This systematic review and meta-analysis aimed to analyse negative effects of smoking in orthopaedic and trauma patients.

A PubMed search was carried out for studies published until July 2020 regarding effects of smoking on fracture risk, nonunion, infection after orthopaedic surgery, and persisting nonunion after scaphoid nonunion surgery. Random effects models calculated for outcome parameters, and relative risks (RR) with 95% confidence intervals are provided. No adjustments for covariates were made. Heterogeneity was assessed with Higgins’ I², publication bias with Harbord’s p (Hp), sensitivity analysis performed on funnel plots and quality of studies was analysed using the Newcastle-Ottawa Scale.

Of 3362 retrieved entries, 69 were included in the final analysis. Unadjusted RR for smokers to develop vertebral (six studies, seven entries; RR: 1.61; p = 0.008; I² = 89.4%), hip (11 studies, 15 entries; RR: 1.28; p = 0.007; I² = 84.1%), and other fractures (eight studies, 10 entries; RR: 1.75; p = 0.019; I² = 89.3%) was significantly higher. Postoperative infection risk was generally higher for smokers (21 studies; RR: 2.20; p < 0.001; I² = 58.9%), and remained upon subgroup analysis for elective spinal (two studies; RR: 4.38; p < 0.001; I² = 0.0%) and fracture surgery (19 studies; RR: 2.10; p < 0.001; I² = 58.5%). Nonunion risk after orthopaedic (eight studies; RR: 2.15; p < 0.001; I² = 35.9%) and fracture surgery (11 studies; RR: 1.85; p < 0.001; I² = 39.9%) was significantly higher for smokers, as was persisting nonunion risk after surgery for scaphoid nonunion (five studies; RR: 3.52; p < 0.001; I² = 0.0%). Sensitivity analysis for each model reduced heterogeneity whilst maintaining significance (all I² < 20.0%).

Smoking has a deleterious impact on fracture incidence, and (subsequent) development of nonunions and postoperative infections.

Keywords: fracture risk; nonunion risk; smoking

Introduction

Since the 1960s, tobacco smoking has been a well-known risk factor for development of malignancies and cardiovascular disease, and has been associated with increased mortality rates.1–3 According to the World Health Organization (WHO), the prevalence of tobacco smoking in 2018 was 13.0% in Norway, 19.2% in the United Kingdom, 25.1% in the United States, and 29.1% in Austria.4 As further detrimental effects of smoking were recognized, the negative effects of tobacco smoking on the musculoskeletal system, including bone healing, became likewise apparent.5–8 In active smokers, among other factors, bone metabolism is reduced by tissue hypoxia, reduced blood supply, altered activity of osteoblasts and osteoclasts resulting in overall impaired bone turnover, and decreased calcium absorption.8–13 More than 4000 toxins released by cigarettes have been identified that could have a negative effect on bone metabolism.14

Previous meta-analyses have reported on a negative impact of smoking regarding various outcome parameters in orthopaedics and trauma, including incidence of fracture, risk for lateral epicondylitis, fracture nonunion and postoperative complication rate.15–18
The aim of the current systematic review and meta-analysis was to comprehensively analyse the potential negative effect of smoking on fracture risk, nonunion risk after elective orthopaedic procedures and fracture surgery in general, postoperative infection risk after trauma and orthopaedic surgery, and persisting nonunion after surgical correction of scaphoid nonunion.

**Methods**

**Search strategy and selection criteria**

For this systematic review and meta-analysis, the review process was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search in PubMed was performed, using the search terms: (smoking) AND (fracture), (smoking) AND (traumatology), and (smoking) AND (bone healing). Any study published until July 2020 and being available in PubMed was potentially eligible, with no retrospective time limit determined. Full search codes are listed in Supplemental Table 1.

All English or German studies dealing with the effect of smoking on bone quality, fracture incidence, fracture healing, fracture treatment outcome and prognosis, as well as incidence, complications and outcome of elective orthopaedic and traumatological procedures were included.

Studies not analysing the effect of smoking on bone quality, elective orthopaedic or traumatological procedures, fracture healing, incidence, outcome of fracture treatment, or prognosis of patients with fractures, bone healing, studies with maxillofacial surgery topics, preclinical studies, reviews, editorials, case reports, insufficient data regarding the effect of smoking on fractures, surveys as well as articles not written in English or German were excluded. Searches and data extraction were performed by one of the co-authors (MAS), and the underlying data subsequently re-evaluated by another author (LL).

**Data analysis**

The following information was collected from each study finally included: main topic (i.e. orthopaedics, traumatology), outcome measure (e.g. fracture incidence, union rate), type of study (e.g. retrospective cohort study, randomized controlled trial), gender (i.e. male, female, or both), number of patients analysed, number of patients exposed and not exposed to the outcome parameter, and level of evidence as defined by the Oxford Centre for Evidence-Based Medicine (OCEBM).19

Studies were grouped into four categories according to their main outcome parameter, i.e. fracture incidence by localization (subdivided into hip fracture, vertebral fracture, and fracture at other sites), postoperative infection risk, nonunion after fracture surgery or elective orthopaedic procedures in general, and persistent nonunion after scaphoid nonunion. Crude values rather than variable-adjusted results were used in order not to skew the meta-analysis based on different multivariate models demonstrated in individual studies.

Quality of the studies finally included in the meta-analysis was assessed using the Newcastle-Ottawa Scale (NOS) for non-randomized cohort and case-control studies.20 This tool allows assessment of studies based on three items, i.e. selection (maximum 4 points), comparability (maximum 2 points), and exposure (for case-control studies; maximum 3 points) or outcome (for cohort studies; maximum 3 points). By adding the points of each category, a total score ranging from 0 to 9 can be obtained, with higher scores being indicative of studies of higher quality.20 Of note, level III and level II studies were also analysed using the NOS, as randomization had been performed for smoking in one study only.21

Random effects models using the restricted maximum likelihood method were calculated for each outcome parameter of interest. No adjustment for potential confounders such as age or gender were made. Higgins’ $I^2$ was calculated for each model to assess heterogeneity between studies.22 Small, medium and large heterogeneity was defined as $I^2$ being $\leq 25\%$, $\leq 50\%$, and $\leq 75\%$, respectively.22 Presence of publication bias was assessed with Harbord’s test.23 Sensitivity analyses were performed to assess the robustness of findings, based on funnel plots identifying outlier studies. All statistical analyses were performed with Stata Version 16.1 (StataCorp, College Station, TX, USA).

**Results**

The search retrieved 3362 studies, of which 3258 were screened after exclusion of 104 duplicates. Subsequently, 2789 studies not meeting the inclusion criteria according to the title and abstract were excluded. The full-text articles of the remaining 469 studies were further screened, with 343 studies being thoroughly analysed for outcome parameters and variables of interest. Of these, 274 had to be excluded due to insufficient information or outcome parameters other than the ones defined. Thus, 69 articles could be included in the quantitative analysis (Fig. 1). Mean NOS score over all 69 studies was $6.5 \pm 1.3$ points (Supplemental Table 2). Fifty articles comprised level IV studies (72.5%), 16 level III studies (23.2%), and three level II studies (4.3%). Twenty-four (34.8%), 21 (30.4%), 19 (27.5%), and five (7.2%) studies reported on fracture risk, postoperative infection risk, nonunion risk, and persisting scaphoid nonunion risk, respectively.
Records identified through database searching  
\( n = 3362 \)  

Records after duplicates removed  
\( n = 3258 \)  

Records screened  
\( n = 3258 \)  

Full-text articles assessed for eligibility  
\( n = 469 \)  

Full-text articles assessed for variables and outcome parameters  
\( n = 343 \)  

Studies excluded due to insufficient information or alternative outcome parameter  
\( n = 274 \)  

Records excluded  
\( n = 2789 \)  

Smoking effect not specifically addressed (\( n = 76 \))  
No full-text article available (\( n = 47 \))  
Meta-analysis (\( n = 1 \))  
Review (\( n = 1 \))  
Non-English article (\( n = 1 \))

Fig. 1 Flow chart of studies included.

**General fracture risk**

Twenty-four studies were analysed regarding impact of smoking on fracture risk.\(^{24-47}\) Mean NOS score for these studies was 6.9 ± 1.5 points. Six of these studies reported separate results for males and females,\(^{26,28,30,46,47}\) one provided individual results for fractures at the trochanteric region and femoral neck,\(^{32}\) and one study presented different results for fractures at any location and hip fractures.\(^{33}\) The resulting meta-analysis thus comprised 32 study entries, involving 2,037,159 patients, of whom 518,995 (25.5%) were active smokers. Notably, these numbers also included three study entries reporting on identical patient cohorts (Table 1).\(^{25,28,30}\) Of the 24 studies analysed, 11 were retrospective studies (45.8%; level IV),\(^{25,27-30,34,36,39,40,42,43}\) one was a prospective study (4.2%; level III),\(^{24}\) and one a large retrospective study (4.2%; level III).\(^{26}\) Overall relative risk (RR) for smokers (regardless of fracture site) was 1.46 (95% confidence interval [CI]: 1.23–1.72; \( p < 0.001 \); Fig. 2), with high heterogeneity between studies (\( I^2 = 89.3\% \)), and no significant publication bias (Harbord’s \( p = 0.267 \)). Subsequent subgroup analyses were performed for studies focusing on vertebral fractures, hip fractures, and other fracture sites.

**Vertebral fracture risk**

Meta-analysis of the six studies (seven study entries)\(^{16,39,42,43,45,47}\) with vertebral fractures as the primary endpoint showed a significant association for smoking (RR: 1.61; 95% CI: 1.13–2.29; \( p = 0.008 \); Fig. 2). Heterogeneity between studies was high (\( I^2 = 89.4\% \)), and a significant publication bias was present (Harbord’s \( p = 0.016 \)). Sensitivity analysis was performed after excluding one study reporting on presence of vertebral fractures and abdominal aortic calcification,\(^{39}\) one study assessing vertebral re-fracture risk after already having sustained a vertebral fracture,\(^{43}\) and one study analysing vertebral fracture risk in women > 65 years of age.\(^{45}\) This analysis revealed a significant association for smoking (RR: 1.51; 95% CI: 1.19–1.92; \( p < 0.001 \)), whilst heterogeneity could be diminished (\( I^2 = 0.0\% \)).

**Hip fracture risk**

For 11 studies (15 study entries)\(^{24,26,27,31-34,37,38,44,46}\) reporting on hip fracture risk, meta-analysis showed a strong association between active smoking and risk for hip fracture (RR: 1.28; 95% CI: 1.07–1.53; \( p = 0.007 \); Fig. 2). Heterogeneity between studies was large (\( I^2 = 84.1\% \)). No significant publication bias was present (Harbord’s \( p = 0.894 \)).
| Author                      | Study type                  | Gender | Smokers total | Non-smokers total | Outcome factor | Evidence level |
|-----------------------------|-----------------------------|--------|---------------|-------------------|----------------|----------------|
| Ji et al (2019)             | Retrospective study         | Female | 7106          | 208,499          | Humerus fracture risk | IV             |
| Hannan et al (2019)         | Longitudinal population-based cohort study | Female | 237           | 2539             | Nonvertebral fracture risk | III            |
| Givon et al (2000)          | Retrospective study         | Both   | 552           | 1450             | Stress fracture risk | IV             |
| Olofsson et al (2005)       | Longitudinal population-based cohort study | Male   | 1185          | 1134             | Any fracture risk | III            |
| Zhu et al (2019)            | Longitudinal population-based cohort study | Both   | 104,753       | 324,676          | Calcaneal fracture risk | III            |
| Michaëllson et al (1999)    | Longitudinal population-based cohort study | Female | 798           | 3099             | Cervical hip fracture risk | III            |
| Liu et al (2019)            | Retrospective study         | Both   | 104,766       | 324,694          | Clavicula fracture risk | IV             |
| Liu et al (2017)            | Longitudinal population-based cohort study | Male   | 778           | 2849             | Trochanteric hip fracture risk | IV             |
| Lack et al (2015)           | Retrospective study         | Both   | 185           | 721              | Postoperative infection following ORIF for ankle fractures | IV             |
| Li et al (2020)             | Retrospective study         | Both   | 84            | 131              | Postoperative infection following ORIF for open tibial fracture | IV             |
| Khan et al (2019)           | Retrospective study         | Both   | 10            | 14               | Postoperative infection after spinal surgery | IV             |
| Xu et al (2019)             | Retrospective study         | Both   | 130           | 304              | Postoperative infection after ORIF for distal femoral fracture | IV             |
| Bai et al (2019)            | Retrospective study         | Both   | 148           | 517              | Postoperative infection following ORIF for distal femoral fracture | IV             |
| Lu et al (2019)             | Retrospective study         | Both   | 135           | 589              | Postoperative infection after ORIF for distal femoral fracture | IV             |
| Meng et al (2018)           | Retrospective study         | Both   | 554           | 2063             | Postoperative infection following ORIF for ankle fractures | IV             |
| Sun et al (2018)            | Retrospective study         | Both   | 355           | 1155             | Postoperative infection following ORIF for ankle fractures | IV             |

(continued)
| Author                  | Study type               | Gender | Smokers total | Non-smokers total | Outcome factor                                                                 | Evidence level |
|-------------------------|--------------------------|--------|---------------|-------------------|--------------------------------------------------------------------------------|----------------|
| Ma et al (2018)          | Retrospective study      | Both   | 73            | 603               | Postoperative infection following ORIF for tibial plateau fracture              | IV             |
| Su et al (2017)          | Retrospective study      | Both   | 114           | 204               | Postoperative infection after ORIF for calcaneal fracture                      | IV             |
| Iqbal et al (2017)       | Retrospective study      | Both   | 63            | 187               | Postoperative infection after ORIF for acetabular fracture                     | IV             |
| Olsen et al (2017)       | Retrospective study      | Both   | 283           | 760               | Postoperative infection following ORIF for ankle fractures                     | IV             |
| Saeedinia et al (2015)   | Prospective non-randomized study | Both | 132          | 846               | Postoperative infection after spinal surgery                                   | III            |
| Claessen et al (2016)    | Retrospective study      | Both   | 343           | 977               | Postoperative infection after ORIF for elbow fracture                         | IV             |
| Lin et al (2014)         | Retrospective study      | Both   | 105           | 151               | Postoperative infection following ORIF for tibial plateau fracture             | IV             |
| Morris et al (2013)      | Retrospective study      | Both   | 137           | 165               | Postoperative infection following ORIF for tibial plateau fracture             | IV             |
| Kamath et al (2005)      | Prospective non-randomized study | Both | 31           | 61                | Postoperative infection after surgery for hip fracture                          | III            |
| Zhu et al (2017)         | Prospective non-randomized study | Both | 22           | 213               | Postoperative infection following ORIF for tibial plateau fracture             | III            |
| Singh et al (2018)       | Retrospective study      | Both   | 26            | 77                | Postoperative infection following ORIF for open tibial fracture                | IV             |

**Nonunion risk**

| Author                  | Study type               | Gender | Smokers total | Non-smokers total | Outcome factor                                                                 | Evidence level |
|-------------------------|--------------------------|--------|---------------|-------------------|--------------------------------------------------------------------------------|----------------|
| McKee et al (2003)      | Retrospective study      | Both   | 47            | 39                | Nonunion after Ilizarov reconstruction                                        | IV             |
| Dailey et al (2018)     | Retrospective study      | Both   | 244           | 261               | Nonunion after tibial fracture                                                  | IV             |
| Murray et al (2013)     | Retrospective study      | Both   | 219           | 722               | Nonunion after mid-clavicular fractures                                         | IV             |
| Kim et al (2005)        | Retrospective study      | Both   | 15            | 81                | Nonunion after spinal fusion                                                   | IV             |
| Glassman et al (2000)   | Retrospective study      | Both   | 188           | 169               | Nonunion after spinal fusion                                                   | IV             |
| Tay et al (2014)        | Retrospective study      | Both   | 161           | 262               | Nonunion after diaphyseal femoral and tibial fracture                           | IV             |
| Rodríguez et al (2014)  | Retrospective study      | Both   | 34            | 249               | Nonunion after distal femoral fracture                                         | IV             |
| Özbek et al (2017)      | RCT                      | Both   | 19            | 56                | Nonunion after thoracolumbar fractures                                         | II             |
| Bydon et al (2014)      | Retrospective study      | Both   | 50            | 231               | Nonunion after lumbar fusion                                                   | IV             |
| Krause et al (2016)     | RCT                      | Both   | 44            | 326               | Nonunion after hindfoot and ankle fusion                                       | II             |
| Nappo et al (2019)      | Retrospective study      | Both   | 34            | 42                | Nonunion after open forearm fracture                                          | IV             |
| Giuseffi et al (2015)   | Retrospective study      | Both   | 17            | 72                | Nonunion after high tibial osteotomy                                           | IV             |
| Meidinger et al (2011)  | Retrospective study      | Both   | 46            | 140               | Nonunion after high tibial osteotomy                                           | IV             |
| Hoffmann et al (2018)   | Retrospective study      | Both   | 32            | 161               | Nonunion after intertrochanteric femoral fracture                               | IV             |
| Gaspar et al (2016)     | Retrospective study      | Both   | 17            | 55                | Nonunion after ulnar shortening osteotomy                                      | IV             |
| Neuhaus et al (2014)    | Retrospective study      | Both   | 19            | 60                | Nonunion after mid-diaphyseal humeral fractures                                 | IV             |
| Ding et al (2014)       | Retrospective study      | Both   | 165           | 494               | Nonunion after diaphyseal humeral fractures                                     | IV             |
| Liu et al (2015)        | Retrospective study      | Both   | 155           | 649               | Nonunion after mid-clavicular fractures                                         | IV             |
| Giannoudis et al (2000) | Retrospective study      | Both   | 31            | 68                | Nonunion after diaphyseal femoral fractures                                     | IV             |

**Persisting nonunion risk in scaphoid nonunion**

| Author                  | Study type               | Gender | Smokers total | Non-smokers total | Outcome factor                                                                 | Evidence level |
|-------------------------|--------------------------|--------|---------------|-------------------|--------------------------------------------------------------------------------|----------------|
| Dinah et al (2007)      | Retrospective study      | Both   | 20            | 17                | Re-nonunion after surgery for scaphoid nonunion                                | IV             |
| Little et al (2006)     | Retrospective study      | Both   | 30            | 34                | Re-nonunion after surgery for scaphoid nonunion                                | IV             |
| Rahimnia et al (2018)   | Retrospective study      | Both   | 19            | 22                | Re-nonunion after vascularized bone graft for scaphoid nonunion                | IV             |
| Hirche et al (2014)     | Retrospective study      | Both   | 13            | 15                | Re-nonunion after vascularized bone graft for scaphoid nonunion                | IV             |
| Chang et al (2006)      | Retrospective study      | Both   | 13            | 35                | Re-nonunion after vascularized bone graft for scaphoid nonunion                | IV             |

Note. RCT, randomized controlled trial; ORIF, open reduction and internal fixation.
**Fig. 2** Forest plot of studies analysing risk of smoking on fracture incidence, divided into hip fractures, vertebral fractures, and other fracture sites. Orange diamonds depict effect sizes for subgroups, and the red diamond shows overall effect size. The dashed black line depicts the no-effects line. The solid red line marks overall effect size value.
Sensitivity analysis was performed after excluding two retrospective studies (i.e., three study entries). This analysis revealed a significant association between smoking and increased hip fracture risk (RR: 1.32; 95% CI: 1.24–1.40; p < 0.001). Heterogeneity could be diminished (I² = 0.0%).

Other fracture risk

Meta-analysis of eight studies (10 study entries) reporting on fracture risk at any anatomical site revealed a significant association between smoking and risk for any fracture (RR: 1.25; 95% CI: 1.10–2.80; p = 0.019; Fig. 2). Between-study heterogeneity was high (I² = 89.3%). No significant publication bias was found (Harbord’s p = 0.505). After excluding four studies investigating fracture incidences in a large Chinese population (> 400,000 patients), and one study with stress fracture as the endpoint, a significant association was revealed between smoking and increased risk for fractures at other sites than vertebrae or hip (RR: 1.50; 95% CI: 1.25–1.80; p < 0.001), and low heterogeneity (I² = 16.9%).

Postoperative infection risk

Altogether, 21 studies analysed risk for postoperative infection after fracture surgery (n = 19), or elective orthopaedic surgery (n = 2), involving 13176 patients of whom 3030 were smokers (23.0%; Table 1). Mean NOS score was 6.6 ± 1.2 points. Three studies were prospective non-randomized cohort studies (14.3%; level III), and 18 were retrospective studies (85.7%; level IV). The overall RR for smokers to develop postoperative infections was 2.20 (95% CI: 1.69–2.86; p < 0.001; Fig. 3). Heterogeneity was high (I² = 58.9%), and a significant publication bias was found (Harbord’s p = 0.001). Subgroup meta-analysis of two studies analysing infection risk after elective spinal surgery revealed a significant association between smoking and risk for postoperative infection (RR: 4.38; 95% CI: 2.17–8.85; p < 0.001; Fig. 3). Heterogeneity between studies was low (I² = 0.0%).

Nineteen studies assessed infection risk following surgery for fractures, including five studies on tibial plateau fractures, four studies on ankle fractures, three studies on open tibial fractures, three studies on distal femoral fractures, and one study each on elbow fractures, hip fractures, acetabular fractures, and calcaneal fractures. The subgroup meta-analysis for this cohort revealed a significant association between smoking and elevated risk for postoperative infections (RR: 2.10; 95% CI: 1.61–2.74; p < 0.001; Fig. 3). Heterogeneity was high (I² = 58.5%), and a significant publication bias was observed (Harbord’s p = 0.001). Sensitivity analysis for this subgroup, after excluding four studies, revealed a significant association between smoking and infection risk (RR: 2.01; 95% CI: 1.65–2.45; p < 0.001), and heterogeneity could be reduced (I² = 15.2%).

General nonunion risk

Nineteen studies, involving 5805 patients of whom 26.5% were smokers, reported on nonunion risk following either elective orthopaedic procedures (n = 8), or fractures (n = 11; Table 1). Of these, 17 were retrospective studies (89.5%; level IV), and two were randomized controlled trials (10.5%; level II). Mean NOS score was 6.3 ± 1.1 points. Meta-analysis of the 19 studies revealed an overall RR of 1.89 (95% CI: 1.60–2.24; p < 0.001) for smokers to develop nonunion (Fig. 4). Moderate heterogeneity was present (I² = 58.5%). A significant publication bias was found (Harbord’s p = 0.003).

Nonunion risk after orthopaedic procedures

Subgroup meta-analysis of the eight studies evaluating nonunion risk following elective orthopaedic procedures revealed a significant association for smoking (RR: 2.15; 95% CI: 1.46–3.17; p < 0.001; Fig. 4), with moderate heterogeneity (I² = 35.9%), and no significant publication bias (Harbord’s p = 0.237). Sensitivity analysis, after exclusion of one study, showed a significant association between smoking and increased nonunion risk (RR: 1.79; 95% CI: 1.36–2.36; p < 0.001), with low heterogeneity (I² = 0.9%).

Nonunion risk after fractures

Subgroup meta-analysis of 11 studies analysing nonunion risk after fractures also showed a significant positive association for smoking (RR: 1.85; 95% CI: 1.51–2.27; p < 0.001; Fig. 4). Heterogeneity was moderate (I² = 39.9%). A significant publication bias was found (Harbord’s p = 0.047). After exclusion of two studies, sensitivity analysis revealed a significant association between smoking and nonunion risk (RR: 1.76; 95% CI: 1.49–2.08; p < 0.001). Heterogeneity could be diminished (I² = 0.0%).

Persisting nonunion risk after scaphoid nonunion

Five studies investigated the risk for persisting nonunion after surgical revision for scaphoid nonunion (Table 1). Mean NOS score for these studies was 4.8 ± 0.4 points. Altogether, 218 patients were included, of whom 43.6% were smokers. All studies were retrospective studies (level IV). Meta-analysis revealed a significant association between smoking and an increased risk for persistent nonunion after surgical revision for scaphoid nonunion (RR: 3.52; 95% CI: 2.14–5.79; p < 0.001; Fig. 5). Heterogeneity was low (I² = 0.0%), and no significant publication bias was detected (Harbord’s p = 0.472). Therefore, no sensitivity analysis was performed.
**Discussion**

According to the present meta-analysis, smoking is not only significantly associated with an overall higher fracture risk, hip fracture risk and vertebral fracture risk, but also with increased risk for nonunion following fracture surgery, postoperative infection risk, and persistent nonunion after surgery for scaphoid nonunions.

One limitation of the current study is the partially vague description of variables in individual studies, wherefore crude values of smoking and non-smoking patients, as well as those with or without an outcome event, could
not be ascertained. This was true for 274 of 343 studies thoroughly analysed for variables of interest and outcome parameters. Consequently, only 69 studies were finally eligible for the meta-analysis. Of these, merely 27.5% were level III or level II studies, and only one study had randomized for smoking. Another limitation of the study has to be seen in the overall moderate NOS score, being 6.5 points on average. Therefore, the mostly retrospective studies may be prone to bias regarding cohort definition, covariate adjustment, and outcome assessment. In order not to further skew results, the authors thus decided to perform meta-analyses on unadjusted crude values of each study. Considering that a large proportion of studies had to be excluded due to lack of disaggregated data, the

| Study | Smokers | Non smokers | Risk ratio for nonunion with 95% CI | Weight (%) |
|-------|---------|-------------|-----------------------------------|------------|
|       | Nonunion | Union | Nonunion | Union |                          |            |
| Fractures | | | | | | |
| Neuhaus V, 2014 | 8 | 11 | 8 | 52 | 3.16 [1.37, 7.26] | 3.42 |
| Ding L, 2014 | 11 | 154 | 13 | 481 | 2.53 [1.16, 5.55] | 3.78 |
| Liu W, 2015 | 30 | 125 | 66 | 583 | 1.90 [1.28, 2.82] | 9.62 |
| Giannoudis PV, 2000 | 14 | 17 | 18 | 50 | 1.71 [0.98, 2.97] | 6.36 |
| Dailey HL, 2018 | 38 | 206 | 36 | 225 | 1.13 [0.74, 1.72] | 8.96 |
| Murray IR, 2013 | 37 | 182 | 52 | 800 | 2.77 [1.87, 4.11] | 9.61 |
| Tay WH, 2014 | 66 | 95 | 72 | 190 | 1.49 [1.14, 1.95] | 13.32 |
| Rodriguez EK, 2014 | 7 | 27 | 34 | 215 | 1.51 [0.73, 3.13] | 4.23 |
| Ozbek Z, 2017 | 14 | 5 | 24 | 32 | 1.72 [1.15, 2.58] | 9.36 |
| Nappo KE, 2019 | 7 | 26 | 4 | 38 | 2.23 [0.71, 6.97] | 1.98 |
| Hoffmann MF, 2019 | 5 | 27 | 7 | 156 | 3.64 [1.23, 10.75] | 2.17 |

| Heterogeneity: T² = 0.04, I² = 39.91%, H² = 1.66 |
| Test of θ₁ = θ₂: Q(10) = 15.72, p = 0.11 |

Orthopaedic procedures

| Study | Smokers | Non smokers | Risk ratio for nonunion with 95% CI | Weight (%) |
|-------|---------|-------------|-----------------------------------|------------|
|       | Nonunion | Union | Nonunion | Union |                          |            |
| McKee MD, 2003 | 10 | 37 | 2 | 37 | 4.15 [0.97, 17.82] | 1.26 |
| Kim YL, 2005 | 3 | 12 | 13 | 68 | 1.25 [0.40, 3.85] | 2.02 |
| Glassman SD, 2000 | 39 | 149 | 24 | 145 | 1.46 [0.92, 2.32] | 8.00 |
| Bydon M, 2014 | 9 | 41 | 24 | 207 | 1.73 [0.86, 3.50] | 4.50 |
| Krause F, 2016 | 14 | 30 | 53 | 273 | 1.96 [1.19, 3.22] | 7.34 |
| Giuseffi SA, 2015 | 2 | 15 | 3 | 69 | 2.82 [0.51, 15.60] | 0.93 |
| Meidinger G, 2011 | 5 | 41 | 5 | 135 | 3.04 [0.92, 10.04] | 1.82 |
| Gaspar MP, 2016 | 10 | 7 | 2 | 53 | 16.18 [3.92, 66.75] | 1.33 |

| Heterogeneity: T² = 0.10, I² = 35.92%, H² = 1.56 |
| Test of θ₁ = θ₂: Q(7) = 12.50, p = 0.09 |

Overall

| Study | Smokers | Non smokers | Risk ratio for nonunion with 95% CI | Weight (%) |
|-------|---------|-------------|-----------------------------------|------------|
|       | Nonunion | Union | Nonunion | Union |                          |            |
|       | | | | | | |
|       | | | | | | |
|       | | | | | | |
|       | | | | | | |

| Heterogeneity: T² = 0.04, I² = 30.19%, H² = 1.43 |
| Test of θ₁ = θ₂: Q(18) = 28.55, p = 0.05 |

Test of group differences: Qb (1) = 0.47, p = 0.49

Decreased risk for smokers

Fig. 4 Forest plot of studies analysing the effect of smoking on nonunion risk following elective orthopaedic surgical procedures or traumatic fracture surgery. Orange diamonds depict effect sizes for subgroups, and the red diamond shows overall effect size. The dashed black line depicts the no-effects line. The solid red line marks overall effect size value.
provision of basic results in observational studies and clinical trials should be emphasized in the future. This would enable researchers to eventually draw further conclusions regarding the role of smoking and other risk factors in orthopaedic patients.

Due to the negative effect of tobacco products on bone metabolism, smokers are known to have an overall lower bone mineral density (BMD), wherefore their susceptibility to fractures may be increased. However, reduced BMD alone does not seem to explain the overall higher fracture risk of smokers in comparison to non-smokers. Indeed, according to the present meta-analysis, smokers had a 1.46 times higher risk of sustaining any fracture in comparison to non-smokers. Our findings are comparable to those reported in the meta-analysis by Kanis et al back in 2005. However, we did not account for potential differences in BMD depending on smoking status. Furthermore, factors such as long-term prescription of corticosteroids, (family) history of fractures and secondary osteoporosis are known to significantly increase fracture risk. As the simultaneous occurrence of these risk factors and smoking cannot be ruled out in this meta-analysis, the negative effect of smoking alone has to be interpreted bearing this limitation in mind.

Surgical site infections are regarded as the most common type of hospital-acquired infection. Any surgical site infection may be associated with increased patient morbidity, reduced subjective quality of life, prolonged hospitalization time, and increased costs to the healthcare system. Smoking leads to decreased microperfusion and tissue hypoxia. Moreover, the direct effect of carbon monoxide on oxyhaemoglobin leads to a leftwards shift of the oxygen dissociation curve. Consequently, wound healing may be impaired in smokers. In line with this, we discovered an RR of 2.20 for smokers to develop postoperative infections after elective orthopaedic and trauma surgeries in comparison to non-smokers. More specifically, the risk of smokers developing infections after fracture surgery was 2.1 times higher than for non-smokers, which is higher than the RR of 1.29 described in a previous meta-analysis including patients with open fractures.

Depending on fracture site and treatment, risk for nonunion after bone fractures ranges between 5% and 10%. Development of nonunion is not only associated with prolonged and often complex treatment, but also a significant financial burden and negative impact on patients’ quality of life. Bearing in mind the non-modifiable risk factors eventually contributing to development of nonunion, such as type of fracture and site, bone morphology, and associated infection, potentially modifiable factors including treatment approach, (postoperative) mobilization protocols, steroid intake, and smoking should be particularly addressed by treating healthcare professionals. Notably, in the present meta-analysis, the RR of active smokers to develop nonunions following fractures or elective orthopaedic procedures was 1.89, being comparable to the RR reported by Pearson et al in a meta-analysis involving 40 studies. Likewise, Scolaro et al discovered a significantly higher risk for smokers to develop nonunions after open fractures (odds ratio: 1.95) and fractures in general (odds ratio: 2.32). Scaphoid fractures in particular are at high risk of nonunion, occurring in 10–15% of both operatively and conservatively treated patients, owing to the limited blood supply via blood vessels entering the bone distally. Revision surgery of scaphoid nonunions is
challenging and usually requires harvesting of autologous bone grafts.\textsuperscript{111,112} It is noteworthy that the present meta-analysis of five studies investigating persisting nonunion risk after surgery for scaphoid nonunions revealed an RR of 3.52 for smokers in comparison to non-smokers, in line with a previous meta-analysis comparing surgical flaps for scaphoid nonunion and healing depending on smoking status.\textsuperscript{113}

According to the results of this meta-analysis, smoking is associated with significant increases in fracture incidences, postoperative complications, and nonunions. Yet, whilst diabetes is known as a significant risk factor for these outcomes, and special attention is usually paid to these patients perioperatively, the awareness among orthopaedic and trauma surgeons towards the risk of smokers likewise developing nonunions and infections is less well pronounced. However, according to Zura et al, past or current smoking seems (multivariate OR: 1.20) to increase nonunion risk to a greater extent than diabetes mellitus type 2 (multivariate OR: 1.15). Also, postoperative infection risk in open fractures is likewise increased in diabetic (RR: 1.72) and smoking patients (RR: 1.29).\textsuperscript{101}

Conclusions

Considering the deleterious effects of smoking on risk of developing fractures, subsequent nonunion and postoperative infection risk, any orthopaedic or trauma surgeon should strongly advise patients to quit smoking and encourage their participation in smoking cessation programmes.

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ICMJE CONFLICT OF INTEREST STATEMENT

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SUPPLEMENTAL MATERIAL

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