Impact of Smoking On Surgical Outcomes For Patients Undergoing Cervical Surgery: A Systematic Review And Meta-Analysis

Li-ming Zheng
Hubei University of Chinese Medicine
Zhi-wen Zhang
Hubei Provincial Hospital of Traditional Chinese Medicine
Yang Li
Hubei University of Chinese Medicine
Feng Wen
Hubei Provincial Hospital of Traditional Chinese Medicine
Wei Wang (hbzyww@hotmail.com)
Hubei Provincial Hospital of Traditional Chinese Medicine

Research Article

Keywords: Smoking, Cervical surgery, Meta-analysis, Outcomes

Posted Date: October 12th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-953208/v1

Abstract

Objective: To determine whether smoking has adverse effects on outcomes following cervical surgery.

Methods: We searched PubMed, Embase, Cochrane Library, and Web of Science through 13 July 2021 for cohort and case-control studies that investigated the effect of smoking on outcomes after cervical surgery. Two researchers independently screened the studies and extracted data according to the selection criteria.

Results: The meta-analysis included 43 studies, including 27 case-control studies and 16 cohort studies, with 10020 patients. Pooled estimates showed that smoking was associated with higher rates of overall complications (odds ratio [OR]=2.00, 95% confidence interval [CI]: 1.63-2.44, p<0.00001), respiratory complications (OR=3.14, 95% CI: 1.94-5.08, p<0.00001), reoperation (OR=2.22, 95% CI: 1.41-3.49, p=0.005), dysphagia (OR=1.49, 95% CI: 1.07-2.07, p=0.02), wound infection (OR=3.19, 95% CI: 1.64-6.21, p=0.0006), axial neck pain (OR=1.97, 95% CI: 1.25-3.10, p=0.003), and a lower rate of fusion (OR=0.63, 95% CI: 0.49-0.81, p=0.0003). There were no significant differences between smoking and non-smoking groups in terms of operation time (mean difference [MD]=0.08, 95% CI: - 5.54 to 5.71, p=0.98), estimated blood loss (MD=-5.31, 95% CI: -148.83 to 139.22, p=0.94), length of hospital stay (MD=1.01, 95% CI: -2.17 to 4.20, p=0.53), Visual Analog Scale-neck pain (MD=-0.19, 95% CI: -1.19 to 0.81, p=0.71), Visual Analog Scale-arm pain (MD=-0.50, 95% CI: -1.53 to 0.53, p=0.34), Neck Disability Index (MD=11.46, 95% CI: -3.83 to 26.76, p=0.14), and Japanese Orthopaedic Association Scores (MD=-1.75, 95% CI: -5.27 to 1.78, p=0.33).

Conclusions: Smokers appear to be more likely than non-smokers to suffer higher rates of overall complications, respiratory complications, reoperation, longer hospital stay, dysphagia, wound infection, axial neck pain, and a lower fusion rate following cervical surgery. It is essential to provide timely smoking cessation advice and explanation to patients before selective cervical surgery.

1. Introduction

Cigarette smoking is a significant public health concern worldwide. Approximately 20% of adults in the US currently smoke cigarettes, responsible for up to 20% of all deaths each year [1]. In some cervical surgeries, more than half of the patients are smokers [2–4]. Smoking is highly detrimental to health and associated with cancer, respiratory disease, and cardiovascular disease [5]. A growing body of evidence shows that smoking is a significant risk factor for adverse surgical outcomes after spine surgery [5–8].

The relationship between smoking and outcomes of cervical surgery has not been well evaluated. Some studies suggest that smoking may be associated with poorer outcomes after cervical surgery, including lower fusion rates [9,10]. Smoking has been independently linked to higher blood loss [11], longer lengths of stay [2,11], and higher reoperation rates [12,13]. There is also an increased risk of perioperative complications, including dysphagia, airway obstruction, nerve palsy, reintubation, axial neck pain, wound infection, deep venous thrombosis, pneumonia, and pseudarthrosis [7,11,12,14–17]. Pain control and functional outcomes have also been shown to be less favorable in smoking patients [18,19].

Nevertheless, some studies disputed these findings and suggest no relationship between smoking and adverse surgical outcomes after cervical surgery [18,20,21]. Some researchers even found that the incidence of complications in smokers was lower than that of non-smokers after posterior cervical fusion [22]. We performed the present study to resolve these discrepancies. To the best of our knowledge, there have been no previous systematic reviews and meta-analyses assessing the association between smoking and outcomes of cervical surgery.

2. Materials And Methods

2.1. Literature Search Strategy

This meta-analysis was performed following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement [23]. PubMed, Embase, Cochrane Library, and Web of Science electronic databases were searched from inception to 13 July 2021 using the MeSH terms “smoking,” “cervical vertebrae,” “surgical procedures, operative,” and their corresponding free terms (Appendix S1). The search was restricted to human subjects. In addition, we also review the list of references for retrieved papers and recent reviews.

2.2. Inclusion And Exclusion Criteria

The inclusion criteria were as follows: (1) The study design was cohort or case-control; (2) the study population consisted of smokers and non-smokers who underwent cervical surgery; (3) the study compared outcomes, including operating time, pain score, functional score, reoperation rate, length of hospital stay, estimated blood loss, fusion rate, and postoperative complications. Exclusion criteria were as follows: (1) reviews, letters, case reports, systematic reviews, animal studies, non-comparative studies, and studies that were unrelated to our topics; (2) the study did not involve any of the outcomes listed in the inclusion criteria; (3) duplicated publications from the same hospital or research center. For accepted articles covering the same population or subpopulation, the most informative articles or complete studies were used to avoid duplication of information. Disagreements between investigators were resolved by discussion and consensus.

2.3. Data Extraction

Data extraction was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and data were extracted independently by two reviewers and examined by the other authors. Any disagreements were resolved by consensus or discussion with a third reviewer. The following information was extracted from the studies: (1) the general study information (name of the first author, publishing date, country, study design, sample size, age, gender, surgical procedure, follow-up time, and definition of smoking); (2) perioperative parameters, including operative time, estimated blood loss, and length of hospital stay; (3) clinical outcomes, including visual analog scale (VAS) of both neck pain and arm pain, Neck Disability Index (NDI), and Japanese Orthopaedic Association Scores (JOA); (4) complications, fusion rate and reoperation rate; the complications included dysphagia, airway obstruction, nerve palsy, reintubation, axial neck pain, wound infection, deep venous thrombosis, pneumonia, and pseudarthrosis. For continuous outcomes, we extracted the mean and standard deviation, and participant numbers were extracted. For dichotomous outcomes, we extracted the total numbers and the numbers of events of both groups. The data in other forms was recalculated when possible to enable pooled analysis.

2.4. Methodological Quality

Two reviewers independently applied the Newcastle-Ottawa Scale (NOS) to evaluate the methodological quality of the included studies [24]. The NOS is a scoring checklist for solving design and implementation issues of a cohort or case-control study, consisting of participant selection, comparability of cases and controls, exposure, and outcomes. If the study is awarded six or more stars, it was considered a high-quality study and was analyzed.

2.5. Statistical Analysis

We used Review Manager version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) [25] to generate forest plots and the funnel plot to determine whether there was a statistical association between the case and control groups and to assess heterogeneity of the included studies. Dichotomous outcomes were expressed as odds ratios (ORs) with 95% confidence intervals (CIs); continuous outcomes are expressed as the mean differences (MDs). Heterogeneity was quantified evaluated using the chi-square based Cochran's Q statistic [26] and the I^2 statistic, which yields results ranged from 0 to 100% (I^2 = 0-25%, no heterogeneity; I^2 = 25-50%, moderate heterogeneity; I^2 = 50-75%, large heterogeneity; and I^2 = 75-100%, extreme heterogeneity) [27]. In cases of substantial heterogeneity, the random-effects model was applied. Otherwise, the fixed-effects model was used. When heterogeneity was present, a 'leave-one-out sensitivity analysis was performed by iteratively removing one study at a time to confirm the source of the heterogeneity. Analysis was then performed without the study to determine if heterogeneity was still present and if so, random-effects modeling was used. For the primary outcomes, subgroup analyses were carried out according to surgical approach (anterior or posterior cervical surgery). Publication bias was assessed using visual inspection of the funnel plot with the Begg [28] and Egger tests [29]. STATA version 12.0 (StataCorp, College Station, TX) was used for Begg and Egger tests. All statistical tests were two-sided, and p-values of <0.05 were considered statistically significant.

3. Results

3.1. Identification of Eligible Studies

A flowchart of the search and study selection process is shown in Fig. 1. The electronic search identified a total of 352 citations (69 from PubMed, 212 from EMBASE, 20 from the Cochrane Library, and 51 from the Web of Science). After screening titles and abstracts and removal of duplicates, 122 were considered of interest; the full text of these 122 studies was retrieved for detailed evaluation; 79 studies were excluded, and 43 studies were ultimately included in the meta-analysis [2–4,7,9–16,18–21,30–56].

3.2. Characteristics Of Included Studies

Characteristics of the studies are summarized in Table 1. The 43 independent observational studies included in this meta-analysis were published from 1995 to 2021. These forty-three studies included 10,020 patients, including 3,107 smokers and 6,913 non-smokers. Twenty-seven studies were conducted in the United States and seven in China. The other nine were conducted in India, Japan, Czech Republic, Italy, Korea, Singapore, and Taiwan. Of these, 16 were cohort studies, and 27 were case-controls. Patients in twenty-eight studies underwent anterior cervical surgery [57], eight underwent posterior cervical surgery [4,12,14,15,36,40,41,48], and the remaining seven underwent anterior and posterior cervical surgery [2,7,13,21,35,42,50].

Table 1
Baseline Characteristics of Included Studies

Series (Year)	Country	Design	Number of patients		Age (mean±SD, year)	Gender,number		Surgery	Definition of smoking	follow-up (mean±SD)	N sc
			Smoker	Nonsmoker		Male	Female				
Agrillo et al., 2002[31]	Italy	Case-control	19	26	49.7 (28-77)	26	19	ACDF	Smoking history	6 months	6
An et al., 1995[32]	USA	Cohort	34	43	47.1	NR		Anterior cervical fusion	NR	12-13 months	6
Badiee et al., 2021[12]	USA	Case-control	27	232	63.2±10.8	129	130	Posterior cervical decompression and fusion	NR	90 days	8
Bergin et al., 2021[33]	USA	Case-control	48	278	53.8	149	177	ACDF	NR	27.6±19.0 months	8
Bose et al., 2001[20]	USA	Cohort	46	60	50.12±11.72(27-80)	47	59	ACDF	NR	>12 months	8
Cerier et al., 2019[19]	USA	Cohort	23	38	50.4	32	29	ACDF	Smoking within 6 months before surgery	6 months	7
Chen et al., 2015[34]	China	Case-control	68	189	NR	138	119	Single-level anterior cervical fusion	Smoking history	6-24 months	8
Dube et al., 2018[35]	India	Case-control	44	163	3 mo–86 y	160	47	Cervical Spine Surgery	NR	NR	7
Eubanks et al., 2011[36]	USA	Cohort	41	117	61	93	65	Posterior cervical fusion	NR	14.5(3-72) months	8
Goldberg et al., 2002[37]	USA	Cohort	30	50	44.6	43	37	ACDF	NR	4(2-7) years	6
Groff et al., 2003[38]	USA	Case-control	55	89	49	119	25	Partial corpectomy and fusion	Smoking within 3 months before surgery	34(>24) months	6
Hilibrand et al., 2001[9]	USA	Cohort	55	135	NR	NR		ACDF	NR	68(24-183) months	7
Huang et al., 2020[16]	China	Case-control	51	130	52.15±9.32	104	77	ACDF	NR	18(12-24) months	8
Kang et al., 2014[39]	Korea	Case-control	41	31	47.1±7.8	50	22	ACDF	Smoking history	1 year	7

NR=not reported; NOS=Newcastle-Ottawa Scale; ACDF=Anterior cervical discectomy and fusion; SD=Standard Deviation; NDI=Neck Disability Index;

VAS=Visual Analog Scale; JOA=Japanese Orthopaedic Association Scores for Assessment of Cervical Myelopathy; EBL=estimated blood loss;

CSF=cerebrospinal fluid; DVT=deep venous thrombosis

Series (Year)	Country	Design	Number of patients		Age (mean±SD, year)	Gender,number		Surgery	Definition of smoking	follow-up (mean±SD)	N sc
			Smoker	Nonsmoker		Male	Female				
Kimura et al., 2018[40]	Japan	Case-control	39	117	64	108	48	Laminoplasty	Current smoking	2 years	7
Klement et al., 2016[41]	USA	Case-control	2	27	63	8	21	Cervical laminectomy and fusion	NR	26.9 months	8
Lau et al., 2014[11]	USA	Cohort	62	70	NR	77	55	Anterior cervical corpectomy and fusion	Smoking history	1 year	8
Lee et al., 2014[42]	USA	Case-control	403	955	51(20-91)	729	629	Cervical Spine surgery	NR	12-168 months	7
Lee et al., 2015[43]	Korea	Case-control	333	705	50 (22-89)	514	524	Anterior cervical surgery	NR	50 (12-168) months	7
Liang et al., 2017[44]	China	Case-control	59	158	55.4	109	108	Anterior cervical corpectomy and fusion	Smoking history	NR	7
Liu et al., 2019[45]	China	Case-control	39	49	60.4	45	43	ACDF	NR	1 year	8
Luszczyk et al., 2013[46]	USA	Cohort	156	417	NR	NR		ACDF	Current smoking	>24 months	6
Mangan et al., 2021[47]	USA	Cohort	63	87	53	123	141	ACDF	Smoking history	19.8(9-20.6) months	8
Martin et al., 1999[10]	USA	Cohort	75	214	NR	162	127	ACDF	Smoking history	33(24-51) months	8

NR=not reported; NOS=Newcastle-Ottawa Scale; ACDF=Anterior cervical discectomy and fusion; SD=Standard Deviation; NDI=Neck Disability Index;

VAS=Visual Analog Scale; JOA=Japanese Orthopaedic Association Scores for Assessment of Cervical Myelopathy; EBL=estimated blood loss;

CSF=cerebrospinal fluid; DVT=deep venous thrombosis

Series (Year)	Country	Design	Number of patients		Age	Gender,number		Surgery	Definition	follow-up (mean±SD)	N sc
			Smoker	Nonsmoker	(mean±SD, year)	Male	Female		of smoking		
Nakashima et al., 2013[48]	Japan	Case-control	55	109	44.9 (14-90)	142	22	Posterior cervical surgery	Smoking history	59.9 months	7
Pahys et al., 2013[14]	USA	Case-contorl	126	357	53.7	268	215	Posterior cervical spine surgery	Smoking history	>3 months	8
Patel et al., 2019[49]	USA	Cohort	25	167	48.7	115	77	ACDF	NR	6 months	8
Plano et al., 2019[50]	USA	Case-control	128	175	57.7±12.6(27-86)	200	103	Cervical Spine surgery	NR	75.35±27.1(16-126) months	7
Reinard et al., 2016[2]	USA	Case-control	47	30	55.1±12.88(20-86)	50	27	Combined anterior-posterior cervical spinal fusions	Smoking history	NR	8
Ren et al., 2020[51]	China	Case-control	106	189	59.7	139	156	ACDF	NR	6 months	8
Riederman et al., 2017[7]	USA	Case-control	36	164	52.4(28-87)	112	88	ACDF	Smoking history	NR	7
Sagi et al., 2002[53]	USA	Case-control	127	184	47	169	142	Anterior cervical surgery	NR	NR	7
Schnee et al., 1997[30]	USA	Case-control	66	78	48.1(27-82)	71	73	Anterior cervical fusion	NR	8.1(2.7-34.2) months	6
Siemionow et al., 2014[7]	USA	Case-control	16	19	60(37-82)	21	14	Combined anterior-posterior cervical spinal fusions	NR	>12 months	6
Suchomel et al., 2004[54]	Czech Republic	Cohort	48	31	47.8(37-73)	49	30	ACDF	Smoking history	39.4(24-48) months	7

NR=not reported; NOS=Newcastle-Ottawa Scale; ACDF=Anterior cervical discectomy and fusion; SD=Standard Deviation; NDI=Neck Disability Index;

VAS=Visual Analog Scale; JOA=Japanese Orthopaedic Association Scores for Assessment of Cervical Myelopathy; EBL=estimated blood loss;

CSF=cerebrospinal fluid; DVT=deep venous thrombosis

Series (Year)	Country	Design	Number of patients		Age	Gender,number		Surgery	Definition	follow-up (mean±SD)	N
			Smoker	Nonsmoker	(mean±SD, year)	Male	Female		of smoking		sc
Tu et al., 2019[18]	Taiwan, China	Cohort	20	89	47.5	56	53	Cervical disc arthroplasty	Smoking within 6 months before surgery	42.3(>24) months	8
Vasquez et al., 2016[21]	USA	Cohort	123	350	18-70	267	206	Cervical Spine Surgery	Current smoking	12 months	8
Wang et al., 1999[55]	USA	Cohort	12	68	43.3(19-70)	33	74	ACDF	NR	2.3(1-6) years	6
Wang et al., 2000[56]	USA	Case-control	6	52	47.6(25-90)	26	34	ACDF	NR	2.7(1-6) years	6
Wang et al., 2017[3]	China	Case-control	46	22	67.6	29	39	Anterior cervical surgery	NR	1 year	8
Wen-Shen et al., 2020[13]	Singapore	Cohort	20	117	45.8	66	71	Cervical artificial disc replacement	Current smoking	74(>24) years	8
Woodroffe et al., 2020[4]	USA	Case-control	219	151	57.8	231	139	Posterior cervical fusion	Smoking history	NR	8
Zhang et al., 2020[15]	China	Case-control	68	181	60.5±7.6	120	129	Laminoplasty	NR	12-108 months	8

NR=not reported; NOS=Newcastle-Ottawa Scale; ACDF=Anterior cervical discectomy and fusion; SD=Standard Deviation; NDI=Neck Disability Index;

VAS=Visual Analog Scale; JOA=Japanese Orthopaedic Association Scores for Assessment of Cervical Myelopathy; EBL=estimated blood loss;

CSF=cerebrospinal fluid; DVT=deep venous thrombosis

3.3. Quality Of Included Studies

Because all included studies were cohort studies or case-control studies, the quality of each study was evaluated using the NOS (maximum of nine stars) in three categories: selection, comparability, and exposure or outcomes. According to the NOS scale, all included studies were considered to be of high-quality: 21 were awarded eight stars, 13 were awarded seven stars, and 9 were awarded six stars (Table 2).

Table 2
Quality Assessment of Included Studies According to Newcastle-Ottawa Scale

Study	Selection	Comparability	Outcome/Exposure	Total
Agrillo et al., 2002	★★★★		★★	6
An et al., 1995	★★★		★★★	6
Badiee et al., 2021	★★★★	★★	★★	8
Bergin et al., 2021	★★★★	★★	★★	8
Bose et al., 2001	★★★	★★	★★★	8
Cerier et al., 2019	★★★	★	★★★	7
Chen et al., 2015	★★★★	★★	★★	8
Dube et al., 2018	★★★★	★★	★	7
Eubanks et al., 2011	★★★	★★	★★★	8
Goldberg et al., 2002	★★★		★★★	6
Groff et al., 2003	★★★★	★	★	6
Hilibrand et al., 2001	★★★	★	★★★	7
Huang et al., 2020	★★★★	★★	★★	8
Kang et al., 2014	★★★★	★★	★	7
Kimura et al., 2018	★★★★	★★	★	7
Klement et al., 2016	★★★★	★★	★★	8
Lau et al., 2014	★★★★	★	★★★	8
Lee et al., 2014	★★★★	★★	★	7
Lee et al., 2015	★★★★	★★	★	7
Liang et al., 2017	★★★★	★★	★	7
Liu et al., 2019	★★★★	★★	★★	8
Luszczyk et al., 2013	★★★		★★★	6
Mangan et al., 2021	★★★	★★	★★★	8
Martin et al., 1999	★★★★	★	★★★	8
Nakashima et al., 2013	★★★★	★★	★	7
Pahys et al., 2013	★★★★	★★	★★	8
Patel et al., 2019	★★★	★★	★★★	8
Plano et al., 2019	★★★★	★	★★	7
Reinard et al., 2016	★★★★	★★	★★	8
Ren et al., 2020	★★★★	★★	★★	8
Riederman et al., 2017	★★★★	★	★★	7
Sagi et al., 2002	★★★★	★	★★	7
Schnee et al., 1997	★★★★		★★	6
Siemionow et al., 2014	★★★★		★★	6
Suchomel et al., 2004	★★★★		★★★	7
Tu et al., 2019	★★★	★★	★★★	8
Vasquez et al., 2016	★★★	★★	★★★	8
Wang et al., 1999	★★★		★★★	6
Wang et al., 2000	★★★★		★★	6
Wang et al., 2017	★★★★	★★	★★	8
Wen-Shen et al., 2020	★★★	★★	★★★	8

Study	Selection	Comparability	Outcome/Exposure	Total
Woodroffe et al., 2020	□□□□	□□	□□	8
Zhang et al., 2020	□□□□	□□	□□	8

3.4. Meta-analysis

3.4.1. Overall Complications

The primary outcomes in our meta-analysis were complications, including dysphagia, airway obstruction, nerve palsy, reintubation, axial neck pain, wound infection, deep venous thrombosis, pneumonia, deltoid weakness, tracheobronchitis, and pseudarthrosis. At least one postoperative complication was reported in 20 studies [2,3,11,12,14,16,18,20,21,30,34–36,39,41,43,44,48,52,53]. Significant heterogeneity was observed, and the random-effects model was used (I^2=52%, p=0.003). The meta-analysis revealed that the incidence of postoperative complications in smokers was significantly higher than that of non-smokers (OR=1.88, 95% CI: 1.46-2.76, p<0.0001). Because of the heterogeneity (I^2=52%), a sensitivity analysis was performed. The study of Reinard et al. [2] excluded patients with a recombinant human bone morphogenetic protein associated with dysphagia after cervical surgery [58]. It may affect the incidence of postoperative dysphagia. Excluding this paper reduced I^2 to 47% (Fig. 2). Re-analysis using a fixed-effects model revealed that, compared with non-smokers, smokers had a higher incidence of complications (OR=2.00, 95% CI: 1.63-2.44, p<0.00001).

3.4.2. Respiratory Complications

Six studies reported the postoperative incidence of respiratory complications, including dyspnea, reintubation, airway obstruction, pneumonia, and tracheotomy [7,11,20,35,48,53]. There was significant heterogeneity (I^2=54%, p=0.06); therefore, the random-effects model was used. Pooling of the results demonstrated that the incidence of respiratory complications in smokers was significantly higher than that of non-smokers (OR=2.34, 95% CI: 1.04-5.26, p=0.04). After performing sensitivity analysis and removing the study by Sagi et al. [53] a higher proportion of patients who had exposure of C4 or above compared with other studies, the heterogeneity was reduced to 37% (Fig. 3). Fixed-effects modeling showed that the incidence of respiratory complications in smokers was significantly higher than that of non-smokers (OR=3.14, 95% CI: 1.94-5.08, p<0.00001).

3.4.3. Reoperation

The number of patients who underwent reoperation was provided in eight studies [4,11–13,20,42,47,50]. Significant heterogeneity was observed, and a random-effects model was used (I^2=58%, p=0.02). Pooling of the results demonstrated that the incidence of reoperation in the smoking group was significantly higher than that of the non-smoking group (OR=1.94, 95% CI: 1.0-3.80, p=0.05). When performing statistical analysis of Mangan et al. [47], we defined the sum of current and former smokers as the total number of smokers. We then removed Mangan et al., performed a sensitivity analysis, and found that heterogeneity was reduced to 39% (Fig. 4). Re-analysis using a fixed-effects model revealed that the incidence of reoperation in the smoking group was significantly higher than that of the non-smoking group (OR=2.22, 95% CI: 1.41-3.49, p=0.005).

3.4.4. Fusion Rate

Sixteen studies reported the fusion rate or the incidence of pseudarthrosis and nonunion [9–11,19,20,31–33,37,38,46,47,51,54–56]. No significant heterogeneity was observed, and a fixed-effects model was used (I^2=16%, p=0.0003). Pooling of the results demonstrated that the fusion rate of smokers after cervical surgery was significantly lower than that of non-smokers (OR=0.63, 95% CI: 0.49-0.81, p=0.0003; Fig. 5).

3.4.5. Dysphagia

Seven studies reported the postoperative incidence of dysphagia [2,3,16,18,20,34,52]. No significant heterogeneity was observed, and a fixed-effects model was used (I^2=47%, p=0.07). Pooling of the results demonstrated that the incidence of dysphagia in the smoking group was significantly higher than that of the non-smoking group (OR=1.49, 95% CI: 1.07-2.07, p=0.02; Fig. 6).

3.4.6. Wound Infection

Seven studies reported the postoperative incidence of wound infection [7,11,12,14,18,30,36]. No significant heterogeneity was observed, and a fixed-effects model was used (I^2=17%, p=0.30). Pooling of the results demonstrated that the incidence of wound infection in the smoking group was significantly higher than that of the non-smoking group (OR=3.19, 95% CI: 1.64-6.21, p=0.0006; Fig. 7).

3.4.7. Axial Neck Pain

Three studies reported the postoperative incidence of axial neck pain [15,40,45]. Significant heterogeneity was observed, and a random-effects model was used (I^2=64%, p=0.06). Pooling of the results shows no significant difference in the incidence of axial neck pain after cervical surgery between smokers and non-smokers. (OR=1.54, 95% CI: 0.75-3.16, p=0.24). After performing sensitivity analysis and removing the study by Liu et al. [45] the only article on anterior cervical surgery, the heterogeneity was reduced to 39% (Fig. 8). Fixed-effects modeling revealed that the incidence of axial neck pain in the smoking group was significantly higher than that of the non-smoking group (OR=1.97, 95% CI: 1.25-3.10, p=0.003).

3.4.8. Operation Time

The operation time was provided in two studies [21,49]. No significant heterogeneity was observed, and a fixed-effects model was used (I^2=0, p=0.96). Pooling of the results revealed no significant difference in operation time after cervical surgery between smokers and non-smokers (MD=0.08, 95% CI: - 5.54 to 5.71, p=0.98; Fig. 9).

3.4.9. Estimated Blood Loss

The estimated blood loss was provided in three studies [2,11,49]. Significant heterogeneity was observed, and a random-effects model was used (I^2=66%, p=0.05). Pooling of the results revealed no significant difference in estimated blood loss after cervical surgery between smokers and non-smokers (MD=-5.31, 95% CI: -148.83 to 139.22, p=0.94; Fig. 10). After performing leave-one-out sensitivity analysis, the heterogeneity did not change substantially and remained significant.

3.4.10. Length Of Hospital Stay

The length of hospital stay was provided in four studies [2,11,21,49]. Significant heterogeneity was observed, and a random-effects model was used (I^2=88%, p<0.0001). Pooling of the results revealed no significant difference in length of hospital stay after cervical surgery between smokers and non-smokers (MD=1.01, 95% CI: -2.17 to 4.20, p=0.53; Fig. 11). After performing leave-one-out sensitivity analysis, the heterogeneity did not change substantially and remained significant.

3.4.11. VAS: Neck Pain

VAS-neck pain was reported in two studies [18,49]. No significant heterogeneity was observed, and a fixed-effects model was used (I^2=0, p=0.53). Pooling of the results revealed no significant difference in VAS-neck pain after cervical surgery between smokers and non-smokers (MD=-0.19, 95% CI: -1.19 to 0.81, p=0.71; Fig. 12).

3.4.12. VAS: Arm Pain

VAS-arm pain was reported in two studies [18,49]. No significant heterogeneity was observed, and a fixed-effects model was used (I^2=0, p=1.00). Pooling of the results revealed no significant difference in VAS-arm pain after cervical surgery between smokers and non-smokers (MD=-0.50, 95% CI: -1.53 to 0.53, p=0.34; Fig. 13).

3.4.13. NDI

NDI was reported in four studies [18,19,21,49]. Significant heterogeneity was observed, and a random-effects model was used (I^2=96%, p<0.00001). Pooling of the results revealed no significant difference in NDI after cervical surgery between smokers and non-smokers (MD=11.46, 95% CI: -3.83 to 26.76, p=0.14; Fig. 14). After performing leave-one-out sensitivity analysis, the heterogeneity did not change substantially and remained significant.

3.4.14.JOA

JOA was reported in two studies [18,21]. Significant heterogeneity was observed, and a random-effects model was used (I^2=89%, p=0.002). Pooling of the results revealed no significant difference in JOA after cervical surgery between smokers and non-smokers (MD=-1.75, 95% CI: -5.27 to 1.78, p=0.33; Fig. 15). After performing leave-one-out sensitivity analysis, the heterogeneity did not change substantially and remained significant.

3.5. Subgroup Analysis

For primary outcomes, we conducted subgroup analysis based on the type of surgical approach. In patients who underwent anterior cervical surgery, smoking had adverse effects on overall complications (OR=1.71, 95% CI: 1.35-2.16, p<0.00001), respiratory complications (OR=3.81, 95% CI: 1.81-8.05, p=0.0004), fusion rate (OR=0.63, 95% CI: 0.49-0.81, p=0.0003), dysphagia (OR=1.70, 95% CI: 1.19-2.42, p=0.003). For outcomes including reoperation (OR=0.65, 95% CI: 0.32-1.31, p=0.23), wound infection (OR=1.37, 95% CI: 0.52-3.62, p=0.52), and axial neck pain (OR=0.68, 95% CI: 0.26-1.78, p=0.43), smoking had no effect.

In patients who underwent posterior cervical surgery, smoking had adverse effects on overall complications (OR=4.88, 95% CI: 2.72-8.74, p<0.00001), wound infection (OR=8.95, 95% CI: 3.23-24.76, p<0.0001), and axial neck pain (OR=1.97, 95% CI: 1.25-3.10, p=0.003). For reoperation (OR=3.65, 95% CI: 1.15-11.58, p=0.03), smoking had no effect.

3.6. Publication Bias

Begg rank correlation test and Egger linear regression test indicated no evidence of significant publication bias among the included studies (Egger p=0.266; Begg p=0.266; Fig. 17, Fig. 18), and funnel plots showed a symmetric distribution, indicating no publication bias. (Fig. 16).

4. Discussion

The major purpose of the present meta-analysis was to determine whether smoking has adverse effects on surgical outcomes after cervical surgery. Our results suggest that smoking is associated with a higher risk of reoperation and postoperative complications, including dysphagia, axial neck pain, and wound infection. Smokers had a higher incidence of overall complications and respiratory complications and a lower fusion rate. There were no significant differences among smokers and non-smokers concerning outcomes, including operation time, estimated blood loss, length of hospital stays, VAS-neck pain, VAS-arm pain, NDI, or JOA. Our results suggest that smoking might have adverse effects on surgical outcomes in patients who undergo cervical surgery.

Complications were the primary outcome to evaluate the safety of cervical surgery among smoking patients. Siemionow et al. conducted a study of 35 patients undergoing anterior and posterior cervical decompression and fusion and reported that smoking appeared to be the most critical factor related to perioperative complications; the risks for at least one perioperative complication were 50% and 31.6% for smokers and non-smokers, respectively [7]. Lau et al. studied 160 patients undergoing anterior cervical corpectomy and found that smoking patients had longer hospital stays, more bleeding, a higher rate of pseudarthrosis, and more complications at 30 days than non-smoking patients [11]. By contrast, Fehlings et al. analyzed data from the AOSpine North America Cervical Spondylotic Myelopathy Study and concluded that perioperative complications were not associated with smoking status [59]. Medvedev et al. reported that the complication rates in smoking and non-smoking patients of 23.5% and 39.8% (p<0.0001), respectively [22]. Our pooled data showed that smoking was associated with increased postoperative complications, including dysphagia, airway obstruction, nerve palsy, reintubation, axial neck pain, wound infection, deep venous thrombosis, pneumonia, and pseudarthrosis.

We assessed perioperative outcomes, including operation time, estimated blood loss, and length of hospital stay in our meta-analysis and failed to find any significant difference between the smoking and non-smoking groups. As measured by NDI, JOA, and VAS, functional recovery was similar between the two groups. This finding indicates that cervical surgery might offer similar functional outcomes in smoking patients. However, the relatively small sample size limited the generalizability of this conclusion.

After cervical surgery, smokers had a higher reoperation rate and a lower fusion rate. In this meta-analysis, given that functional improvement between the groups was similar, it is possible that higher reoperation rates were directly related to the higher incidence of complications in smoking patients, including wound infection, respiratory complications, and pseudarthrosis. Through subgroup analysis, we found that smoking did not influence reoperation rates for patients undergoing anterior cervical surgery, while higher rates were found for smoking patients undergoing posterior cervical surgery. Due to limited data, we did not perform a subgroup analysis based on the type of surgical procedure.

There are several potential explanations for the observed association between smoking and adverse effects on the surgical outcomes for patients after cervical surgery. First, cigarette smoke products have been shown to inhibit prostacyclin production, a potent vasodilator, and an inhibitor of platelet aggregation. This effect can lead to impaired blood flow and increased blood viscosity, resulting in impaired blood supply [60-64], leading to decreased angiogenesis and epithelialization [65]. Moreover, inhibition of revascularization by nicotine was observed in a rabbit study, and this mechanism may retard cellular metabolism and promote tissue degeneration [66].

Second, at the cellular level, nicotine has been shown to inhibit proliferation, differentiation, and collagen synthesis in osteoblasts [67], which was the primary determinant of the tensile strength of a surgical wound [68]. Free radicals produced by burning cigarettes have been associated with cell membrane destabilization, impair osteoblasts' mitochondrial oxidative function and lead to local tissue hypoxia [60,69-73].

Third, it is well-documented that smoking harms bone physiology, resulting in decreased bone mineral density, impaired bone metabolism, and accelerated osteoporosis, with resulting lower fusion rates [74]. Animal and in vitro studies found that nicotine impaired bone healing, retarded bone formation and growth, and decreased graft biomechanical properties [75,76].

Finally, cigarette smoke contains many toxic ingredients. Nicotine, tar, and other components irritate mucous membranes of the respiratory tract and cause cilia of bronchial epithelial cells to become shorter and irregular, which can hinder the movement of ciliary bodies, reduce local resistance, weaken phagocytosis and sterilization functions of alveolar phagocytes, leading to bronchospasm and increased airway resistance [77]. For these reasons, smokers are susceptible to respiratory complications after cervical surgery. In addition, carbon monoxide combines with hemoglobin, reducing the oxygen-carrying capacity of the blood, and hydrogen cyanide inhibits cytochrome c, which leads to inhibition of aerobic metabolism [78].

To the best of our knowledge, our meta-analysis, on the basis of 16 cohort studies and 27 case-control studies, is the first, also the largest and most comprehensive assessment to investigate the association between smoking and outcomes of cervical surgery. The main strength of this systematic review and meta-analysis is the thorough literature search, careful study selection with strict inclusion criteria, and comprehensive assessment of methodological quality of included studies using the NOS, which is the accepted standard currently. In addition, we performed subgroup analysis according to the surgical approach for the primary outcomes. Although we found significant heterogeneity in several outcomes among the included studies, the sensitivity analysis showed no significant change, suggesting that the pooled estimate in our study was stable. Finally, publication bias was assessed by visually inspecting funnel plots and quantitatively evaluated using Begg and Egger linear regression tests.

This systematic review and meta-analysis has several limitations that are worthy of comment. First, studies included in our review span over two decades (1995 to 2021), during which advancements in cervical surgery techniques might have improved outcomes. Despite this, point estimates for earlier and more recent studies were similar. Second, all of the included studies were retrospective observational trials rather than randomized controlled trials. The inherent nature of observational trials may be associated with selective bias, which might have influences on our results. Third, in most studies, the definition of smoking was not standardized, and self-reporting introduces recall bias or response bias because non-smokers may be current or former smokers. Therefore, the true impact of smoking may be larger than we have reported here. Moreover, the definition of complications was not uniform and might introduce an additional source of bias. Fourth, since most of the information collected was not used to answer specific questions, all characteristics of smoker and non-smoker cohorts such as age, sex, BMI, ethnic group, indications for surgery, and comorbidities were not necessarily consistently matched, leaving some possible residual confusion. What's more, due to the limited number of articles, we did not compare the various types of cervical surgeries in detail. Nevertheless, we attempted to perform a subgroup analysis for the primary outcomes via the surgical approach. Finally, we do not know how investigators confirmed that their patients did not smoke before or after surgery or even if they quitted smoking before surgery, which may have impacted the evaluated results.

One study analyzed the pack-year history and found that, after lumbar surgery, nicotine exposure was associated with an increased risk of disease, and there was a dose-response trend; but this trend was not significant [79]. On the contrary, another study did not support this view and found that after anterior cervical discectomy and fusion, pack-years were not significantly associated with greater odds of developing any one complication or any major complication [80]. This may be related to differences in the number, characteristics, surgical sites, and follow-up time of the population included in the study. Therefore, there is an urgent need for further high-quality studies that are sufficiently prepared and designed with sufficient detail to adjust for multiple confounders and allow exploration of dose-response relationships.

Some researchers reported that preoperative smoking cessation might improve surgery outcomes and could lower medical costs by decreasing postoperative complications and length of post-surgical hospital stay among smokers [11,81]. Sørensen et al. performed a meta-analysis and found that smoking cessation reduced the risk of surgical site infection in plastic and general surgery patients by more than half [82]. Andersen et al. found that quitting smoking significantly increased the rate of fusion after spinal surgery compared to those who continued to smoke, bringing it close to the level of non-smokers [83]. This may be related to the rapid recovery of tissue local oxygenation and metabolism after smoking cessation [84]. Therefore, it is theoretically necessary to quit smoking before elective surgery.

Nevertheless, the optimal timing to quit smoking remains a matter of considerable debate. A study showed that quitting smoking 1 to 2 months before surgery can significantly reduce the perioperative risk [79]. Another report indicated that smoking cessation must be at least 4 weeks before surgery to be effective [12]. Thus, exploring the optimal timing to quit smoking before the operation should determine future efforts.

5. Conclusions

We found significant differences in overall complications, respiratory complications, reoperation rate, fusion rate, dysphagia, wound infection, and axial neck pain between smokers and non-smokers after cervical surgery. Our results suggest that smoking increases the rate of adverse outcomes after neck surgeries. It is crucial to provide timely smoking cessation advice and explanation to patients before selective cervical surgery.

Abbreviations

CIs=confidence intervals; **ORs**=odds ratios; **NR**=not reported; **NOS**=Newcastle-Ottawa Scale; **ACDF**=Anterior cervical discectomy and fusion; **SD**=Standard Deviation; **NDI**=Neck Disability Index; **JOA**=Japanese Orthopaedic Association Scores; **VAS**=Visual Analog Scale; **EBL**=estimated blood loss; **CSF**=cerebrospinal fluid; **DVT**=deep venous thrombosis.

Declarations

Acknowledgments

This work was supported by the Natural Science Foundation of Hubei Province [Grant No. 2019CFC901]

Authors' contributions

Li-ming Zheng: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft

Zhi-wen Zhang: Formal analysis, Investigation, Writing - original draft

Yang Li: Formal analysis, Writing - original draft

Feng Wen: Formal analysis, Writing - original draft

Wang Wei: Writing-review & editing, Supervision.

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Figures

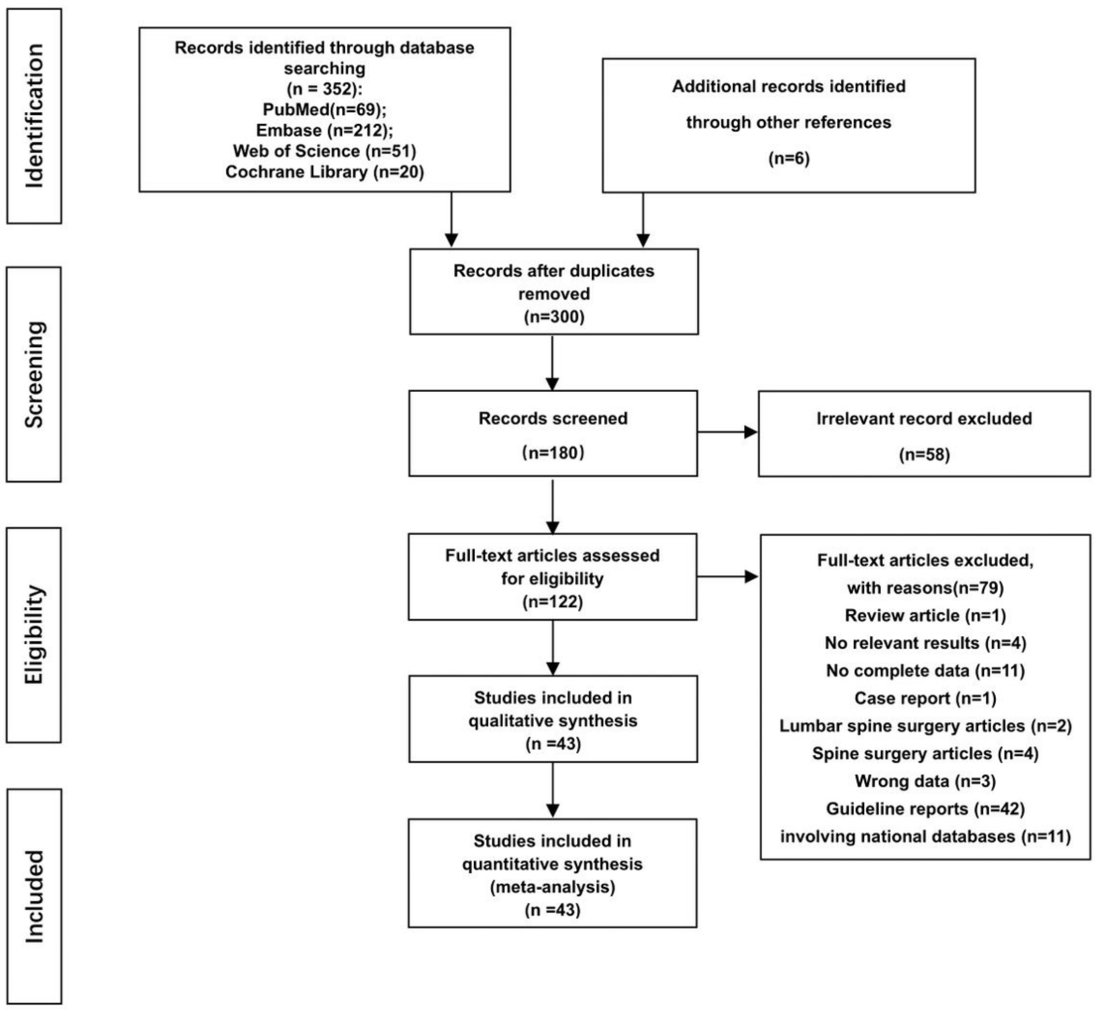

Figure 1

Flow diagram of study selection

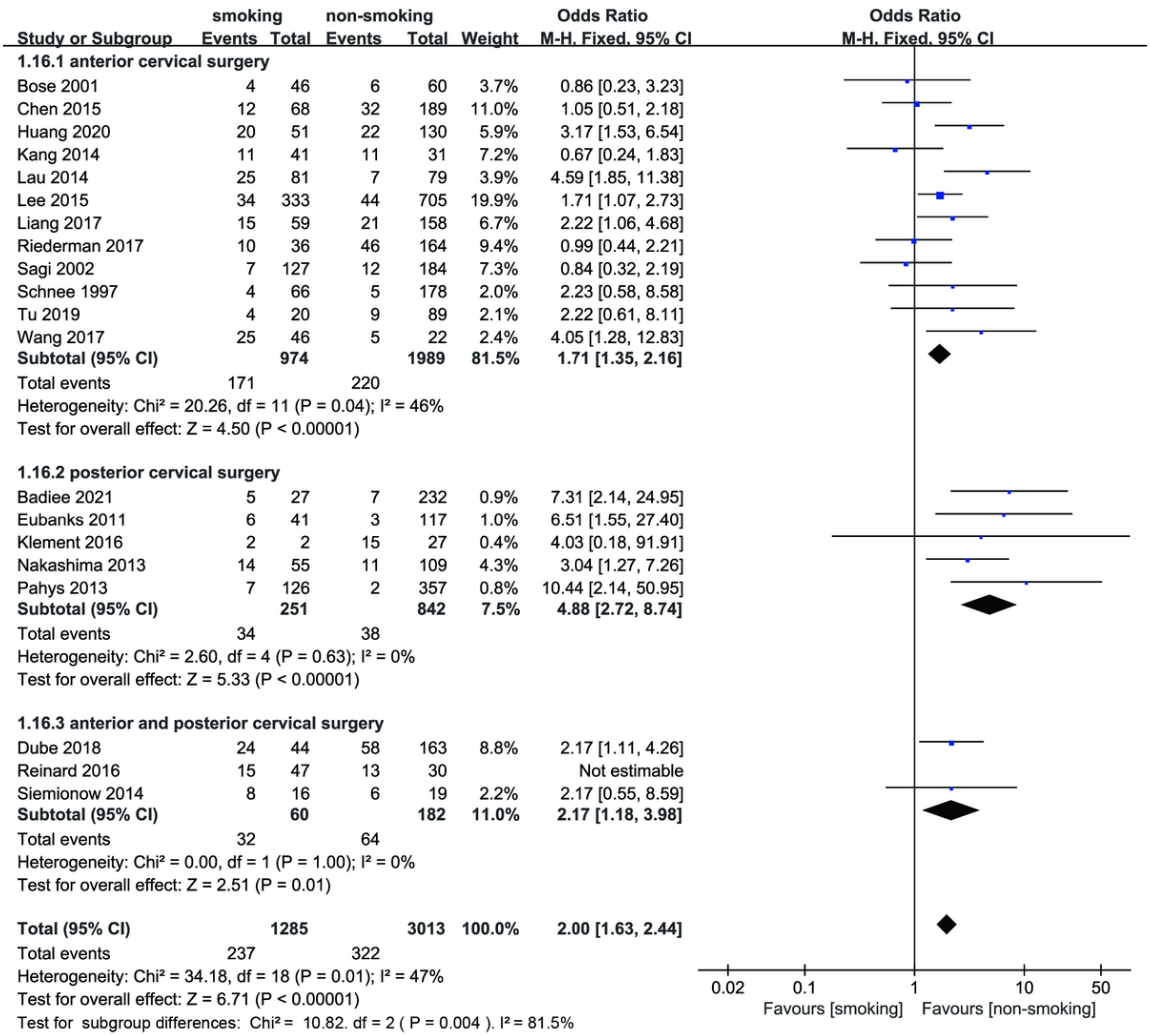

Figure 2

Forest plot showing the effect of smoking on overall complications. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

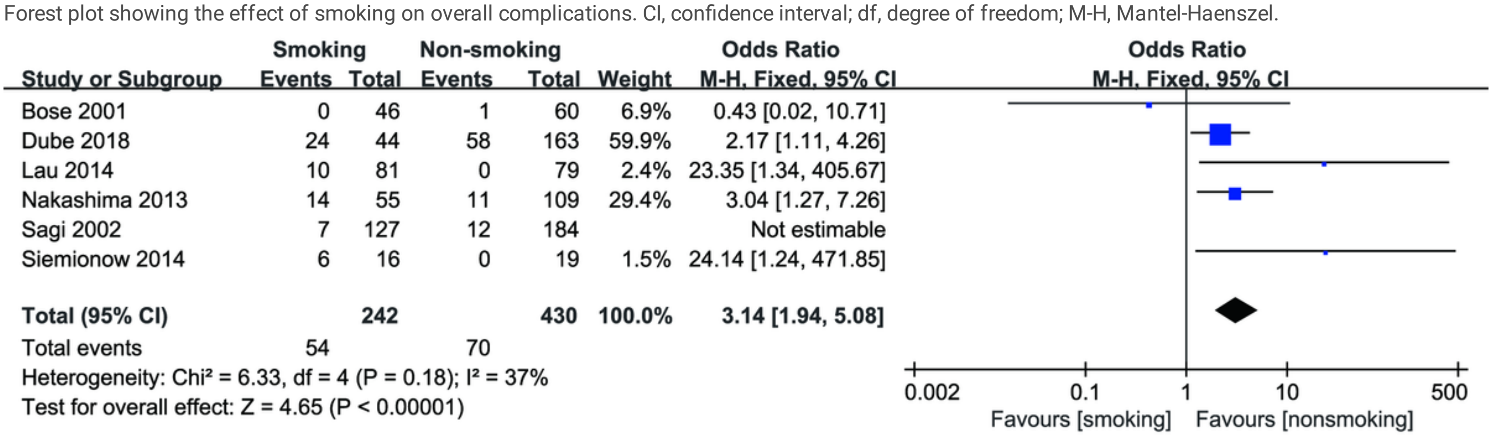

Figure 3

Forest plot showing the effect of smoking on respiratory complications. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

	Smoking		Non-smoking			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Badiee 2021	5	27	7	232	4.7%	7.31 [2.14, 24.95]
Bose 2001	2	46	4	60	13.0%	0.64 [0.11, 3.64]
Lau 2014	4	81	5	79	18.9%	0.77 [0.20, 2.97]
Lee 2014	3	20	6	117	5.8%	3.26 [0.75, 14.30]
Mangan 2021	7	112	15	152		Not estimable
Plano 2019	5	128	3	175	9.6%	2.33 [0.55, 9.94]
Wen-Shen 2020	4	20	5	117	4.6%	5.60 [1.36, 23.06]
Woodroffe 2020	33	219	11	151	43.4%	2.26 [1.10, 4.62]
Total (95% CI)		**541**		**931**	**100.0%**	**2.22 [1.41, 3.49]**
Total events	56		41			

Heterogeneity: Chi² = 9.86, df = 6 (P = 0.13); I² = 39%
Test for overall effect: Z = 3.46 (P = 0.0005)

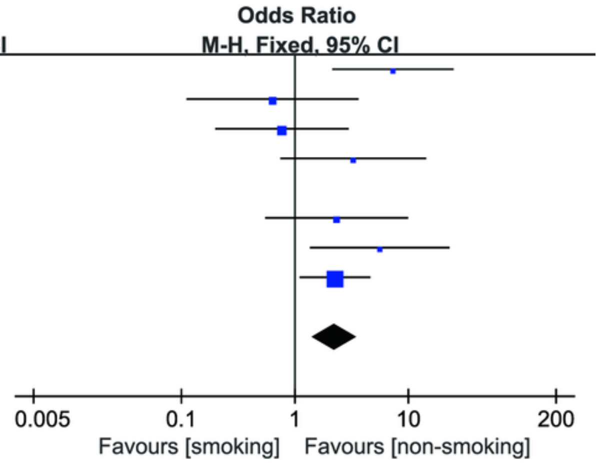

Figure 4

Forest plot showing the effect of smoking on reoperation. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

	Smoking		Non-smoking			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Agrillo 2002	13	19	23	26	4.2%	0.28 [0.06, 1.32]
An 1995	18	34	31	43	8.9%	0.44 [0.17, 1.12]
Bergin 2021	41	48	242	278	7.2%	0.87 [0.36, 2.09]
Bose 2001	45	46	58	60	0.8%	1.55 [0.14, 17.66]
Cerier 2019	14	23	21	38	4.3%	1.26 [0.44, 3.61]
Goldberg 2002	15	30	35	50	9.0%	0.43 [0.17, 1.09]
Groff 2003	50	55	88	89	4.2%	0.11 [0.01, 1.00]
Hilibrand 2001	34	55	110	135	16.7%	0.37 [0.18, 0.74]
Lau 2014	55	62	67	70	4.9%	0.35 [0.09, 1.42]
Luszczyk 2013	142	156	382	417	12.8%	0.93 [0.49, 1.78]
Mangan 2021	56	63	73	87	4.7%	1.53 [0.58, 4.05]
Martin 1999	62	75	193	214	12.0%	0.52 [0.25, 1.10]
Ren 2020	100	106	177	189	5.0%	1.13 [0.41, 3.10]
Suchomel 2004	44	48	30	31	2.1%	0.37 [0.04, 3.44]
Wang 1999	11	12	64	68	1.1%	0.69 [0.07, 6.74]
Wang 2000	4	6	47	52	2.2%	0.21 [0.03, 1.47]
Total (95% CI)		**838**		**1847**	**100.0%**	**0.63 [0.49, 0.81]**
Total events	704		1641			

Heterogeneity: Chi² = 17.91, df = 15 (P = 0.27); I² = 16%
Test for overall effect: Z = 3.59 (P = 0.0003)

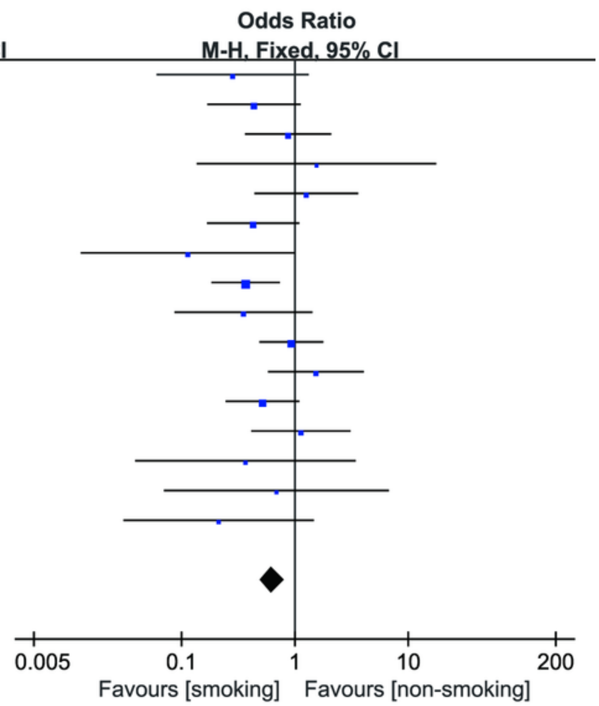

Figure 5

Forest plot showing the effect of smoking fusion rate. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

	Smoking		Non-smoking			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Bose 2001	1	46	2	60	3.1%	0.64 [0.06, 7.33]
Chen 2015	12	68	32	189	25.1%	1.05 [0.51, 2.18]
Huang 2020	20	51	22	130	13.5%	3.17 [1.53, 6.54]
Kang 2014	11	38	11	64	10.5%	1.96 [0.75, 5.10]
Reinard 2016	15	47	13	30	19.4%	0.61 [0.24, 1.58]
Riederman 2017	9	36	42	164	20.4%	0.97 [0.42, 2.22]
Tu 2019	1	20	4	89	2.5%	1.12 [0.12, 10.58]
Wang 2017	25	46	5	22	5.6%	4.05 [1.28, 12.83]
Total (95% CI)		**352**		**748**	**100.0%**	**1.49 [1.07, 2.07]**
Total events	94		131			

Heterogeneity: Chi² = 13.16, df = 7 (P = 0.07); I² = 47%
Test for overall effect: Z = 2.35 (P = 0.02)

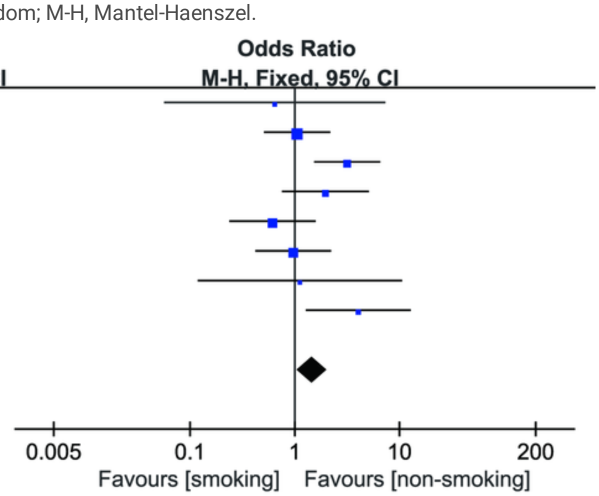

Figure 6

Forest plot showing the effect of smoking on dysphagia. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

Study or Subgroup	Smoking Events	Smoking Total	Non-smoking Events	Non-smoking Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Badiee 2021	3	27	5	232	9.8%	5.67 [1.28, 25.23]
Eubanks 2011	2	41	0	117	2.6%	14.87 [0.70, 316.48]
Lau 2014	4	81	2	79	20.3%	2.00 [0.36, 11.24]
Pahys 2013	7	125	2	358	10.3%	10.56 [2.16, 51.53]
Schnee 1997	4	66	5	78	45.3%	0.94 [0.24, 3.66]
Siemionow 2014	1	16	0	19	4.4%	3.77 [0.14, 99.24]
Tu 2019	1	20	2	89	7.3%	2.29 [0.20, 26.56]
Total (95% CI)		**376**		**972**	**100.0%**	**3.19 [1.64, 6.21]**
Total events	22		16			

Heterogeneity: Chi² = 7.20, df = 6 (P = 0.30); I² = 17%
Test for overall effect: Z = 3.42 (P = 0.0006)

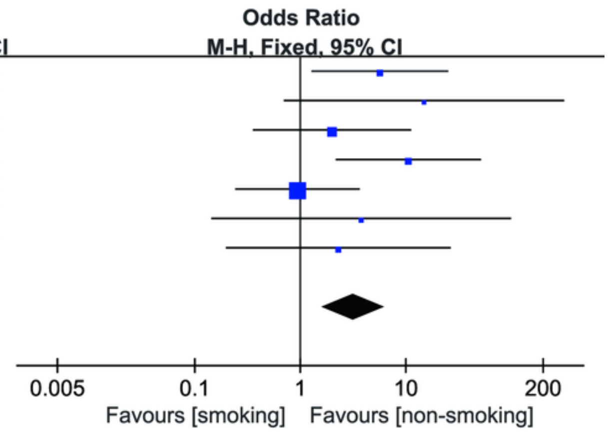

Figure 7

Forest plot showing the effect of smoking on wound infection. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

Study or Subgroup	Smoking Events	Smoking Total	Non-smoking Events	Non-smoking Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kimura 2018	20	39	31	117	29.4%	2.92 [1.38, 6.18]
Liu 2019	9	39	15	49		Not estimable
Zhang 2020	29	68	58	181	70.6%	1.58 [0.89, 2.80]
Total (95% CI)		**107**		**298**	**100.0%**	**1.97 [1.25, 3.10]**
Total events	49		89			

Heterogeneity: Chi² = 1.64, df = 1 (P = 0.20); I² = 39%
Test for overall effect: Z = 2.94 (P = 0.003)

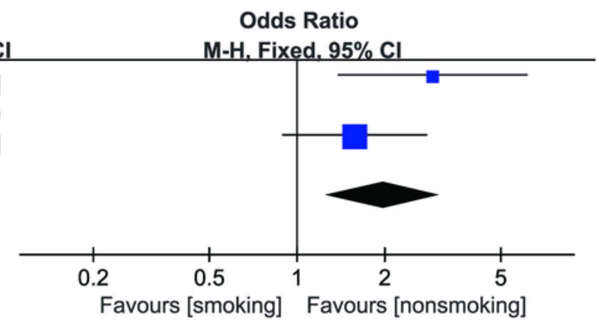

Figure 8

Forest plot showing the effect of smoking on axial neck pain. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

Study or Subgroup	smoking Mean	smoking SD	smoking Total	non-smoking Mean	non-smoking SD	non-smoking Total	Weight	Mean Difference IV, Fixed, 95% CI
Patel 2019	51.5	14.8	25	51.5	16.3	167	79.5%	0.00 [-6.31, 6.31]
Vasquez 2016	162	60	123	161.6	62	350	20.5%	0.40 [-12.03, 12.83]
Total (95% CI)			**148**			**517**	**100.0%**	**0.08 [-5.54, 5.71]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)

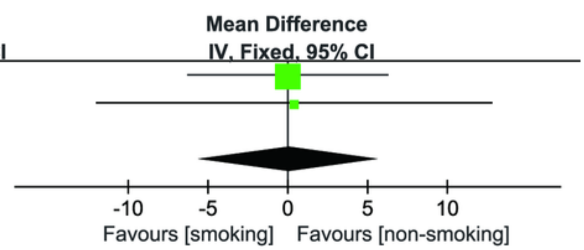

Figure 9

Forest plot showing the effect of smoking on operation time. CI, confidence interval; df, degree of freedom; SD, standard deviation.

Study or Subgroup	Smoking Mean	Smoking SD	Smoking Total	Non-smoking Mean	Non-smoking SD	Non-smoking Total	Weight	Mean Difference IV, Random, 95% CI
Lau 2014	518.9	1,035.8	40	249.6	199.6	79	14.5%	269.30 [-54.70, 593.30]
Patel 2019	34	22.7	25	30	12.7	167	53.0%	4.00 [-5.10, 13.10]
Reinard 2016	340.43	339.88	47	483.17	347.68	30	32.5%	-142.74 [-300.60, 15.12]
Total (95% CI)			**112**			**276**	**100.0%**	**-5.31 [-149.83, 139.22]**

Heterogeneity: Tau² = 10235.88; Chi² = 5.89, df = 2 (P = 0.05); I² = 66%
Test for overall effect: Z = 0.07 (P = 0.94)

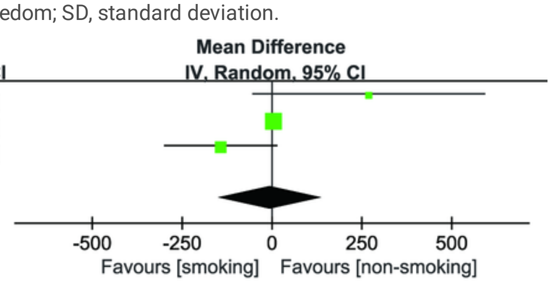

Figure 10

Forest plot showing the effect of smoking on estimated blood loss. CI, confidence interval; df, degree of freedom; SD, standard deviation.

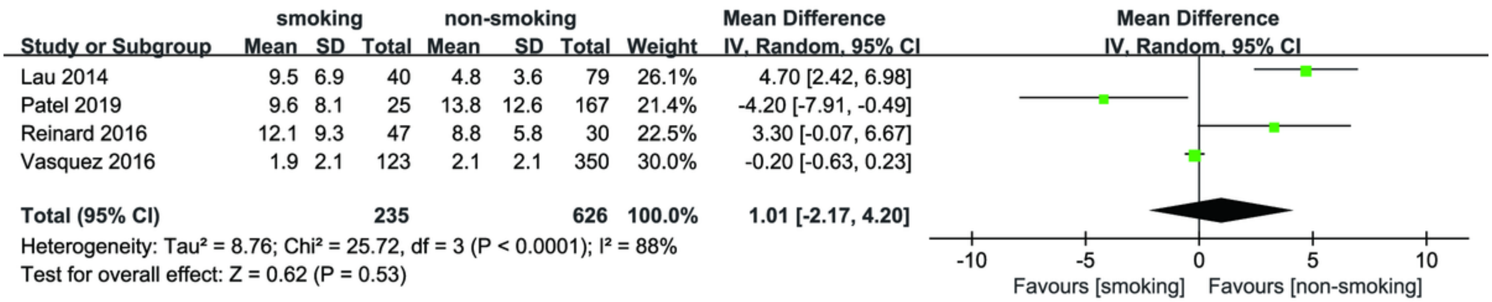

Figure 11

Forest plot showing the effect of smoking on length of hospital stay. CI, confidence interval; df, degree of freedom; SD, standard deviation.

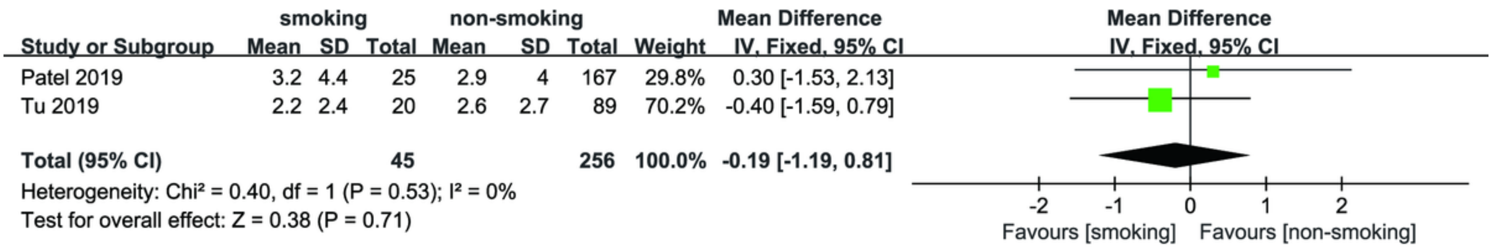

Figure 12

Forest plot showing the effect of smoking on VAS-neck pain. CI, confidence interval; df, degree of freedom; SD, standard deviation.

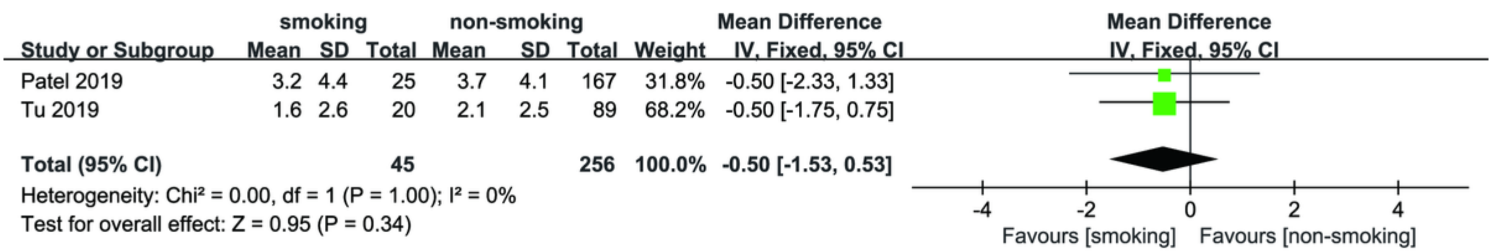

Figure 13

Forest plot showing the effect of smoking on VAS-arm pain. CI, confidence interval; df, degree of freedom; SD, standard deviation.

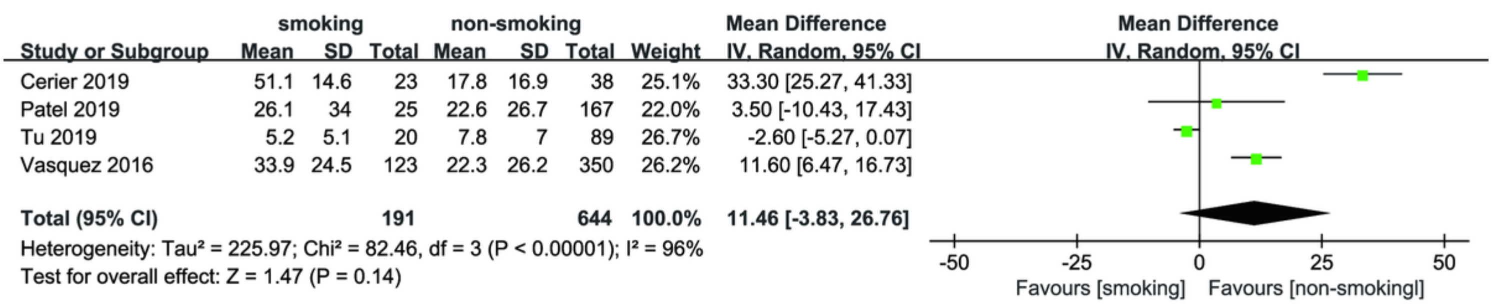

Figure 14

Forest plot showing the effect of smoking on NDI. CI, confidence interval; df, degree of freedom; SD, standard deviation.

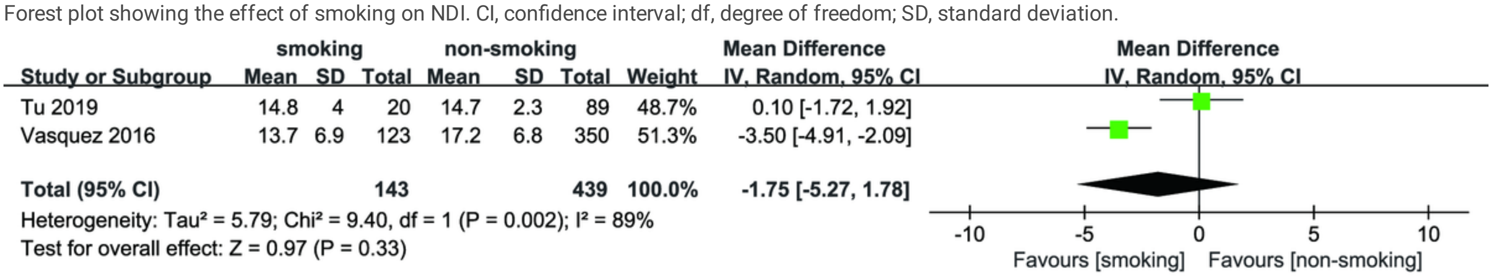

Figure 15

Forest plot showing the effect of smoking on JOA. CI, confidence interval; df, degree of freedom; SD, standard deviation.

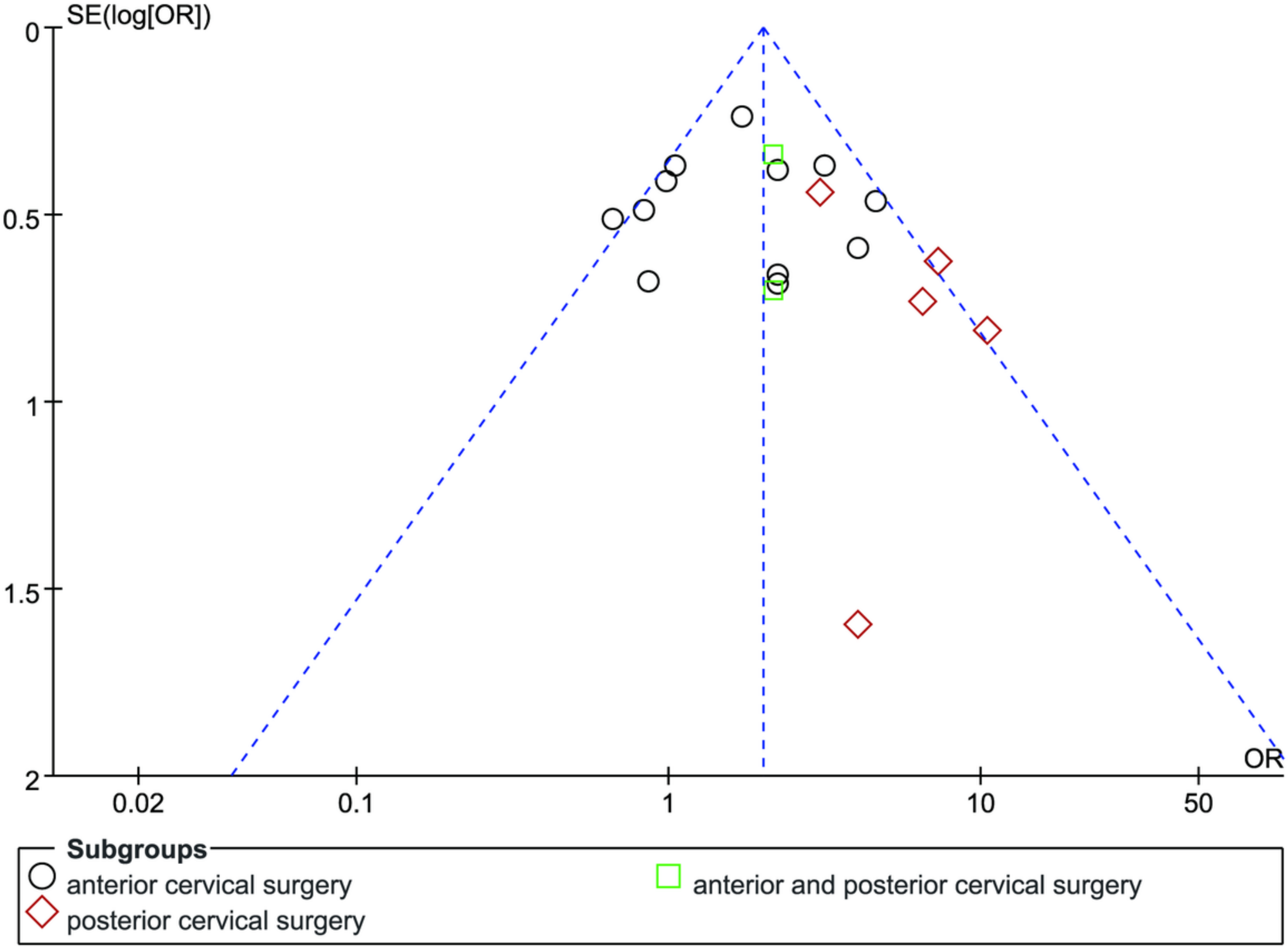

Figure 16

Funnel plot to evaluate the publication bias of overall complications. OR, odds ratio; SE, standard error.

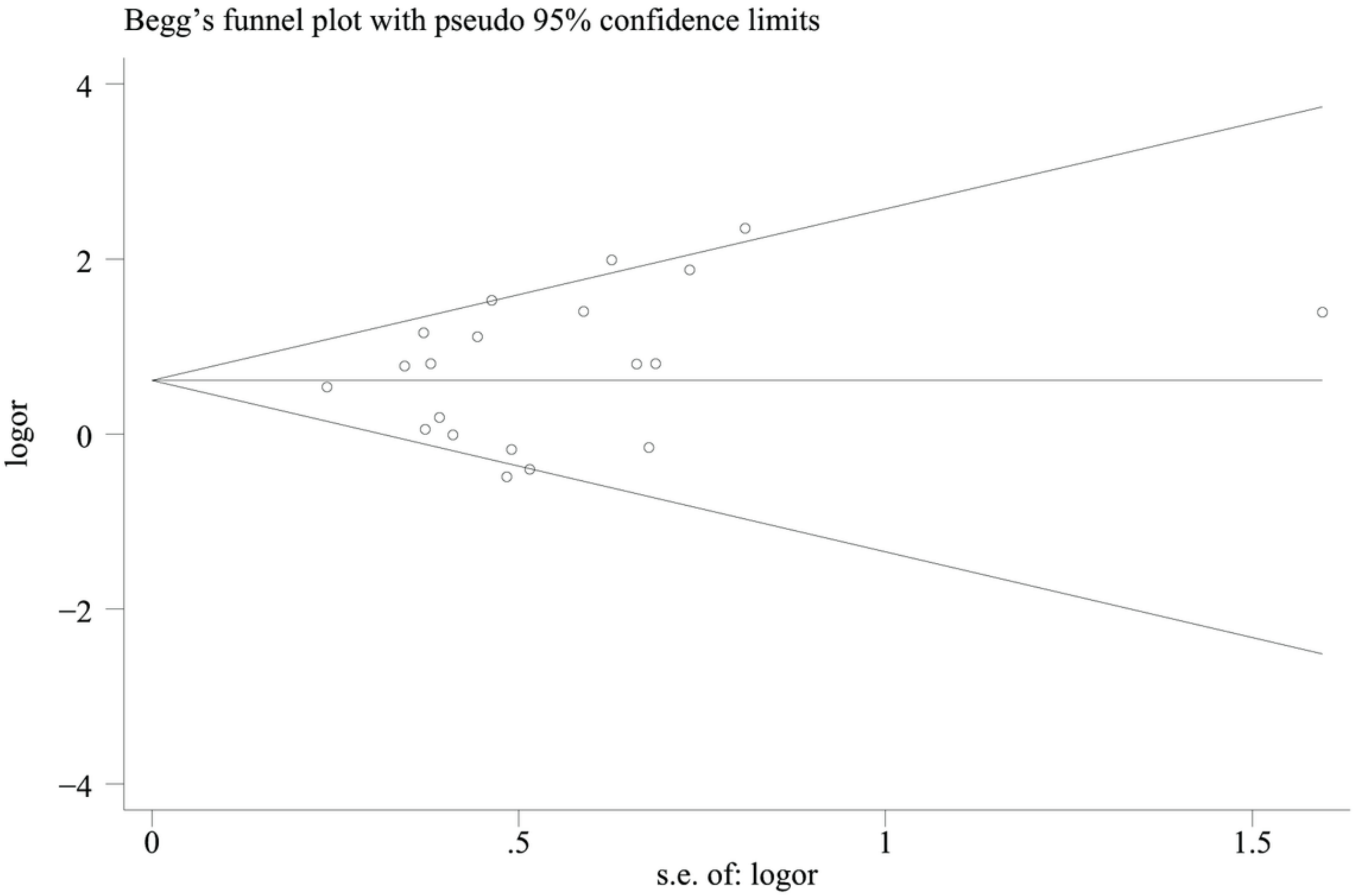

Figure 17

Begg's funnel plot to evaluate the publication bias of overall complications.

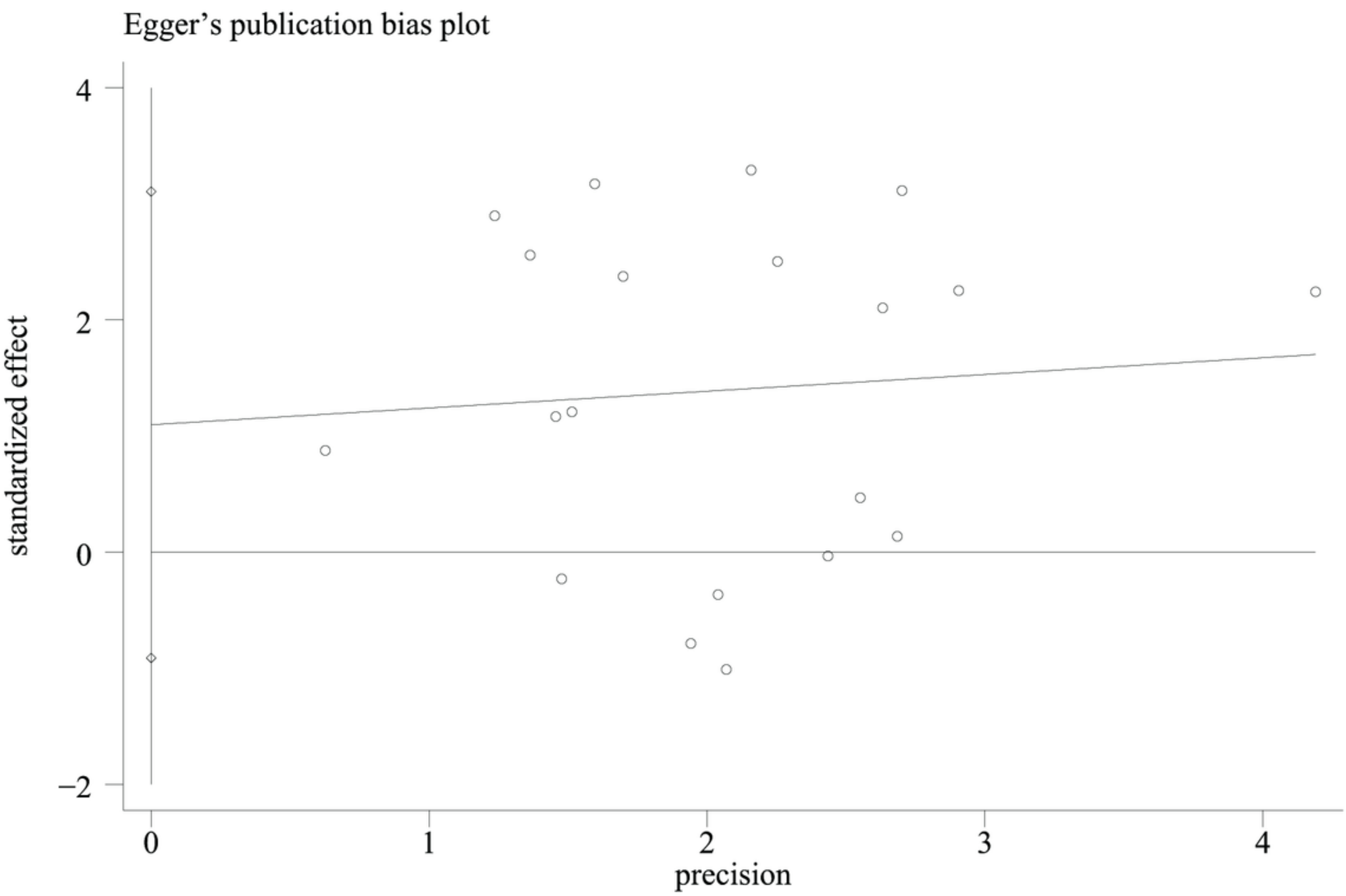

Figure 18

Egger's publication bias plot to evaluate the publication bias of overall complications.

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