EFORT open reviews

TRAUMA | 7:7 | 516–525

Risk factors for nonunion following surgically managed, traumatic, diaphyseal fractures: a systematic review and meta-analysis

Signe Steenstrup Jensen[1,6], Niels Martin Jensen[1], Per Hviid Gundtoft[3], Søren Kold[4], Robert Zura[5] and Bjarke Viberg[1,2,6]

[1]Department of Orthopedic Surgery and Traumatology, Lillebaelt Hospital, Kolding, Denmark
[2]Department of Orthopedic Surgery and Traumatology, Odense University Hospital, Odense, Denmark
[3]Department of Orthopedic Surgery and Traumatology, Aarhus University Hospital, Aarhus, Denmark
[4]Department of Orthopedic Surgery, Aalborg University Hospital, Aalborg, Denmark
[5]Department of Orthopedic Surgery, Louisiana State University Medical Center, New Orleans, Louisiana, USA
[6]Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark

Correspondence should be addressed to S S Jensen
Email signe.steenstrup.jensen2@rsyd.dk

- *Background:* There are several studies on nonunion, but there are no systematic overviews of the current evidence of risk factors for nonunion. The aim of this study was to systematically review risk factors for nonunion following surgically managed, traumatic, diaphyseal fractures.
- *Methods:* Medline, Embase, Scopus, and Cochrane were searched using a search string developed with aid from a scientific librarian. The studies were screened independently by two authors using Covidence. We solely included studies with at least ten nonunions. Eligible study data were extracted, and the studies were critically appraised. We performed random-effects meta-analyses for those risk factors included in five or more studies. PROSPERO registration number: CRD42021235213.
- *Results:* Of 11,738 records screened, 30 were eligible, and these included 38,465 patients. Twenty-five studies were eligible for meta-analyses. Nonunion was associated with smoking (odds ratio (OR): 1.7, 95% CI: 1.2–2.4), open fractures (OR: 2.6, 95% CI: 1.8–3.9), diabetes (OR: 1.6, 95% CI: 1.3–2.0), infection (OR: 7.0, 95% CI: 3.2–15.0), obesity (OR: 1.5, 95% CI: 1.1–1.9), increasing Gustilo classification (OR: 2.2, 95% CI: 1.4–3.7), and AO classification (OR: 2.4, 95% CI: 1.5–3.7). The studies were generally assessed to be of poor quality, mainly because of the possible risk of bias due to confounding, unclear outcome measurements, and missing data.
- *Conclusion:* Establishing compelling evidence is challenging because the current studies are observational and at risk of bias. We conclude that several risk factors are associated with nonunion following surgically managed, traumatic, diaphyseal fractures and should be included as confounders in future studies.

Keywords
- nonunion
- healing
- trauma
- pseudoarthrosis
- risk factors

EFORT Open Reviews (2022) **7**, 516–525

Introduction

Nonunion is a severe complication in the treatment of fractures and can lead to a reduced quality of life and generate substantial healthcare costs related to prolonged hospital stays, reoperations, and an inability to return to work (1, 2, 3, 4). Early identification of nonunion is therefore important and one possibility is to identify risk factors. This could result in earlier recognition of patients at risk, leading to closer follow-up and lowering the threshold for further intervention.

Establishing compelling evidence of risk factors associated with nonunion is challenging, since existing studies are predominantly small and retrospective. This underscores the need to combine results from multiple studies in order to complete an exhaustive investigation (5, 6). The extensive review on risk factors and quality of scientific evidence only included studies in which risk factors demonstrated a significant impact. Therefore, all other studies were excluded from this review, resulting in a potential risk of bias (5). To our knowledge, no previous studies have systematically reviewed the complete body

www.efortopenreviews.org
https://doi.org/10.1530/EOR-21-0137

of existing studies on risk factors for nonunion, while including a risk of bias analysis, nor has any meta-analysis been performed previously.

This study aimed to systematically review risk factors for nonunion following surgically treated diaphyseal fractures in adults.

Materials and methods

Protocol and registration

The study was based upon the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2020 (7, 8). Before data extraction began, the protocol was registered in the International Register of Systematic Reviews, PROSPERO (Registration number: CRD42021235213 XX). No review protocol was prepared beforehand.

Eligibility criteria

The search string was based on the PECO criteria:

P: Adults with at least one surgically managed, traumatic, diaphyseal bone fracture
E: Risk factors associated with the development of nonunion
C: Patients who did not develop nonunion
O: Patients with nonunion

Inclusion criteria: patients with a mean age >18 years suffering from traumatic diaphyseal fractures, >10 patients that developed nonunion following surgery, at least one risk factor, and peer-reviewed literature. Exclusion criteria: articles not written in English, German, French, Danish, Swedish, or Norwegian, pooling of data from surgically and conservatively treated fractures, animal or cadaveric studies, tumor or cancer surgery, periprosthetic fractures, and gunshot fractures.

Definition of risk factors and outcome

Risk factors were considered as either patient-related or fracture-related. The outcome was defined as the indicated presence of nonunion in each study, regardless of the definition of nonunion in the study.

Information sources

The literature search was executed using four electronic bibliographic databases on April 14, 2020, including Embase (1947–present), MEDLINE (1946–present), Scopus (1940–present), and Cochrane Library. We did not hand search references or contact specific authors. Embase and MEDLINE were searched through Ovid, whereas Scopus and Cochrane were searched through their own respective platforms.

Search strategy

The search string was built with the help of a librarian from the University of Southern Denmark. A block building strategy was used with three individual blocks. To achieve a high recall/sensitivity rate, we implemented a broad search with a low precision rate (9), as advised in the 'Cochrane Handbook for Systematic Reviews of Interventions' (10).

We used both Medical Subject Headings and free text words, combined with Boolean operators and truncations when suitable. No search limitations were added, and the exact search strategy for each database can be found in Supplementary Digital Content 1 (see section on supplementary materials given at the end of this article).

Selection process

All records were transferred to Endnote (Clarivate Analytics, Philadelphia, PA, USA), and duplicates were removed using the built-in software. Data selection and screening was performed using Covidence (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org).

All records were screened independently by two of the authors (S S and N J). Records approved by both authors went through a full-text screening, which was also done independently by the two authors.

Data collection

Data extraction was performed by the two authors collaboratively, using a prefabricated Excel spreadsheet. Discrepancies were reviewed, and disagreements were settled by conferring with the senior author. Authors were contacted in case of missing data, such as the number of patients in each exposure group or doubts regarding the cohort. Nineteen authors were contacted via email and one via LinkedIn; 11 did not answer, 7 did not have further data, and 2 supplied further data. To include as many studies and data as possible in the meta-analyses, we contacted three authors for further data; however, no one replied.

Data items

Records were sought for the following variables: study design, publication year, mean age, number of nonunions, patient demographics, surgical procedures, follow-up time, and risk factors as defined by the study.

Risk of bias assessment

Only those studies included in the meta-analyses were assessed for risk of bias. The studies were assessed by two authors (S S and N J) in collaboration, using the Joanna Briggs Institute critical appraisal checklists for case control

and cohort studies (11). The first study was evaluated as a pilot study and blindly assessed by the senior author and the two main authors to ensure a common baseline.

The assessments were based on the primary aim of the study, although nonunion was always assessed as the outcome. Two orthopedic professors from the author group (S K and R Z) selected five critical confounders, that is known risk factors for nonunion: open/closed fractures, fracture complexity (i.e. AO classification), diabetes, smoking, and age. According to the Social Security Administration final rules for evaluating musculoskeletal disorders in 2021, nonunion is defined as 'a fracture that has failed to unite completely. Nonunion is usually established when a minimum of 9 months has elapsed since the injury and the fracture site has shown no, or minimal, progressive signs of healing for a minimum of 3 months' (12). Therefore, a 9-month follow-up period was defined as sufficient in the risk of bias assessments. The outcome was assessed as valid and reliable if it was clearly stated that nonunion was defined as a lack of progression of healing in the radiographs for 3 months and considered that the fracture would not heal without further intervention (12, 13). It was considered a 'no' if nonunion was exclusively defined by the treating surgeon and no guidelines or radiographic findings were defined, or if nonunion was not defined. 'Unclear' was used when there was a timely or radiographic definition of nonunion, but it did not meet our specified criteria or those defined by CPT/ICD-10/ICD-9 codes.

Effect measures

Nonunion and risk factors were assessed as a binary outcome. The odds ratio (OR) was used as an effect measure. If only the OR and CI were reported in a study, that study could still be eligible for inclusion in the meta-analysis, provided that data had been derived from a univariate analysis. Analyses were carried out using Stata® 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Data syntheses and reporting bias

Meta-analyses were only performed when more than five studies examined the same risk factor. Data are reported using a random-effects model and a restricted maximum likelihood variance estimator to assess the heterogeneity between studies. Meta-analyses are displayed as forest plots. Meta-analyses were done using the built-in Meta function in Stata® 16. Summary data are presented in a table, and an overview of risk factors in a graphical chart. The risk of bias for the studies included in the meta-analyses is depicted in a colored table. A funnel plot and Egger's test were used to assess potential publication bias in the meta-analyses.

Results

Study selection

A total of 11,738 records were included for screening, of which 30 studies were included in the review (Fig. 1).

Study characteristics

The included studies were designed as follows: one was prospective (14), one was uncertain (15), and the remaining 28 were retrospective (16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43) (Table 1). The studies included 38 465 patients, of which 3,975 suffered from nonunion. The patients' ages ranged from 13 to 100 years.

Five studies were not included in the meta-analyses due to missing information (e.g. no data from the univariate analysis) or because the study examined risk factors included in fewer than five studies (21, 25, 29, 30, 36). Authors were contacted regarding the missing information, but they did not reply. One study included

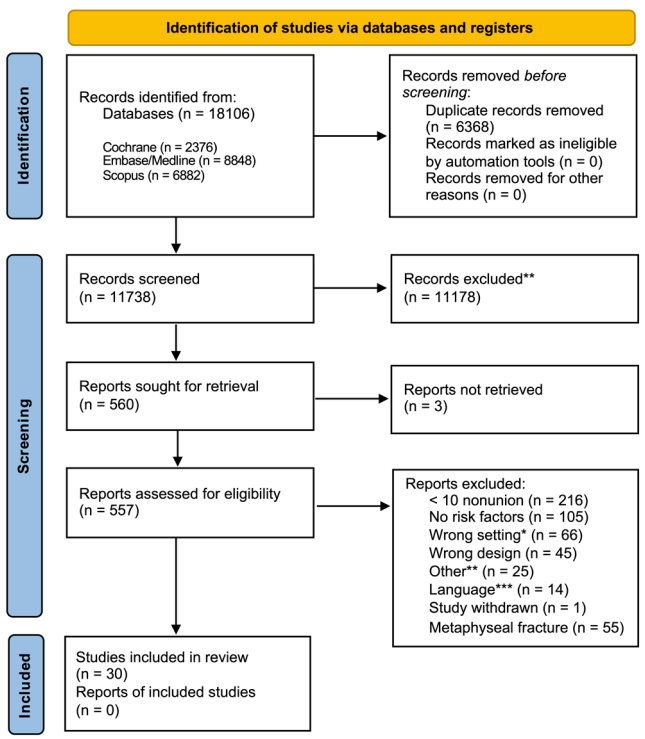

Figure 1

PRISMA 2020 flow diagram for new systematic reviews (8). *Wrong setting includes eight conservative fracture treatment, six periprosthetic fractures, five pediatric, two gunshots, one fusion study, one pathological fractures, one osteotomy, six pooling of data from conservative and operative treatments, thirty-six other wrong setting. **Other: contact to authors, and duplicates found when full-text were retrieved. ***Language includes one Persian, one Turkish, one Japanese, two Chinese, four Russian, one Spanish, one Hebrew, and two Czech.

Table 1 General characteristics of the included studies.

Reference	Publication year	Country	Study design	Participants, *n*	Age†	Minimum follow-up	Patients with nonunion	Patient-related risk factors	Bone***	Open/closed fractures
Aslanoglu *et al.* (15)	1984	Turkey	Uncertain	57	40 (13–79)	5 weeks	11	3	T	Open
Burrus *et al.* (16)	2016	USA	Retrospective	14638	Uncertain	6 months	1758	1	T	Both
Chitnis *et al.* (17)	2019	USA	Retrospective	15962	(18–75+)	30 days	1241	10	T	Both
Dailey *et al.* (18)	2018	UK	Retrospective	1003	34*	Uncertain	121	9	T	Both
Ding *et al.* (19)	2014	China	Retrospective	659	52	9 months	24	18	H	Both
Donohue *et al.* (20)	2016	USA	Retrospective	328	41 (18–97)	1 year	34	6	T, F	Both
Douglas *et al.* (21)	2010	USA	Retrospective	107	Uncertain	6 months	10	1	T, F	Closed
Fong *et al.* (22)	2013	Canada	Retrospective	200	42 ± 16.5	Uncertain	37	3	T	Both
Giannoudis *et al.* (23)	2000	UK	Retrospective	99	Uncertain	11.5 months	32	2	F	Uncertain
Haines *et al.* (24)	2016	USA	Retrospective	40	36	6 months	21	5	T	Open
Haller *et al.* (25)	2017	USA	Retrospective	231	45 (18–100)	1 year	12	2	T	Closed
Hernigou & Schuind (26)	2013	Belgium	Case control	108	47 (16–85)	1 year	35	4	T, F, H	Both
Joseph *et al.* (14)	2020	India	Prospective	255	42 (17–77)	9 months	80	6	T,F	Open
Lack *et al.* (27)	2014	USA	Retrospective	176	35/37**	Every 2–3 months	13	6	T	Both
Leroux *et al.* (28)	2014	Canada	Retrospective	1350	33 ± 12.7	2 years	35	3	C	Closed
Ma *et al.* (29)	2016	China	Retrospective	425	38 (21–56)	Uncertain	12	1	F	Closed
Metsemakers *et al.* (30)	2015	Belgium	Retrospective	480	39 (17–90)	18 months	58	9	T	Both
Metsemakers *et al.* (31)	2015	Belgium	Retrospective	232	35 ± 19 (16–96)	1 year	27	8	F	Both
Millar *et al.* (32)	2018	Australia	Retrospective	211	33	1 year	23	5	F	Both
Noumi *et al.* (33)	2005	Japan	Retrospective	89	25 (15–62)	2 years	12	6	F	Open
Olesen *et al.* (34)	2015	Denmark	Retrospective	45	41 (15–80)	1 year	19	5	T	Open
Papaioannou *et al.* (35)	2001	Greece	Retrospective	207	40 (15–75)	Uncertain	42	4	T	Both
Pourfeizi *et al.* (36)	2013	Iran	Case control	62	36 (20–50)	6 months	30	5	T	Closed
Santolini *et al.* (37)	2020	UK	Case control	200	46	3 months	100	7	T, F	Both
Taitsman *et al.* (38)	2009	USA	Case control	137	34 (16–87)	3 months	45	7	F	Both
Thakore *et al.* (39)	2017	USA	Retrospective	486	36 ± 15 (16–90)	Uncertain	56	7	T	Open
Watanabe *et al.* (40)	2013	Japan	Case control	105	27/25**	1 year	35	5	F	Both
Wu *et al.* (41)	2013	Taiwan	Retrospective	337	41 ± 14.95	6 months	19	7	C	Closed
Wu *et al.* (42)	2019	Taiwan	Retrospective	152	53 ± 12	9 months	16	11	F	Closed
Yokoyama *et al.* (43)	2008	Japan	Retrospective	84	35 (15–86)	1.6 years	17	8	T	Open

*Median, **Median for nonunion/union, ***Tibia(T), Femur(F), Humerus(H), Clavicle(C); †Presented as mean ± S.D. or range.

three different patient cohorts according to insurance type, including Commercial, Medicare, and Medicaid (17). We could not get access to the raw data, and the three cohorts were therefore registered individually in the meta-analyses and the distribution of risk factors.

Risk of bias in studies

The studies were generally assessed to be of poor quality, mainly because of the possible risk of bias due to confounding, unclear measurement of outcome, and missing data. The risk of bias assessments are depicted in Figs 2 and 3. Only one study included all of the five predefined confounders (24, 41, 42). However, most studies did include a multivariable regression analysis (Q5).

Results of individual studies

Thirty-nine risk factors were identified in the 30 studies included in this systematic review (Fig. 4). Risk factors such as age, sex, smoking, open/closed fracture, Gustilo, diabetes, AO/OTA, infection, and obesity were included in more than five studies and were eligible for meta-analysis. A summary of the meta-analysis can be found in Table 2, the funnel and forest plots can be found in Supplementary Digital Content 2. One study was consistently excluded from the meta-analyses because no data were available from the univariate analysis (30).

Age

It was not possible to perform a meta-analysis on age, because data were presented with great heterogeneity, including medians, means, ranges, and ORs from different group comparisons. Five out of 19 studies (17, 19, 27, 28, 41) found that age was a significant risk factor for nonunion.

Sex

Male sex was not associated with nonunion. Two out of 18 studies were excluded from the meta-analysis because they did not include data from the univariate analysis (30, 39), but both of their multiple logistic regression analysis (MLRA) showed a nonsignificant OR.

Smoking

Smoking was significantly associated with nonunion. The excluded study showed an OR of 0.96 (95% CI: 0.48–1.95) in MLRA (30). Smoking was clearly defined in five studies: 20 cigarettes a day (23), 5 cigarettes a day (37), 1 pack of cigarettes a day (41), and lastly using ICD-9 and ICD-10 codes (17).

Open fracture

Open fracture was significantly associated with nonunion. The excluded study showed an OR of 1.44 (95% CI: 0.49–4.2) in the MLRA (30).

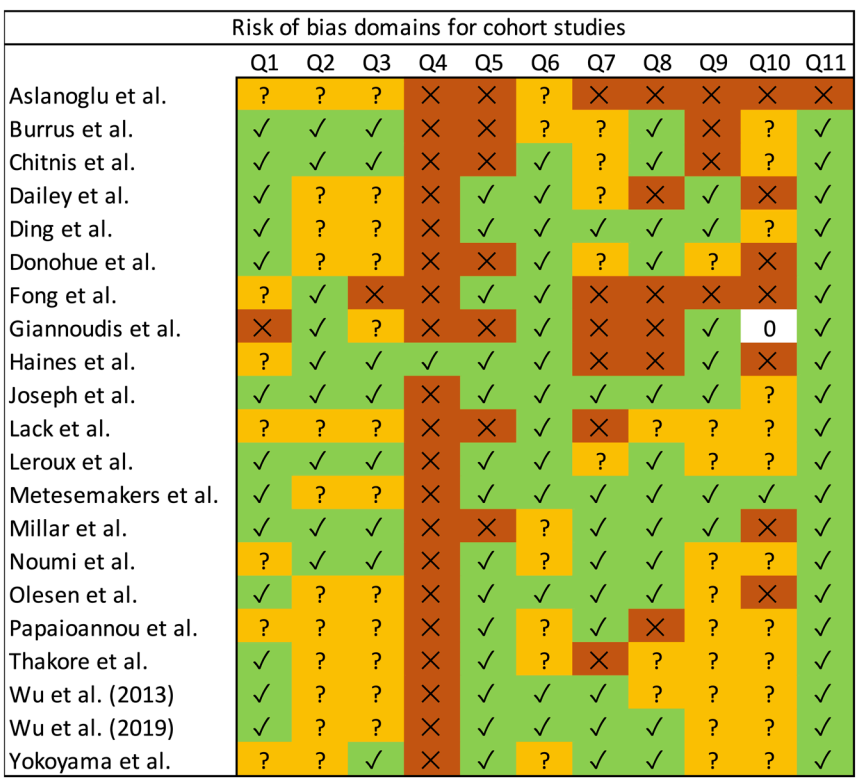

Figure 2
Risk of bias assessment in the cohort studies. Domains were selection Q1, exposure Q2–Q3, confounding Q4–Q5, outcome Q6–Q8, missing data Q9–Q10, and reported results Q11. Green (✓) indicates the best possible answer, yellow (?) is 'unclear', red (×) is 'no', and white (0) is 'non-applicable'.

Risk of bias domains for case control studies										
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Hernigou et al.	✓	✓	✓	✗	✓	✗	✓	✓	✗	✓
Santolini et al.	✓	?	✓	✓	✓	✗	✓	✓	?	✓
Taitsman et al.	?	✓	✓	?	✓	✗	✓	?	?	✓
Watanabe et al.	✓	✓	?	✓	✓	✗	✓	✓	✓	✓

Figure 3
Risk of bias assessment in the case–control studies. Domains were selection Q1–Q3, exposure Q4–Q5+Q9, confounding Q6–Q7, outcome Q8, and reported results Q10. Green (✓) indicates the best possible answer, yellow (?) is 'unclear', and red (✗) is 'no'.

Gustilo

Higher Gustilo classification was significantly associated with nonunion when comparing type II and III fractures. There was no significant difference between type I and II. Thirteen studies included Gustilo classification in their analyses; nine and ten studies were eligible for the meta-analysis comparing type I vs II and type II vs III, respectively. The studies that were not included in the meta-analyses supplied the following evidence: one study stated that Gustilo type was significantly associated with nonunion in the univariate analysis ($P<0.0001$), but not in the multiple logistic regression analysis ($P=0.085$) (30), another study pooled data into two groups, over and under type IIIc (OR: 2.41, 95% CI: 1.26–4.76) (14), and the last study pooled type I+II and compared this to type III (OR: 6.06, 95% CI: 1.67–24.50) (43).

Diabetes

Diabetes was significantly associated with nonunion. The excluded study showed an OR of 0.86 (95% CI: 0.15–4.90) in the MLRA (30). Diabetes was clearly defined in 1 out of 11 studies (17), and 3 studies specified the type of diabetes (30, 31, 41).

AO

Higher AO classification was significantly associated with nonunion when comparing wedge type B to simple type A fractures. However, there was no significant difference between multifragmentary type C and wedge fractures. Ten studies included AO-classification, and nine were eligible for the meta-analysis comparing type A and B fractures. One study did not include any type C fractures and could therefore not be included in the meta-analysis comparing type B and C fractures (42). One study pooled data from AO types B and C and compared these to type A, and found that higher AO was a risk factor for nonunion with an OR of 3.94 (95% CI: 2.00–7.76) (37).

Infection

Infection was significantly associated with nonunion. Infection was clearly defined in four studies: two studies defined infection according to Dellinger *et al.* (33, 43, 44), another defined it as an elevated CRP and/or white cell count in combination with pus, discharge, or wound breakdown (34), and the last one defined infection according to the Centers for Disease Control and Prevention criteria (37).

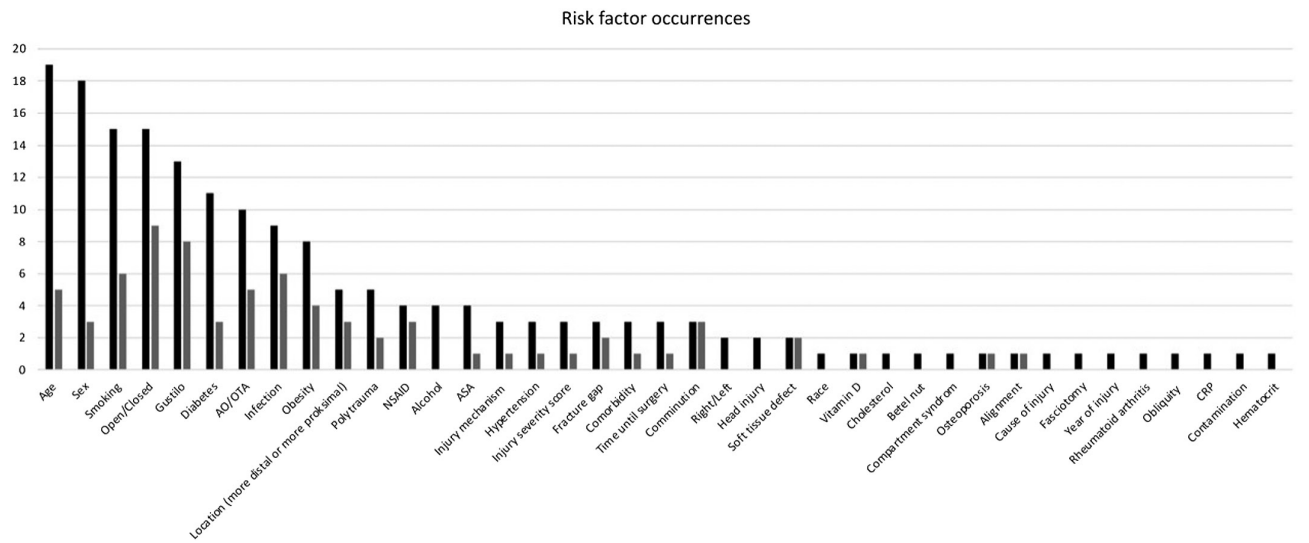

Figure 4
Number of each risk factor occurrences (black bar) and number of significant risk factor occurrences (gray bar). Data stem from the univariate analyses, unless only data from the multivariable analysis were reported.

Table 2 Overview of the results from the meta-analysis.

Risk factor	Studies included	OR (95% CI)	*P*-value	I^2 (%)	Number of	
					Fractures	Nonunions
Sex	16	1.0 (0.90–1.3)	0.80	64	20 856	1750
Smoking	14	1.7* (1.2–2.4)	<0.01	53	17 183	4113
Open vs closed fracture	14	2.6* (1.8–3.9)	<0.01	80	19 216	1745
Gustilo II vs I	9	1.6 (0.95–2.7)	0.07	0.0	720	88
Gustilo III vs II	10	2.2* (1.4–3.7)	<0.01	22	964	210
Diabetes	10	1.6* (1.3–2.0)	<0.01	0.0	17 954	1409
AO B vs A	9	2.4* (1.5–3.7)	<0.01	44	2520	318
AO C vs B	8	1.4 (0.99–1.9)	0.05	0.0	2386	302
Infection	9	7.0* (3.2–15.0)	<0.01	51	1859	389
Obesity	7	1.5* (1.1–1.9)	<0.01	28	31 643	3066

*Significant results with *P*-values < 0.05.

Obesity

Obesity was significantly associated with nonunion. The excluded study showed an OR of 2.57 (95% CI: 0.71–9.31) in the MLRA (30). Obesity was clearly defined in all studies as either a BMI of ≥25 kg/m^2 (42) or ≥30 kg/m^2 (19, 30, 31) or by using ICD-9 and ICD-10 codes (16, 17). We combined the obese and morbidly obese groups in one study (16).

Other risk factors

Among the risk factors that could not be included in the meta-analyses, it was found that fracture gap (20, 24, 37), comminution (22, 32, 41), soft tissue defects (15, 22), NSAIDs (19, 20, 23, 42), and location of the fracture (25, 29, 32, 42, 43) were associated with nonunion in more than 50% of the studies. By contrast, polytrauma (18, 19, 26, 30, 31), ASA score (14, 19, 30, 39), injury mechanism (25, 27, 35), hypertension (19, 41, 42), injury severity score (33, 38, 43), comorbidity (17, 28, 39), and time until surgery (14, 15, 43) were associated with nonunion in less than 50% of the studies. Vitamin D deficiency (36), osteoporosis (19), and fracture alignment (21) were also associated with nonunion, but each risk factor was only included in a single study. No studies found that alcohol (17, 19, 41, 42), fracture location (right vs left) (19, 41), head injury (19, 26), race (39), cholesterol (36, 42), betel nuts (42), compartment syndrome (24), cause of injury (19), fasciotomy (18), year of injury (17), rheumatoid arthritis (17), obliquity (19), CRP (14), contamination (14), or hematocrit (14) were associated with nonunion.

Reporting biases

There was no evidence of asymmetry in the funnel plots due to publication bias. However, to quantify this observation, we used the Egger's regression test, which was in line with our perception and showed no risk of publication bias across all risk factors (Supplementary Digital Content 2).

Definition of nonunion

Nonunion was defined with great variability, as seen in Table 3. The most common definitions were a combination of radiological criteria (77%), specific time constraints (50%), and clinical criteria (43%).

Discussion

In this systematic review, we reviewed the total quantity of existing studies on risk factors for nonunion, which included 38,465 patients and 3,975 nonunions. To our knowledge, this has not been done before, and during our extensive search we did not find any systematic reviews with a risk of bias or meta-analysis on risk factors for nonunion.

Thirty observational studies were included in the review, and these showed that nonunion was significantly associated with smoking, open fracture, diabetes, infection, obesity, increasing Gustilo, and AO classification. Regarding the studies not included in the meta-analyses, we found that fracture gap, comminution, soft tissue defects, NSAID, location of the fracture, vitamin D deficiency, osteoporosis, and fracture alignment were associated with nonunion in more than 50% of the studies.

Our findings are consistent with the results from the most comprehensive epidemiological study on bone nonunion that included information on 309,330 fractures (45). That study found, among other results, that NSAIDs

Table 3 Overview of the criteria used to define nonunion in the included studies.

Criteria used to define nonunion	Articles, *n* (%)
Clinical criteria (e.g. nonpainful weight bearing)	13 (43)
Need for further intervention	11 (37)
Radiographical criteria	23 (77)
Diagnosis codes (e.g. ICD-10)	3 (10)
As defined by the FDA	3 (10)
By the attending senior surgeons	7 (23)
Time specific (e.g. 9 months)	15 (50)
Not described	2 (7)

plus opioids, osteoarthritis, type 1 diabetes, osteoporosis, male gender, smoking, obesity, open fracture, and vitamin D deficiency were significant risk factors for nonunion. By contrast, the male gender was not found to be a risk factor in our study. Unfortunately, this study could not be included in the systematic review, since information about treatment was missing in roughly 50% of cases, and we aimed to determine risk factors in surgically treated fractures. Another review on the level of the existing scientific evidence on risk factors concluded that open fracture, smoking, infection, wedge or comminuted type of fracture, high degree of initial displacement, and location of the fracture contributed to an impaired fracture healing (5). This is also in line with our results.

A limitation of this study is that only observational studies were available for inclusion; therefore, the study was merely able to make conclusions on associations, not causal relations (46). Observational studies are at higher risk of bias compared to other study types, making the establishment of causal relationships inadequate (47). Not surprisingly, this was consistent within our review, as the majority of the included studies were in fact limited by the risk of bias due to confounding, unclear measurements of outcome, and missing data. Only one study included our predefined confounders; it analyzed 16 covariates in the multivariable regression model based on 40 patients and 21 nonunions (24). They concluded that no covariates predicted healing outcomes asides from the cortical gap. Another study that was not included in the meta-analyses and thus not included in the risk of bias assessment did include all five confounders in its analysis (30). The researchers performed a multivariable analysis on 13 variables, based on 486 fractures including 58 nonunions, and did not find any significant results. The study could not be included in the meta-analysis and risk of bias assessment because there were no results from the univariate analysis and no raw data available in the article.

The definition of nonunion varied substantially across the included studies, which has been pointed out previously in a cross-sectional survey of 577 orthopedic surgeons carried out in 2002 and again in 2012 (48, 49). The definition and description of risk factors (exposures) varied considerably among the included studies. As an example, smoking was only defined in 5 (17, 23, 37, 41) out of 15 studies (18, 19, 20, 26, 27, 31, 34, 38, 42). Diabetes and infection had the same issues. To improve future research, agreeing on common definitions of exposures and outcomes would be beneficial.

The comparison of healing in different anatomical locations, such as the humerus and tibia, may give rise to bias, but it also broadens the applicability of the study. The low heterogeneity of our meta-analyses, however, indicated that the studies were comparable. Only two analyses had an I^2 higher than 60%.

A major strength of this review is that two authors dually screened all 11,738 abstracts and did full-text evaluations, data extraction, and risk of bias assessment. This decreased the risk of bias and increased the objectivity of the evaluations.

For inclusion in this systematic review, each study was required to report at least ten cases of nonunion. This criterion substantially reduced the pool of literature, but it was a necessary limitation. Methodological studies suggest that to reduce the risk of bias and misleading associations, events per variable should be no fewer than ten (50, 51, 52).

The five confounding factors we decided on in the risk of bias analysis were consistent with an article from 2012, in which orthopedic surgeons had to list the risk factors they believed resulted in an increased risk of nonunion (49). However, they did not identify age as a major factor, but we believe that increasing age could be a proxy measurement for increased comorbidity.

Conclusion

This systematic review forms the basis for identifying risk factors in clinical practice and conducting improved studies and to some extent serves as a decision tool to optimize fracture healing. In summary, this systematic review found that smoking, open fracture, diabetes, infection, obesity, increasing Gustilo, and AO classification were associated with nonunion in the meta-analyses. The included studies were of poor quality and at risk of bias.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EOR-21-0137.

ICMJE Conflict of Interest Statement
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding Statement
The main author has received a PhD Scholarship and was granted a 1-year Faculty scholarship from the University of Southern Denmark. This investigation has not received any other funding and the decision to publish was made by the authors.

Availability
The data from this systematic review, including excel sheets with data on risk factors for the various studies, are available upon request to the corresponding author via email. Materials can be shared, provided that it is apparent that they were obtained from the authors, approved for the purpose, and correctly quoted.

Author contribution statement
S S, B V, S K, R Z, and P G conceptualized the research idea and method, while S S and N M conducted data collection and formal analyses. R Z contributed with external supervision. S S wrote the initial draft but all author performed critically review and accepted the final draft.

References

1. Antonova E, Le TK, Burge R & Mershon J. Tibia shaft fractures: costly burden of nonunions. *BMC Musculoskeletal Disorders* 2013 **14** 42. (https://doi.org/10.1186/1471-2474-14-42)

2. Brinker MR, Trivedi A & O'Connor DP. Debilitating effects of femoral nonunion on health-related quality of life. *Journal of Orthopaedic Trauma* 2017 **31** e37–e42. (https://doi.org/10.1097/BOT.0000000000000736)

3. Brinker MR, Hanus BD, Sen M & O'Connor DP. The devastating effects of tibial nonunion on health-related quality of life. *Journal of Bone and Joint Surgery: American Volume* 2013 **95** 2170–2176. (https://doi.org/10.2106/JBJS.L.00803)

4. Tay WH, de Steiger R, Richardson M, Gruen R & Balogh ZJ. Health outcomes of delayed union and nonunion of femoral and tibial shaft fractures. *Injury* 2014 **45** 1653–1658. (https://doi.org/10.1016/j.injury.2014.06.025)

5. Santolini E, West R & Giannoudis PV. Risk factors for long bone fracture non-union: a stratification approach based on the level of the existing scientific evidence. *Injury* 2015 **46** (Supplement 8) S8–S19. (https://doi.org/10.1016/S0020-1383(15)30049-8)

6. Zura R, Mehta S, Della Rocca GJ & Steen RG. Biological risk factors for nonunion of bone fracture. *JBJS Reviews* 2016 **4** e5. (https://doi.org/10.2106/JBJS.RVW.O.00008)

7. Moher D, Liberati A, Tetzlaff J, Altman DG & PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009 **6** e1000097. (https://doi.org/10.1371/journal.pmed.1000097)

8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021 **372** n71. (https://doi.org/10.1136/bmj.n71)

9. Buckland M & Gey F. The relationship between recall and precision. *Journal of the American Society for Information Science* 1994 **45** 12–19. (https://doi.org/10.1002/(SICI)1097-4571(199401)45:1<12::AID-ASI2>3.0.CO;2-L)

10. Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Marshall C, Metzendorf MI, Noel-Storr A, Paynter R, Rader T, *et al.* Chapter 4: Searching for and selecting studies. In *Cochrane Handbook for Systematic Reviews of Interventions Version 60* (updated July 2019). Eds **JPT Higgins, J Thomas, J Chandler, M Cumpston, T Li, MJ Page & VA Welch**. Cochrane, 2019.

11. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Lisy K, Qureshi R, Mattis P, *et al.* Chapter 7: Systematic reviews of etiology and risk. In *JBI Manual for Evidence Synthesis*. Eds **E Aromataris & Z Munn**. JBI, 2020. (available at: https://wiki.jbi.global/display/MANUAL)

12. Social Security Administration. *Revised Medical Criteria for Evaluating Musculoskeletal Disorders*. Federal Register United States Government, 2020 [updated 4 February 2021]. (available at: https://www.federalregister.gov/d/2020-25250/p-550)

13. Schmal H, Brix M, Bue M, Ekman A, Ferreira N, Gottlieb H, Kold S, Taylor A, Toft Tengberg P, Ban I, *et al.* Nonunion – consensus from the 4th annual meeting of the Danish Orthopeadic Trauma Society. *EFORT Open Reviews* 2020 **5** 46–57. (https://doi.org/10.1302/2058-5241.5.190037)

14. Joseph CM, Jepegnanam TS, Ramasamy B, Cherian VM, Nithyananth M, Sudarsanam TD & Premkumar PS. Time to debridement in open high-grade lower limb fractures and its effect on union and infections: a prospective study in a tropical setting. *Journal of Orthopaedic Surgery* 2020 **28** 2309499020907558. (https://doi.org/10.1177/2309499020907558)

15. Aslanoglu O, Ayas I, Kaymak O, Atik OS & Kunak F. Treatment of open fractures with external fixation. *Orthopedics* 1984 **7** 996–999. (https://doi.org/10.3928/0147-7447-19840601-14)

16. Burrus MT, Werner BC & Yarboro SR. Obesity is associated with increased postoperative complications after operative management of tibial shaft fractures. *Injury* 2016 **47** 465–470. (https://doi.org/10.1016/j.injury.2015.10.026)

17. Chitnis AS, Vanderkarr M, Sparks C, McGlohorn J & Holy CE. Complications and its impact in patients with closed and open tibial shaft fractures requiring open reduction and internal fixation. *Journal of Comparative Effectiveness Research* 2019 **8** 1405–1416. (https://doi.org/10.2217/cer-2019-0108)

18. Dailey HL, Wu KA, Wu PS, McQueen MM & Court-Brown CM. Tibial fracture nonunion and time to healing after reamed intramedullary nailing: risk factors based on a single-center review of 1003 patients. *Journal of Orthopaedic Trauma* 2018 **32** e263–e269. (https://doi.org/10.1097/BOT.0000000000001173)

19. Ding L, He Z, Xiao H, Chai L & Xue F. Factors affecting the incidence of aseptic nonunion after surgical fixation of humeral diaphyseal fracture. *Journal of Orthopaedic Science* 2014 **19** 973–977. (https://doi.org/10.1007/s00776-014-0640-1)

20. Donohue D, Sanders D, Serrano-Riera R, Jordan C, Gaskins R, Sanders R & Sagi HC. Ketorolac administered in the recovery room for acute pain management does not affect healing rates of femoral and tibial fractures. *Journal of Orthopaedic Trauma* 2016 **30** 479–482. (https://doi.org/10.1097/BOT.0000000000000620)

21. Douglas L, Benson D & Seligson D. The incidence of nonunion after nailing of distal tibial and femoral fractures. *Current Orthopaedic Practice* 2010 **21** 49–53. (https://doi.org/10.1097/BCO.0b013e3181b66ac0)

22. Fong K, Truong V, Foote CJ, Petrisor B, Williams D, Ristevski B, Sprague S & Bhandari M. Predictors of nonunion and reoperation in patients with fractures of the tibia: an observational study. *BMC Musculoskeletal Disorders* 2013 **14** 103. (https://doi.org/10.1186/1471-2474-14-103)

23. Giannoudis PV, MacDonald DA, Matthews SJ, Smith RM, Furlong AJ & De Boer P. Nonunion of the femoral diaphysis. The influence of reaming and non-steroidal anti-inflammatory drugs. *Journal of Bone and Joint Surgery: British Volume* 2000 **82** 655–658. (https://doi.org/10.1302/0301-620x.82b5.9899)

24. Haines NM, Lack WD, Seymour RB & Bosse MJ. Defining the lower limit of a 'critical bone defect' in open diaphyseal tibial fractures. *Journal of Orthopaedic Trauma* 2016 **30** e158–e163. (https://doi.org/10.1097/BOT.0000000000000531)

25. Haller JM, Githens M, Scolaro J & Firoozabadi R. Does provisional plating of closed tibia fractures have higher complication rates? *Journal of Orthopaedic Trauma* 2017 **31** 554–558. (https://doi.org/10.1097/BOT.0000000000000874)

26. Hernigou J & Schuind F. Smoking as a predictor of negative outcome in diaphyseal fracture healing. *International Orthopaedics* 2013 **37** 883–887. (https://doi.org/10.1007/s00264-013-1809-5)

27. Lack WD, Starman JS, Seymour R, Bosse M, Karunakar M, Sims S & Kellam J. Any cortical bridging predicts healing of tibial shaft fractures. *Journal of Bone*

and Joint Surgery: American Volume 2014 **96** 1066–1072. (https://doi.org/10.2106/JBJS.M.00385)

28. Leroux T, Wasserstein D, Henry P, Khoshbin A, Dwyer T, Ogilvie-Harris D, Mahomed N & Veillette C. Rate of and risk factors for reoperations after open reduction and internal fixation of midshaft clavicle fractures: a population-based study in Ontario, Canada. *Journal of Bone and Joint Surgery: American Volume* 2014 **96** 1119–1125. (https://doi.org/10.2106/JBJS.M.00607)

29. Ma YG, Hu GL, Hu W & Liang F. Surgical factors contributing to nonunion in femoral shaft fracture following intramedullary nailing. *Chinese Journal of Traumatology: English Edition* 2016 **19** 109–112. (https://doi.org/10.1016/j.cjtee.2016.01.012)

30. Metsemakers WJ, Handojo K, Reynders P, Sermon A, Vanderschot P & Nijs S. Individual risk factors for deep infection and compromised fracture healing after intramedullary nailing of tibial shaft fractures: a single centre experience of 480 patients. *Injury* 2015 **46** 740–745. (https://doi.org/10.1016/j.injury.2014.12.018)

31. Metsemakers WJ, Roels N, Belmans A, Reynders P & Nijs S. Risk factors for nonunion after intramedullary nailing of femoral shaft fractures: remaining controversies. *Injury* 2015 **46** 1601–1607. (https://doi.org/10.1016/j.injury.2015.05.007)

32. Millar MJ, Wilkinson A, Navarre P, Steiner J, Vohora A, Hardidge A & Edwards E. Nail fit: does nail diameter to canal ratio predict the need for exchange nailing in the setting of aseptic, hypertrophic femoral nonunions? *Journal of Orthopaedic Trauma* 2018 **32** 245–250. (https://doi.org/10.1097/BOT.0000000000001110)

33. Noumi T, Yokoyama K, Ohtsuka H, Nakamura K & Itoman M. Intramedullary nailing for open fractures of the femoral shaft: evaluation of contributing factors on deep infection and nonunion using multivariate analysis. *Injury* 2005 **36** 1085–1093. (https://doi.org/10.1016/j.injury.2004.09.012)

34. Olesen UK, Juul R, Bonde CT, Moser C, McNally M, Jensen LT, Elberg JJ & Eckardt H. A review of forty five open tibial fractures covered with free flaps. Analysis of complications, microbiology and prognostic factors. *International Orthopaedics* 2015 **39** 1159–1166. (https://doi.org/10.1007/s00264-015-2712-z)

35. Papaioannou N, Mastrokalos D, Papagelopoulos PJ, Tyllianakis M, Athanassopoulos J & Nikiforidis PA. Nonunion after primary treatment of tibia fractures with external fixation. *European Journal of Orthopaedic Surgery and Traumatology* 2001 **11** 231–235. (https://doi.org/10.1007/BF01686895)

36. Pourfeizi HH, Tabrizi A, Elmi A & Aslani H. Prevalence of vitamin D deficiency and secondary hyperparathyroidism in nonunion of traumatic fractures. *Acta Medica Iranica* 2013 **51** 705–710.

37. Santolini E, West RM & Giannoudis PV. Leeds-Genoa Non-Union Index: a clinical tool for asessing the need for early intervention after long bone fracture fixation. *International Orthopaedics* 2020 **44** 161–172. (https://doi.org/10.1007/s00264-019-04376-0)

38. Taitsman LA, Lynch JR, Agel J, Barei DP & Nork SE. Risk factors for femoral nonunion after femoral shaft fracture. *Journal of Trauma* 2009 **67** 1389–1392. (https://doi.org/10.1097/TA.0b013e318182afd0)

39. Thakore RV, Francois EL, Nwosu SK, Attum B, Whiting PS, Siuta MA, Benvenuti MA, Smith AK, Shen MS, Mousavi I, ***et al.*** The Gustilo–Anderson classification system as predictor of nonunion and infection in open tibia fractures. *European Journal of Trauma and Emergency Surgery* 2017 **43** 651–656. (https://doi.org/10.1007/s00068-016-0725-y)

40. Watanabe Y, Takenaka N, Kobayashi M & Matsushita T. Infra-isthmal fracture is a risk factor for nonunion after femoral nailing: a case-control study. *Journal of Orthopaedic Science* 2013 **18** 76–80. (https://doi.org/10.1007/s00776-012-0316-7)

41. Wu CL, Chang HC & Lu KH. Risk factors for nonunion in 337 displaced midshaft clavicular fractures treated with Knowles pin fixation. *Archives of Orthopaedic and Trauma Surgery* 2013 **133** 15–22. (https://doi.org/10.1007/s00402-012-1631-3)

42. Wu KJ, Li SH, Yeh KT, Chen IH, Lee RP, Yu TC, Peng CH, Liu KL, Yao TK, Wang JH, ***et al.*** The risk factors of nonunion after intramedullary nailing fixation of femur shaft fracture in middle age patients. *Medicine* 2019 **98** e16559. (https://doi.org/10.1097/MD.0000000000016559)

43. Yokoyama K, Itoman M, Uchino M, Fukushima K, Nitta H & Kojima Y. Immediate versus delayed intramedullary nailing for open fractures of the tibial shaft: a multivariate analysis of factors affecting deep infection and fracture healing. *Indian Journal of Orthopaedics* 2008 **42** 410–419. (https://doi.org/10.4103/0019-5413.43385)

44. Dellinger EP, Miller SD, Wertz MJ, Grypma M, Droppert B & Anderson PA. Risk of infection after open fracture of the arm or leg. *Archives of Surgery* 1988 **123** 1320–1327. (https://doi.org/10.1001/archsurg.1988.01400350034004)

45. Zura R, Xiong Z, Einhorn T, Watson JT, Ostrum RF, Prayson MJ, Della Rocca GJ, Mehta S, McKinley T, Wang Z, ***et al.*** Epidemiology of fracture nonunion in 18 human bones. *JAMA Surgery* 2016 **151** e162775. (https://doi.org/10.1001/jamasurg.2016.2775)

46. Varady NH, Feroe AG, Fontana MA & Chen AF. Causal language in observational orthopaedic research. *Journal of Bone and Joint Surgery: American Volume* 2021 **103** e76. (https://doi.org/10.2106/JBJS.20.01921)

47. Egger M, Schneider M & Davey Smith G. Spurious precision? Meta-analysis of observational studies. *BMJ* 1998 **316** 140–144. (https://doi.org/10.1136/bmj.316.7125.140)

48. Bhandari M, Guyatt GH, Swiontkowski MF, Tornetta P, 3rd, Sprague S & Schemitsch EH. A lack of consensus in the assessment of fracture healing among orthopaedic surgeons. *Journal of Orthopaedic Trauma* 2002 **16** 562–566. (https://doi.org/10.1097/00005131-200209000-00004)

49. Bhandari M, Fong K, Sprague S, Williams D & Petrisor B. Variability in the definition and perceived causes of delayed unions and nonunions: a cross-sectional, multinational survey of orthopaedic surgeons. *Journal of Bone and Joint Surgery: American Volume* 2012 **94** e1091-6. (https://doi.org/10.2106/JBJS.K.01344)

50. Peduzzi P, Concato J, Kemper E, Holford TR & Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology* 1996 **49** 1373–1379. (https://doi.org/10.1016/s0895-4356(96)00236-3)

51. Harrell Jr FE, Lee KL, Matchar DB & Reichert TA. Regression models for prognostic prediction: advantages, problems, and suggested solutions. *Cancer Treatment Reports* 1985 **69** 1071–1077.

52. Concato J, Feinstein AR & Holford TR. The risk of determining risk with multivariable models. *Annals of Internal Medicine* 1993 **118** 201–210. (https://doi.org/10.7326/0003-4819-118-3-199302010-00009)