# **BMJ Open** Risk factors for surgical site infection (SSI) in patients undergoing hysterectomy: a systematic review and meta-analysis

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## ABSTRACT

Objective Surgical site infections (SSI) after hysterectomy constitute significant postoperative complications, affecting patient recovery and healthcare costs. We conducted a systematic review of risk factors for SSI in patients undergoing hysterectomy.

Design The current study conducted a systematic review with meta-analysis to identify and summarise risk factors for SSI following hysterectomy.

Data sources PubMed, Medline, Embase, Web of Science and Cochrane Central Register of Controlled Trials were searched through 1 November 2023.

Eligibility criteria The inclusion criteria were (1) population: female participants who had post-

hysterectomy SSI; (2) intervention: hysterectomy surgeries; (3) comparators: the number of participants who had or had not post-hysterectomy SSI; (4) outcomes: the number of participants exposed and not exposed to the risk factors of SSI. The exclusion criteria were (1) non-English studies and (2) studies that provided insufficient data.

Data extraction and synthesis Two reviewers conducted the screening process independently. Articles that did not meet the inclusion criteria were excluded. For those that met the criteria, full-text papers were procured. Any discrepancies between the reviewers were resolved through discussion. The meta-analysis synthesised risk factors reported in  $\geq$ 4 datasets via random-effects models, assessing heterogeneity, sensitivity (leave-one-out), publication bias (Egger's test/funnel plots) and subgroup analyses (incision types).

Results Blood transfusion emerged as the largest risk factor (OR=2.55, 95% CI (1.84, 3.56)), followed by tumour presence (OR=2.23, 95% CI (1.86, 2.66)), obesity (OR=1.79, 95% CI (1.43, 2.23)), diabetes (OR=1.70, 95% CI (1.26, 2.29)) and tobacco use (OR=1.43, 95% CI (1.26, 1.63)). The ORs varied by incision type.

**Conclusions** The study establishes blood transfusion, tumour presence, obesity, diabetes and tobacco use as significant risk factors for SSI after hysterectomy, with variations in risk evident across different incision types. The findings also suggest vaginal and laparoscopic hysterectomies as preferable alternatives to abdominal hysterectomy in mitigating SSI risk. Future research should aim for more granular data to untangle the interplay between comorbidities and further elucidate the differential risk across SSI types.

# STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The current systematic review synthesised evidence on ORs of risk factors for posthysterectomy surgical site infection (SSI).
- $\Rightarrow$  The current systematic review included 152 993 patients who underwent hysterectomy, including 2887 who had posthysterectomy SSI.
- $\Rightarrow$  The major limitation was that we found the case numbers exposed to each risk factor were counted, respectively, such that the ORs were not solely attributed to a single risk factor and might be overestimated.

# **INTRODUCTION**

Protected by copyright, including for uses related to text Hysterectomy is a very common procedure in and which the uterus is surgically removed, and it is an optional treatment for leiomyoma, å endometriosis, abnormal bleeding, benign ovarian neoplasms, pelvic organ prolapse 3 and gynaecologic cancer.<sup>1</sup> Epidemiological research estimated that the lifetime prev-≥ alence of hysterectomy surgery is approximately 236/1 000 000 in Germany, 143/1 000 000 in the USA,<sup>2 3</sup> 80/1 000 000 in China<sup>4</sup> and  $42/1\ 000\ 000$  in the UK<sup>2</sup> among the female population, depending on waitlist queuing time of different regions.<sup>2</sup> Among S patients who had hysterectomies, 2.1% are estimated to develop surgical site infections (SSI) worldwide,<sup>5</sup> which has been one of the most common complications after hysterectomy surgery.<sup>6</sup> According to the Centers for **Q** Disease Control and Prevention, SSI is an & infection that develops in the portion of the **3** body where the operation was performed. It might be superficial, affecting simply the skin, or more serious, involving tissues beneath the skin, organs or implanted material. The currently accepted risk factors of hysterectomy SSI are age, body mass index (BMI), smoking and diabetes.<sup>7</sup> However, many studies have shown different results. One study from Spain only considered obesity

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and inadequate prophylaxis as meaningful indicators,<sup>8</sup> whereas another study from the UK also suggested that the operative time should be considered an independent risk factor.<sup>9</sup> The evidence from current research appears to be diverse, isolated and lacking in quantitative power. One study analysed the risk factors for SSI after obstetric and gynaecological surgery; in fact, the types of obstetric and gynaecological surgeries are varied; for example, breast-conserving surgeries are cleansing surgeries, and breast reconstruction may use silicone implants, so the factors affecting SSI for these surgeries may be different than for hysterectomies.<sup>10</sup>

Consequently, the current study aims to summarise the results of risk factors of hysterectomy SSI through a quantitative approach.

#### **METHOD**

#### **Study registration**

The protocol of the current study was registered and reviewed by the PROSPERO International Prospective Register of Systematic Reviews (No. CRD42023411668). The protocol is available at: https://www.crd.york.ac.uk/ PROSPERO/export\_details\_pdf.php

Patient and public involvement None.

#### Search strategy

The data were extracted from published empirical study reports retrieved from the databases, including Pubmed (central), Medline (Ovid), Embase (Ovid), Web of Science and Cochrane Central Register of Controlled Trials. The search terms followed the standard PICO guideline (population, intervention, comparator, outcome) and were adapted according to Medical Subject Headings terms.<sup>11</sup> The search was conducted on the completion of study registration.

#### **Eligibility criteria**

The inclusion criteria were (1) population: women undergoing hysterectomy; (2) intervention: hysterectomy surgeries; (3) comparators: the number of participants who had or had not posthysterectomy SSI; (4) outcomes: SSI. The exclusion criteria were (1) non-English studies and (2) studies that provided insufficient data.

#### Study screening and data extraction

The report articles were retrieved in RIS format and managed with Endnote (Bld13966, EndNote V.X9.3.3, 2023). The screening process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>12</sup> Two reviewers conducted the screening process independently. Initially, they removed all duplicate articles. Then, articles that did not meet the inclusion criteria were excluded. For those that met the criteria, full-text papers were procured. Any discrepancies between the reviewers were resolved through

discussion. Data from the selected articles were subsequently extracted.

#### Risk of bias assessment

Two reviewers independently scored the studies using the Newcastle-Ottawa quality assessment (NOS).<sup>13 14</sup> NOS is a validated, easy-to-use scale containing eight items organised into three dimensions: selection, comparability and exposure/outcome, which has been endorsed for use in systematic reviews of non-randomised studies by The Protected Cochrane Collaboration.<sup>14</sup> Studies rated 0-2 as poor quality, 3-5 as fair quality and 6-9 as good/high quality.

#### **Data synthesis**

by copy Data synthesis requires at least four sets of data according to the general conduct suggested by the Cochrane Handbook.<sup>15</sup> The effect size of each identified risk factor will be pooled in a quantitative meta-analysis using STATA V.18. The risk factors were expected to be reported as binary data about whether or not the patients were exposed to the risk factor and were infected. Consequently, ORs В would be calculated as the effect size with the following for uses related formula:

$$OR = \frac{a}{b} \div \frac{c}{d}$$

Where *a* represents cases exposed to the risk factor and infected, b represents those exposed but not infected, c represents unexposed but infected and d represents unexposed and uninfected cases. And the LogOR is the natural log of the OR.

#### Statistical analysis plan

The meta-analysis was conducted with STATA V.18. Only risk factors reported in over four datasets were synthesised into meta-analysis. A random effects model meta-analysis with the restricted maximum likelihood method was used  $\boldsymbol{\bar{\omega}}$ to evaluate the pooled ORs (LogORs). The heteroge- ≥ tra neity was also assessed with the random effects model, where heterogeneity I<sup>2</sup> is considered moderate when I  $^{2}$ >50% and high when I<sup>2</sup> >75%.<sup>15</sup> Sensitivity analysis was conducted using the Leave-one-out approach by omitting one dataset each time and evaluating the pooled effect one dataset each time and evaluating the pooled effect sizes. Egger's test and funnel plots were used to assess potential publication bias<sup>16</sup>.

The pooled effect sizes were also entered into subgroup analysis based on the SSI types (superficial, deep, organ space) with available datasets. BMI was entered into the meta-regression analysis with pooled effect sizes of **B** diabetes to explore the relationship between obesity and diabetes and its influence on SSI risk prediction.

# RESULTS

#### Systematic review

Initially, searching the keywords in PubMed, Medline (Ovid), Embase (Ovid), Web of Science and the Cochrane Central Register of Controlled Trials produced 3821 records. 14 studies met the inclusion criteria after

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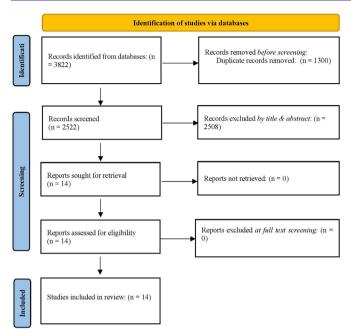


Figure 1 The PRISMA flow. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

screening based on the PRISMA guidelines. The PRISMA procedure is shown in figure 1.

All identified studies were retrospective observations to record the case numbers of SSI after hysterectomy surgeries with or without the occurrence of each risk factor. In total, 152993 female patients (age: 47.53±8.29) who underwent hysterectomy were included in the current 14 studies, of whom 2887 had SSI in different types, and 150106 had no SSI taken as controls. The details of all studies are described in table 1 (More detailed information can be found at online supplemental material 1).

Among these studies, seven only reported infection cases in mixed three SSI types (superficial, deep or organ space),<sup>8 17-22</sup> two only reported in mixed two SSI (deep or organ space),<sup>23 24</sup> one study reported each SSI type separately<sup>25</sup> and one study reported superficial and organ space SSIs separately,<sup>26</sup> one study reported superficial SSI independently but mixed deep or organ space SSIs,<sup>27</sup> one study reported deep SSI independently but mixed superficial or deep SSIs,<sup>5</sup> one study reported only organ space SSIs.<sup>28</sup> Since it requires at least four datasets to conduct meta-analyses,<sup>15</sup> the studies reporting cases in independent SSI types were combined into three mixed SSI types (superficial, deep or organ space) to synthesise with those only reporting the mixed SSI types. The NOS risk of bias assessment rated three studies scored 6,<sup>8 20 25</sup> seven scored 7,  $5 \frac{17-19}{22} \frac{22}{24} \frac{28}{28}$  two scored  $8^{21} \frac{26}{26}$  and the other two scored 9.<sup>23 27</sup> All 14 studies are ranked as good/high quality and were included in the following review.

Among the 14 studies, there were 11 risk factors identified in total, including age, antimicrobial, blood loss, blood transfusion, BMI, diabetes (both type I or type II), obesity, surgery duration, tobacco use, tumour and wound cleanness. However, antimicrobial and blood loss were

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reported in less than four datasets. Wound cleanness and age were reported in different classification standards. Only five factors reported in more than four datasets are available for quantitative analysis, including blood transfusion, diabetes, obesity, tobacco use and tumour. Age, high BMI and surgery duration reported continued data and thus could not be directly synthesised.

#### Meta-analyses

The identified risk factors with sufficient datasets were entered into meta-analyses respectively. As shown in table 2, pooled effect sizes revealed significant overall logORs of blood transfusion (OR=2.55, 95% CI (1.84, 3.56), p<0.001), obesity (OR=1.79, 95% CI (1.43, 2.23), p<0.001), diabetes (OR=1.70, 95% CI (1.26, 2.29), p<0.001), tobacco use (OR=1.43, 95% CI (1.26, 1.63), p<0.001), but not tumour (OR=1.35, p=0.362), as the risk factors for SSI infections. However, after removing each dataset one at a time, leave-one-out sensitivity analysis on all risk factors suggested no changes except for tumour (OR=2.33, 95% CI (1.86, 2.66), p<0.001), where one dataset changed the results.<sup>8</sup> Further analysis with publication bias suggested no publication bias in all factors. use However, as shown in figure 2A, the funnel plot suggested three outlier datasets.<sup>8</sup> <sup>21</sup> <sup>25</sup> One border dataset was decided to be kept.<sup>21</sup> and the other two were excluded **a** from the analysis.

After exclusion, data from the tumour were entered into the meta-analysis again and reported a significant e pooled effect size predicting SSI infections (logOR=0.80, OR=2.23, p<0.001), and, as shown in figure 2B, there were no outliers. As shown in figure 3A–C, the estimation of heterogeneity suggested that the chance of inconsistent distribution of the pooled logORs was not significant in blood transfusion datasets ( $I^2=0\%$ ,  $Q_{(3)}=0.17$ , p=0.983), tumour ( $I^2=0\%$ ,  $Q_{(4)}=1.34$ , p=0.850) or tobacco use  $(I^2=0\%, Q_{(5)}=5.78, p=0.330)$ . However, figure 3D,E suggested significant moderate heterogeneity in obesity  $(I^2=67.56\%, Q_{(4)}=11.58, p<0.001)$  and diabetes datasets ğ  $(I^2=64.07\%, Q_{(7)}=21.13, p<0.001)$ . These results suggested that blood transfusion, tumour, tobacco use, obesity and diabetes were significant risk factors predicting posthysterectomy SSI. Patients who underwent blood transfusion had a 155% increased likelihood of experiencing posthysterectomy SSI. Similarly, individuals with tumours had a 123% increased risk, obese individuals 79%, diabetics 70% and tobacco users 43%.

Subgroup analysis between studies reporting different  $\ensuremath{\mathring{\mathbf{G}}}$ SSI types (mixed superficial or deep or organ space vs 🖁 mixed deep or organ space) was conducted among tobacco use and diabetes, for they obtained more than four datasets under each subgroup. The difference was whether they included superficial SSI. A significant group difference in pooled ORs between mixed superficial and deep and organ space cases and mixed deep or organ space among tobacco use,  $Q_{(1)} = 11.59$ , p<0.001, but not among diabetes,  $Q_{(1)} = .71$ , p=0.400. The impact of tobacco use on the risk of SSI varied significantly depending on

Authors	Sample origin	Study design	Surgery method	Blood transfusion	Diabetes	Obesity	Tobacco use	Tumour
Molina-Cabrillana et al <sup>8</sup>	2000–2004 Hospital Universitario Materno- Infantil de Canarias, Spain	Cohort study	Abdominal and vaginal	NR	Y/N	Y/N	NR	Y/N
Olsen <i>et al<sup>25</sup></i>	2003–2005 CDC Prevention Epicenter Program hospitals, USA	Case-control study	Abdominal and vaginal	NR	Y/N	NR	Y/N	Y/N
Lake <i>et al<sup>27</sup></i>	2005–2009 ACS- NSQIP, USA	Case-control study	Abdominal and vaginal and laparoscopic	Y/N	Y/N	BMI≥30 (Obesity)	Y/N	Y/N
Savage et al <sup>17</sup>	2007–2010 University of Iowa Hospitals and Clinics, USA	Case-control study	Abdominal	Median	Y/N	Y/N	NR	Y/N
Coleman <i>et al</i> <sup>18</sup>	1999–2012 Johns Hopkins Medical Institution, USA	Cohort study	Abdominal and vaginal and laparoscopic	Y/N	Y/N	BMI≥30 (Obesity)	Y/N	NR
Mahdi <i>et al<sup>19</sup></i>	2005–2011 ACS- NSQIP, USA	Cohort study	Laparoscopic	>4 units of packed red blood cells	Y/N	BMI≥30 (Obesity)	Y/N	NR
Pop-Vicas <i>et al<sup>20</sup></i>	2012–2015 University of Wisconsin Hospitals, USA	Case-control study	Abdominal and vaginal and laparoscopic	NR	NR	NR	Y/N	Y/N
Uppal <i>et al<sup>21</sup></i>	2012–2015 MSQC, USA	Cohort study	Abdominal and vaginal and laparoscopic	NR	NR	BMI≥30 (Obesity)	Y/N	Y/N
Morgan <i>et al<sup>5</sup></i>	2012–2014 MSQC, USA	Case–control study	Abdominal	Y/N	Y/N	BMI≥30 (Obesity)	Y/N	Y/N
Tuomi <i>et al<sup>26</sup></i>	2007–2013 Helsinki University Hospital, Finland	Cohort study	Abdominal and vaginal and laparoscopic	NR	Y/N	NR	Y/N	NR
Till et al <sup>28</sup>	2012–2015 MSQC, USA	Cohort study	Abdominal and vaginal and laparoscopic	NR	Y/N	BMI≥30 (Obesity)	Y/N	Y/N
Brown <i>et al<sup>23</sup></i>	2012–2014 ACS- NSQIP, USA	Cohort study	Laparoscopic	Y/N	Y/N	NR	Y/N	NR
Tsuzuki <i>et al<sup>24</sup></i>	2014–2018 Teine Keijinkai Hospital, Japan	Cohort study	Laparoscopic	Y/N	Y/N	NR	Y/N	NR
Wang et al <sup>22</sup>	2012–2022 Two Grade A Tertiary Hospitals, China	Case-control study	Abdominal	NR	Y/N	NR	NR	Y/N

The content under each risk factor was how these studies presented their data. The detailed case numbers are in online supplemental material 1.

ACS-NSQIP, American College of Surgeons National Surgical Quality Improvement Program; BMI, body mass index; CDC, Centres for Disease Control and Prevention; MSQC, Michigan Surgical Quality Collaborative; NR, not reported; Y/N, yes or no.

the type of SSI, see online supplemental material table 2. As shown in figure 4, while tobacco use was associated with a 143% increased risk for combined superficial, deep and organ space SSIs, this risk escalated to a 272%

increase when considering only deep and organ space SSIs. This suggests that the influence of smoking may be more pronounced for deep and organ space infections than superficial ones. Given the observed discrepancy in

	Risk factor	Blood transfusion	Tumour	Obesity	Diabetes	Tobacco use
Case number	RF+SSI+	39	226	720	229	340
	RF+SSI-	998	3924	28717	5330	13645
	RF- SSI+	1075	769	531	1314	938
	RF- SSI-	62830	44733	36398	62893	54500
Meta-analysis	LogOR	0.94	0.8	0.58	0.53	0.36
	OR	2.55	2.23	1.79	1.7	1.43
	SE	0.17	0.09	0.12	0.15	0.07
	Z	5.57	8.8	5.07	3.5	5.54
	P value	<0.001	<0.001	<0.001	<0.001	<0.001
Heterogeneity test	12	0.00%	0.00%	67.56%	64.07%	0.00%
	Q (df)	0.17 (3)	1.34 (4)	11.58 (4)	21.13 (7)	5.78 (5)
	P value	0.983	0.85	0.02	<0.001	0.33
Leave-one-out sensitivity	lowest LogOR	0.88	0.7	0.54	0.44	0.32
	Highest LogOR	0.96	0.86	0.66	0.64	0.43
Egger's publication bias	β	0.09	0.05	1.79	-1.21	0.76
	SE	1.08	0.81	7.6	0.89	0.73
	Z	0.08	0.06	1.12	-1.35	0.91
	P value	0.934	0.95	0.263	0.178	0.363

The presenting data of the tumour were after exclusions of outliers.

I<sup>2</sup> refers, Heterogeneity index; RF+, exposure to the risk factor; RF–, no exposure to the risk factor; SSI, surgical site infections; SSI+, SSI positive; SSI–, SSI negative.

risk between the combined three types of SSIs and the combined two types (deep or organ space) for tobacco use, it is plausible that other risk factors might also exhibit differential effects across various SSI categories.

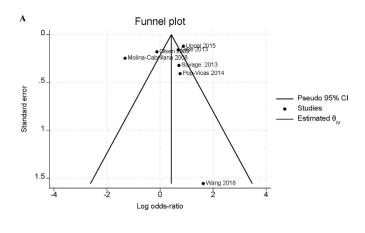
Continuous BMI data were incorporated into a metaregression analysis alongside the ORs of diabetes to evaluate the relationship between obesity and diabetes. Given the absence of group differences or heterogeneity discrepancies across SSI types in the effect sizes associated with diabetes, datasets from both SSI types (though not originating from identical studies) were incorporated into the meta-regression. The results suggested that BMI did not significantly predict the ORs of diabetes ( $\beta$ =0.001, SE=0.08, t=0.02, p=0.989). While this does not suggest that BMI (or obesity) is not correlated with the incidence of diabetes, it does affirm that high BMI did not affect the outcomes in this particular analysis.

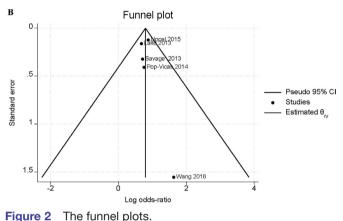
#### DISCUSSION

The current study conducted a systematic review with meta-analysis to summarise the evidence of risk factors of SSI after hysterectomy surgeries. To our knowledge, this is the first quantitative review of the topic. In total, 14 retrospective observational studies were identified with 2887 SSI positive and 150106 negative cases under 11 risk factors, including age, antimicrobial, blood loss, blood transfusion, high BMI, diabetes, obesity, surgery duration, tobacco use, tumour and wound cleanness. However,

only five were available for meta-analysis synchronisation. Among which, blood transfusion, tumour, obesity, diabetes and tobacco use were factors that significantly increased the risk of SSI. The estimated ORs also seemed to vary between different SSI types (superficial, deep or organ space). The details of the quantitative analysis are discussed as follows.

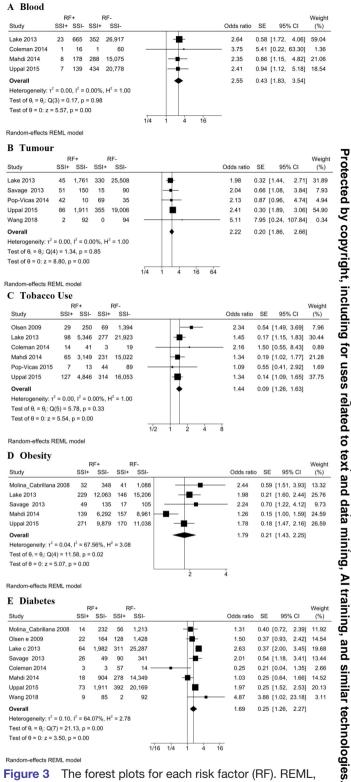
The largest risk factor for SSI is blood transfusion (OR=2.55), with a 155% increased likelihood of SSI. Blood transfusion has always been identified as a major source of postsurgical infections.<sup>29 30</sup> Administrative errors, such as bacterial contamination in platelet products, are believed to be responsible for infections induced by blood transfusion.<sup>29</sup> These issues are related to the healthcare service environment and beyond the current paper's discussion. Instead, the need for blood transfusion deserves further nologies elaboration from the patients' site. For example, blood loss was reported to be positively correlated with BMI.<sup>31 32</sup> Apart from obesity, severe abnormal uterine bleeding and cancer-related anaemia are also important reasons that patients require extra blood transfusion. However, none of the included studies attempted to isolate these factors, nor did they report preoperative haemoglobin. Consequently, we could not address whether blood transfusion was an independent factor or it was attributed to other factors such as obesity, severe abnormal uterine bleeding, cancer-related anaemia, preoperative haemoglobin or whether its estimated ORs were inflated. Future studies





should consider reporting more comprehensive data to precisely estimate the ORs for blood transfusion as the SSI risk factor.

Likewise, one may argue that obesity and diabetes are comorbid, where obesity-induced insulin resistance is one of the major sources of type 2 diabetes.<sup>33</sup> This might explain the moderate heterogeneity of the ORs in obesity (OR=1.79, I<sup>2</sup>=67.56%) and diabetes (OR=1.70,  $I^2$ =64.07%). This is, in fact, a methodological issue, where all studies directly counted the case number that was exposed and not exposed to the specific risk factors, but none attempted to distinguish whether the case was exposed to multiple risk factors. That is, one might suffer from obesity or diabetes or both, and the case would be counted in each risk factor respectively when they suffer from both. Consequently, the estimated ORs were not solely attributed to one risk factor and might be overestimated. Hypothetically, in the current case, the heterogeneity of the ORs in obesity and diabetes was moderate because some studies included more patients suffering from both obesity and diabetes and reported higher ORs than those with fewer such patients. As a result, although both obesity and diabetes are significant risk factors, their estimated ORs should be considered cautiously and



restricted maximum likelihood; SSI, surgical site infection.

require further clarification in future studies by reporting cases separately.

To further address this issue, the current study conducted a meta-regression analysis to investigate whether BMI predicts the ORs of diabetes. The analysis found no significant relationship between continuous BMI values and the ORs of diabetes. Notably, the absence

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	F	(F+	F	RF-					Weight
Study	SSI+	SSI-	SSI+	SSI-		Odds ratio	SE	95% CI	(%)
Deep or Organ space									
Olsen 2009	18	178	27	1,005		3.76	1.19	[2.03, 6.98]	8.20
Lake 2013	47	2,675	107	10,993		1.81	0.32	[1.28, 2.55]	11.70
Brown 2019	112	333	4,126	42,184		3.44	0.38	[2.77, 4.27]	13.27
Tsuzuki 2021	26	45	281	1,207		2.48	0.63	[1.51, 4.09]	9.64
Heterogeneity: $\tau^2$ = 0.08, $I^2$ = 68.56%,	$H^2 = 3.18$	3			-	2.72	0.48	[1.93, 3.84]	
Test of $\theta_i = \theta_j$ : Q(3) = 10.66, p = 0.01									
Test of $\theta$ = 0: z = 5.69, p = 0.00									
Superficial or Deep or Organ space									
Olsen 2009	29	250	69	1,394		2.34	0.54	[1.49, 3.69]	10.25
Lake 2013	98	5,346	277	21,923		1.45	0.17	[1.15, 1.83]	13.09
Coleman 2014	14	41	3	19		2.16	1.50	[0.55, 8.43]	3.06
Mahdi 2014	65	3,149	231	15,022		1.34	0.19	[1.02, 1.77]	12.56
Pop-Vicas 2015	7	13	44	89	<b>_</b>	1.09	0.55	[0.41, 2.92]	4.88
Uppal 2015	127	4,846	314	16,053		1.34	0.14	[1.09, 1.65]	13.35
Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$				•	1.44	0.09	[1.26, 1.63]		
Test of $\theta_i = \theta_j$ : Q(5) = 5.78, p = 0.33									
Test of $\theta$ = 0: z = 5.54, p = 0.00									
Overall					↓	1.95	0.27	[1.49, 2.55]	
Heterogeneity: $\tau^2 = 0.13$ , $I^2 = 81.56\%$ ,	$H^2 = 5.42$	2							
Test of $\theta_i = \theta_j$ : Q(9) = 58.63, p = 0.00									
Test of θ = 0: z = 4.90, p = 0.00									
Test of group differences: $Q_b(1) = 11.8$	59, p = 0.	00							
					1/2 1 2 4 8				

#### Random-effects REML model

Figure 4 Tobacco use subgroup forest plot between SSI types. REML, restricted maximum likelihood; RF, risk factor; SSI, surgical site infection.

of a significant predictive relationship between BMI and the OR for diabetes does not imply that these two factors were unrelated or that obesity does not influence the estimation of OR for diabetes. On the one hand, the absence of a significant predictive relationship might arise from including both type I and type II diabetes in the studies, with type I diabetes having less direct relevance to obesity. On the other hand, the estimation of ORs may still have been elevated due to the repeated counting of cases exposed to multiple risk factors. Instead, this result might be interpreted as the pathologies of obesity and diabetes are relatively independent in the context of SSI risk.

Apart from obesity and diabetes, the second-largest risk factor was tumour (OR=2.23), with a 123% increased likelihood of SSI. The immune system in patients afflicted with malignant tumours was generally compromised.<sup>34</sup> This impairment in the primary immune function directly results from the tumour's pervasive influence on the natural defence mechanisms. Furthermore, the standard therapeutic interventions for tumours, including surgery, chemotherapy and radiotherapy, also contribute to the weakened immune state.<sup>35</sup>

Tobacco use was the last risk factor (OR=1.43), with a 43% increased likelihood of SSI. Nicotine and carbon monoxide, two primary agents produced in tobacco use, contribute to the constriction of peripheral blood vessels. This vasoconstriction reduces the oxygen supply to tissues, vital for cellular function and healing processes.<sup>36</sup> Consequently, this oxygen deficit can precipitate the formation of microthrombi, which are small clots that can impair blood flow and further hinder tissue repair and regeneration.

However, the estimated ORs of tobacco use seemed to vary between SSI types. A subgroup comparison was conducted between studies that reported all mixed SSI and those that only reported deep or organ space SSI for tobacco use and diabetes, where only these two risk factors were reported repeatedly in distinguishing between SSI types. Significant subgroup differences were observed exclusively in the context of tobacco use. Specifically, tobacco use was associated with a 43% increased risk for superficial, deep or organ space SSIs. This risk escalated to a 172% increase when focusing solely on deep or organ space SSIs. The pronounced impact of tobacco use appears more substantial in increasing the risk of deep or organ space infections compared with superficial ones. This discrepancy may also be attributed to tobaccoinduced vasoconstriction. The vascular system supporting superficial cells, such as those in the skin, is more prosperous than the vasculature of deep and organ space cells. Consequently, cells in deeper tissues and organ spaces are more vulnerable to oxygen supply alterations exacerbated by tobacco use. However, this was merely a hypothetical explanation without solid evidence, which requires further investigation.

There are five limitations in the current study. First, some procedures performed in conjunction with hysterectomy can also affect SSI, but this was not explored in this paper. Second, the included studies did not differentiate cases based on the number of risk factors present, counting each instance for all identified risks. This approach likely inflated the ORs, particularly for comorbid conditions like patients with severe abnormal uterine bleeding or cancer-related anaemia and obesity and diabetes. Third, there was no distinction between type I and type II diabetes in the studies, potentially contributing to moderate heterogeneity in the pooled OR estimates. Therefore, the estimated ORs for obesity and diabetes as risk factors for SSIs should be interpreted cautiously. Then, since none of the studies isolated patients with severe abnormal uterine bleeding, suffered from cancerrelated anaemia or reported preoperative HbA1, it is unclear whether these factors also inflated the estimation ORs for blood transfusion, and thus, they should be interpreted cautiously as well. Lastly, few studies specified the types of SSI (superficial, deep or organ space). Given that our analysis indicates variation in tobacco use ORs across different SSI types, it is crucial to ascertain if similar variations apply to other risk factors. Addressing these issues in future research, with more detailed data reporting, is essential for a clearer understanding of the risk factors for SSIs. Future studies should report more comprehensive data to address these limitations.

In summary, the current study conducted a systematic review with meta-analysis of the risk factors of SSI after hysterectomy surgeries. In total, 11 risk factors were mentioned, whereas only blood transfusion, tumour, obesity, diabetes and tobacco use had sufficient data to be entered into meta-analysis and yield statistical significance. With limited available data, the ORs of tobacco use seemed to vary between different SSI types, suggesting potential diversity in other risk factors. This approach offers valuable insights into the varying risks associated with each surgical method.

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