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The effect of smoking on bone healing

A SYSTEMATIC REVIEW

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Objectives
To review the systemic impact of smoking on bone healing as evidenced within the orthopaedic literature.

Methods
A protocol was established and studies were sourced from five electronic databases. Screening, data abstraction and quality assessment was conducted by two review authors. Prospective and retrospective clinical studies were included. The primary outcome measures were based on clinical and/or radiological indicators of bone healing. This review specifically focused on non-spinal orthopaedic studies.

Results
Nine tibia studies and eight other orthopaedic studies were considered for systematic review. Of these 17 studies, 13 concluded that smoking negatively influenced bone healing.

Conclusions
Smoking has a negative effect on bone healing, in terms of delayed union, nonunion and more complications.

Keywords: Smoking, Bone healing, Systematic review, Fracture healing, Bone healing, Bone repair

Article focus
- To review the systemic impact of smoking on bone healing as evidenced within the non-spinal orthopaedic literature

Key messages
- Smoking has a negative impact on bone healing

Strengths and limitations
- This study sets out to review bone healing in a systematic manner
- A meta-analysis could not be performed due to differences in study designs, methods of measuring bone healing and presentation of data between studies

Introduction
Bone healing is a complex process that is influenced by biological, mechanical and systemic factors. There is growing evidence that smoking delays or inhibits bone healing after surgery or trauma. This evidence has largely been derived from animal studies and human studies focusing on spinal fusion.[1-4]

Giannoudis, Einhorn and Marsh[5] described a 'Diamond Model' for successful fracture healing; osteogenic cells, osteoconductive scaffold, mechanical stability and adequate growth factors. While it is unlikely that smoking affects the mechanical stability, it may have an effect on the other three aspects of this diamond. There is still much to be understood about the exact mechanism and effect of smoking on bone healing.

Overall a number of studies in the medical literature have investigated the effects of smoking on bone healing, however predominantly this information is dispersed across multiple surgical specialties. Little emphasis has been placed on summarising these findings.

This review aims to systematically assess the effect of smoking on bone healing. Bone healing will be objectively assessed through clinical, radiological and patient-centered outcomes.

The impact of smoking on spinal fusion has been extensively researched and reviewed. Consequently this review will focus on other bone sites that have also been studied. Conclusions applicable to the effect of smoking on bone healing in general will be drawn.

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Materials and Methods

The systematic review followed many of the recommendations as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[6] The PRISMA statement is primarily aimed at helping authors improve the reporting of reviews of randomised control trials. However, the PRISMA statement can also be used as a basis for reporting systematic reviews of other types of research, as in the present review.

A protocol specifying all aspects of the review method was developed before initiation of this review. This protocol included criteria for considering studies for this review, search methods for identification of studies, data collection and analysis.

The protocol was planned to minimise the effect of author bias on the review and, in particular, the potential to alter the method or data analysis based on study findings. The protocol was peer-reviewed by the Periodontal team at King's College London (London, United Kingdom) before commencing the study.

Search strategy. Five electronic databases were searched: MEDLINE, Web of Science, The Cochrane Library, SCOPUS and EMBASE. All databases were searched from their earliest records until August 2012. The full search strategy developed for MEDLINE is shown in Table I. This search strategy was customised according to the database being used. The searches were restricted to English language publications.

The bibliographies of all relevant papers and review articles were manually searched. Unpublished data was not sought.

The search strategy was designed to examine the effect of smoking on bone healing generally. Spinal studies were excluded from this review, due to the complicated nature of healing at this site across intervertebral spaces. This review focused instead only on the non-spinal orthopaedic literature.

Study inclusion and exclusion criteria. Prospective and retrospective clinical studies assessing bone healing in smokers and non-smokers were included. The studies involved clinical interventions, ranging from conservative treatment such as cast immobilisation to surgical interventions, for example internal fracture fixation. In addition, arms of clinical trials comparing different interventions that reported results separately for smokers and non-smokers were included. The following inclusion criteria were applied: 1) publications written in the English language; 2) human studies; and 3) studies categorising subjects into at least two groups (non-smokers and smokers).

Studies were excluded if they contained inadequate data to allow a clear comparison of bone healing in smokers and non-smokers following treatment.

Outcome measures. Included studies needed to report one or more of the following primary outcomes, which were: 1) clinical indicators of bone healing (including measures of time to clinical union and diagnoses of non-, delayed or malunion); and 2) radiological indicators of bone healing (including measures of time to radiologically defined union).

Secondary outcomes were: 1) complications of bone healing (including diagnoses of infection or osteomyelitis); and 2) patient based-outcomes (when not used as part of a clinical indicator for bone healing), which included pain and functional status.

Study selection, data collection and analysis. In the first phase of study selection, the titles and abstracts of all identified publications were independently screened by two reviewers (RAP and RMP). Disagreement between reviewers was resolved by discussion.

The full texts of all studies of possible relevance were obtained for independent assessment against the inclusion criteria stated. Studies rejected at this stage were recorded in a rejection table with reasons for rejection. Again disagreement between reviewers was resolved by discussion.

Inter-reviewer agreement was calculated with Cohen's κ score for each screening stage. Where possible, authors of studies were contacted to resolve doubts about study design, patient populations and to request missing information.

A data extraction form was used to collect information from the included studies. The data collected included

Table I. Search strategy developed for MEDLINE

	Search strategies
	Main heading
1	Bone and bones
2	Fracture healing
3	Bone regeneration
4	Bone transplantation
	(mp = Title, original title, abstract, name of substance word, subject heading, word):
5	Fracture healing. mp
6	Bone healing. mp
7	Bone regeneration. mp
8	Fracture repair. mp
9	Bone repair. mp
10	Bone grafting. mp
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
	Main heading
12	Smoking
	(mp = Title, original title, abstract, name of substance word, subject heading, word):
13	smok*. mp
14	nicotine. mp
15	tobacco. mp
16	cigar. mp
17	12 or 13 or 14 or 15 or 16
18	11 and 17
19	Limit 18 to Humans and English language

study characteristics, outcome measures, treatment characteristics, results, quality assessment data and other general information.

Quality assessment. The quality of the included studies was assessed according to: 1) similarity of the smoking and non-smoking groups at baseline; 2) masking of smoking status to the clinician(s) assessing the outcome(s); 3) reproducibility of the outcome measure(s); and 4) completeness of follow-up and explanations for dropouts. Studies with a retrospective design were not assessed with reference to completeness of follow-up.

When all criteria were met the risk of bias was estimated as low. A moderate risk of bias was assigned when one or more criteria were partly fulfilled and a high risk assigned when one or more criteria were not met. The quality assessment was not used to exclude any studies qualifying for the review on the basis of their inclusion criteria.

Data synthesis. A summary table was constructed using information collected on the data extraction forms. The pooled data was analysed in a descriptive format. Studies were analysed for similarities and suitability for meta-analysis.

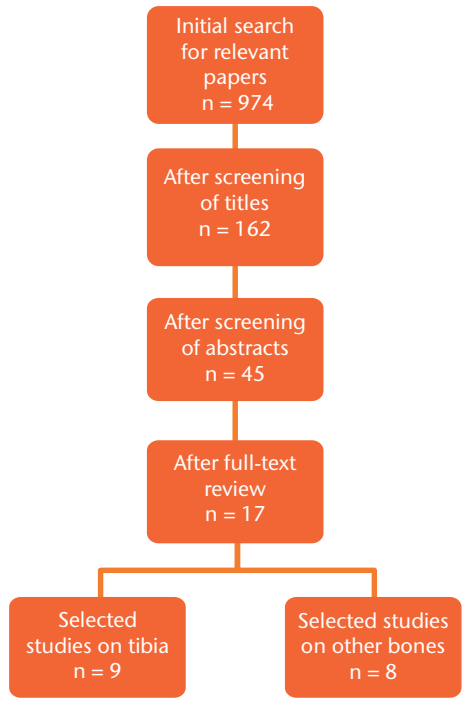

Fig. 1

Flow diagram for the systematic review.

Results

Literature search. The search of the five databases initially resulted in a total of 974 studies (Fig. 1). After screening of article titles and excluding spinal studies, 162 studies remained. The abstracts of these studies were reviewed and 45 studies were selected for full-text evaluation. No additional studies were identified through hand searching of bibliographies of relevant papers or review articles.

The screening of abstracts had a selection agreement defined by a κ score of 0.94 and the screening of full text had a selection agreement defined by a κ score of 0.47. The low κ score for the full text review was largely attributed to discussions at the time as to whether to include or exclude revision surgery.

Of the full-text articles evaluated, 28 were excluded. After reading all full-text articles, the protocol was adapted to exclude all studies based on revision surgery, in view of the high number of confounders associated with patients in this group. Other common reasons for exclusion included studies not measuring bone healing and insufficient data being presented in the paper.

The 17 remaining studies where categorised into two groups: studies based on the tibia (n = 9) and studies base on other bones (n = 8). These two groups were analysed separately. Table II summarises the nine included tibia studies, and Table III summarises the eight included studies on other bones.

Summary of tibial studies

Characteristics of study designs and settings. Smoking was reported as a primary focus in all the studies. One study was multi-centred with eight participating centres.[7] Six studies were conducted within single institutions.[8-13] Two studies were unclear as to whether they were multi-centred or conducted in single institutions.[14,15]

Two studies[14,15] were published by the same authors and included similar patients treated at the same institution at overlapping times. After contacting the authors it was established that there was an overlap in the patients used between these two studies.

Characteristics of participants. One study[15] only included male patients, whereas all others included both male and female patients. The mean age of participants was provided in six studies.[7,9,10,12,14,15] This ranged from 33 years[9] to 53 years.[14,15] Schmitz et al[11] reported the mean age of the smoking group as 35.6 years and the non-smoking group as 35.8 years. Adams et al[8] reported the mean age of smokers was 38.7 years and non-smokers was 39.2 years. One study reported the mean age seperately for men and women (40.3 years and 43.7 years, respectively).[13]

One study[7] used a subgroup of patients who were participating in a lower extremity assessment project. This project was a cohort study of lower extremity trauma patients who were at risk of amputation.

The number of patients in the studies ranged from 33[12] to 273.[8] The number of smokers in the studies ranged from 13[12] to 140.[8]

The studies categorised patients based on a self-reported smoking history, but the definition of 'smoking' varied. Six studies were unclear on their reported definition of a smoker,[7,10,12-15] but more definite descriptions included

Table II. Summary of included tibia studies (IM, intramedullary; AP, anteroposterior; CI, confidence interval; OR, odds ratio)

Author/s	Design	Smoker definition	Patients/fractures/ smokers (n)	Intervention	Follow-up (mths)	Diagnostic criteria	Findings	Conclusions
Schmitz et al[11]	Prospective cohort study. Closed and grade 1 open fractures	> 5 cigarettes/day	190/190/76	IM rod fixation. External fixation. Cast immobilisation	12 (or healing)	Clinical union: ability to ambulate and bear full weight on the affected tibia without pain at the fracture site and no pain or motion at the fracture site with manual stressing of the fracture. Nonunion: lack of clinical union after at least 1 year follow-up. Radiological union: healing of 3 or 4 of 4 cortices on AP and lateral radiographs	Median time to clinical union 269 days for smokers *vs* 136 days for non-smokers (p = 0.0001). Median time to radiological union 244 days for smokers *vs* 144 days for non-smokers (p < 0.001). Statistically significant differences were noted in the clinical and radiological time to union between smokers and non-smokers when treated by IM and external fixation	Significantly delayed clinical and radiological union in smokers with closed and Grade 1 open tibial fractures compared with non-smokers
Ristiniemi et al[10]	Possibly retrospective study. Open and closed distal tibial fractures (all < 5 cm from ankle joint)	Unclear. Data obtained from patient records	52/52/16	Two-ring hybrid external fixation	Until fractures united	Clinical and radiological union: bridging of ≥ 3/4 cortices on AP and lateral radiographs, or disappearance of fracture line with no pain in the fracture on weight-bearing. Delayed union: additional operation required to promote fracture union	Smokers comprised 26% of those without delayed union and 58% of those with delayed union. Smoking was significantly associated with a longer time to fracture union (p = 0.013). Smoking seen to delay union by 10 weeks (regression coefficient 10.1 (95% CI 1 to 21); p = 0.070). Number of cigarettes per day significantly associated with re-operation because of delayed healing (p = 0.043)	Current smoking was associated with a longer time to fracture union and the number of cigarettes smoked a day was found to be a risk factor for re-operation
Alemdaroglu et al[12]	Prospective cohort study. Open & closed tibial shaft-fractures	Unclear	33/34/13	Circular external fixation	6 to 12 after union	Radiological union: evidence of bridging callus between the main fragments on ≥ 3 cortices on AP and lateral views. Delayed union: consolidation after 26 weeks	Mean consolidation time 27.54 weeks (SD 11.61) for smokers *vs* 21.37 weeks (SD 5.08) for non-smokers (p = 0.158)	No significant difference in the healing time for tibial shaft fractures for smokers and non-smokers treated by circular external fixation
Adams et al[8]	Partly prospective, partly retrospective. Open tibial fractures	≥ 10 cigarettes/day (self-reported)	273/273/140	IM rod fixation. External fixation. Cast immobilisation	Until union or clinical intervention for nonunion	Clinical and radiological union: when a patient could bear full weight with no pain at fracture site and radiological evidence of bridging of 3/4 cortices on standard AP and lateral views. Nonunion: fractures that required revision surgery to achieve healing	Mean time to union of 32.3 weeks for smokers and 27.8 weeks for non-smokers (p < 0.05). Union times were more prolonged in smokers in each Gustilo subtype. The difference was greatest in grade IIIA injuries (37 weeks *vs* 27 weeks; p < 0.05). Surgery for nonunion was required in 33% of smokers and 25% of non-smokers (p = 0.14), and deep infection occurred in 10% of smokers and 11% of non-smokers	Smokers had a significant delay in union of open tibial fractures. The delay in union was most evident in Grade IIIA fractures
Castillo et al[7]	Prospective study. Open tibial fractures	Current smokers	268/268/105	Fracture debridement, antibiotic coverage, fracture stabilisation, repeat debridement & early soft-tissue coverage	24	Clinical and radiological union: bridging of the fracture site and when the patient could weight bear and perform activities without pain	Mean time to fracture healing 41.9 weeks for smokers *vs* 40.1 weeks for non-smokers. Nonunion rate at 24 months was 24.1% for smokers and 9.9% for non-smokers. After adjusting for covariates, current smokers were 37% less likely to be healed after 2 years than non-smokers (p = 0.01). Rate of osteomyelitis of 17.1% for smokers and 4.9% for non-smokers. After adjusting for covariates, current smokers were 3.7 times as likely to develop an osteomyelitis than non-smokers (p = 0.01)	Nonsmokers appear more likely to heal by 24 months and appear less likely to develop osteomyelitis than smokers
Harvey et al[9]	Retrospective study. Open tibial fractures	Any use of tobacco	105/110/59	External fixation. IM fixation	Unclear	Clinical and radiological union: if united clinically & if 2 orthogonal radiographs showed union with bridging callus	Rate of union 84% for smokers *vs* 94% for non-smokers (p = 0.10). Rate of union after 270 days or nonunion was 71% in smokers *vs* 43% in non-smokers (p = 0.09). Rate of deep infection 13% in smokers *vs* 16% in non-smokers (p = 0.49)	Union rate was not significantly different for smokers and non-smokers for open tibial fractures
W-Dahl and Toksvig-Larsen[14]	Prospective cohort study. Tibial Osteotomy	Unclear (self-reported)	200/207/34	Hemicallotasis osteotomy	Unclear	Clinical and radiological union: radiological investigation and upon completion of a weight-bearing test without developing symptoms. Delayed healing: > 16 weeks in external fixation	Mean time in external fixation was 110 days (SD 25.2) for smokers and 94 days (SD 18) for non-smokers (p < 0.001). Delayed healing occurred in 41% (14/34) of smokers *vs* 15% (25/166) of non-smokers. Multivariate analysis showed smoking was the greatest preoperative risk factor for delayed healing: OR 4.0 (95% CI 1.7 to 9.5); p = 0.004	Smokers operated on by the hemicallotasis techniques needed a longer time in external fixation & were more likely to have delayed healing
W-Dahl and Toksvig-Larsen[15]	Prospective cohort study. Tibial Osteotomy	Unclear (self-reported)	175/200/41	Hemicallotasis osteotomy	Unclear	Clinical and radiological union: radiological investigation and upon completion of a weight-bearing test without developing symptoms. Delayed healing: > 16 weeks in external fixation	Mean time in external fixation was 100 days for smokers and 93 days for non-smokers. Significant difference in the time in external fixation (unadjusted 7 days (p = 0.03), adjusted 6 days (p = 0.05). Delayed healing in 20% (8/41) of smokers *vs* 9% (10/113) of non-smokers (p > 0.05)	Cigarette smoking delays bone healing following hemicallotasis osteotomies for knee deformities
Meidinger et al[13]	Retrospective cohort study. Tibial Osteotomy	Unclear	186/186/46	Medial open wedge high tibial osteotomy	Unclear	Clinical nonunion: persistence of load-dependent pain over the osteotomy and focally over the lateral hinge for > 6 months. Radiological nonunion: missing bony consolidation in conventional radiographs as well as the appearance of defects and a sclerosis of the bony osteotomy boundaries in CT-scans	50% of nonunions were smokers. 23.3% of consolidations were smokers. There was a significant difference in the percentage of smokers in the nonunion group compared with the percentage in the consolidation group (p < 0.05)	Smoking is a risk factor for nonunion after high tibial osteotomies

> five cigarettes per day,[11] ≥ ten cigarettes per day,[8] or the use of any amount of tobacco in the form of cigarettes, a pipe or cigars.[9] The two studies by W-Dahl and Toksvig-Larsen[14,15] clearly defined non-smokers as patients who at a pre-operative examination stated they had never smoked or had stopped smoking > six months ago.

Table III. Summary table of included studies based on other bones (IM, intramedullary; CI, confidence interval)

Author/s	Design	Definition of smoker	Patients/ fractures/smokers (n)	Intervention	Follow-up (mths)	Diagnostic criteria	Results	Conclusions
Femoral fractures								
Giannoudis et al[16]	Retrospective case-controlled study	Heavy smoker > 20 cigarettes/day	99/99/31	IM nailing	Unclear	Nonunion was defined by routine clinical and radiological criteria, and the need for further surgery	14/32 nonunions (43.8%) and 17/67 unions (25.3%) were heavy smokers. Odds ratio of smoking on nonunion was 2.29 (95% CI 0.85 to 6.08; p = 0.107)	Smoking was not a statistically significant factor for nonunion of femoral fractures
Femoral distraction								
Kenawey et al[17]	Prospective cohort study	Unclear	35/37/5	Femoral lengthening procedure	≥ 12	Regenerate failure defined as insufficient bone regenerate requiring surgery	2/29 cases (7%) in the normal regenerate group were smokers. 3/8 cases (38%) in the insufficient regenerate group were smokers. Risk ratio of smoking = 3.8 (p = 0.025)	Smoking was associated with a higher risk of insufficient bone regeneration
Fibular fractures								
Krannitz et al[18]	Retrospective cohort study	Current smoker (any quantity)	52/52/27	Internal fixation. Cast immobilisation	Unclear	Radiological assessment based on presence of cortical bridging and resolution of fracture line	Mean time to healing following cast immobilisation 96.9 days (SD 30.3) for smokers and 80.7 days (SD 33.3) for non-smokers (p = 0.034). Mean time to healing following external fixation 54.9 days (SD 11.9) for smokers and 42.5 days (SD 6.5) for non-smokers (p = 0.034). The positive predictive value of smoking increasing time to heal was 100%	Smokers had an increased time to radiological bone healing in minimally displaced fibular fractures
Ulnar osteotomy								
Chen et al[19]	Retrospective cohort study	Unclear	39/40/19	Elective ulna-shortening osteotomy (oblique osteotomy stabilised with compression plate)	Mean 13.7	Radiological union: presence of trabeculation across the osteotomy site & of confluent bony bridging across both cortices. Delayed union: incomplete healing at seven months. Nonunion: lack of evidence of progressive healing by 12 months	Mean time to union 7.1 months for smokers and 4.1 months for non-smokers (p = 0.016). Delayed or nonunion occurred in 6/20 fractures (30%) in smokers and 0/20 fractures in non-smokers (p = 0.02)	Smokers had a longer time to union and higher incidence of delayed union or nonunion after ulna osteotomies
Subtalar arthrodesis								
Chahal et al[20]	Retrospective cohort study	Any smoking 1 week pre- or post-operatively	87/87/38	Elective primary subtalar arthrodesis. Bone graft used in some cases	Mean 35.5 months	Union: complete bridging callus or trabeculation across the subtalar joint as identified on radiological examination, with no pain when stress applied to the subtalar joint during clinical examination. Nonunion: the lack of radiological bridging callus or trabeculation & continued clinical symptoms when stress was applied to the subtalar joint	Rate of union was 68.4% (26/38) for smokers and 89.8% (44/49) for non-smokers. Smokers were 3.8 times more likely to experience nonunion (p < 0.05)	Smokers had a significantly lower union rate after subtalar arthrodesis
Ankle arthrodesis								
Perlman and Thordarson[22]	Retrospective cohort study	Current tobacco use	61/67/40	Ankle arthrodesis. Fixation with cancellous screws or external fixation	Unclear	Radiological union: absence of radiolucent lines and visualisation of trabeculae crossing the fusion site. Radiological nonunion: persistence of a complete radiolucency on plain radiographs	Rate of nonunion was 32.5% for smokers and 22% for non-smokers	No statistical significant difference was noted between the rates of nonunion
Collman et al[21]	Retrospective cohort study	History of smoking or tobacco use	39/39/11	Arthroscopic ankle arthrodesis	Union: mean 1 year; nonunion: mean 610 days	Radiological union: the presence of unequivocal trabeculation across the tibiotalar joint space	Rate of union was 82% (9/11) in smokers and 89% (25/28) in non-smokers	Smokers did not show a trend towards nonunion
Foot surgery								
Krannitz et al[23]	Prospective cohort study	Self-reported. Also confirmed with a urine cotinine dipstick test	46/46/17	Austin bunionectomy with internal fixation screw	Up to 4 months after return to activity	Radiological union: assessment of cortical bridging consistent with consolidation of the osteotomy site	Mean bone healing time was 120 days (SD 55.3) for smokers and 69 days (SD 26.0) for non-smokers (p < 0.001). There was a mean 42% increase in time to bone healing in smokers. As the concentration of cotinine in urine increased, the healing time increased (Pearson correlation = -0.314, p < 0.01)	Smokers had delayed radiological healing when compared with non-smokers following bunion surgery. The urine cotinine level in the smokers was highly correlated with prolonged bone healing

Characteristics of clinical state and intervention. Six studies investigated fractures of the tibia[7-12] and three were based on tibial osteotomies.[13-15] Of the fracture studies, three included open and closed fractures,[10-12] whereas the remaining three studies [7-9] included only open fractures.

Schmitz et al[11] investigated closed and Gustillo Grade I open fractures, whereas Castillo et al[7] investigated only Grade III open fractures. Harvey et al[9] included only Gustillo Grade II, IIIA and IIIB fractures.

Three studies[9,11,12] investigated fractures in the tibial shaft while Ristiniemi et al[10] investigated distal tibia fractures (defined as fractures within 5 cm of the ankle joint).

In two studies.[8,11] fractures were treated by intramedullary rod fixation, external fixation or cast immobilisation. Fractures in Harvey et al[9] were treated with external fixation or intramedullary nailing. In one study[10] fractures were treated with two-ring Ilizarov hybrid external fixation. One study[7] did not state the form of fracture stabilisation used.

Characteristics of outcome measures. The majority of studies investigating tibia fractures assessed union based on clinical and radiological data.[7-10] In these four studies fractures were described as united when there was radiological evidence of bridging of cortices and there was no pain at the fracture site upon weight bearing. One study[11] defined and measured clinical union and radiological union separately. Alemdaroglu et al[12] assessed consolidation based on radiographic measures only.

All studies investigating tibia fractures described in some format the time to union for smokers and non-smokers.

Several studies described an average time to union while one study[9] grouped the time to union into three different time periods (< six months, six to nine months and > nine months). One study[10] did not provide data on time to union between smoking and non-smoking groups, but included the results from a univariate analysis of the difference.

Harvey et al[9] also described union rates between smokers and non-smokers. Four other studies investigating tibia fractures described the proportion of delayed unions or nonunions in the smoking and non-smoking groups.[7,8,10,11]

Two studies based on tibial osteotomies presented data on the mean time in external fixation.[14,15] The time in external fixation was once again based on both a clinical and radiological assessment of healing. Both studies also described the incidence of delayed healing amongst smokers and non-smokers. Meidinger et al[13] reported the percentage of nonunions and consolidations.

Secondary outcomes. Three studies reported on infection as a secondary outcome. These studies documented the incidence of infection amongst smokers and non-smokers, defined as deep infection in two studies,[8,9] and osteomyelitis in one study.[7]

Length of follow-up. The exact length of follow-up was not clearly specified in several studies.[9,12-15] Schmitz et al[11] described follow-up until complete healing or for at least a year. Adams et al[8] described follow-up until fracture union or clinical intervention for non-union was required, this study had a mean follow-up of 21.6 months. Ristiniemi et al[10] document a mean follow-up time of 41 months, while Castillo et al[7] had a mean follow-up of 24 months. Alemdaroglu et al[12] described follow-up for at least six months after union.

Conclusions drawn on the effect of smoking on bone healing. Details of the conclusions drawn on the effect of smoking on bone healing for each tibia study are presented in Table II.

Five of the nine studies concluded that smokers took significantly longer to heal than non-smokers.[8,10,11,14,15] Two of these studies also noted that smokers were more likely to have delayed healing.[14,15] These two studies defined delayed healing as > 16 weeks in external fixation.

Castillo et al[7] did not present a direct stastistical analysis of the time to fracture healing between smokers and non-smokers. The study however reported that non-smokers are more likely to heal by 24 months than smokers ($p = 0.01$).

Meidinger et al[13] reported the percentage of smokers in the nonunion and consolidation groups. They reported a significant difference in the the percentage of smokers in the nonunion group compared with the percentage in the consolidation group ($p < 0.05$).

Harvey et al[9] did not describe the average time to union, instead results were presented as four different healing groups; timely union, delayed union, late union and un-united. The study reported that more smokers had late union or un-united fractures than non-smokers. The union rate was not significantly different between the smokers and non-smokers ($p = 0.10$).

Adams et al[8] found a non-statistically significant difference in the percentage of smokers and non-smokers with nonunions. Alemdaroglu et al[12] noted no significant difference in the healing time for smokers and non-smokers treated by circular external fixation.

Overall all tibia studies except one[12] reported a negative effect of smoking on bone healing.

One study,[7] concluded that smokers were more likely to develop osteomyelitis. Harvey et al[9] noted no significant difference in the incidence of deep infections in smokers and non-smokers. Adams et al[8] did not include a statistical analysis of the incidence of deep infections among smokers and non-smokers.

Risk of bias in included studies. Details of the quality assessment for each included tibia study is presented in Table IV. Fracture characteristics among other things were noted not to be significantly different between smokers and non-smokers in three studies.[8,9,11] It was unclear in six studies[7,10,12-15] whether the smoking and non-smoking groups were comparable at baseline. Although two studies[14,15] provided baseline data on the mean age and BMI of the smoking and non-smoking groups, a statistical analysis to assess a significant difference between the two groups was not reported.

The reproducibility of outcome measures was unclear in eight studies. One study[12] reported inter- and intra-observer reliability of the outcome measure. In all studies except two[9,11] it was unclear as to whether the examiner was masked to the smoking status of the patients.

Of the five prospective studies, two had a 100% follow-up[14,15] and one had a 77% follow-up but all drop-outs were accounted for.[11] In was unclear as to whether one study[10] was prospective or retrospective in design.

Studies based on other bones

Table III summarises the eight included studies based on other bones and Table V details the quality assessment of these included studies.

Femoral fractures. Giannoudis et al[16] presented a retrospective study aimed to assess the factors that affected union of the diaphysis of the femur by comparing 32 patients with nonunion and 67 patients with united fractures. The fracture union and nonunion groups were comparable regarding gender, Injury Severity Score and soft-tissue injury. The assessment of healing was poorly described, but the definition of nonunion was based on clinical and radiological criteria. Overall the study concluded that smoking was not a statistically significant factor for nonunion of the femoral diaphysis.

Femoral distraction. Kenawey et al[17] studied 35 patients treated with intramedullary femoral lengthening at a single institution. This prospective study assessed regenerate

Table IV. Quality assessment of included tibial studies

Authors	Smoking and non-smoking groups not significantly different at baseline*	Assessor blinded to smoking status	Reproducibility of outcome measure	Proportion followed-up	Risk of bias
Schmitz et al[11]	Yes. The smoking and non-smoking groups were statistically similar in relation to demographics, fracture characteristics and fracture treatment tendencies	Yes. Radiological union interpreted by a radiologist blinded to the smoking status	Unclear	77% (all drop-outs accounted for)	Moderate
Ristiniemi et al[10]	Unclear	Unclear	Unclear but all radiographs were interpreted by one clinician	Unclear (study possibly retrospective)	Moderate
Alemdaroglu et al[12]	Unclear	Unclear	The inter- and intra-observer reliability of the consolidation time was 0.9660 (95% confidence interval (CI) 0.9400 to 0.9821) and 0.9564 (95% CI 0.9237 to 0.9769), respectively	94% (all drop-outs accounted for)	Moderate
Adams et al[8]	Yes. The smoking and non-smoking groups were broadly comparable in regards to the mean age and gender distribution. The median ISS was the same in both groups, and the groups were well-matched by fracture causation, fracture morphology classified by the AO system and distribution of Gustilo subtypes	Unclear	Unclear	N/A† (study partially retrospective)	Moderate
Castillo et al[7]	Unclear	Unclear	Unclear. Fracture healing was assessed by different surgeons at different sites	91.4% non-smokers, 76.2% smokers	Moderate
Harvey et al[9]	Yes. Smokers and non-smokers were statistically similar for baseline characteristics, injury type or implant type	Yes	Unclear	N/A (retrospective)	Moderate
W-Dahl and Toksvig-Larsen[14]	Unclear. Data provided on the mean age, mean BMI and gender distribution in the smoking and non-smoking groups, but no statistical analysis reported	Unclear	Unclear	100%	Moderate
W-Dahl and Toksvig-Larsen[15]	Unclear. Data provided on the mean age and BMI of the smoking and non-smoking groups, but no statistical analysis reported	Unclear	Unclear	100%	Moderate
Meidinger et al[13]	Unclear	Unclear	Unclear	N/A	Moderate

* ISS, Injury Severity Score; BMI, body mass index
† N/A, not available

failure. Insufficient bone regenerate developed in eight cases, three of whom were smokers. Normal regenerate developed in 29 cases, of which two were smokers. It was concluded that smoking was associated with a higher risk of insufficient bone regeneration.

Fibular fractures. One study investigated fibular fractures.[18] This study retrospectively examined 52 patients with minimally displaced isolated fibular fractures treated by either internal fixation or cast immobilisation. Healing was based on radiological assessment. The study concluded that smokers displayed an increased time to radiological bone healing compared with non-smokers ($p = 0.034$).

Ulna osteotomy. One study was conducted on patients who had undergone an elective procedure on the ulna.[19] This retrospective study involved ulna-shortening osteotomies on 39 patients to treat ulna impaction syndrome. Union was defined by radiological assessment and a clinician masked to the patient's smoking status interpreted all radiographs. One smoker underwent bilateral procedures and bilateral results were included. Smokers had a longer time to union and higher incidence of delayed union or nonunion. The mean time to union was 7.1 months in smokers and 4.1 months in non-smokers ($p = 0.016$), and 30% of smokers experienced delayed union or nonunion compared with none of the non-smokers ($p = 0.02$).

Subtalar arthrodesis. Chahal et al[20] investigated subtalar arthrodesis. This multicentre study was carried out at two hospitals. Radiological outcomes were independently assessed by musculoskeletal radiologists. The

Table V. Quality assessment of included studies based on other orthopaedic bones

Authors	Smoking and non-smoking groups not significantly different at baseline	Assessor blinded to smoking status	Reproducibility of outcome measure	Proportion followed-up*	Risk of bias
Giannoudis et al[16]	Unclear	Unclear	Unclear	N/A - retrospective	Moderate
Kenaway et al[17]	Unclear	Unclear	Unclear	100%	Moderate
Krannitz et al[18]	Unclear	Unclear	Unclear. However radiological review was performed individually by researchers and radiologists. No disagreement between the two was encountered	N/A - retrospective	Moderate
Chen et al[19]	Unclear	Yes	Unclear. Single examiner	N/A - retrospective	Moderate
Chahal et al[20]	Unclear	Yes	Unclear	N/A - retrospective	Moderate
Perlman and Thordarson[22]	Unclear	Unclear	Unclear	N/A - retrospective	Moderate
Collman et al[21]	Unclear	Unclear	Unclear	N/A - retrospective	Moderate
Krannitz et al[23]	Unclear	Yes	Unclear	100%	Moderate

* N/A, not applicable

results showed that smokers were 3.8 times more likely to have a nonunion than non-smokers. The study concluded that smokers had a significantly lower rate of union after subtalar arthrodesis.

Ankle arthrodesis. Two retrospective cohort studies investigated arthrodesis of the ankle.[21,22] The majority of patients in the study by Collman et al[21] were diagnosed with post-traumatic ankle arthritis. As the study was based on a small patient population (11 smokers and 28 non-smokers), analysis of results was limited to observational trends. Smokers attained union in almost all cases and did not show a trend towards nonunion. In the study the term 'smokers' was poorly defined, and may have included individuals with a previous smoking history. The authors also acknowledge that the outcome analysis was limited by a small patient population. Non-significant differences between the groups may have been due to the small study size rather than a lack of association.

Perlman and Thordarson[22] studied 67 fusions in 61 patients. The rate of nonunion was higher in the smoking group (32.5% of smokers *vs* 22% of non-smokers), but statistical significance was not reached. However, p-values were not reported in the study, and the results from bilateral fusions in the same patient were included.

Elective foot surgery. Krannitz et al[23] investigated the effect of cigarette smoking on radiological bone healing after elective Austin bunionectomies with internal screw fixation. The study included 17 self-reported smokers and 17 non-smokers. This study was unique among those included in this review in that it confirmed smoking status with a urine cotinine test. The study concluded that smokers displayed an increased time to radiological bone healing compared with non-smokers ($p < 0.001$). The urine cotinine level in the smoking group was highly correlated with prolonged bone healing.

Meta-analysis of the data presented in the studies. A meta-analysis was not possible for any of the orthopaedic studies, due to heterogeneity in study design, data collection and data presentation.

Discussion

This systematic review has shown that smoking can have a negative effect on bone healing. Eight of the nine included tibia studies reported a negative effect of smoking on bone healing. Five of the eight other orthopaedic studies reported a statistical difference in healing or bone regeneration between smokers and non-smokers. It is concluded that smoking has a negative effect on bone healing.

Analysis of study designs. It is important to note that the effect of smoking was reported as a primary focus for all the included studies. However the studies were less clear in regards to their design. It could not be established whether one study conducted by Risiniemi et al[10] was prospective or retrospective. The study by Adams et al[8] was partially prospective and partially retrospective. Overall the studies were predominantly retrospective and cohort in design.

Analysis of study participants. The number of patients in the studies ranged from 33 to 273.[12] The only study to report no negative effect of smoking on bone healing was also the study with the smallest sample size,[12] and the authors acknowledged that this may have prevented a statistical difference in healing times from being recorded.

The conclusions drawn in this review are based on studies of middle-aged adults. It is however interesting to note the conclusions of Rajan et al.[24] Their study retrospectively reviewed patients who were found to have a prolonged bone healing index (BHI) after limb deformity corrective surgery. The study demonstrated that BHI was increased in both active and passive smokers. The 17 smoking patients in their study comprised 16 adolescents and one nine-year-old, an age distribution substantially different to the studies included in this review.

The definition of a smoker varied significantly between the studies in this review, ranging from any history of tobacco use to thresholds of ten or 20 cigarettes a day. A surprisingly large proportion of studies (eight of the 17) did not define a smoker in their publications.

All of the included studies categorised patients based on self-reported smoking status. Krannitz et al[23] acknowledged in their discussion that smoking status could be misclassified when based on statements by the patient, and that patients could mislead physicians about their tobacco use. Lores Obradors et al[25] investigated patients attending a clinic for respiratory medicine, and demonstrated that 21 of 125 patients (17%) smoked while denying doing so.

Scott, Palmer and Stapleton[26] identified that most studies rely on patient reported smoking habits, which can be unreliable. They recommended biochemical analysis as the gold standard of assessing smoking status. Biochemical assessment of current smoking status can be achieved by measurement of systemic levels of cotinine,[23,27] which provides the most accurate assessment of the level of exposure. It is also important to record the number of years a patient has smoked to provide an estimate of pack-years, as the duration and magnitude of smoking exposure will have a greater impact on healing.[26] Misclassification of the smoking status of patients would tend to favour smokers being included in the non-smoking group, which would reduce the chances of finding an effect of smoking upon outcomes. This may also be affected by inclusion of former smokers in the study.

The study by Krannitz et al[23] was the only one to confirm smoking status with a biochemical analysis. A urine cotinine test was performed on patients pre-operatively and during the post-operative healing period. It involved a urine dipstick, with the strip changing colour depending on the concentration of cotinine in the urine. Results showed a correlation between the concentration of cotinine in the urine and the time to healing.[23]

Finally the participants also differed between trials in terms of their initial clinical diagnoses.

Analysis of interventions. The majority of studies were based on fractures, and studies that included revision surgery were excluded. The tibial fractures were treated either by internal fixation, external fixation or cast immobilisation. Internal fixation was achieved by different methods.

Several studies reported on elective procedures, such as osteotomies. These procedures are good models to assess bone healing as the surgical procedure performed is standardised and weight-bearing can be assessed at regular intervals.

Analysis of outcome measures. The assessment of union was similar in the studies dealing with tibial fractures, based on both clinical and radiological assessment. The other studies commonly defined union through radiological assessment only.

Schmitz et al[11] when investigating the effect of smoking on tibial shaft healing, only included closed and Grade I open tibial fractures. The reason for excluding Grade II and III open fractures was to avoid confounding variables such as the severity of soft-tissue damage and the timing of wound coverage. A review in the medical literature has noted that smokers presenting with an open tibial fracture will in particular suffer the negative effects of their smoking behaviour, because these fractures also involve significant soft-tissue injury.[28] This demonstrates that healing of bone should not be considered as an independent process and undoubtedly events within the soft tissues influence bone healing.

Overview of conclusions. The findings of this review are in agreement with the recent literature review by Al-Hadithy et al.[1] This paper concludes that smoking has a significant effect on fracture union, particularly in tibial shaft fractures, spinal and foot and ankle fusions. The delay in union was reported to be more apparent in those cases requiring bone grafts, as there is an increased chance of devascularising the graft. The paper suggests smokers have a 40% increased time to union and chance of nonunion compare with non-smokers.

Another recent study of note is that of Moghaddam et al.[29] This study was excluded as it combined the results of smoker and ex-smokers, however, it demonstrated similar finding to that of this review. Current and previous smokers exhibited a significantly higher proportion of delayed union and nonunion of tibial shaft fractures. This difference was highly significant ($p = 0.0007$), which indicated that the time that was necessary for bone healing was significantly increased ($p = 0.0008$).

Overview of quality assessment. Three of the 17 studies reported on the degree of difference at baseline in the smoking and non-smoking groups. This information, required to establish whether the groups were comparable, was provided in less than half of the included studies.

The included prospective studies had a high level of follow-up and generally all dropouts were accounted for. The reproducibility of outcome measures was poorly reported. Also in general the smoking status of the patient was not concealed from the examiner. Due to the less than ideal methodological quality of the included studies, the results presented in this review should be interpreted with caution.

In several studies bilateral defects were treated, and these were managed statistically in different ways. Schmitz et al[11] randomly excluded a tibia from bilateral patients in their study in order to avoid statistical dependence between the observations. In comparison, Harvey et al[9] reported on a cohort of 105 patients and analysed data from 110 tibial fractures. Bilateral fractures were included in this study, and data analysed based on fractures rather than patients.

Overview of the effect on ex-smokers. One study considered the effect on bone healing on previous smokers.

Castillo et al[7] reported that previous smokers were at increased risk of delayed union after tibia fractures, but their risk was not as great as current smokers.

Conclusion. Smoking negatively influences healing of the tibia. It is difficult to draw conclusions on the effect of smoking on bone healing in general. The evaluation of other orthopaedic studies provided less definitive conclusions and did not strengthen the findings seen in the tibia studies. Differences in study designs, methods of measuring bone healing and presentation of data precluded a complete pooling of data for a more robust analysis of all the information.

Clinical implications. The review strengthens our knowledge of the impact of smoking on bone healing. The reduced bone healing potential in smokers, suggests that smoking cessation advice should be offered to smokers before elective procedures. This review however has not investigated the effect of smoking cessation on bone healing potential, and so the advantages can only be speculated.

Implications for future research. One recurring problem in this review was the variability in study design and outcome measures. It would be recommended that future studies record time to healing and present data transparently using mean values with a measure of the spread of data.

Studies evaluating the effect of smoking on treatment response should be based on more reliable methods of assessing smoking exposure rather than sole reliance on patient-reported data. Other methods include the measurement of exhaled carbon monoxide or assessment of salivary/serum levels of cotinine.

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- R. M. Palmer: Data collection, Data analysis, Writing the paper

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