	Colorectal	Laparoscopic	<30 vs ≥ 30	1.33 [0.78, 2.25]
Bokey et al 2014 [26].	Australia	Retrospective	255	Rectal	Open /laparoscopic	<30 vs ≥ 30	2.31 [1.03, 5.18]
Amri et al 2014 [27].	America	Retrospective	1048	Colon	Open/ laparoscopic	<30 vs ≥ 30	2.54 [1.66, 3.91]
Chand et al 2015 [28].	U.K	Prospective	254	Colorectal	Laparoscopic	≤30 vs. >30	2.09 [0.37, 11.77]
Frasson et al 2016 [29].	Spain	Prospective	1102	Colon	Open /laparoscopic	≤30 vs. >30	2.39 [1.17, 4.87]

BMI body mass index, *OR* odds ratio, *CI* confidence interval

Figures and legends

Figure1: Flow chart of studies selection process**.**

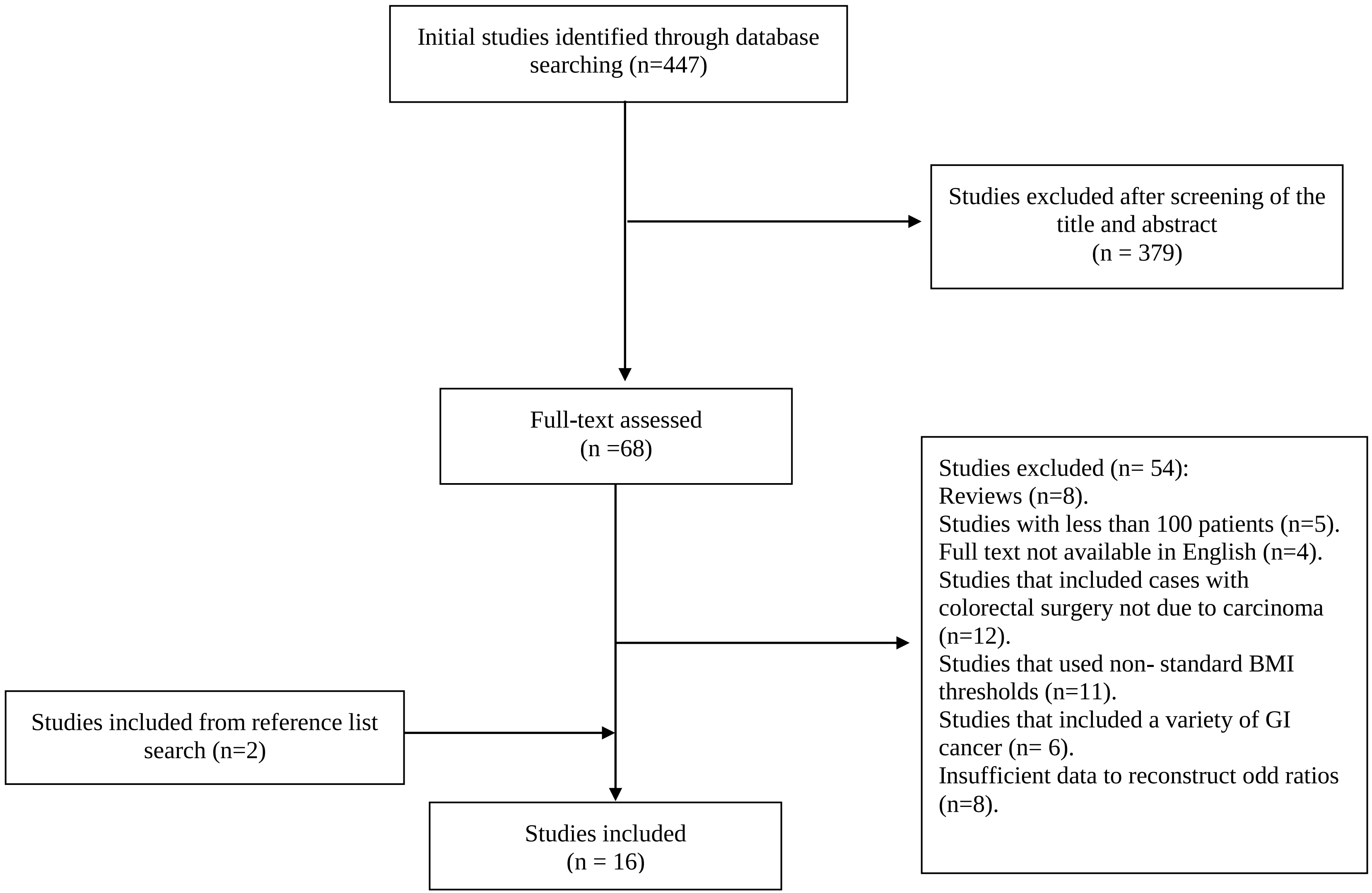

Figure 2: Forest plot of studies that compared BMI <25 vs. $\geq$ 25 kg/m^2 and association with surgical site infection in Asian countries following colorectal surgery.

	>25		<25			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Tsujinaka et al	5	27	12	106	4.0%	1.78 [0.57, 5.58]	2008
Nakamura et al	6	39	11	105	4.5%	1.55 [0.53, 4.53]	2008
Park et al	7	337	9	645	5.2%	1.50 [0.55, 4.06]	2010
Akiyoshi et al	19	268	36	926	14.3%	1.89 [1.06, 3.35]	2011
Itatsu et al	59	399	174	1581	36.1%	1.40 [1.02, 1.93]	2014
Xia et al	10	156	29	371	8.9%	0.81 [0.38, 1.70]	2014
Miayamoto et al	26	140	34	421	15.3%	2.60 [1.50, 4.51]	2014
Watanabe et al	19	91	28	247	11.7%	2.06 [1.09, 3.92]	2014
Total (95% CI)		**1457**		**4402**	**100.0%**	**1.63 [1.29, 2.06]**	
Total events	151		333				

Heterogeneity: Tau^2 = 0.01; Chi^2 = 7.83, df = 7 (P = 0.35); I^2 = 11%

Test for overall effect: Z = 4.13 (P < 0.0001)

Odds Ratio
M-H, Random, 95% CI

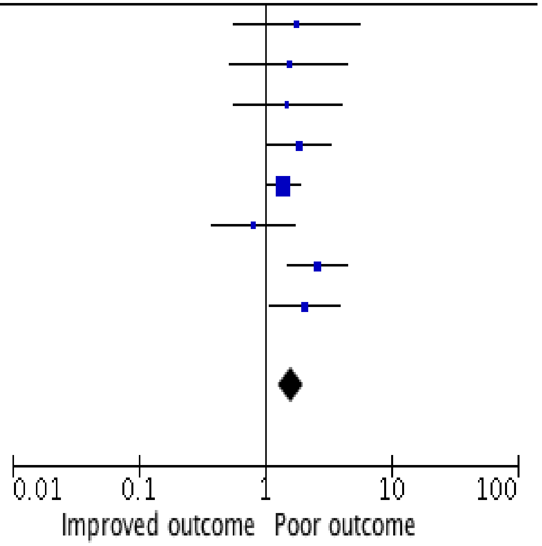

Figure 3: Forest plot of studies that compared BMI <30 vs. ≥ 30 kg/m^2 and association with surgical site infection in Western countries following colorectal surgery.

Study or Subgroup	>30 Events	>30 Total	<30 Events	<30 Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Bege et al	3	24	7	186	2.9%	3.65 [0.88, 15.21]	2009
Healy et al	9	75	29	339	9.5%	1.46 [0.66, 3.22]	2010
Singh et al	16	62	17	172	10.4%	3.17 [1.49, 6.77]	2011
Poulsen et al	25	93	72	332	21.5%	1.33 [0.78, 2.25]	2012
Amri et al	46	301	48	725	32.5%	2.54 [1.66, 3.91]	2014
Bokey et al	15	95	12	160	9.2%	2.31 [1.03, 5.18]	2014
Chand et al	2	50	4	205	2.0%	2.09 [0.37, 11.77]	2015
Frasson et al	11	42	137	1060	11.9%	2.39 [1.17, 4.87]	2016
Total (95% CI)		**742**		**3179**	**100.0%**	**2.13 [1.66, 2.72]**	
Total events	127		326				

Heterogeneity: Tau² = 0.00; Chi² = 6.38, df = 7 (P = 0.50); I² = 0%

Test for overall effect: Z = 6.04 (P < 0.00001)

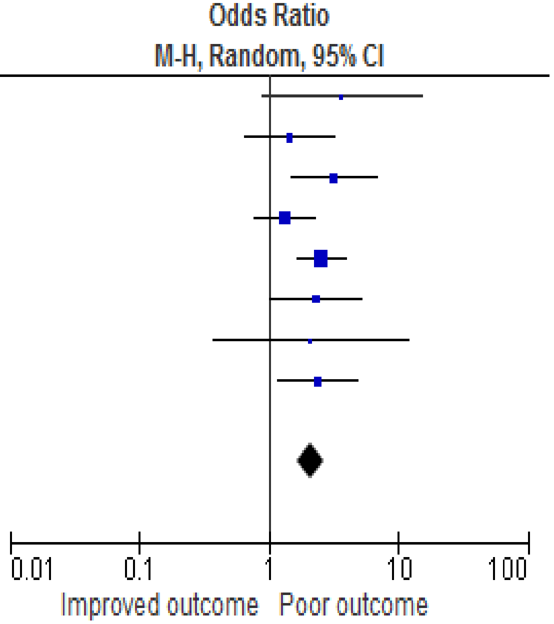

Figure 4: Forest plot of studies that compared obese vs. non-obese patients in relation to postoperative wound infection after colorectal surgery.

Study or Subgroup	Obese Events	Obese Total	Nonobese Events	Nonobese Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Tsujinaka et al	5	27	12	106	4.1%	1.78 [0.57, 5.58]	2008
Nakamura et al	6	39	11	105	4.7%	1.55 [0.53, 4.53]	2008
Bege et al	3	24	7	186	2.6%	3.65 [0.88, 15.21]	2009
Park et al	6	337	6	645	4.1%	1.93 [0.62, 6.03]	2010
Healy et al	7	75	18	339	6.5%	1.84 [0.74, 4.57]	2010
Akiyoshi et al	16	268	27	926	13.4%	2.11 [1.12, 3.99]	2011
Singh et al	7	62	6	172	4.2%	3.52 [1.13, 10.93]	2011
Amri et al	40	301	34	725	23.5%	3.11 [1.93, 5.03]	2014
Xia et al	5	156	13	371	4.9%	0.91 [0.32, 2.60]	2014
Bokey et al	15	95	12	160	8.3%	2.31 [1.03, 5.18]	2014
Miayamoto et al	17	140	22	421	12.2%	2.51 [1.29, 4.87]	2014
Chand et al	1	50	2	205	0.9%	2.07 [0.18, 23.31]	2015
Frasson et al	11	42	137	1060	10.6%	2.39 [1.17, 4.87]	2016
Total (95% CI)		**1616**		**5421**	**100.0%**	**2.32 [1.84, 2.92]**	
Total events	139		307				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.67$, $df = 12$ ($P = 0.88$); $I^2 = 0\%$

Test for overall effect: $Z = 7.11$ ($P < 0.00001$)

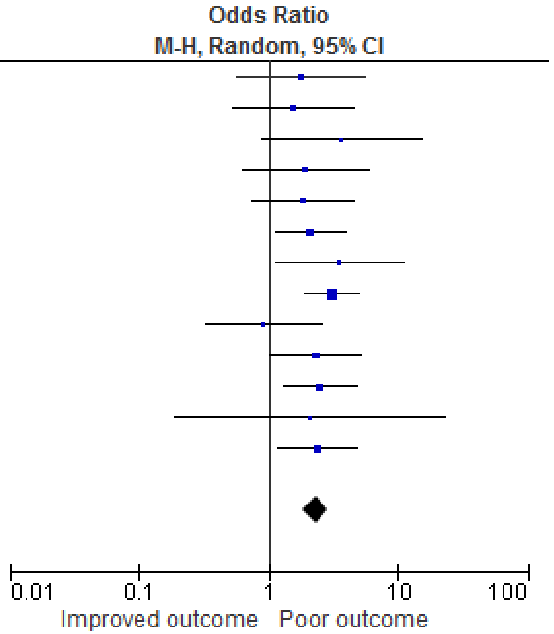

Figure 5: Forest plot of studies that compared obese vs. non-obese patients in relation to postoperative deep/organ space infection after colorectal surgery.

	Obese		Nonobese			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Tsujinaka et al	3	27	2	106	3.1%	6.50 [1.03, 41.07]	2008
Healy et al	6	75	16	339	11.1%	1.76 [0.66, 4.65]	2010
Park et al	1	337	3	645	2.0%	0.64 [0.07, 6.15]	2010
Akiyoshi et al	3	268	9	926	6.1%	1.15 [0.31, 4.29]	2011
Singh et al	9	62	11	172	12.0%	2.49 [0.98, 6.32]	2011
Poulsen et al	10	93	30	332	18.4%	1.21 [0.57, 2.58]	2012
Xia et al	4	156	11	371	7.8%	0.86 [0.27, 2.75]	2014
Miayamoto et al	9	140	12	421	13.3%	2.34 [0.97, 5.68]	2014
Amri et al	6	301	14	725	11.2%	1.03 [0.39, 2.71]	2014
Bokey et al	9	95	13	160	13.2%	1.18 [0.49, 2.88]	2014
Chand et al	1	50	2	205	1.8%	2.07 [0.18, 23.31]	2015
Total (95% CI)		**1604**		**4402**	**100.0%**	**1.50 [1.08, 2.07]**	
Total events	61		123				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.44$, df = 10 (P = 0.68); $I^2 = 0\%$

Test for overall effect: Z = 2.45 (P = 0.01)

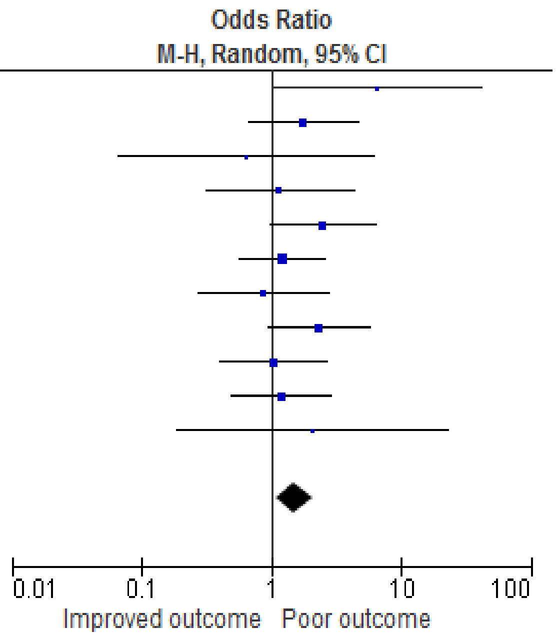

Figure 6: Funnel plot of studies that compared BMI <25 vs. ≥ 25 kg/m^2 and association with surgical site infection in Asian countries following colorectal surgery

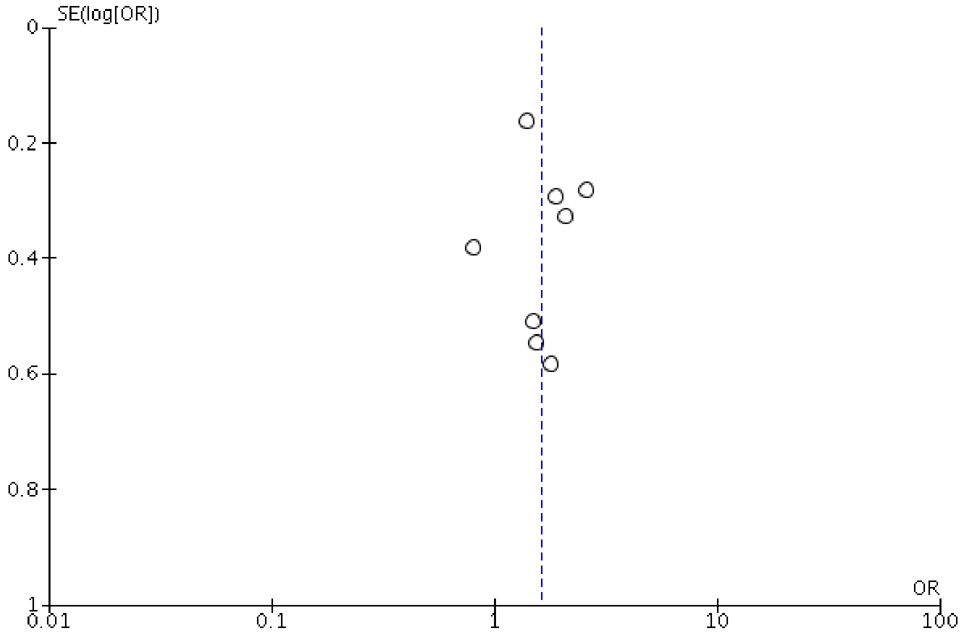

Figure 7: Funnel plot of studies that compared BMI <30 vs. ≥ 30 kg/m^2 and association with surgical site infection in Western countries following colorectal surgery