TITLE PAGE

Title: Systematic Review with Meta-analysis: The Adverse Effect of Tobacco Smoking on the Natural History of Crohn's Disease.

Short "running" title: Adverse Effects of Tobacco Smoking on Crohn's Disease.

Authors: Natalie To[1, 2], David J. Gracie[1, 2], Alexander C. Ford.[1, 2]

[1]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

[2]Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK.

Abbreviations:	CI	confidence interval
	MeSH	medical subject headings
	OR	odds ratio

Correspondence: Dr. Alex Ford

Leeds Gastroenterology Institute

Room 125

4th Floor

Bexley Wing

St. James's University Hospital

Beckett Street

Leeds

United Kingdom

LS9 7TF

Email: alexf12399@yahoo.com

Telephone: +441132684963

Facsimile: +441132429722

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SUMMARY

Background: Tobacco smoking is a well-established risk factor for the development of Crohn's disease, and this may lead to a more complicated disease course. However, recent evidence suggests that many patients with Crohn's disease are unaware of this fact.

Aims: To perform a systematic review and meta-analysis of the effects of smoking on disease course in Crohn's disease.

Methods: A search of MEDLINE, EMBASE, and EMBASE classic was carried out (up to July 2015) to identify observational studies reporting data on smoking and rates of surgery or flares of disease activity in patients with Crohn's disease. Dichotomous data were pooled to obtain odds ratios (ORs) for flares of disease activity or need for surgery, with 95% confidence intervals (CIs).

Results: The search identified 33 eligible studies. Compared with non-smokers, smokers had increased odds of flare of disease activity (OR 1.56; 95% CI 1.21-2.01), flare after surgery (OR = 1.97; 95% CI 1.36-2.85), need for first surgery (OR = 1.68; 95% CI 1.33-2.12), and need for second surgery (OR = 2.17; 95% CI 1.63-2.89). The odds of these outcomes among ex-smokers diminished upon smoking cessation, with ORs comparable to those among non-smokers and, in the case of flare or second surgery, significantly lower than smokers.

Conclusions: Smokers with Crohn's disease have a more complicated disease course than non-smokers, and quitting smoking may ameliorate this. Patients should be reminded of the detrimental effects of smoking on the course of their disease, and smoking cessation advice should be provided to reduce disease burden and costs in these patients.

INTRODUCTION

Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract, with an incidence of 6 to 8 per 100,000 population,(1, 2) and a prevalence of 130 to 200 per 100,000. (1-3) It affects both sexes equally, most commonly in the productive second to fourth decade of life, resulting in a high burden to both patients and society. (4) The condition runs a relapsing and remitting course, with flares of disease activity requiring medical therapy and/or surgery, and is associated with long term morbidity, impacting on psychological, social, and physical aspects of a patient's life.

Crohn's disease is extremely costly to health services with a recent study estimating that nearly €30billion is spent annually in the USA and Europe combined. (5) In selected European countries, direct health care costs per patient, such as the cost of medication and hospitalisation, were between €2,898 and €6,960 annually. (6) The financial cost of the disease can increase two to three-fold during flares of disease activity, and up to 20 times if hospitalisation is required. (7) In addition, patients with Crohn's disease have an impaired health related quality of life compared with healthy controls, with those in remission having a markedly improved quality of life compared with individuals with active Crohn's disease. (5)

The aetiology of Crohn's disease is complex, and involves environmental, immunological, and genetic factors. (8) A much-investigated environmental factor is the impact of tobacco smoking on the risk of developing Crohn's disease, and its subsequent natural history. The correlation between smoking and an increased risk of Crohn's disease was identified more than 30 years ago. (9, 10) The mechanisms involved are not completely understood, but may include alterations in the immune system, abnormal cytokine levels, and changes in gut permeability and motility. (11)

Tobacco smoking in Crohn's disease is therefore a potentially modifiable environmental risk factor, and this is supported by studies that show smoking cessation in patients with Crohn's disease is associated with a milder subsequent disease course. (12, 13) Other investigators have examined the relationship between smoking status and the rate of complications, such as flares of disease activity or the need for surgical intervention during extended follow-up. (14-17) However, the effect of tobacco smoking on the likelihood of flares of disease activity, need for surgery, recurrence of disease activity after surgical intervention, or need for further surgical intervention is variable in these studies.

If clinicians were able to communicate more clearly to patients the detrimental effects of continued tobacco consumption on the course of Crohn's disease this may lead not only to a higher likelihood that they will cease smoking, but it could also help to reduce the burden of the disease. It may also serve as a mandate for further randomised controlled trials of smoking cessation as a medical intervention in Crohn's disease. We have therefore conducted a systematic review and meta-analysis in order to address this issue.

MATERIALS AND METHODS

Search Strategy and Study Selection

A literature search was performed using MEDLINE, EMBASE, and EMBASE classic (from 1947 to July 2015) to identify observational studies with longitudinal follow-up that investigated the effect of tobacco smoking on the natural history of Crohn's disease, including the risk of flares of disease activity or need for surgical intervention. In order to be eligible, studies had to recruit at least 50 adult patients (aged 16 years and over) with Crohn's disease, and report data on smoking status at study entry, and the subsequent occurrence of flares of disease activity, or need for surgical intervention (with focus on intestinal resection). Studies could either be prospective in their design, or a retrospective analysis of prospectively collected data. The diagnosis of Crohn's disease had to be made using histological, radiological, surgical, or endoscopic methods. These eligibility criteria were defined prospectively and are summarised in Table 1.

We performed a search of the medical literature using the words: *Crohn disease*, *inflammatory bowel disease*, *colitis*, or *ileitis* (both as a medical subject heading (MeSH) and free text term), *Crohn$ disease*, or *regional enteritis* (as free text terms). These were combined using the set operator AND with studies identified using the terms: *tobacco*, *tobacco products*, or *smoking* (both as a medical subject heading (MeSH) and free text term), *cigarettes*, or *smoker* (as free text terms). There were no language restrictions applied and foreign articles were translated if required. All titles and abstracts generated from the search were screened for inclusion into the study, and were examined further if they appeared to be relevant. In addition, a recursive search identified other potentially eligible studies among the bibliographies of selected articles. Finally, we searched the bibliographies of previous systematic reviews in this area. (18-25) Eligibility was judged by two independent investigators with any disagreements resolved by a third investigator.

Data Extraction

Extraction of data was carried out independently by two investigators onto a Microsoft excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA) as total number of patients with Crohn's disease who were current smokers with either a flare of disease activity or needing surgical intervention, total number of patients with Crohn's disease who were ex-smokers with either a flare of disease activity or needing surgical intervention (where reported), and total number of patients with Crohn's disease who were non-smokers with either a flare of disease activity or needing surgical intervention. Any discrepancies were resolved by a third investigator. Data collected included year of study, country of origin, number of centres, setting (primary, secondary, or tertiary care), study design (prospective, or retrospective analysis of prospectively collected data), outcomes assessed, whether studies recruited consecutive patients, sample size, mean age of participants, and proportion of male subjects.

The quality of included studies was judged according to the Newcastle-Ottawa scale, (26) with a total possible score of 9, higher scores indicating higher quality studies.

Data Synthesis and Statistical Analysis

The degree of agreement between the two investigators, in terms of judging study eligibility, was measured using the Kappa statistic. Data in the studies identified were analysed according to the reported outcomes of interest, including flare of disease activity, flare of disease activity after surgery, need for any surgery (where investigators did not report whether this was a first or second operation), need for first surgery, or need for second surgery. The proportion of patients with a flare of disease activity or needing surgical intervention were compared between current smokers, ex-smokers (where reported), and non-smokers using an odds ratio (OR) with a 95% confidence interval (CI). An analysis of heterogeneity between studies was carried out using the I^2 statistic with a cut off of 50%, (27) and the χ^2 test with a P value <0.10, used to define a statistically significant degree of heterogeneity.

Data were pooled using a random effects model, (28) to give a more conservative estimate of the effect of tobacco smoking on the natural history of Crohn's disease. StatsDirect version 2.7.2 (StatsDirect Ltd, Sale, Cheshire, England) was used to generate Forest plots of pooled ORs with 95% CIs. Evidence of publication bias was assessed for by applying Egger's test to funnel plots, (29) where a sufficient number of studies were available. (30)

RESULTS

The search generated 4271 citations, of which 195 appeared relevant and were retrieved for further detailed analysis (Figure 1). In total, 33 articles met all eligibility criteria and were included in the meta-analysis. (13-17, 31-58) Agreement between reviewers was substantial (Kappa statistic = 0.75). Detailed characteristics of individual studies, including study quality, are provided in Table 2.

Flares of Disease Activity According to Smoking Status

There were nine studies recruiting a total of 4013 patients with Crohn's disease that reported information on flares of disease activity in 1788 smokers versus 2225 non-smokers. (14, 16, 32, 36-38, 51, 52, 57) Overall, 1243 (69.5%) smokers developed a flare of disease activity, compared with 1431 (64.3%) non-smokers. The odds of a flare of disease activity was significantly higher among smokers (OR 1.56; 95% CI 1.21 to 2.01) (Figure 2), with borderline significant heterogeneity between studies (I^2 = 40.9%, P = 0.09). There were too few studies to assess for publication bias.

Four studies of these studies, containing 1115 patients, reported data on flares of disease activity in 510 current smokers, 180 ex-smokers, and 425 non-smokers. (14, 16, 37, 38) In total, 260 (51.0%) smokers developed a flare of disease activity, compared with 166 (39.1%) non-smokers (OR = 1.85; 95% CI 1.33 to 2.57), with no significant heterogeneity between studies (I^2 = 13.2%, P = 0.33). There were 63 (35.0%) ex-smokers developing a flare of disease activity (OR compared with non-smokers = 0.90; 95% CI 0.59 to 1.39), with no heterogeneity between studies (I^2=0%, P = 0.66). The odds of a flare was significantly increased in smokers, compared with ex-smokers (OR = 2.05; 95% CI 1.38 to 3.04), again with no heterogeneity between studies (I^2=0%, P = 0.53). There were too few studies to assess for publication bias.

Flares of Disease Activity After Surgery According to Smoking Status

The occurrence of first flare of disease activity after surgery in Crohn's disease was reported by five studies, containing 538 patients. (46, 48, 50, 53, 54) There were 152 (60.6%) of 251 smokers, compared with 126 (43.9%) of 287 non-smokers experiencing a flare of disease activity (OR = 1.97; 95% CI 1.36 to 2.85), with no heterogeneity between studies (I^2 = 0%, P = 0.89). There were too few studies to assess for publication bias. Only one of these studies reported first flare of disease activity in smokers, ex-smokers, and non-smokers, (50) so meta-analysis was not possible, although overall 70 (63.6%) of 110 smokers experienced a flare of disease activity after surgery, compared with 6 (31.6%) of 19 ex-smokers, and 23 (43.4%) of 53 non-smokers.

Need for Any Surgery According to Smoking Status

Twelve studies, containing 4864 patients, reported need for any surgery in smokers and non-smokers. (14, 15, 31-38, 55, 57) Overall, 648 (29.6%) of 2190 smokers required any surgery, compared with 765 (28.6%) of 2674 non-smokers. The pooled OR for any surgery in smokers compared with non-smokers was 1.12 (95% CI 0.91 to 1.38) (Figure 3), with no significant heterogeneity between studies (I^2= 26.4%, P = 0.18), and no evidence of publication bias (Egger test, P = 0.71).

Five studies of these studies, containing 1532 patients, reported data on flares of disease activity in 712 current smokers, 219 ex-smokers, and 601 non-smokers. (14, 15, 36-38) There were 111 (15.6%) smokers requiring any surgery, compared with 101 (16.8%) non-smokers (OR = 0.99; 95% CI 0.72 to 1.35), with no heterogeneity between studies (I^2 = 0%, P = 0.78). Among ex-smokers, 36 (16.4%) required any surgery, (OR compared with non-smokers = 0.97; 95% CI 0.60 to 1.57), again with no heterogeneity between studies (I^2=0%, P = 0.48). The odds of requiring any surgery was not significantly increased in smokers, compared with ex-smokers (OR = 1.07; 95% CI 0.67 to 1.70), with no heterogeneity between studies (I^2=0%, P = 0.68). There were too few studies to assess for publication bias.

Need for First Surgery According to Smoking Status

Rates of first surgery according to smoking status were reported by nine studies, containing 3389 patients. (13, 17, 39-44, 58) In total, 585 (51.2%) of 1142 smokers required a first operation, compared with 714 (31.8%) of 2247 non-smokers (OR = 1.68; 95% CI 1.33 to 2.12) (Figure 4), with no significant heterogeneity between studies (I^2= 37.8%, P = 0.12), but with too few studies to assess for publication bias.

Five studies, containing 1747 patients, reported rates of first surgery among 335 smokers, 255 ex-smokers, and 1157 non-smokers. (41-44, 58) There were 158 (47.2%) smokers undergoing first surgery, compared with 306 (26.4%) non-smokers. The pooled OR for first surgery in smokers compared with non-smokers was 1.54 (95% CI 1.17 to 2.03), with no heterogeneity between studies (I^2=0%, P = 0.82). Among ex-smokers, 106 (41.6%) underwent a first surgery (OR compared with non-smokers = 1.32; 95% CI=0.90 to 1.94), with no significant heterogeneity between studies (I^2=24.1%, P = 0.26). The odds of first surgery was not significantly increased in smokers, compared with ex-smokers (OR = 1.21; 95% CI 0.86 to 1.72), again with no heterogeneity between studies (I^2=0%, P = 0.51). Again, there were too few studies to assess for publication bias.

Need for Second Surgery According to Smoking Status

Eleven studies, containing 1893 patients, reported on rates of second surgery according to smoking status. (13, 41, 44-50, 56, 58) There were 425 (47.3%) of 899 smokers requiring a second surgery, compared with 330 (33.2%) of 994 non-smokers (OR = 2.17; 95% CI 1.63 to 2.89) (Figure 5), but with significant heterogeneity between studies (I^2 = 41.2%, P = 0.07). This was driven by one Australian study, (58) and disappeared with its exclusion from the analysis (OR = 2.31; 95% CI 1.86 to 2.86, I^2 = 0%, P = 0.65). There was no evidence of publication bias (Egger test, P = 0.25).

Six studies, containing 1398 patients, reported rates of second surgery among 559 smokers, 212 ex-smokers, and 627 non-smokers. (13, 41, 44, 50, 56, 58) There were 251 (44.9%) smokers undergoing a second operation, compared with 225 (35.9%) non-smokers. The pooled OR for second surgery in smokers compared with non-smokers was 1.97 (95% CI 1.23 to 3.15), but with significant heterogeneity between studies (I^2=59.4%, P = 0.03). The effect was attenuated among ex-smokers once more, with 74 (34.9%) undergoing a second surgery (OR compared with non-smokers = 1.08; 95% CI=0.67 to 1.74), with no significant heterogeneity between studies (I^2=34.6%, P = 0.18). The odds of second surgery was significantly increased in smokers, compared with ex-smokers (OR = 1.64; 95% CI 1.04 to 2.57), again with no heterogeneity between studies (I^2=25.6%, P = 0.24). Again, there were too few studies to assess for publication bias.

DISCUSSION

In this systematic review and meta-analysis, we pooled data from observational studies that examined the rate of flares of disease activity or need for surgical intervention in smokers of tobacco, ex-smokers, and non-smokers. We demonstrated that the course of Crohn's disease is more complicated among active smokers compared with non-smokers. There was a 56% to 85% increase in flares of disease activity, a nearly two-fold increase in clinical recurrence of disease activity after surgery, a 54% to 68% increase in the need for first surgery, and a two-fold or greater increase in rates of second surgery. Stopping smoking appeared to ameliorate this, with rates of flare, clinical recurrence, and need for first or second surgery no higher than among non-smokers, although patient numbers were smaller in these analyses. In addition, there were significantly higher rates of flare of disease activity and need for second surgery among smokers, compared with ex-smokers.

We conducted a comprehensive and contemporaneous search of the medical literature, which included a recursive search of the bibliographies of relevant articles. We also included foreign language studies, and translated these. The judging of study eligibility and data extraction were performed by two investigators working independently, with any discrepancies resolved with the aid of a third independent investigator. The quality of the selected studies was also assessed, using the Newcastle-Ottawa scale, a well-accepted quality assessment scale, with 24 of the selected articles scoring 7 or more out of a possible 9. Finally, we used a random effects model to pool data from eligible studies in order to provide a more conservative estimate of the effect of tobacco smoking on the natural history of Crohn's disease, and assessed for evidence of publication bias in the analyses, where there sufficient studies.

Limitations of this meta-analysis include the fact that the majority of eligible studies were conducted in tertiary referral centres. This could mean that the results may not be applicable to patients with Crohn's disease in the community, or in primary care. In addition, there was some variability in the methods that individual studies used to classify smokers, non-smokers, and ex-smokers. Not all studies stated their criteria for defining smoking status, especially those whose primary aim was not to investigate the effect of tobacco smoking on the natural history of Crohn's disease. A further, and related, problem was that some articles pooled ex-smokers with non-smokers, rather than reporting rates of flare of disease activity or need for surgery separately in these two groups. If there were an increased in the likelihood of either flare or surgery among ex-smokers in these studies this would have underestimated the effect of smoking on these outcomes in some of our analyses. We tried to circumvent this by performing analyses with only smokers, non-smokers, and ex-smokers compared, wherever trial reporting allowed. There was also heterogeneity between studies in some of our analyses, suggesting there are factors other than smoking that may affect the natural history of Crohn's disease. Multiple other factors have been associated with a worsened disease course, including stress or anxiety. (59) These could be potentially confounding factors, as higher stress levels are associated with increased smoking. (60, 61) As we extracted and pooled raw data from all of the included studies we could not adjust for the influence of confounding variables in our analyses. Finally, in this meta-analysis it was not possible to assess the effect of smoking on the course of

Crohn's disease according to disease location, or to estimate the time point at which stopping smoking has a beneficial effect on the natural history of Crohn's disease.

Crohn's disease is a chronic condition, and can affect multiple aspects of a patient's wellbeing, causing disruption to their personal and working life, due to flares of disease activity, which can result in hospitalisation. Although there are medical therapies of proven benefit, such as biological agents or immunosuppressant drugs to reduce flares of disease, (62, 63) these are not universally effective and, even with timely use, as many as one in four patients will ultimately require an intestinal resection within 5 years of diagnosis. (64) Building on the knowledge that smoking is a risk factor for the development of the disease, (9) the results of this meta-analysis provide an overall estimate of the deleterious effects of continuing to smoke tobacco on the natural history of Crohn's disease, as well as some evidence to suggest that smoking cessation is beneficial to the subsequent disease course, as ex-smokers appeared to be at a reduced risk of flares of disease activity or need for second surgery compared with smokers. Although the studies we included were not randomised, using these data to calculate a number needed to treat suggests that only seven people with Crohn's disease would need to stop smoking to prevent one flare of disease activity, and 10 would need to stop smoking to prevent one person undergoing a second operation, which compares favourably to many of the available medical therapies. (62, 63, 65-67)

There are several potential explanations for the deleterious effects of smoking tobacco in Crohn's disease. Smoking may alter the intestinal microbiota, (68) and it has also been shown that mononuclear cells from patients with Crohn's disease who smoke are functionally impaired. (69) In addition, cigarette smoke is associated with an altered immune response, with studies linking the addictive component nicotine with immunosuppression of the innate and adaptive immune system. (70) Finally, smoking can lead to altered epigenetic events, thereby altering protein expression, and potentially leading to an abnormal cascade of inflammation in the intestinal mucosa. (71)

As a modifiable risk factor, this study therefore provides support for healthcare practitioners to encourage smoking cessation among all their patients with Crohn's disease. A recent study found that there are low levels of awareness of the detrimental effects of continued smoking among patients with Crohn's disease, with less than one-third of patients aware of increased rates of surgery, and increased risk of post-operative recurrence. (72) However, educating patients with Crohn's disease as to the harmful effects of smoking may not be sufficient, with studies suggesting that an intervention has to be actively pursued in order for there to be a successful alteration in smoking behaviour. (73) Smoking cessation programmes are already integrated into health services such as the NHS, which runs public health campaigns like "smoke-free". (74) These programmes can act as a starting point that could be used to reach out to aid smokers with Crohn's disease to stop smoking. In addition, it is well known that smoking carries many other harmful effects that could also be reduced if such programmes were implemented. (75) However, other investigators have shown that the willingness of patients with Crohn's disease to engage with measures to facilitate smoking cessation is suboptimal. (76)

Interventions to aid smoking cessation with known efficacy include antidepressants, such as buproprion and nortriptyline, telephone counselling, varenicline, physician advice, and nicotine replacement therapy(77-80). With the ever increasing financial constraints on healthcare systems in the future, some providers may choose to decline to pay for the continued use of expensive therapy among patients with Crohn's disease who do not engage with smoking cessation interventions, or even implement surveillance for continued tobacco use, employing methods such as salivary cotinine or carbon monoxide testing as a means of restricting access to such drugs.

This approach is supported by a study from France, (12) where active smokers were provided with repeated counselling to help stop smoking, and their subsequent risk of flare of disease activity or need for glucocorticosteroids returned to a similar level to that of non-smokers, although it is important to point out that only 12% of smokers were able to remain abstinent for more than 1 year. In addition, a recent cost-utility analysis that compared four different smoking cessation strategies with no intervention, using Markov modelling with 5 years of follow-up, found that all smoking cessation strategies, including varenicline, nicotine replacement, counselling, or nicotine replacement and counselling combined, were all more cost-effective than no active intervention. (81) After probabilistic sensitivity analysis no active intervention was the most cost-effective option <1% of the time.

In summary, this meta-analysis has demonstrated that smokers, compared with non-smokers, have 55% to 85% higher rates of flares of disease activity, clinical recurrence rates after surgery that are two-fold higher, between 54% and 68% higher rates of need for first surgery, and are twice as likely to need a second operation (Figures 6 and 7). In the studies we identified, quitting smoking appeared to have a beneficial effect on disease course, particularly for flare of disease activity or need for a second operation. This study therefore provides summary estimates of the adverse effect of smoking on the natural history of Crohn's disease that can be communicated easily to patients with Crohn's disease who smoke, and used to encourage smoking cessation as a management strategy. The magnitude of the increase in odds of flare of disease activity or need for surgery seen in this meta-analysis among smokers, compared with non-smokers and ex-smokers, suggests that there is a need for trials of smoking cessation strategies as a primary medical intervention among patients with Crohn's disease who smoke.

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Table 1. Eligibility Criteria.

Prospective studies, or retrospective analyses of prospectively collected data, with longitudinal follow-up.
≥50 adult patients with Crohn's disease (participants aged ≥ 16 years).
Diagnosis of Crohn's disease based on histological, radiological, surgical, or endoscopic criteria.
Studied the effect of smoking on the natural history of Crohn's disease including: Flare of disease activity; Flare of disease activity after surgery; Need for any surgery; Need for first surgery; or Need for second surgery.

Table 2. Characteristics of Studies Reporting Effects of Tobacco Smoking on the Natural History of Crohn's Disease.

Study name and year	Country (no. of centres)	Setting	Method of assessment of smoking status	Outcome studied	No. of patients (% male)	Duration of follow up	Quality score
Sutherland 1990 (45)	Canada (1)	Secondary care	Questionnaire	Second surgery	174 (33.3%)	5 years	6
Duffy 1990 (36)	USA (2)	Secondary and tertiary care	Recorded on a database	Flare of disease activity Any surgery	74 (48.6%) 74 (48.6%)	6 months	7
Wright 1992 (51)	South Africa (1)	Tertiary care	Documented by the physician at diagnosis	Flare of disease activity	234 (32.6%)	10 years	7
Lindberg 1992 (35)	Sweden (1)	Tertiary care	Questionnaire	Any surgery	173 (not reported)	9-12 years	5

Cottone 1994 (50)	Italy (2)	Tertiary care	Questionnaire	Flare of disease activity after surgery Second surgery	182 (55.5%) 182 (55.5%)	98 months	8
Breuer-Katschinski 1996 (49)	Germany (1)	Tertiary care	Questionnaire	Second surgery	161 (45.6%)	10 years	7
Russel 1998 (15)	Pan-European (19)	Secondary and tertiary care	Recorded on a database	Any surgery	457 (47.7%)	1 year	7
Timmer 1998 (16)	Canada (31)	Secondary and tertiary care	Face-to-face interview	Flare of disease activity	152 (48.0%)	1 year	8
Cosnes 1999 (14)	France (1)	Tertiary care	Questionnaire	Flare of disease activity Any surgery	622 (39.3%) 622 (39.3%)	12-18 months	6
Moskovitz 1999 (46)	Canada (1)	Tertiary care	Recorded on a database	Flare of disease activity after surgery Second surgery	92 (52.2%) 92 (52.2%)	90 months	7

Yamamoto 1999 (47)	UK (1)	Tertiary care	Medical records, face-to-face interview, or questionnaire	Second surgery	141 (36.9%)	97 months	7
Cheikh 2002 (57)	Tunisia (4)	Secondary and tertiary care	Unclear	Flare of disease activity Any surgery	109 (53.7%) 109 (53.7%)	30 months	6
Fidder 2003 (31)	Israel (1)	Tertiary care	Medical records	Any surgery	162 (59.2%)	7.5 years	6
Sands 2003 (17)	USA (16)	Secondary and tertiary care	Recorded on a database	First surgery	237 (44.7%)	3 years	9
Ryan 2004 (56)	UK and USA (2)	Tertiary care	Questionnaire	Second surgery	264 (36.7%)	18.7 years	6
Kane 2005 (53)	USA (1)	Tertiary care	Medical records	Flare of disease activity after surgery	59 (33.9%)	250 weeks	7

De Diego 2006 (55)	Spain (1)	Secondary care	Unclear	Any surgery	178 (57.9%)	6 years	6
Kurer 2007 (54)	UK (1)	Secondary care	Medical records	Flare of disease activity after surgery	85 (68.2%)	36 months	7
Cullen 2007 (48)	Ireland (1)	Tertiary care	Recorded on a database	Flare of disease activity after surgery Second surgery	139 (39.6%) 139 (39.6%)	16.4 years	8
Solberg 2007 (37)	Norway (15)	Secondary and tertiary care	Recorded on a database	Flare of disease activity Any surgery	193 (not estimable) 231 (50.2%)	5 years	9
Renda 2008 (41)	Italy (1)	Tertiary care	Face-to-face interview	First surgery Second surgery	182 (59.3%) 110 (not estimable)	7 years	7
Picco 2009 (42)	USA (1)	Tertiary care	Medical records	First surgery	159 (57.2%)	5-6 years	8
Seksik 2009 (32)	France (1)	Tertiary care	Questionnaire	Flare of disease activity Any surgery	2443 (41.1%) 2443 (41.1%)	85-96 months	7

Radwan-Kwiatek 2009 (38)	Poland (1)	Tertiary care	Face-to-face interview	Flare of disease activity Any surgery	148 (54.1%) 148 (54.1%)	12-18 months	5
Szamosi 2010 (39)	Hungary (3)	Secondary and tertiary care	Face-to-face interview	First surgery	340 (45.6%)	Up to 300 months	8
Bernstein 2010 (52)	Canada (not applicable)	Population-based	Questionnaire	Flare of disease activity	218 (35.7%)	1 year	7
Song 2011 (40)	China (1)	Tertiary care	Medical records	First surgery	205 (68.9%)	5 years	8
Harper 2012 (33)	USA (1)	Tertiary care	Recorded on a database	Any surgery	240 (48.4%)	5 years	8
Lawrance 2013 (13)	Australia and New Zealand (6)	Secondary and tertiary care	Medical records	First surgery Second surgery	1115 (42.9%) 556 (not estimable)	16.6 years	9

Zabana 2013 (34)	Spain (3)	Tertiary care	Medical records or telephone call	Any surgery	246 (54.9%)	91 months	8
Moon 2014 (43)	South Korea (13)	Tertiary care	Questionnaire and medical records	First surgery	728 (71.2%)	5 years	8
Karczewski 2014 (44)	Poland (1)	Tertiary care	Medical records	First surgery Second surgery	55 (41.8%) 55 (41.8%)	average 2.4 years	3
Lunney 2015 (58)	Australia (6)	Secondary and tertiary care	Recorded on a database	First surgery Second surgery	623 (45.5%) 257 (not estimable)	9 years	9

FIGURES

Figure 1. Flow Diagram of Studies Identified in the Systematic Review and Meta-analysis.

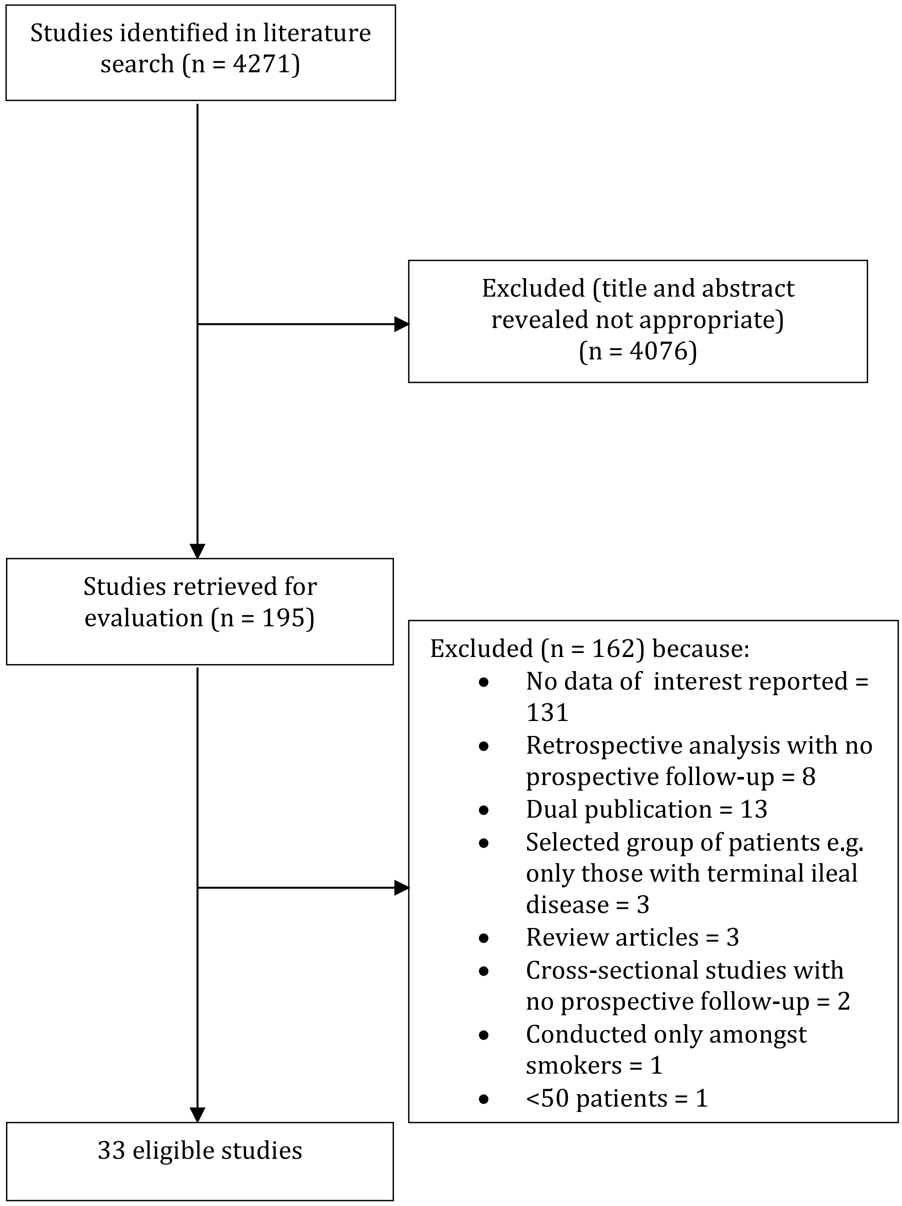


Figure 2. Forest Plot of Effect of Smoking on Flares of Disease Activity.

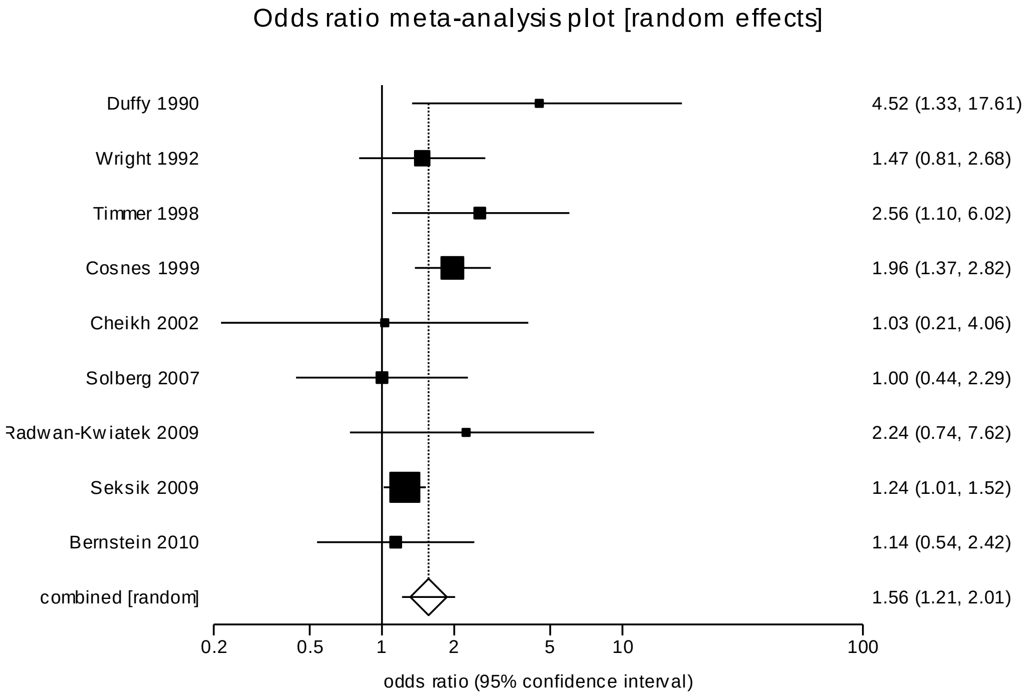


Figure 3. Forest Plot of Effect of Smoking on Need for Any Surgery.

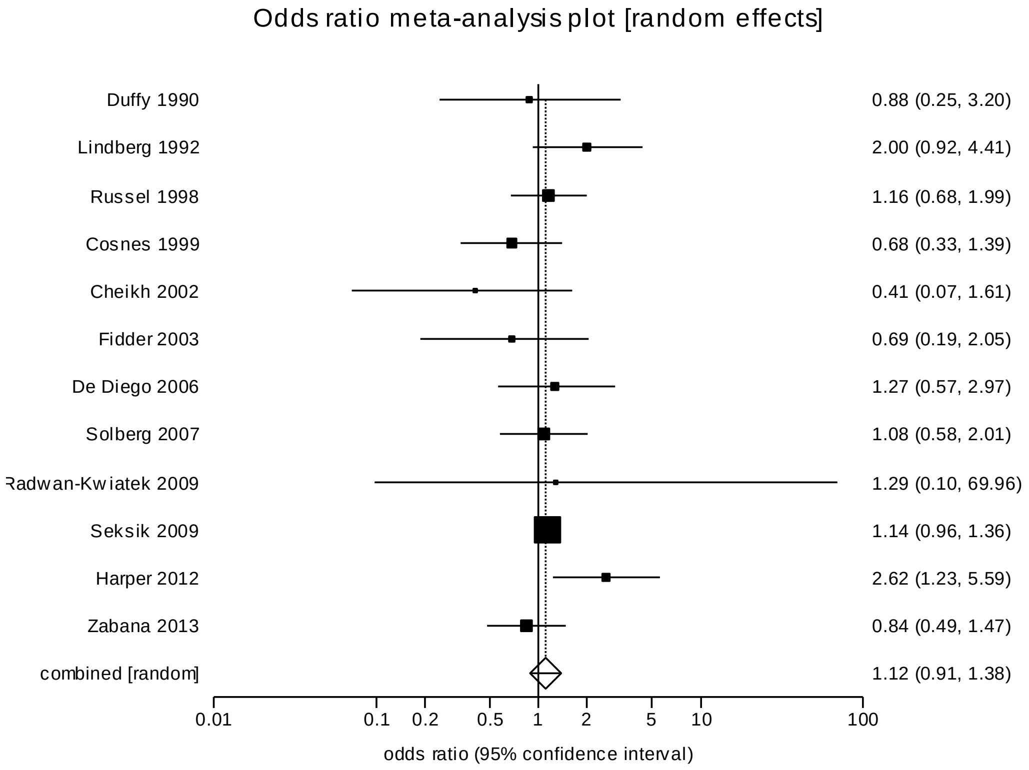


Figure 4. Forest Plot of Effect of Smoking on Need for First Surgery.

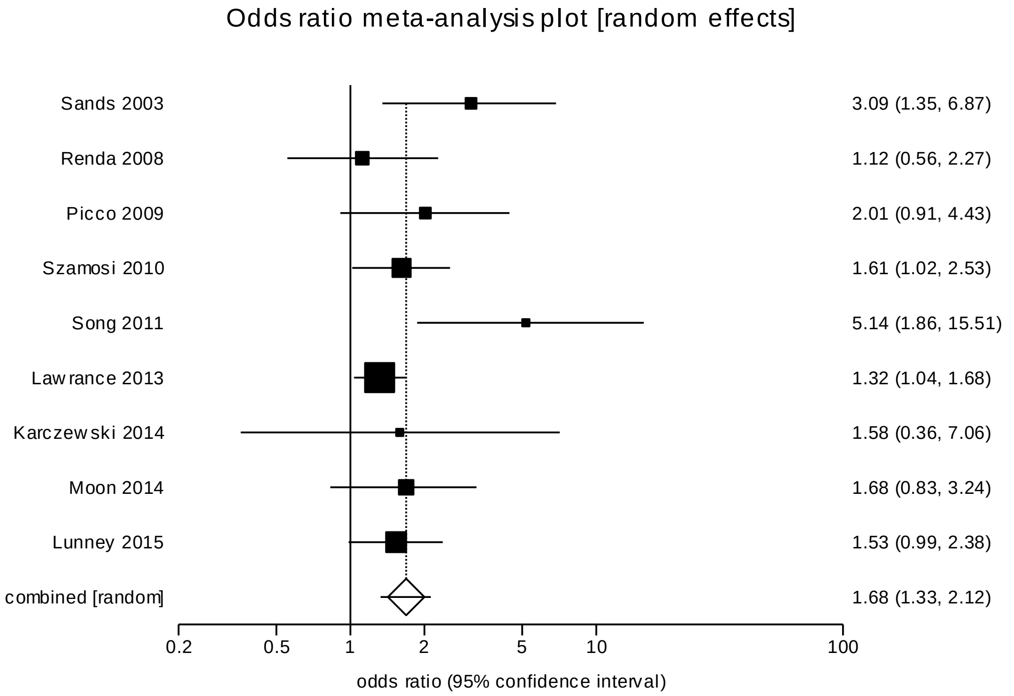


Figure 5. Forest Plot of Effect of Smoking on Need for Second Surgery.

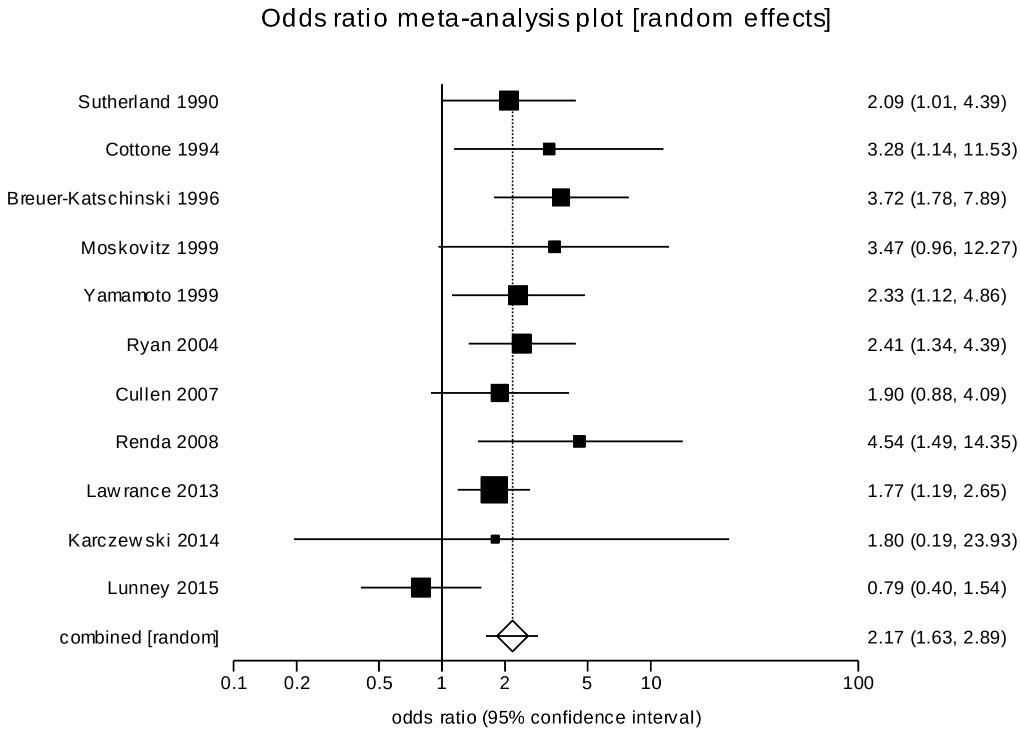


Figure 6. Summary Effects of Tobacco Smoking on Flare of Disease Activity.

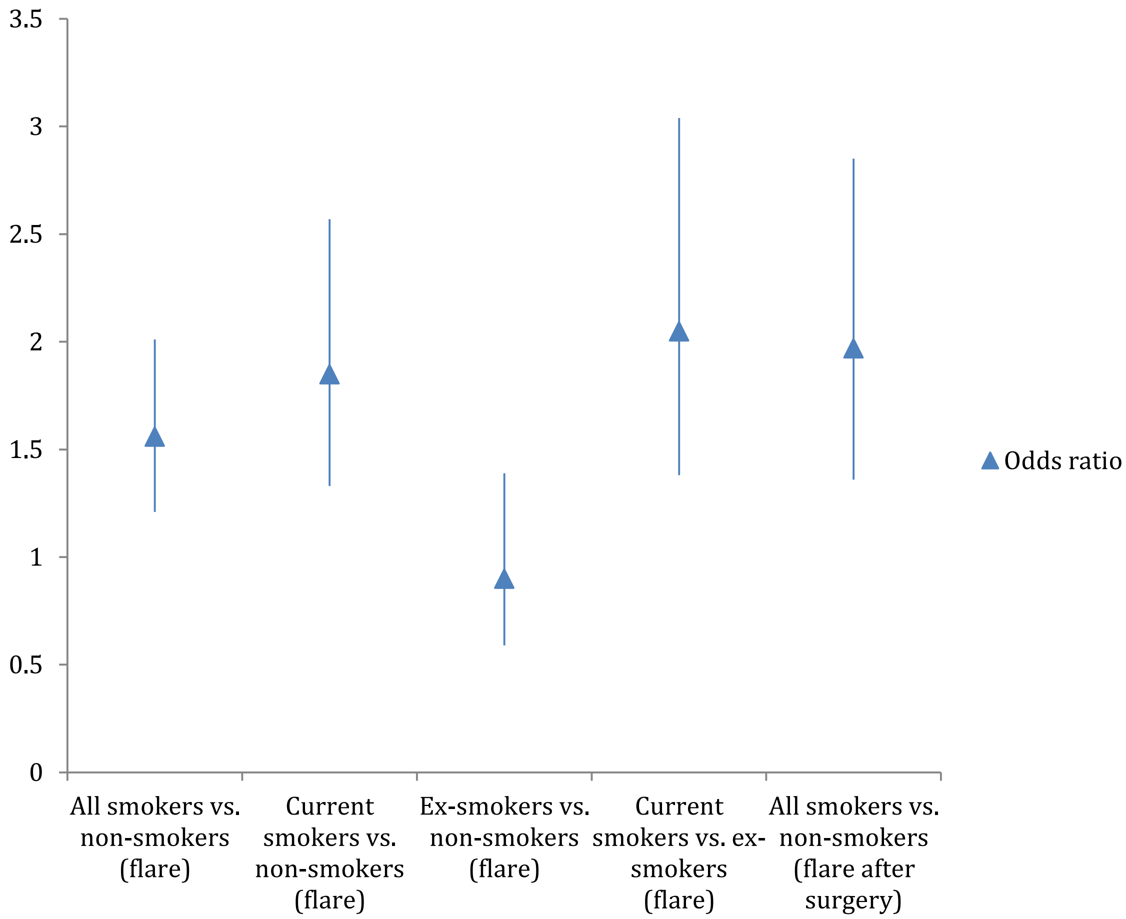
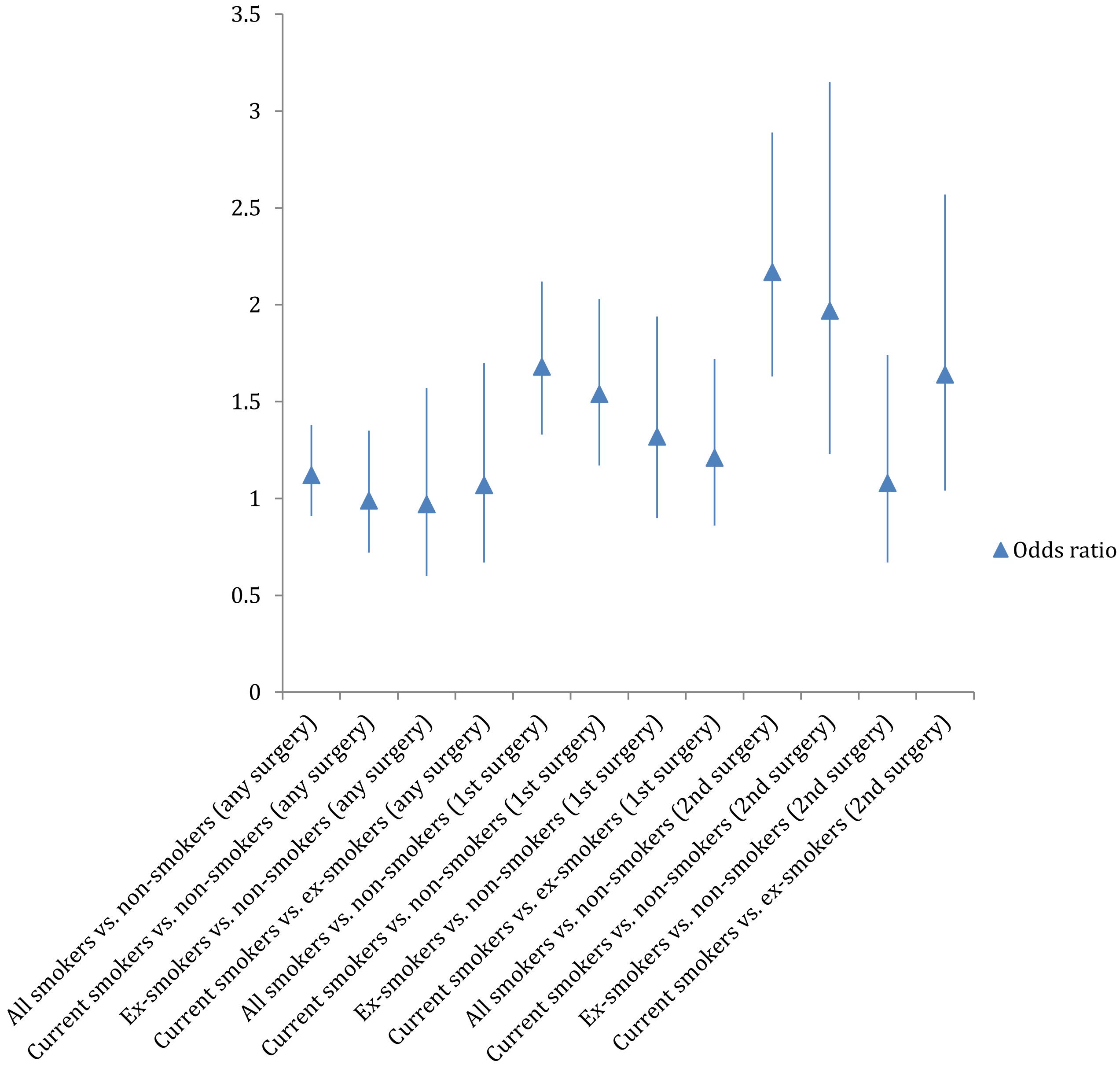


Figure 7. Summary Effects of Tobacco Smoking on Need for Surgery.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6 and 26
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6 and 26
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6-7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9, 27-32
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 and 33
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	27-32
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	27-32
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	27-32
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-12 and 34-37
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	27-32
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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