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# Adverse effect of smoking on surgical site infection following ankle and calcaneal fracture fixation: a meta-analysis

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- *Purpose:* Studies have reported conflicting findings on the relationship between smoking and surgical site infection (SSI) post fixation for ankle and calcaneal fractures. This meta-analysis explored the effect of smoking on SSI incidence following open reduction and internal fixation (ORIF) of these fractures.
- *Methods:* Full-text studies on smoking's influence on post-ORIF SSI rates for closed ankle and calcaneal fractures were sourced from the PubMed, Embase, and Cochrane databases, with no consideration given to language or publication date. Study quality was appraised using the Newcastle–Ottawa Scale. Odds ratios (OR) and the corresponding 95% CIs were determined using random-effects models. This meta-analysis adhered to the PRISMA guidelines and was registered with PROSPERO (CRD42023429372).
- *Results:* The analysis incorporated data from 16 cohort and case–control studies, totaling 41 944 subjects, 9984 of whom were smokers, with 956 SSI cases. Results indicated smokers faced a higher SSI risk (OR: 1.62; 95% CI: 1.32–1.97, $P < 0.0001$) post ORIF, with low heterogeneity ($I^2 = 26\%$). Smoking was identified as a significant deep SSI risk factor (OR: 2.09; 95% CI: 1.42–3.09; $P = 0.0002$; $I^2 = 31\%$). However, the subgroup analysis revealed no association between smoking and superficial SSI (OR: 1.05; 95% CI: 0.82–1.33; $P = 0.70$; $I^2 = 0\%$).
- *Conclusion:* Smoking is associated with increased SSI risk after ORIF for closed ankle and calcaneus fractures. Although no clear link was found between superficial SSI and smoking, the data underscore the negative influence of smoking on deep SSI incidence.

Keywords: ankle fractures; calcaneal fractures; meta-analysis; smoking; surgical site infection

## Introduction

Smoking, a widespread habit characterized by the inhalation of nicotine-rich tobacco smoke (1), has few proven benefits, such as stress reduction (2, 3), but multiple established adverse effects, including a detrimental impact on mental health (4, 5, 6, 7, 8). Smoking is associated with impaired wound healing and increased susceptibility to surgical site infections (SSIs) (9, 10, 11).

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SSIs, occurring in 1–20% of patients after ankle and calcaneal fracture surgeries, result in substantial treatment costs and delayed treatment, potentially leading to severe complications, including amputation or mortality (12, 13, 14). Whereas open fractures, diabetes, and obesity are universally acknowledged risk factors (15, 16, 17, 18, 19, 20), the contribution of smoking remains contentious, with conflicting evidence from several studies and meta-analyses (14, 21, 22, 23).

Previous meta-analyses have noted the detrimental influence of smoking on orthopedic and trauma outcomes, including increased fracture rates and delayed healing (24, 25, 26). However, these meta-analyses have overlooked the specific relation between smoking and SSI subcategories and have often failed to exclude open fractures, a significant confounder in wound infections post open reduction and internal fixation (ORIF) (27, 28, 29, 30).

Addressing this research gap, our comprehensive meta-analysis examines the effect of smoking on SSI incidence following ORIF for closed fractures of the ankle and calcaneus, utilizing a corpus of previously published data.

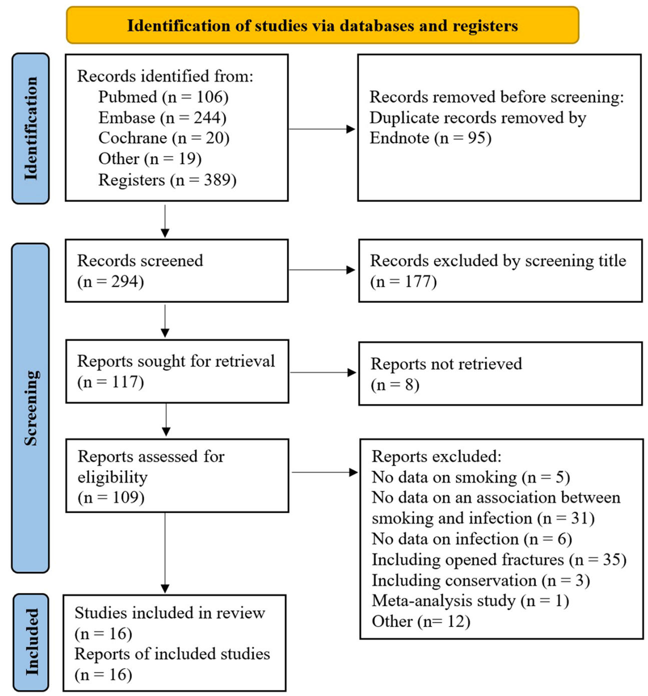


**Figure 1**

PRISMA 2020 flow diagram for new systematic reviews incorporating database and register searches only.

# Methods

## Study design and search strategy

In this meta-analysis, following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (31), investigators DNAT and TTN employed a comprehensive search strategy across PubMed, Embase, and Cochrane databases, Wiley Library online, and Google Scholar. Search terms included 'smoking', 'cigarettes', or 'tobacco' in conjunction with 'ankle fracture', 'foot fracture', or 'calcaneus fracture', and 'infection' or 'SSI'. No time or language restrictions were applied, and studies published through April 2023 were candidates for inclusion. Screening of titles and abstracts was conducted independently by two investigators (YJK and YPC), with conflicts resolved by a third reviewer. Inclusion criteria required studies involving ankle and calcaneal fixation, which reported data on smoking and SSI, allowing calculation of the odds ratio (OR) and 95% CI (Fig. 1). The meta-analysis is registered with the International Prospective Register of Systematic Reviews (CRD42023429372).

## Eligibility criteria

This study included studies with (1) a prospective or retrospective design, (2) a cohort or case–control methodology, (3) data on smoking status, and (4) data on SSI following ORIF for foot or ankle fractures.

Exclusion criteria included studies: (1) involving patients with open fractures, (2) lacking sufficient data for calculating OR and 95% CI in smokers and non-smokers, and (3) unavailable in full-text format.

## Data extraction and management

Two reviewers (DNAT and BTTN) independently extracted data and metadata from the studies; specifically, they extracted data on study identifiers, study characteristics (e.g. design, criteria, follow-up duration, definitions of smoking and SSI), and participant demographics, frequency of smoking, and frequency of SSI.

The methodological quality of each study was assessed on the basis of the Newcastle–Ottawa Scale (NOS) (32). A third author (JYK) adjudicated any discrepancies between the assessments of the two authors. In the NOS, stars are given in three categories: (1) selection, 0–3 stars; (2) comparability, 0–2 stars; and (3) outcome (for cohort studies) or exposure (for case–control studies), 0–3 stars. Studies rated seven or more stars on the NOS were deemed to be of high quality (Supplementary Table 1, see section on supplementary materials given at the end of this article).

## Definition of smoking

A subgroup analysis based on whether the individual is a current or former smoker was conducted for studies with explicit, consistent definitions of 'current smoking'.

## Definition of surgical site infection

Per the Centers for Disease Control and Prevention (CDC) guidelines (33), superficial SSIs were identified

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as infections affecting the skin or subcutaneous tissue around the surgical incision within 30 days postoperatively. Deep SSIs were classified as infections affecting deeper fascial and muscle layers, appearing within 1 year after surgery.

Additional surgical procedures such as debridement were typically required for deep SSI management, whereas superficial SSIs were generally managed in a conservative manner (34).

## Statistical analysis

We used ReviewManager 5.3 software to calculate the OR and 95% CI in analyses of dichotomous data related to smoking and infection status. Significance was indicated by $P < 0.05$. In addition, $P < 0.1$ in a $Q$ test and $I^2 > 50\%$ indicated heterogeneity (35). All forest plots were constructed based on a random-effects model to account for potential variability. Funnel plots were used to visually examine potential publication bias, while Egger's test was used to determine small-study effects; $P < 0.05$ indicated significant publication bias. Meta-regression with Comprehensive Meta-Analysis 3.0 (CMA V3) was performed to identify confounders.

# Results

## Study identification

A thorough search across Embase (224 articles), PubMed (106 articles), Cochrane (20 articles), and additional resources (19 articles) yielded a total of 389 articles. We removed duplicates (95 articles), screened titles and abstracts (177 articles), and were not able to retrieve a few studies (8 articles). A detailed review resulted in the exclusion of 93 studies. Finally, 16 studies were included in our meta-analysis (Fig. 1).

## Quality assessment

The NOS scores for the 16 included studies are presented in Supplementary Table 1. Of these, seven were rated as high quality (≥7 stars), and nine were rated as medium quality (4–6 stars).

## Study characteristics

The meta-analysis included 16 studies, comprising ten cohorts and six case–control studies, totaling 41 944 patients, including 9984 patients who smoked and 956 patients with SSI. The mean age of participants ranged from 38.0 to 54.8 years, and 56.8% of all participants were women. Although some studies did not detail the ascertainment of smoking status, eight provided data on the number of 'current smokers' (13, 19, 36, 37, 38, 39, 40, 41). In addition, six studies conducted follow-up at a period of at least 1 year (13, 14, 36, 37, 42, 43), and eight studies adopted the CDC's definition of SSI (13, 14, 36, 37, 44, 45). Further characteristics of the included studies are available in Table 1.

## Association of smoking and SSI

Our analysis, detailed in Fig. 2, encompasses 16 studies examining the relationship between smoking and post-ORIF SSI in closed ankle and calcaneal fractures. The non-smoking group had a lower risk of SSI; their ORs relative to the smoking group were 1.62 (95% CI: 1.32–1.97; $P < 0.00001$) for SSI, 1.53 (95% CI: 1.26–1.86; $P < 0.0001$) for ankle fractures, and 2.13 (95% CI: 1.14–3.97; $P = 0.02$) for calcaneal fractures. Low heterogeneity was observed among the 16 studies, reflected by a nonsignificant Cochran Q statistic ($P = 0.16$) and an $I^2$ of 26%.

To account for discrepancies in smoking patterns, criteria used to define smoking, and in follow-up duration, we conducted a subgroup analysis where studies were distinguished according to one or some of these criteria. The findings are presented in Table 2 and Supplementary Figs. 1, 2, 3 and 4. Current smokers had an OR of 1.77 (95% CI: 1.25–2.51). The effect size was greater for studies with a follow-up period of 1 year or more (OR: 1.90; 95% CI: 1.41–2.57), relative to studies without, and studies adhering to the CDC's definition of SSI (OR: 1.85; 95% CI: 1.47–2.33), relative to studies that did not. The three studies that met all these criteria had an OR of 2.13 (95% CI: 1.54–2.94), which was higher than that of the entire sample.

## Association of smoking and superficial SSI

Figure 3 provides a summary of the meta-analysis regarding the influence of smoking on superficial SSI rates. The OR for the non-smoking group vs the smoking group was 1.05 (95% CI: 0.82–1.33; $P = 0.70$; $I^2 = 0\%$). Among the studies, four that focused on ankle fractures had an OR of 1.04 (95% CI: 0.80–1.36; $P = 0.38$; $I^2 = 2\%$), whereas two regarding calcaneal fractures had an OR of 1.02 (95% CI: 0.37–2.82; $P = 0.97$; $I^2 = 0\%$). The smoking and non-smoking groups did not significantly differ with respect to superficial SSI rate ($P > 0.05$ in three forest plots).

## Association of smoking and deep SSI

The influence of smoking on the risk of deep SSI was assessed through a meta-analysis of six studies. The results in Fig. 4 demonstrated a significantly elevated risk of deep SSI in smokers (OR: 2.09; 95% CI: 1.42–3.09; $P = 0.0002$). Notably, the influence of smoking was more pronounced in the calcaneal fracture group (OR: 2.89; 95% CI: 1.47–5.69; $P = 0.002$) than in the ankle fracture group (OR: 1.73; 95% CI: 1.07–2.79; $P = 0.02$).

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**Table 1** Characteristics of included studies.

| Study | Year | Country | Study design | Follow-up | Smoking status | SSI definition | Fracture | Patients: Total, *n* | Patients: % Females | Smoker | SSI |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Jensen *et al.* (13) | 2023 | Denmark | PS | ≥1 year | Current | CDC | Ankle | 588 | 53.2 | 59 | 119 |
| Sagherian *et al.* (12) | 2022 | USA | RS | 30 days | Not clear | Self-defining | Ankle | 33741 | 58.7 | 99 | 334 |
| Shen *et al.* (14) | 2022 | China | RS | ≥1 year | Not clear | CDC | Calcaneal | 302 | 41.4 | 10 | 24 |
| Zhao *et al.* (36) | 2022 | China | RS | ≥1 year | Current | CDC | Ankle | 378 | 55.6 | 21 | 70 |
| Lu *et al.* (37) | 2022 | China | RS | ≥1 year | Current | CDC | Calcaneal | 1400 | 40.4 | 8 | 24 |
| Sato *et al.* (44) | 2021 | Japan | RS | ≥6 months | Not clear | CDC | Ankle | 1201 | 42.6 | 23 | 69 |
| Davey *et al.* (38) | 2021 | Ireland | RS | ≥6 months | Current | Self-defining | Calcaneal | 104 | 56.7 | 4 | 5 |
| Braunstein *et al.* (42) | 2020 | Germany | PS | ≥1 year | Not clear | NI | Ankle | 32 | 56.3 | 1 | 2 |
| Liu *et al.* (45) | 2020 | China | RS | ≥4 months | Not clear | CDC | Ankle | 1532 | 42.0 | 10 | 45 |
| Abdelgaid *et al.* (43) | 2018 | Kuwait | PS | ≥34 months | Not clear | NI | Ankle | 47 | 61.7 | 1 | 3 |
| Su *et al.* (40) | 2017 | China | PS | NI | Current | Self-defining | Calcaneal | 999 | 73.3 | 11 | 17 |
| Olsen *et al.* (19) | 2017 | Denmark | RS | >30 days | Current | Self-defining | Ankle | 1043 | 58.7 | 21 | 64 |
| Sun *et al.* (41) | 2017 | China | RS | NI | Current | CDC | Ankle | 1247 | 46 | 11 | 46 |
| Naumann *et al.* (41) | 2017 | Norway | RS | NI | Current | Self-defining | Ankle | 567 | 56.8 | 10 | 29 |
| Soni *et al.* (48) | 2014 | UK | RS | NI | Not clear | Self-defining | Calcaneal | 69 | 27.5 | 6 | 10 |
| Schepers *et al.* (49) | 2013 | Netherlands | RS | ≥6 months | Not clear | CDC | Ankle | 101 | 60.4 | 4 | 14 |

CDC, Centers for Disease Control and Prevention; NI, no information; PS, prospective study; RS, retrospective study; SSI, surgical site infection.

## Publication bias

Publication bias was assessed using a funnel plot, as shown in Fig. 5, which plotted the logarithmic OR for smoking vs non-smoking against their respective standard errors. Visually, the funnel plot displayed symmetry. Further confirmation of the absence of publication bias was obtained through Egger's test, which yielded a *P*-value of 0.53, supporting the lack of publication bias in our study.

# Discussion

Deep infections following ORIF for fractures can lead to significant complications and potential treatment failure. Consequently, understanding and managing the associated risk factors for SSI is imperative. Our meta-analysis demonstrates that smoking significantly heightens the SSI risk in ORIF-treated ankle and calcaneal fractures, with an OR of 1.62 (95% CI: 1.32–1.97; $P < 0.00001$). Notably, the risk of deep SSI was found to be considerably higher than that of superficial SSI among smokers, with ORs of 2.09 (95% CI: 1.42–3.09; $P = 0.0002$) and 1.05 (95% CI: 0.82–1.33; $P = 0.70$), respectively.

Smoking has been shown to negatively affect SSIs by contributing to tissue ischemia and disrupted inflammatory processes (10, 11). A 2022 meta-analysis by Liu *et al.* involving 11 studies with 218 567 participants in total reported an association with non-smoking or smoking cessation with fewer postoperative wound healing complications (OR: 0.59; 95% CI: 0.43–0.82, $P < 0.001$) (48). However, for ORIF-treated ankle and calcaneal fractures, Shao *et al.* and Zhang *et al.* reported nonsignificant smoking effects on SSI rate with ORs of 1.63 (95% CI: 0.95–2.8; $P > 0.05$; $I^2 = 73.7\%$) and 1.79 (95% CI: 0.97–3.30; $P > 0.05$; $I^2 = 79.6\%$), respectively (22, 23). In contrast, our studies jointly demonstrated a substantial correlation of smoking with SSI in the ankle (OR: 1.53; 95% CI: 1.26–1.86; $P < 0.0001$; $I^2 = 21\%$) and calcaneal fractures (OR: 2.13; 95% CI: 1.14–3.97; $P = 0.02$; $I^2 = 36\%$) (Fig. 2). Our study's specificity lies in its focus on smoking in the context of closed fractures and SSI, and we observed low heterogeneity among studies at 21% and 36% for ankle and calcaneal fracture groups, respectively. Our study distinguishes itself from previous works by focusing on smoking in the context of closed fractures and SSI. Zhang's study, though it had a specific definition of SSI, included studies in patients with open fractures. Shao's analysis focused on patients with closed fractures but defined the outcome as 'wound complications', a broader definition than SSI.

Several studies highlight the varying effects of smoking cessation timing on postoperative wound healing. Kuri *et al.* found that patients who abstained from smoking for more than 3 weeks prior to surgery experienced less impaired wound healing (49). Cavichio *et al.*

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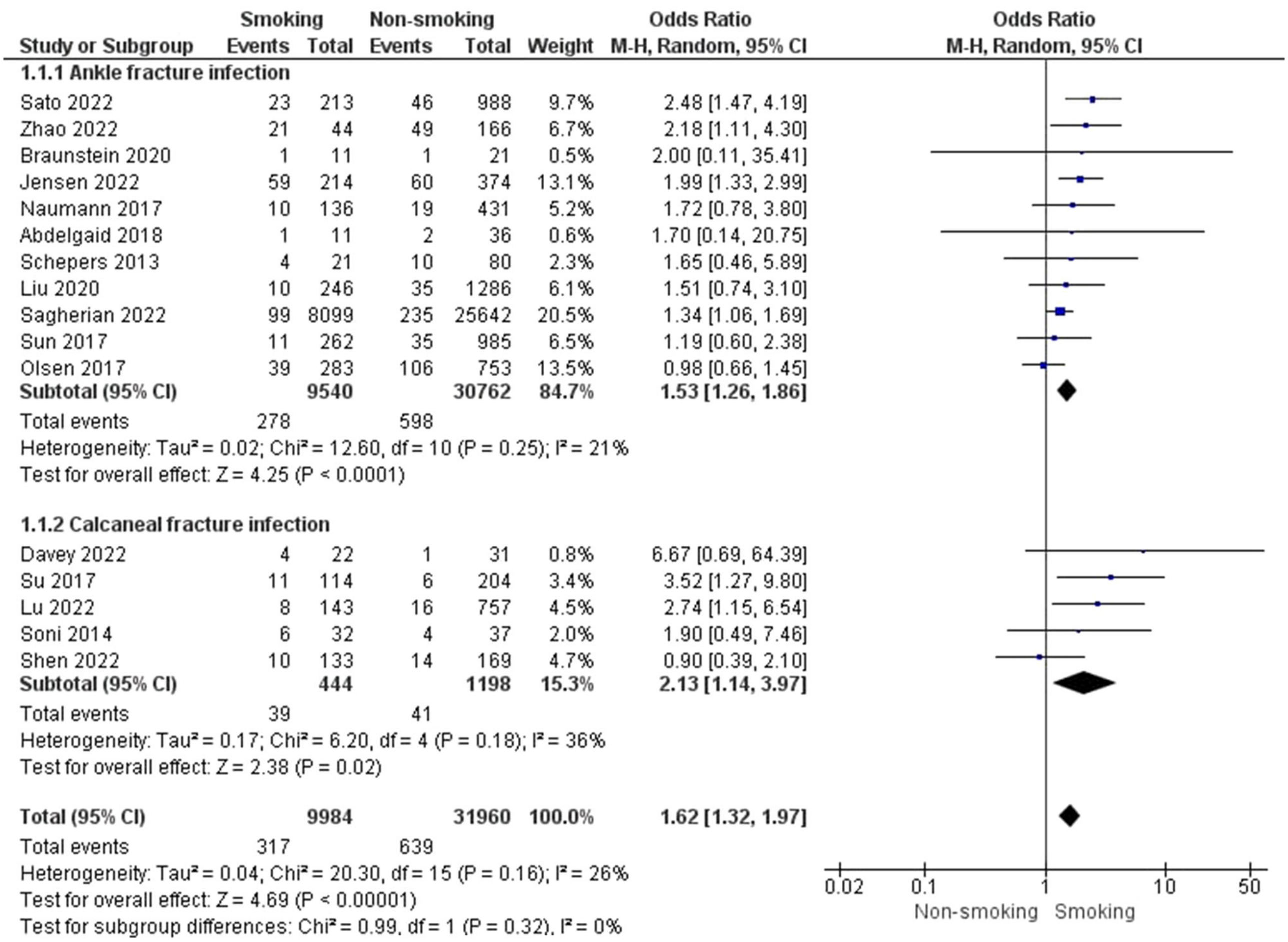


**Figure 2**

Comparison of SSI rates between smoking and non-smoking groups after ORIF of ankle and calcaneal fractures (12, 13, 14, 19, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47).

corroborated this finding in their 2014 meta-analysis, showing that stopping smoking at least 4 weeks before surgery reduced complications related to wound healing (50). Our meta-analysis included a single study with subgroups of smokers, ex-smokers (those who quit for 6 months or longer), and non-smokers (38). Of the 16 studies reviewed, eight identified current smokers, and eight did not specify smoking status. Despite differences in the definitions of smoking between the included studies, the meta-analysis of these nine studies still indicated an increased incidence of SSI in smokers (OR: 1.77; 95% CI: 1.25–2.51; $P = 0.002$; Supplementary Fig. 1).

The CDC issued SSI prevention guidelines in 1999; they defined a 30-day timeframe for superficial or deep SSI without implants and 1 year for those with implants (51). In 2016, the CDC amended these guidelines, reducing the post-discharge surveillance for deep infection with implants to 90 days for more efficient monitoring and prompt feedback (52, 53). This change,

**Table 2** Association between smoking and SSI by subgroups of current smoking, follow-up duration, and CDC-defined SSI.

| | | | | Heterogeneity | | |
|---|---|---|---|---|---|---|
| **Studies included** | **No. of reports** | **OR** (95% CI) | ***P*** | *Q* | *P* | $I^2$, % |
| All studies | 16 | 1.62 (1.32–1.97) | 0.02 | 20.3 | 0.16 | 26 |
| (1) Current smoking | 8 | 1.77 (1.25–2.51) | 0.002 | 13.95 | 0.05 | 50 |
| (2) Follow-up ≥1 year | 6 | 1.90 (1.41–2.57) | <0.00001 | 3.92 | 0.56 | 0 |
| (3) SSI following CDC | 8 | 1.85 (1.47–2.33) | <0.00001 | 7.05 | 0.42 | 1 |
| (1) + (2) + (3) | 3 | 2.13 (1.54–2.94) | <0.00001 | 0.44 | 0.80 | 0 |

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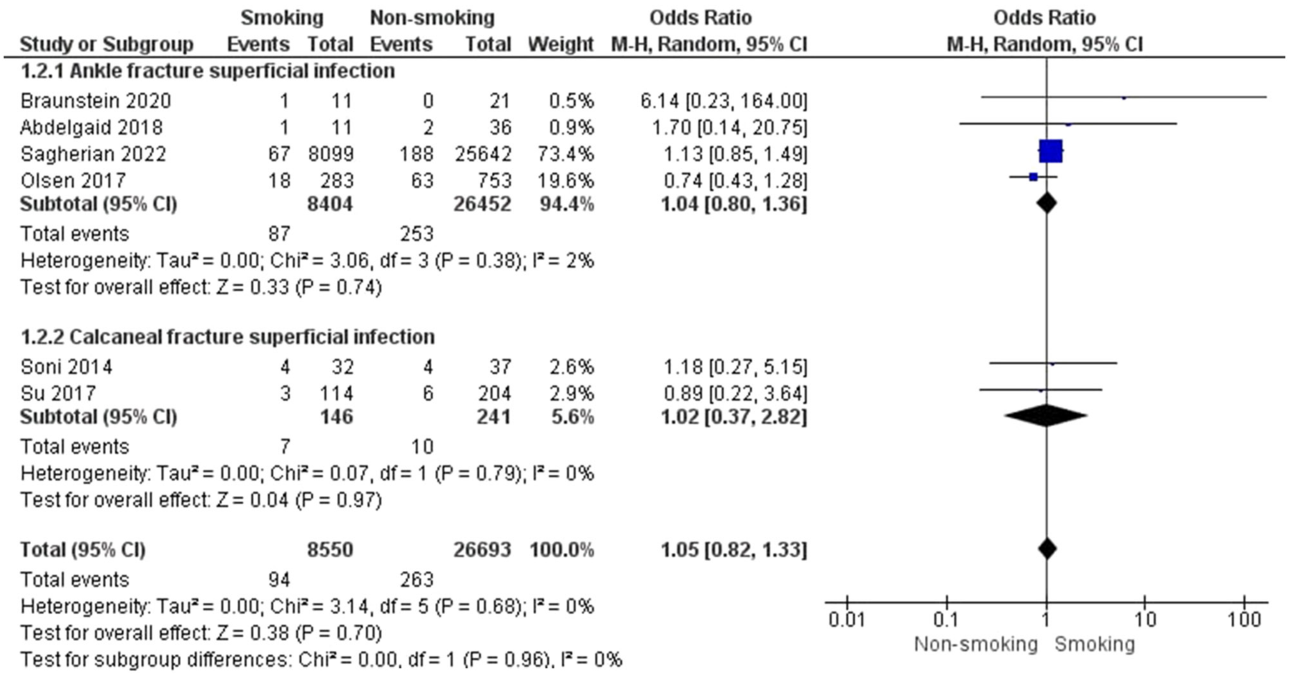


**Figure 3**

Comparison of superficial SSI rates between the smoking and non-smoking groups after ORIF of ankle and calcaneal fractures (12, 19, 40, 42, 43, 46).

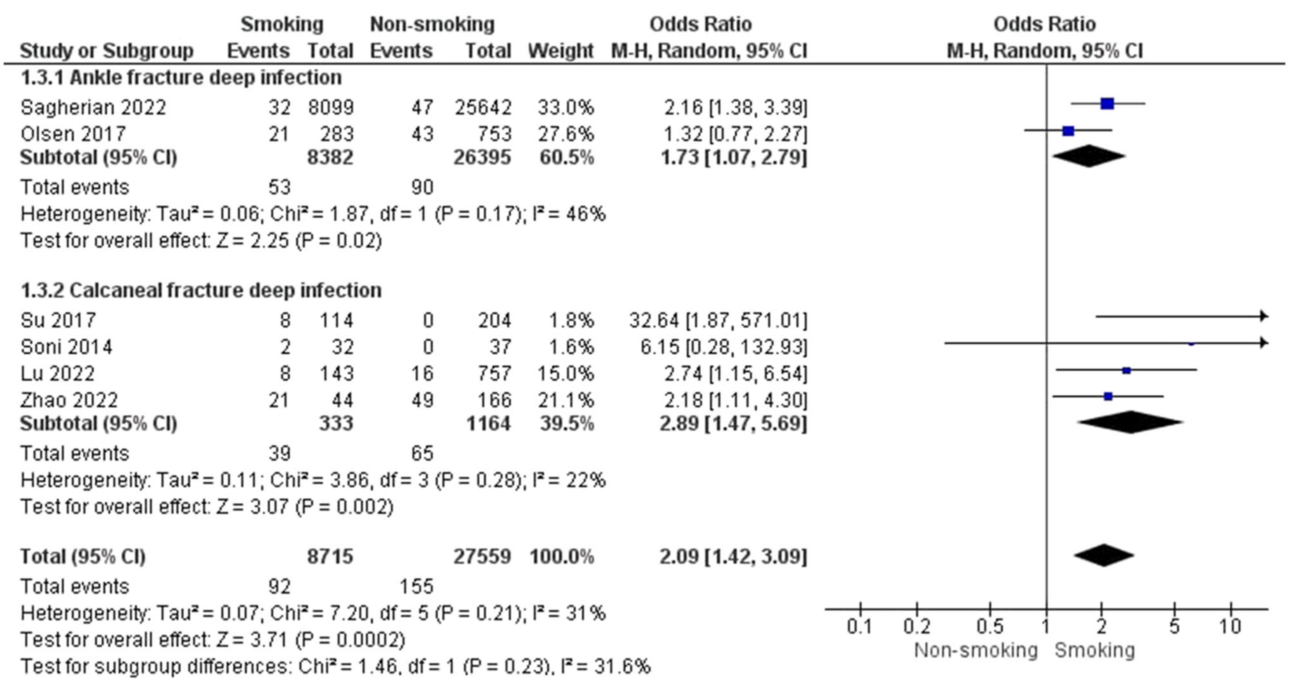


**Figure 4**

Comparison of deep SSI rates between the smoking and non-smoking groups after ORIF of ankle and calcaneal fractures (12, 19, 36, 37, 40, 46).

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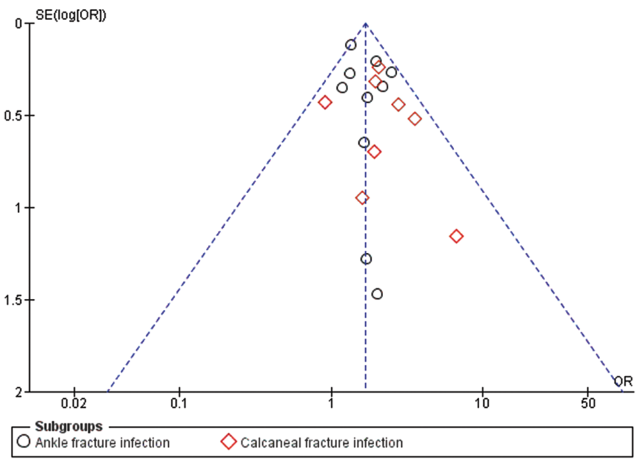


**Figure 5**

Funnel plot for the detection of publication bias.

however, has sparked debate among orthopedists due to concerns that SSIs may be overlooked (53, 54). As such, many orthopedic researchers, including those in our review, adhere to the 1999 CDC definition of SSI. Subgroup analyses based on this definition (eight studies) and a 1-year follow-up period (six studies) demonstrated statistically significant OR greater than 1 when comparing non-smokers to smokers ($P$ < 0.05) (Supplementary Figs. 2 and 3).

Although superficial SSIs are generally milder and can be effectively treated with antibiotics or physiotherapy (51, 54), they can lead to severe complications, including deep SSI, if left untreated (55, 56). In a meta-analysis by Xu *et al.* on 1059 patients with non-pathological fractures, no significant difference in superficial SSI rates was found between smokers and non-smokers (OR: 1.27; 95% CI: 0.73–2.21; $P$ = 0.39, $I^2$ = 0%) (57), consistent with our findings (OR: 1.05; 95% CI: 0.82–1.33; $P$ = 0.70; $I^2$ = 0%; Fig. 3). Nonetheless, larger-scale studies have reported a higher risk of superficial SSI in smokers, including those by Fan Chiang *et al.* (5 337 996 surgical cases) (58) and Turan *et al.* (635 265 patients) (59). Therefore, further investigation into the association between smoking and superficial SSI is warranted.

Sorensen and Xu's meta-analyses have confirmed the negative effect of smoking on deep SSI, both reporting ORs of 1.79 (95% CI: 1.57–2.04; $P$ < 0.001) (57, 60). Our study corroborated their findings, observing a higher risk of deep SSI in smokers undergoing ORIF for ankle and calcaneal fractures (OR: 2.09; 95% CI: 1.42–3.09; $P$ = 0.0002; $I^2$ = 31%; Fig. 4).

Smoking's potential to induce hypoxia and ischemia in fractured bones has led to speculation about its negative impact on the bone-healing process (61, 62). Recent meta-analyses have substantiated this concern, establishing smoking as a risk factor for delayed bone union and non-union (57, 63). While these findings are well-supported, it is noteworthy that research specifically addressing the influence of smoking on ankle fracture surgery is limited. As our finding, only one study of Matson in 2017 revealed that smoking patients exhibited a significantly higher incidence of delayed union compared to their non-smoking counterparts ($P$ = 0.035) following closed ankle fractures treated with ORIF, while no statistically significant difference was observed in the mean time to union (64). Therefore, for a more comprehensive and in-depth understanding, further studies are required to evaluate bone healing in smoking patients following ORIF for ankle and calcaneal fractures.

Our study, however, has some limitations. The retrospective nature of the majority (14 out of 16) of the included studies could introduce biases, potentially affecting evidence quality. Additionally, heterogeneity in the definitions of smoking, SSI, and follow-up time necessitated subgroup analysis. Nevertheless, our study's robustness is supported by consistent findings across subgroups, a low level of heterogeneity, and the absence of publication bias.

## Conclusion

Our study provides strong evidence for the adverse effects of smoking on SSI. Despite a lack of evidence linking smoking to superficial SSI, a substantial correlation between smoking and increased deep SSI risk is evident. We, therefore, recommend for clinicians to adopt treatment strategies that are specific to patients who smoke, especially those undergoing ORIF surgeries for ankle and calcaneal fractures.

**Supplementary materials**

This is linked to the online version of the paper at https://doi.org/10.1530/EOR-23-0139.

**ICMJE Conflict of Interest Statement**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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