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Fracture, nonunion and postoperative infection risk in the smoking orthopaedic patient: a systematic review and meta-analysis

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- 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

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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 surgery for 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 ± 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.

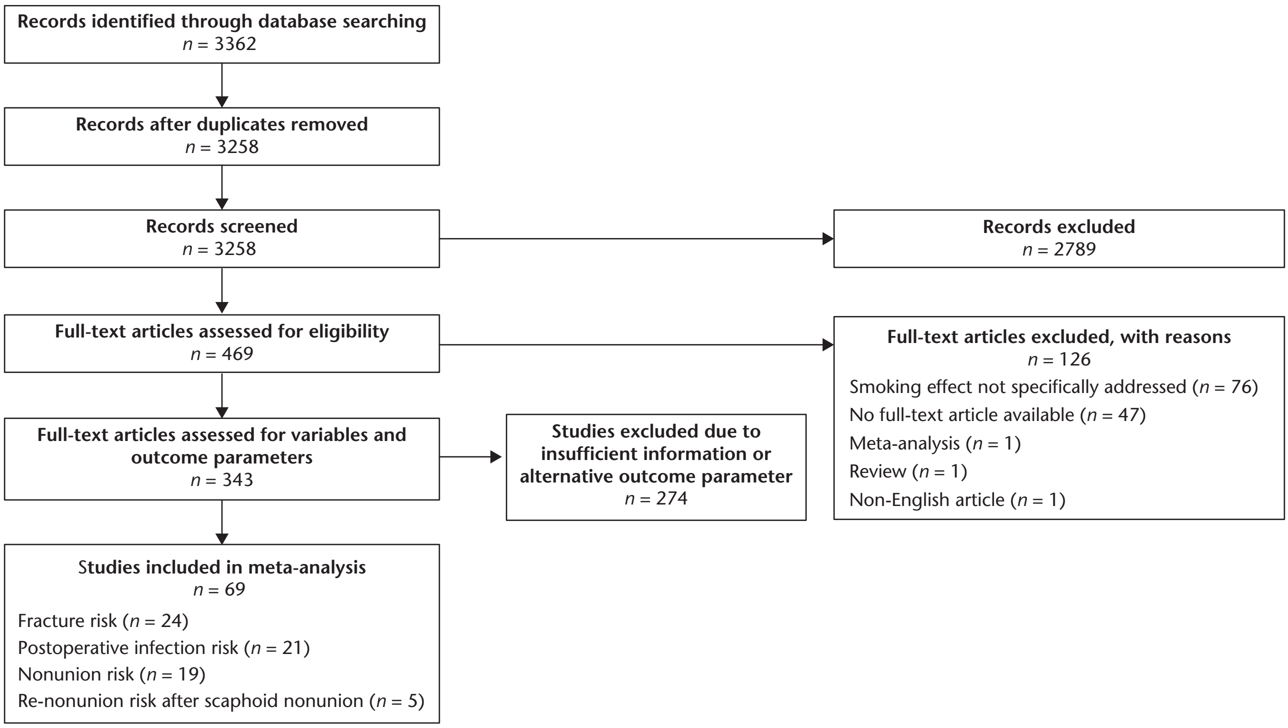


Fig. 1 Flow chart of studies included.

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,[26,28,30,31,46,47] 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] 11 were longitudinal population-based cohort studies (45.8%; level III),[31–33,35,37,38,41,44–47] one 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)[36,39,42,43,45,47] 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 $p = 0.894$).

Table 1. Summary of studies included in meta-analysis

Fracture risk

Author	Study type	Gender	Smokers total	Non-smokers total	Outcome factor	Evidence level
Ji et al (2019)[28]	Retrospective study	Female	7106	208499	Humerus fracture risk	IV
		Male	98190	117226		
Hannan et al (2019)[41]	Longitudinal population-based cohort study	Female	237	2539	Nonvertebral fracture risk	III
Givon et al (2000)[4]	Retrospective study	Both	552	1450	Stress fracture risk	IV
Olofsson et al (2005)[33]	Longitudinal population-based cohort study	Male	1185	1134	Any fracture risk	III
			1185	1134	Hip fracture risk	
Zhu et al (2019)[35]	Longitudinal population-based cohort study	Both	104753	324676	Calcaneal fracture risk	III
Michaëlsson et al (1999)[32]	Longitudinal population-based cohort study	Female	798	3099	Cervical hip fracture risk	III
			727	2849	Trochanteric hip fracture risk	
Chen et al (2018)[25]	Retrospective study	Both	104766	324694	Clavicula fracture risk	IV
Liu et al (2018)[30]	Retrospective study	Female	7081	207860	Foot fracture risk	IV
		Male	97722	116902		
Liu et al (2019)[29]	Retrospective study	Male	37879	38605	Fracture risk (general)	IV
Lobo et al (2017)[31]	Longitudinal population-based cohort study	Female	76	2618	Hip fracture risk	III
		Male	528	1448		
Wiklund et al (2016)[34]	Retrospective study	Both	29	924	Hip fracture risk	IV
Bawab et al (2014)[24]	Prospective cohort study	Both	77	118	Hip fracture risk	III
Jenkins et al (2008)[27]	Retrospective study	Female	56	432	Hip fracture risk	IV
Holmberg et al (2005)[26]	Retrospective study (large)	Female	3808	7094	Hip fracture risk	III
		Male	11041	11403		
Baron et al (2001)[37]	Longitudinal population-based cohort study	Female	940	3470	Hip fracture risk	III
Cornuz et al (1999)[38]	Longitudinal population-based cohort study	Female	36031	115892	Hip fracture risk	III
Mussolino et al (1998)[44]	Longitudinal population-based cohort study	Male	1077	1802	Hip fracture risk	III
Paganini-Hill et al (1991)[46]	Longitudinal population-based cohort study	Female	1081	7512	Hip fracture risk	III
		Male	433	4614		
Bae et al (2019)[36]	Retrospective study	Both	14	232	Vertebral fracture risk	IV
El Maghraoui et al (2012)[39]	Retrospective study	Male	52	657	Vertebral fracture risk	IV
Nevitt et al (2005)[45]	Longitudinal population-based cohort study	Female	667	6571	Vertebral fracture risk	III
van der Klift et al (2004)[47]	Longitudinal population-based cohort study	Female	290	1334	Vertebral fracture risk	III
		Male	354	1023		
Kim et al (2015)[42]	Retrospective study	Both	45	166	Vertebral fracture risk	IV
Ma et al (2019)[43]	Retrospective study	Both	210	345	Vertebral re-fracture risk (following vertebral fracture)	IV

Postoperative infection risk

Author	Study type	Gender	Smokers total	Non-smokers total	Outcome factor	Evidence level
Nåsell et al (2011)[21]	Retrospective study	Both	185	721	Postoperative infection following ORIF for ankle fractures	IV
Lack et al (2015)[50]	Retrospective study	Both	39	98	Postoperative infection following ORIF for open tibial fracture	IV
Li et al (2020)[51]	Retrospective study	Both	84	131	Postoperative infection following ORIF for open tibial fracture	IV
Khan et al (2019)[48]	Retrospective study	Both	10	14	Postoperative infection after spinal surgery	IV
Xu et al (2019)[52]	Retrospective study	Both	130	304	Postoperative infection after ORIF for distal femoral fracture	IV
Bai et al (2019)[53]	Retrospective study	Both	148	517	Postoperative infection after ORIF for distal femoral fracture	IV
Lu et al (2019)[54]	Retrospective study	Both	135	589	Postoperative infection after ORIF for distal femoral fracture	IV
Meng et al (2018)[55]	Retrospective study	Both	554	2063	Postoperative infection following ORIF for ankle fractures	IV
Sun et al (2018)[56]	Retrospective study	Both	355	1155	Postoperative infection following ORIF for ankle fractures	IV

(continued)

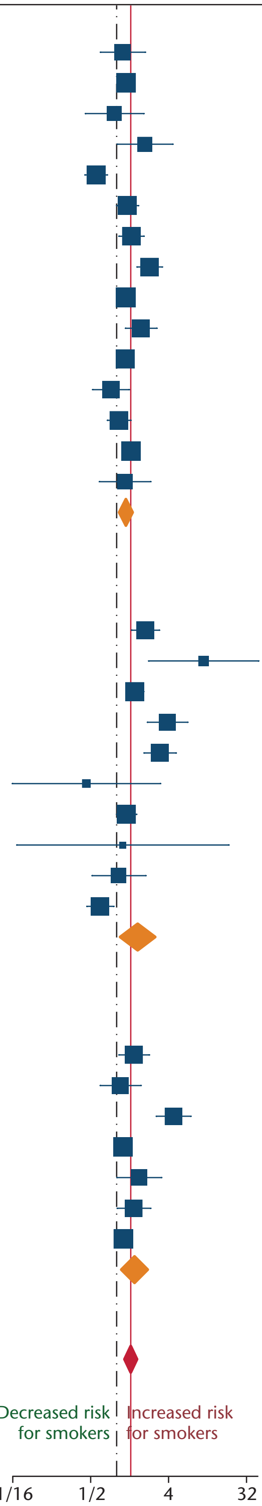
Table 1. (continued)

Postoperative infection risk						
Author	**Study type**	**Gender**	**Smokers total**	**Non-smokers total**	**Outcome factor**	**Evidence level**
Ma et al (2018)[58]	Retrospective study	Both	73	603	Postoperative infection following ORIF for tibial plateau fracture	IV
Su et al (2017)[59]	Retrospective study	Both	114	204	Postoperative infection after ORIF for calcaneal fracture	IV
Iqbal et al (2017)[60]	Retrospective study	Both	63	187	Postoperative infection after ORIF for acetabular fracture	IV
Olsen et al (2017)[61]	Retrospective study	Both	283	760	Postoperative infection following ORIF for ankle fractures	IV
Saeedinia et al (2015)[49]	Prospective non-randomized study	Both	132	846	Postoperative infection after spinal surgery	III
Claessen et al (2016)[62]	Retrospective study	Both	343	977	Postoperative infection after ORIF for elbow fracture	IV
Lin et al (2014)[63]	Retrospective study	Both	105	151	Postoperative infection following ORIF for tibial plateau fracture	IV
Morris et al (2013)[64]	Retrospective study	Both	137	165	Postoperative infection following ORIF for tibial plateau fracture	IV
Kamath et al (2005)[65]	Prospective non-randomized study	Both	31	61	Postoperative infection after surgery for hip fracture	III
Zhu et al (2017)[66]	Prospective non-randomized study	Both	22	213	Postoperative infection following ORIF for tibial plateau fracture	III
Singh et al (2018)[67]	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)[74]	Retrospective study	Both	47	39	Nonunion after Ilizarov reconstruction	IV
Dailey et al (2018)[80]	Retrospective study	Both	244	261	Nonunion after tibial fracture	IV
Murray et al (2013)[81]	Retrospective study	Both	219	722	Nonunion after mid-clavicular fractures	IV
Kim et al (2005)[68]	Retrospective study	Both	15	81	Nonunion after spinal fusion	IV
Glassman et al (2000)[69]	Retrospective study	Both	188	169	Nonunion after spinal fusion	IV
Tay et al (2014)[82]	Retrospective study	Both	161	262	Nonunion after diaphyseal femoral and tibial fracture	IV
Rodriguez et al (2014)[83]	Retrospective study	Both	34	249	Nonunion after distal femoral fracture	IV
Özbek et al (2017)[84]	RCT	Both	19	56	Nonunion after thoracolumbar fractures	II
Bydon et al (2014)[75]	Retrospective study	Both	50	231	Nonunion after lumbar fusion	IV
Krause et al (2016)[70]	RCT	Both	44	326	Nonunion after hindfoot and ankle fusion	II
Nappo et al (2019)[85]	Retrospective study	Both	34	42	Nonunion after open forearm fracture	IV
Giuseffi et al (2015)[71]	Retrospective study	Both	17	72	Nonunion after high tibial osteotomy	IV
Meidinger et al (2011)[72]	Retrospective study	Both	46	140	Nonunion after high tibial osteotomy	IV
Hoffmann et al (2019)[86]	Retrospective study	Both	32	161	Nonunion after intertrochanteric femoral fracture	IV
Gaspar et al (2016)[73]	Retrospective study	Both	17	55	Nonunion after ulnar shortening osteotomy	IV
Neuhaus et al (2014)[76]	Retrospective study	Both	19	60	Nonunion after mid-diaphyseal humeral fractures	IV
Ding et al (2014)[77]	Retrospective study	Both	165	494	Nonunion after diaphyseal humeral fractures	IV
Liu et al (2015)[78]	Retrospective study	Both	155	649	Nonunion after mid-clavicular fractures	IV
Giannoudis et al (2000)[79]	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)[87]	Retrospective study	Both	20	17	Re-nonunion after surgery for scaphoid nonunion	IV
Little et al (2006)[88]	Retrospective study	Both	30	34	Re-nonunion after surgery for scaphoid nonunion	IV
Rahimnia et al (2018)[89]	Retrospective study	Both	19	22	Re-nonunion after vascularized bone graft for scaphoid nonunion	IV
Hirche et al (2014)[90]	Retrospective study	Both	13	15	Re-nonunion after vascularized bone graft for scaphoid nonunion	IV
Chang et al (2006)[91]	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.

Fracture risk - Subgroup analysis for hip, other, and vertebral fractures

Study	Smokers Fracture	Smokers No fracture	Non smokers Fracture	Non smokers No fracture	Risk ratio for fracture with 95% CI	Weight (%)
Hip Fracture						
Lobo E, 2017	15	513	35	1,413	1.18 [0.65, 2.13]	2.75
Michaëlsson K, 1999	202	596	609	2,490	1.29 [1.12, 1.48]	4.12
Lobo E, 2017	6	70	219	2,399	0.94 [0.43, 2.06]	2.20
Wiklund R, 2016	6	23	90	834	2.12 [1.01, 4.45]	2.31
Bawab W, 2014	35	42	30	8	0.58 [0.43, 0.77]	3.74
Jenkins MR, 2008	28	28	162	270	1.33 [1.00, 1.78]	3.76
Holmberg AH, 2005	62	3,751	78	7,016	1.48 [1.06, 2.06]	3.63
Holmberg AH, 2005	114	10,927	49	11,354	2.40 [1.72, 3.35]	3.62
Baron JA, 2001	345	595	979	2,419	1.27 [1.15, 1.41]	4.17
Olofsson H, 2005	64	1,121	32	1,102	1.91 [1.26, 2.90]	3.35
Cornuz J, 1999	106	35,925	271	115,621	1.26 [1.01, 1.57]	3.94
Mussolino ME, 1998	24	1,053	47	1,755	0.85 [0.53, 1.39]	3.12
Paganini-Hill A, 1991	44	1,037	288	7,224	1.06 [0.78, 1.45]	3.69
Michaëlsson K, 1999	131	596	349	2,490	1.47 [1.22, 1.76]	4.03
Paganini-Hill A, 1991	9	424	77	4,536	1.25 [0.63, 2.47]	2.47
Heterogeneity: $\tau^2 = 0.09$, $I^2 = 84.12\%$, $H^2 = 6.30$					1.28 [1.07, 1.53]	
Test of $\theta_i = \theta_j$: Q(14) = 54.97, p = 0.00						
Other Fracture						
Liu S, 2018	79	97,643	44	116,858	2.15 [1.49, 3.11]	3.51
Ji C, 2019	17	98,173	2	117,224	10.15 [2.34, 43.92]	0.99
Olofsson H, 2005	171	1,014	101	1,033	1.62 [1.28, 2.04]	3.92
Zhu Y, 2019	30	104,723	24	324,652	3.87 [2.27, 6.63]	2.94
Chen W, 2018	43	104,723	42	324,652	3.17 [2.07, 4.85]	3.32
Liu S, 2018	1	7,080	66	207,794	0.44 [0.06, 3.20]	0.61
Liu G, 2019	125	37,754	98	38,507	1.30 [1.00, 1.69]	3.83
Ji C, 2019	0	7,106	12	208,487	1.17 [0.07, 19.82]	0.32
Hannan MT, 2019	8	229	81	2,458	1.06 [0.52, 2.16]	2.38
Givon U, 2000	35	517	143	1,307	0.64 [0.45, 0.92]	3.55
Heterogeneity: $\tau^2 = 0.41$, $I^2 = 89.30\%$, $H^2 = 9.35$					1.75 [1.10, 2.80]	
Test of $\theta_i = \theta_j$: Q(9) = 59.33, p = 0.00						
Vertebral Fracture						
van der Klift M, 2004	29	261	84	1,250	1.59 [1.06, 2.38]	3.40
Bae IS, 2019	7	7	107	130	1.11 [0.64, 1.90]	2.93
El Maghraoui A, 2012	18	34	50	607	4.55 [2.87, 7.20]	3.21
Nevitt MC, 2005	152	515	1,264	5,307	1.18 [1.02, 1.37]	4.10
van der Klift M, 2004	17	337	27	996	1.82 [1.00, 3.30]	2.75
Kim GW, 2015	18	27	42	124	1.58 [1.02, 2.46]	3.26
Ma X, 2019	120	90	165	180	1.19 [1.02, 1.40]	4.08
Heterogeneity: $\tau^2 = 0.18$, $I^2 = 89.39\%$, $H^2 = 9.43$					1.61 [1.13, 2.29]	
Test of $\theta_i = \theta_j$: Q(6) = 34.41, p = 0.00						
Overall					1.46 [1.23, 1.72]	
Heterogeneity: $\tau^2 = 0.17$, $I^2 = 89.33\%$, $H^2 = 9.37$						
Test of $\theta_i = \theta_j$: Q(31) = 156.37, p = 0.00						
Test of group differences: $Q_b(2) = 2.42$, p = 0.30						



Random-effects REML model
based on univariate binary outcomes

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).[24,26] 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 ($I^2 = 0.0\%$).

Other fracture risk

Meta-analysis of eight studies (10 study entries)[25,28–30,33,35,40,41] reporting on fracture risk at any anatomical site revealed a significant association between smoking and risk for any fracture (RR: 1.75; 95% CI: 1.10–2.80; p = 0.019; Fig. 2). Between-study heterogeneity was high ($I^2 = 89.3\%$). 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),[25,28,30,35] and one study with stress fracture as the endpoint,[40] sensitivity analysis revealed a significant association 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 ($I^2 = 16.9\%$).

Postoperative infection risk

Altogether, 21 studies analysed risk for postoperative infection after fracture surgery (*n* = 19), or elective orthopaedic surgery (*n* = 2),[48,49] involving 13176 patients of whom 3030 were smokers (23.0%; Table 1).[21,48–67] Mean NOS score was 6.6 ± 1.2 points. Three studies were prospective non-randomized cohort studies (14.3%; level III),[49,65,66] and 18 were retrospective studies (85.7%; level IV).[21,48,50–64,67] 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 ($I^2 = 58.9\%$), 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[48,49] 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 ($I^2 = 0.0\%$).

Nineteen studies assessed infection risk following surgery for fractures,[21,50–67] including five studies on tibial plateau fractures,[57,58,63,64,66] four studies on ankle fractures,[21,55,56,61] three studies on open tibial fractures,[50,51,67] three studies on distal femoral fractures,[52–54] and one study each on elbow fractures,[62] hip fractures,[65] acetabular fractures[60] and calcaneal fractures.[59] 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 ($I^2 = 58.5\%$), and a significant publication bias was observed (Harbord's p = 0.001). Sensitivity analysis for this subgroup, after excluding four studies,[21,56,57,60] 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 ($I^2 = 15.2\%$).

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),[68–75] or fractures (*n* = 11; Table 1).[76–86] Of these, 17 were retrospective studies (89.5%; level IV),[68,69,71–83,85,86] and two were randomized controlled trials (10.5%; level II).[70,84] Mean NOS score was 6.3 ± 1.1 points. Meta-analysis of the 19 studies[68–86] 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 ($I^2 = 58.5\%$). 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[68–75] revealed a significant association for smoking (RR: 2.15; 95% CI: 1.46–3.17; $p < 0.001$; Fig. 4), with moderate heterogeneity ($I^2 = 35.9\%$), and no significant publication bias (Harbord's p = 0.237). Sensitivity analysis, after exclusion of one study,[73] 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 ($I^2 = 0.0\%$).

Nonunion risk after fractures

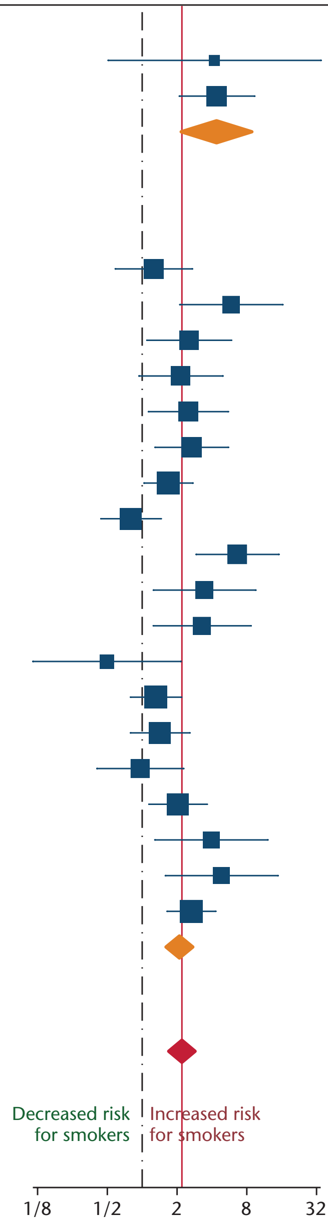
Subgroup meta-analysis of 11 studies analysing nonunion risk after fractures[76–86] also showed a significant positive association for smoking (RR: 1.85; 95% CI: 1.51–2.27; $p < 0.001$; Fig. 4). Heterogeneity was moderate ($I^2 = 39.9\%$). A significant publication bias was found (Harbord's p = 0.047). After exclusion of two studies,[80,81] 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 ($I^2 = 0.0\%$).

Persisting nonunion risk after scaphoid nonunion

Five studies investigated the risk for persisting nonunion after surgical revision for scaphoid nonunion (Table 1).[87–91] 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).[87–91] 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 ($I^2 = 0.0\%$), and no significant publication bias was detected (Harbord's p = 0.472). Therefore, no sensitivity analysis was performed.

Postoperative infection risk - Subgroup Analysis for orthopaedic and trauma studies

Study	Smokers		Non smokers		Risk ratio for infection with 95% CI	Weight (%)
	Infection	No infection	Infection	No infection		
Ortho						
Khan ES, 2019	3	7	1	13	4.20 [0.51, 34.74]	1.32
Saeedinia S, 2015	11	121	16	830	4.41 [2.09, 9.29]	5.17
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$					4.38 [2.17, 8.85]	
Test of $\theta_i = \theta_j$: Q(1) = 0.00, p = 0.97						
Trauma						
Lack WD, 2015	8	31	16	82	1.26 [0.59, 2.70]	5.07
Nåsell H, 2011	9	176	6	716	5.85 [2.11, 16.24]	3.79
Li J, 2020	13	71	8	123	2.53 [1.10, 5.85]	4.67
Xu H, 2019	10	119	11	294	2.15 [0.94, 4.94]	4.70
Bai Y, 2019	10	138	14	503	2.50 [1.13, 5.50]	4.92
Lu K, 2019	11	124	18	571	2.67 [1.29, 5.51]	5.28
Meng J, 2018	23	531	51	2,012	1.68 [1.04, 2.72]	6.81
Sun Y, 2018	13	342	53	1,102	0.80 [0.44, 1.45]	6.09
Li J, 2018	12	50	9	299	6.62 [2.92, 15.04]	4.76
Ma Q, 2018	5	68	12	591	3.44 [1.25, 9.49]	3.82
Su J, 2017	11	103	6	198	3.28 [1.25, 8.64]	4.02
Iqbal F, 2017	2	61	12	175	0.49 [0.11, 2.15]	2.35
Olsen LL, 2017	21	262	43	717	1.31 [0.79, 2.17]	6.68
Claessen FM, 2016	16	327	32	945	1.42 [0.79, 2.56]	6.14
Lin S, 2014	8	97	12	139	0.96 [0.41, 2.26]	4.55
Morris BJ, 2013	27	110	16	149	2.03 [1.14, 3.61]	6.22
Kamath S, 2005	8	23	4	57	3.94 [1.28, 12.06]	3.40
Zhu Y, 2017	4	18	8	205	4.84 [1.58, 14.79]	3.41
Singh A, 2018	17	9	19	58	2.65 [1.64, 4.28]	6.84
Heterogeneity: $\tau^2 = 0.19$, $I^2 = 58.46\%$, $H^2 = 2.41$					2.10 [1.61, 2.74]	
Test of $\theta_i = \theta_j$: Q(18) = 42.23, p = 0.00						
Overall					2.20 [1.69, 2.86]	
Heterogeneity: $\tau^2 = 0.20$, $I^2 = 58.88\%$, $H^2 = 2.43$						
Test of $\theta_i = \theta_j$: Q(20) = 46.99, p = 0.00						
Test of group differences: $Q_b(1) = 3.70$, p = 0.05						



Random-effects REML model
based on univariate binary outcomes

Fig. 3 Forest plot for studies investigating association between smoking status and postoperative infection risk, separated by elective orthopaedic procedures and trauma surgeries. 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.

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

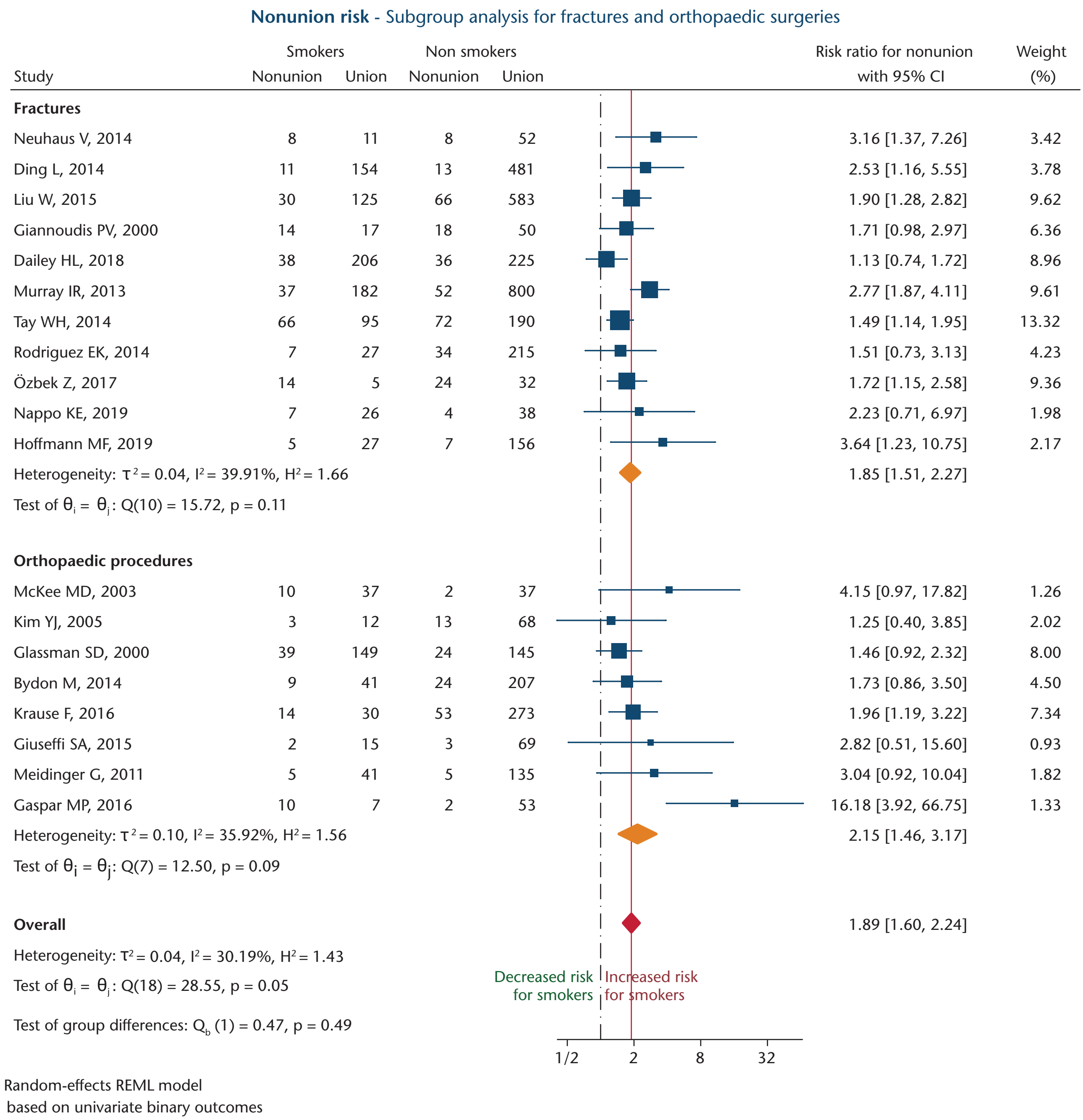


Fig. 4 Forest plot of studies analysing the effect of smoking on nonunion risk following elective orthopaedic surgical procedures or traumatic fracture surgery. Orange diamonds depict effect sizes for subgroups, and the red diamond shows overall effect size. The dashed black line depicts the no-effects line. The solid red line marks overall effect size value.

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

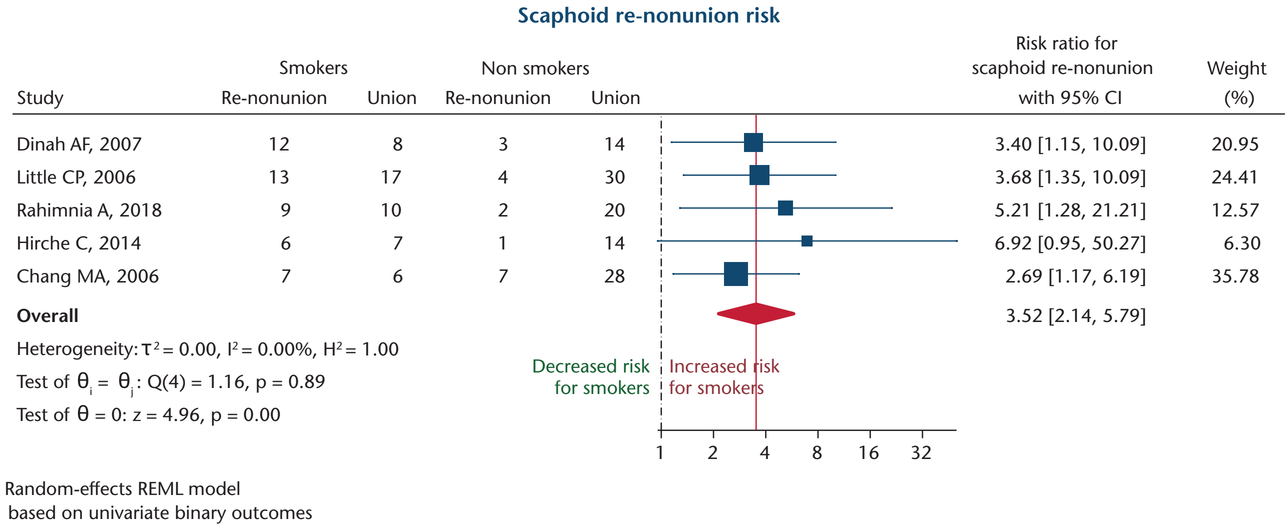


Fig. 5 Forest plot for studies investigating influence of smoking on development of persistent nonunions after surgery for scaphoid nonunions. The dashed black line depicts the no-effects line. The solid red line marks overall effect size value.

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.[92] However, reduced BMD alone does not seem to explain the overall higher fracture risk of smokers in comparison to non-smokers.[16] Indeed, according 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.[16] 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.[16,93–95] 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.[96] 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.[97,98] 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.[7,8,99] 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.[100]

Depending on fracture site and treatment, risk for nonunion after bone fractures ranges between 5% and 10%.[101–103] 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.[104,105] 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.[106,107] 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.[18] 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).[108]

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.[109,110] Revision surgery of scaphoid nonunions is challenging and usually requires harvesting of autologous bone grafts.[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.[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).[101]

Conclusions

Considering the deleterious effects of smoking on risk of developing fractures, subsequent nonunion and post-operative 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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