Patient-related risk factors for fracture-healing complications in the United Kingdom General Practice Research Database

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Background and purpose **A variety of risk factors have been hypothesized to contribute to the development of fracture-healing complications; however, population-based estimates of the strength of these risk factors are limited. In this case-control study, we evaluated patient-related risk factors for fracture-healing complications.**

Methods **Using the United Kingdom General Practice Research Database, we identified patients with a fracture-healing complication (delayed union, nonunion, or malunion) between 1988 and 2008. 4 controls (i.e. patients with normal healing) were matched to each case on general practice, fracture site, fracture date, and length of history in the database. We used conditional logistic regression to estimate odds ratios (ORs) of various risk factors, including demographics, comorbidities, and medication use.**

Results **Diabetes and use of non-steroidal anti-inflammatory drugs (NSAIDs) within 12 months before the initial fracture were associated with a higher odds of a fracture-healing complication (type-I diabetes: adjusted OR = 2.3, 95% CI: 1.3–3.8; type-II diabetes: adjusted OR = 2.3, CI: 1.4–3.7; NSAIDs: adjusted OR = 2.6, CI: 2.1–3.2). Patients who had a motor vehicle accident recorded within 1 month before their initial fracture were also at increased odds of a fracture-healing complication (adjusted OR = 2.6, CI: 1.2–5.4).**

Interpretation **Diabetes, NSAID use, and a recent motor vehicle accident were most consistently associated with an increased risk of a fracture-healing complication, regardless of fracture site or specific fracture-healing complication. This analysis suggests that certain patient-related characteristics influence the development of fracture-healing complications in general, even though specific healing complications may differ by their mechanism.**

While most fractures heal uneventfully, fracture-healing complications such as delayed union, nonunion, and malunion do occur. In tibial shaft fracture, nonunion has been reported to occur in up to 10–20% of patients (Court-Brown et al. 2006). However, because fracture complications are often variably defined and there is a lack of consensus in their assessment (Bhandari et al. 2002), their incidence is difficult to estimate. The frequency of these complications varies depending on the type of complication and the fracture site. For example, the prevalence of nonunion was found to be lower than the prevalence of delayed union in patients with fractures of the clavicle (Edwards et al. 1992, Robinson et al. 2004). Conversely, in patients with femoral neck fracture, the prevalence of nonunion appears to be greater than the prevalence of delayed union (Krastman et al. 2006, Parker et al. 2007). Furthermore, nonunion fractures could be considered delayed unions first, adding additional complexity to estimates of incidence.

Fracture-healing complications can lead to pain and functional impairment. Sanders et al. (2002) found that patients with tibial fracture nonunion who had undergone reconstructive surgery reported more pain than age-matched controls, even after union was achieved. Court-Brown and McQueen (2008) found that patients with nonunion of the proximal humerus had prolonged times to return to some activities of daily living (e.g. shopping and housework) compared to patients who had achieved fracture union. Additionally, patients with fracture-healing complications commonly experience subsequent comorbidities. For example, McKellop et al. (1991) showed that the angulation of a malunion of the tibia may predispose patients to osteoarthritis by altering load transmission through the knee and ankle joints.

Because the etiology or pathophysiology is not always clear, a variety of factors have been hypothesized to contribute to the development of fracture-healing complications. While some of these factors are fracture and/or quality-of-surgery-dependent, many of them are related to patient attributes and lifestyle (e.g. age, sex, diabetes, use of medications such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), smoking, excessive alcohol use, and poor nutrition) (Buckwalter et al. 2006, Court-Brown et al. 2006, Calori et al. 2007). As it is impractical to examine many of these factors in clinical

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trials, much of the evidence comes from case series (which tend to reflect small sample sizes or single-site medical facilities) or from reports that are anecdotal in nature. Furthermore, few authors report estimates of the magnitude of associations between potential risk factors and fracture-healing complications. With the goal of improving understanding of patient-related risk factors, we conducted a population-based case-control study to quantify the association between a variety of patient characteristics and fracture-healing complications.

Patients and methods

Data resource

Data for this study were derived from the United Kingdom (UK)-based General Practice Research Database (GPRD), which has been described in detail previously (Jick et al. 1991, 2003). Briefly, the GPRD is an ongoing longitudinal database that collects data on more than five million patients from over 400 general practices in the UK. The database is population-based and representative of the underlying UK population with respect to age, sex, and geographic distribution. Information recorded in the database is entered by general practitioners (GPs) who function as gatekeepers for hospital and specialist referrals in the UK health system, and it includes patient demographics, diagnoses (recorded using the Oxford Medical Information System codes and/or Read codes), consultant referrals, and drug prescriptions.

Case selection

We identified cases from all individuals registered in the GPRD who had a diagnosis of a fracture-healing complication (i.e. delayed union, nonunion, malunion) between January 1988 and May 2008 and who were aged 18–79 years on the date of diagnosis. We required that cases had a site-specific diagnosis of a fracture within 12 months before their fracture-healing complication diagnosis. We also required that cases had at least 1 year of history recorded in the database before their diagnosis, to ensure that there was sufficient time to capture risk factors.

Because diagnosis codes for fracture-healing complications are not fracture site-specific, we selected the most recent fracture diagnosis before or on the date of the first diagnosis of fracture-healing complication to reflect the eligible fracture site. We combined fracture sites into the following groups: long bones (i.e. humerus, radius, ulna, tibia, fibula, and femur), small bones (i.e. hand, foot, and ankle), trunk (i.e. vertebrae, ribs, sternum, and pelvis), neck of femur, and other (i.e. patella, skull, scapula, and shoulder). Long bones were grouped together because they are similar with respect to mechanical properties, as they are primarily loaded with bending and are composed of mostly cortical bone. Small bones were grouped together because they are loaded with compression and are composed of mostly trabecular bone. Finally, we excluded patients who had 2 or more different fracture diagnosis codes recorded on their fracture date since it was not known which fracture site was associated with the fracture-healing complication.

To validate the cases, we categorized cases as likely if they had more than 1 diagnosis code for a fracture-healing complication recorded in the database. Since some fracture-healing complications undergo treatment, we also categorized cases as likely if they had a procedure code related to treatment of a fracture-healing complication 6 months or less before or 12 months or less after their fracture-healing complication diagnosis. The procedure codes reflected bone grafts, osteotomy, and immobilization. All other cases were categorized as possible. We then reviewed the original clinical records (which are maintained separately from the database) for 26 (8%) and 24 (10%) randomly selected cases categorized as likely and possible, respectively. Based on information from the original clinical records that included notes from both GPs and specialists, we confirmed that the majority of the reviewed cases were indeed true cases (96% of likely and 87% of possible). We also reviewed the original clinical records to validate the fracture site associated with the healing complication and found that we had correctly categorized the fracture site for 87% of the reviewed cases.

Control selection

We selected controls from all patients aged 18–79 years who did not have a diagnosis of a fracture-healing complication. We required controls to have a fracture in the same fracture site group within 1 year of (before or after) the diagnosis date of the fracture-healing complication of their matched case and to be present in the database on the diagnosis date of their matched case. Patients with diagnosis codes for multiple fracture sites recorded on the same day were not eligible to be controls. Controls were matched to their case's general practice and length of history in the database but were not matched on age or sex, so that these characteristics could be evaluated as risk factors. Using these criteria, we were able to match 4 controls for all but 21 cases (due to small general practice size). By removing the criteria of matching on general practice for these cases, we were ultimately able to find 4 controls for all of the cases.

Exposures of interest

Based on a review of the medical literature, we chose to study patient-related risk factors including patient characteristics (age, sex, body mass index), lifestyle factors (smoking, alcohol use), comorbidities (cancer, diabetes, osteoporosis, hypothyroidism, rheumatoid arthritis, peripheral vascular disease), use of outpatient medications (steroids, NSAIDs, anticonvulsants, estrogen-containing hormone therapy, thyroid hormone therapy, bone-loss therapy, anticoagulants, antibiotics, chemotherapy), and external factors (falls, motor vehicle accident). We assessed the presence of comorbidities, falls, and medication use in the year before the fracture date. Additionally,

a notation of a motor vehicle accident was assessed only in the month before the fracture date, while the use of estrogen-containing hormone therapy was assessed only for women.

Statistics

We compared the frequencies of the potential risk factors between cases and controls using descriptive statistics. Because we matched cases to controls, we used conditional logistic regression to estimate odds ratios (ORs) and their 95% confidence intervals (CIs) for the association between each risk factor and fracture-healing complications. We modeled each risk factor separately, with all of the other risk factors that we assessed being potential confounding covariates for that model. We used an iterative process whereby we added each of the covariates to the primary model at hand, one at a time. Any covariate that resulted in at least a 10% change from the prior OR was kept in the model as a confounder (Greenland and Rothman 2008). In addition to any covariates identified from this process, we adjusted all ORs for the matched factors as well as age and sex. Our initial analyses combined all fracture-healing complications, so that we could have large sample size to assess whether risk factors were consistent across complication types. Because malunion typically occurs as a result of surgically-dependent factors (i.e. poor postoperative stability), while nonunion and delayed union typically occur as a result of defects in the healing process (i.e. infection or trauma to the vasculature), we present results separately for the 3 types of fracture-healing complications. We also present results stratified by fracture site. All analyses were conducted using SAS software version 9.1.3.

Results

We initially identified 2,257 cases of fracture-healing complications in the GPRD during the study period. Applying the pre-specified exclusion criteria outlined in Material and Methods, 197 patients were out of age range, 907 patients had less than 12 months of history in the database prior to the first fracture-healing diagnosis, 197 patients did not have a fracture code recorded 12 months or less before the fracture-healing complication, 71 patients had a fracture at multiple or unspecified sites, and 76 patients had a fracture at a site that did not fit into one of our categories of interest. Thus, our case-control study comprised 563 cases and 2,252 controls (n = 2,815).

The most commonly diagnosed fracture-healing complication was nonunion (71%), followed by malunion (18%), and delayed union (11%). Of the nonunion diagnoses, 39% were based on diagnosis codes that stated either "malunion and nonunion" or "malunion or nonunion". For these codes, we assigned the diagnosis of nonunion as this is the most severe healing complication. Fractures of the long bones (45%) were the most prevalent among the cases, followed by fractures of the small bones (32%) and fractures of the trunk (17%). Fractures of the neck of femur (2%) and fractures categorized as other (3%) were the least prevalent among the cases.

The distribution of patient characteristics is given in Table 1. There was a higher proportion of females in both the cases (52%) and the controls (55%). Younger patients (18–49 years) comprised approximately half of both cases (52%) and controls (49%). Additional characteristics that were more prevalent in cases than controls included being overweight (BMI ≥ 25; 37% and 31%, respectively), being a current smoker (42% and 36%, respectively) or a drinker (60% and 54%, respectively), having diabetes (8.4% and 4.0%, respectively) or rheumatoid arthritis (3.4% and 1.9%, respectively), using NSAIDs (40% and 21%, respectively) or estrogen-containing hormone therapy (9.5% and 6.5%, respectively), and being involved in a motor vehicle accident 1 month or less before the fracture (2.1% and 0.8%, respectively).

The conditional and fully adjusted ORs for any fracture-healing complication, by individual risk factors, are also presented in Table 1. Patients aged 65–79 years had a lower odds of having a fracture-healing complication than patients aged 18–29 years (OR = 0.65). Former smokers (OR = 1.4), patients with either type-I diabetes (OR = 2.3) or type-II diabetes (OR = 2.3) diabetes, patients who used NSAIDs (OR = 2.6), and patients who were involved in a motor vehicle accident (OR = 2.6) had a higher odds of having a fracture-healing complication than their respective reference group. Patients with rheumatoid arthritis (OR = 1.6), patients who used estrogen-containing hormone therapy (OR = 1.6) or bone-loss therapy (OR = 1.2), and patients who reported falls (OR = 1.2) had an at least 20% higher odds of having a fracture-healing complication than their respective reference group, although the corresponding confidence intervals included the null value for these estimates.

The fully adjusted ORs for any fracture-healing complication by individual risk factors, stratified by fracture site groups (except for fractures of the neck of femur and fractures grouped as others due to the limited number of cases, and thus a lack of power) are presented in Table 2. Regardless of the fracture site group, patients with type-I or type-II diabetes, patients who used NSAIDs, and patients involved in a motor vehicle accident had a higher odds of having a fracture-healing complication compared to their respective reference group, which is consistent with the overall analysis. In the long bone fracture group, female patients had lower odds of having a fracture-healing complication than men (OR = 0.70). In the short bone fracture group, patients with rheumatoid arthritis had a higher odds of having a fracture-healing complication than patients without such a diagnosis (OR = 5.0). In the trunk fracture group, patients with hypothyroidism (OR = 6.1) and patients who used thyroid hormone therapy (OR = 5.3) had a higher odds of having a fracture-healing complication than their respective reference groups. Because there was probably a large overlap between patients with hypothyroidism and those who used hormone therapy, it is difficult to determine

Table 1. Patient characteristics

Characteristic	Cases (n = 563) n (%)	Controls (n = 2,252) n (%)	Conditional OR [a] (95% CI)	Adjusted OR [b] (95% CI)
Fracture-healing complication				
Delayed union	61 (11)	–	–	–
Nonunion	401 (71)	–	–	–
Malunion	101 (18)	–	–	–
Fracture site				
Long bone	254 (45)	1,016 (45)	–	–
Short bone	182 (32)	728 (32)	–	–
Trunk	98 (17)	392 (17)	–	–
Other	18 (3.2)	72 (3.2)	–	–
Neck of femur	11 (2.0)	44 (2.0)	–	–
Sex				
Male	268 (48)	1,022 (45)	1.0	1.0
Female	295 (52)	1,230 (55)	0.91 (0.75–1.1)	0.89 (0.72–1.1)
Age quartiles [c]				
18–29	111 (20)	488 (22)	1.0	1.0
30–49	183 (33)	623 (28)	1.3 (0.98–1.7)	1.1 (0.81–1.4)
50–64	151 (27)	519 (23)	1.3 (0.95–1.7)	0.95 (0.70–1.3)
65–79	118 (21)	622 (28)	0.81 (0.60–1.1)	0.64 (0.46–0.90)
Smoking status				
Never	238 (42)	953 (42)	1.0	1.0
Former	84 (15)	253 (11)	1.4 (1.0–1.8)	1.4 (1.0–1.9)
Current	153 (27)	556 (25)	1.1 (0.88–1.4)	1.0 (0.82–1.3)
Unknown	88 (16)	490 (22)	0.65 (0.49–0.88)	0.63 (0.47–0.86)
Drinking status [d]				
Never	70 (12)	256 (11)	1.0	1.0
Former	6 (1.1)	20 (0.89)	1.2 (0.45–3.0)	0.84 (0.32–2.2)
Current	337 (60)	1,216 (54)	1.0 (0.77–1.4)	0.99 (0.73–1.3)
Unknown	150 (27)	760 (34)	0.68 (0.49–0.94)	0.69 (0.49–0.99)
BMI category [d]				
< 18.5	11 (2.0)	49 (2.2)	0.85 (0.43–1.7)	0.81 (0.40–1.6)
18.5–24	185 (33)	702 (31)	1.0	1.0
25–30	142 (25)	475 (21)	1.1 (0.89–1.5)	1.1 (0.88–1.5)
> 30	68 (12)	227 (10)	1.1 (0.82–1.6)	0.98 (0.71–1.4)
Unknown	157 (28)	799 (35)	0.72 (0.56–0.92)	0.73 (0.56–0.94)
Comorbidities				
Any malignant cancer	30 (5.3)	136 (6.0)	0.87 (0.58–1.3)	0.98 (0.64–1.5)
Type-I diabetes	23 (4.1)	42 (1.9)	2.2 (1.3–3.8)	2.3 (1.3–3.8)
Type-II diabetes	25 (4.4)	48 (2.1)	2.1 (1.3–3.4)	2.3 (1.4–3.7)
Osteoporosis	18 (3.2)	87 (3.9)	0.82 (0.49–1.4)	0.92 (0.54–1.6)
Hypothyroidism	21 (3.7)	85 (3.8)	0.99 (0.60–1.6)	1.1 (0.66–1.8)
Rheumatoid arthritis [d]	19 (3.4)	43 (1.9)	1.8 (1.0–3.1)	1.6 (0.91–2.9)
Peripheral vascular disease	4 (0.71)	18 (0.80)	0.89 (0.30–2.7)	1.0 (0.34–3.1)
Medication use				
Any steroids [d]	58 (10)	202 (9.0)	1.2 (0.86–1.6)	1.1 (0.81–1.5)
Any NSAIDs [e]	227 (40)	483 (21)	2.5 (2.1–3.1)	2.6 (2.1–3.2)
Anticonvulsants	16 (2.8)	75 (3.3)	0.85 (0.49–1.5)	0.82 (0.47–1.4)
Hormone therapy	28 (9.5)	80 (6.5)	1.7 (0.98–3.0)	1.6 (0.88–2.9)
Thyroid hormone therapy	23 (4.1)	90 (4.0)	1.0 (0.64–1.6)	1.1 (0.70–1.8)
Bone-loss therapy	24 (4.3)	92 (4.1)	1.0 (0.65–1.7)	1.2 (0.75–2.0)
Anticoagulants [d]	8 (1.4)	39 (1.7)	0.82 (0.38–1.8)	1.1 (0.50–2.5)
Antibiotics [d]	224 (40)	834 (37)	1.1 (0.93–1.4)	1.0 (0.83–1.2)
Chemotherapy	5 (0.89)	13 (0.58)		
Falls	27 (4.8)	103 (4.6)	1.1 (0.68–1.6)	1.2 (0.74–1.8)
Motor vehicle accident	12 (2.1)	19 (0.84)	2.6 (1.2–5.4)	2.6 (1.2–5.4)

[a] All conditional odds ratios were adjusted for matched factors (fracture site, GP, and length of history in database).
[b] All adjusted odds ratios were adjusted for age and sex.
[c] Also adjusted for smoking and NSAIDs.
[d] Also adjusted for NSAIDs.
[e] Also adjusted for steroids.

Table 2. Adjusted odds ratios stratified by fracture site group

Characteristic	Long bones Cases n = 254	Long bones Controls n = 1,016	Long bones Adjusted [a] OR (95% CI)	Short bones Cases n = 182	Short bones Controls n = 728	Short bones Adjusted [a] OR (95% CI)	Trunk Cases n = 98	Trunk Controls n = 392	Trunk Adjusted [a] OR (95% CI)
Sex									
Male	97	323	1.0	105	406	1.0	57	230	1.0
Female	157	693	0.70 (0.52–0.96)	77	322	0.97 (0.68–1.4)	41	162	1.2 (0.77–2.0)
Age quartiles [b]									
18–29	29	152	1.0	60	231	1.0	19	79	1.0
30–49	69	237	1.4 (0.83–2.3)	68	237	0.99 (0.65–1.5)	39	121	1.1 (0.56–2.1)
50–64	75	253	1.3 (0.75–2.2)	42	160	0.81 (0.49–1.3)	25	89	0.92 (0.44–1.9)
65–79	81	374	1.0 (0.60–1.7)	12	100	0.34 (0.17–0.71)	15	103	0.50 (0.22–1.1)
BMI category [c]									
< 18.5	7	22	1.4 (0.56–3.6)	2	9	0.66 (0.13–3.5)	2	13	0.62 (0.13–3.0)
18.5–24	77	320	1.0	55	207	1.0	41	143	1.0
25–30	70	216	1.3 (0.89–1.9)	41	163	0.94 (0.59–1.5)	24	70	1.3 (0.70–2.4)
> 30	31	99	0.94 (0.56–1.6)	25	85	1.1 (0.59–1.9)	9	36	0.94 (0.41–2.2)
Unknown	69	359	0.80 (0.54–1.2)	59	264	0.80 (0.50–1.3)	22	131	0.55 (0.29–1.1)
Smoking status									
Never	120	470	1.0	74	287	1.0	33	149	1.0
Former	43	113	1.5 (0.99–2.3)	21	66	1.3 (0.75–2.4)	12	62	0.90 (0.43–1.9)
Current	57	219	0.95 (0.66–1.4)	50	204	0.90 (0.59–1.4)	40	95	1.7 (0.99–2.9)
Unknown	34	214	0.55 (0.34–0.88)	37	171	0.69 (0.41–1.2)	13	86	0.52 (0.22–1.2)
Drinking status [c]									
Never	34	139	1.0	23	75	1.0	9	31	1.0
Former	2	9	0.66 (0.13–3.4)	0	4	Too few cases	2	3	2.7 (0.37–20)
Current	146	529	1.2 (0.75–1.8)	105	388	0.87 (0.50–1.5)	69	234	0.83 (0.35–2.0)
Unknown	72	339	0.95 (0.57–1.6)	54	261	0.59 (0.32–1.1)	18	124	0.30 (0.10–0.85)
Comorbidities									
Any malignant cancer	17	79	0.90 (0.52–1.6)	4	23	0.77 (0.26–2.3)	9	26	2.1 (0.85–5.4)
Type-I diabetes	10	19	2.2 (1.0–4.9)	7	13	2.0 (0.79–5.1)	3	9	1.7 (0.43–6.9)
Type-II diabetes	18	25	2.8 (1.5–5.2)	4	9	1.9 (0.56–6.2)	3	10	1.7 (0.44–6.4)
Osteoporosis	11	49	1.0 (0.51–2.0)	0	10	Too few cases	4	22	0.84 (0.26–2.7)
Hypothyroidism	11	52	0.93 (0.46–1.9)	4	21	0.82 (0.27–2.5)	5	6	6.1 (1.6–23)
Rheumatoid arthritis [c]	13	24	2.0 (0.96–4.3)	5	5	5.0 (1.3–19)	1	11	0.36 (0.04–2.8)
Peripheral vascular disease	2	11	0.71 (0.15–3.4)	1	2	Too few cases	1	4	Too few cases
Medication use									
Any steroids [c]	27	107	0.94 (0.58 – 1.5)	15	39	1.8 (0.92 – 3.5)	12	45	1.1 (0.54 – 2.3)
Any NSAIDs [d]	116	222	3.3 (2.4 – 4.5)	67	122	3.0 (2.1 – 4.4)	38	110	1.5 (0.94 – 2.5)
Anticonvulsants	8	35	0.91 (0.41–2.0)	4	15	1.1 (0.35–3.3)	4	20	0.67 (0.21–2.1)
Hormone therapy	13	39	1.3 (0.68–2.6)	11	28	1.7 (0.76–3.8)	3	12	0.88 (0.22–3.5)
Thyroid hormone therapy	12	55	0.93 (0.48–1.8)	5	21	1.1 (0.39–3.0)	5	7	5.3 (1.5–19)
Bone–loss therapy	13	48	1.3 (0.66–2.5)	1	9	0.59 (0.07–5.0)	6	28	1.1 (0.39–3.0)
Anticoagulants [c]	6	18	1.8 (0.66–5.1)	0	6	Too few cases	1	13	0.41 (0.05–3.3)
Antibiotics [c]	109	381	1.1 (0.80–1.5)	58	265	0.72 (0.50–1.0)	43	151	1.2 (0.75–2.1)
Chemotherapy									
Falls	19	60	1.3 (0.75–2.3)	2	15	0.61 (0.14–2.7)	2	20	0.46 (0.10–2.1)
Motor vehicle accident	2	3	3.5 (0.53–23)	3	3	4.4 (0.88–22)	7	12	2.7 (1.0–7.4)

[a] All odds ratios were adjusted for age and sex.
[b] Also adjusted for smoking and NSAIDs.
[c] Also adjusted for NSAIDs.
[d] Also adjusted for steroids.

whether the observed association was due to the underlying condition itself or to treatment of the condition.

The fully adjusted ORs for the specific type of fracture-healing complication by the individual risk factors are presented in Table 3. As in the overall analysis, patients aged 65–79 years had lower odds of having any of the specific fracture-healing complications than patients aged 18–29 years. Also similar to the overall analysis, patients with either type-I or type-II diabetes and patients who used NSAIDs had higher odds of having any of the specific fracture-healing complications than their respective reference groups. Former smokers (OR = 1.7) and patients with rheumatoid arthritis (OR = 2.1) had a higher odds of having a nonunion than their respective reference group, while patients who were involved in a motor vehicle accident (OR = 7.4) had a higher odds of having a delayed union than patients who were not involved in a motor vehicle accident.

We also ran all analyses stratified by case validation status (likely or possible), and the results were consistent between both strata (data not shown).

Table 3. Adjusted odds ratios stratified by specific fracture–healing complication

Characteristic	Nonunion Cases n = 401	Nonunion Controls n = 1,604	Nonunion Adjusted [a] OR (95% CI)	Malunion Cases n = 101	Malunion Controls n = 404	Malunion Adjusted [a] OR (95% CI)	Delayed union Cases n = 61	Delayed union Controls n = 244	Delayed union Adjusted [a] OR (95% CI)
Sex									
Male	191	728	1.0	48	173	1.0	29	121	1.0
Female	210	876	0.92 (0.72–1.2)	53	231	0.83 (0.51–1.4)	32	123	0.98 (0.51–1.9)
Age quartiles [b]									
18–29	81	355	1.0	22	85	1.0	8	48	1.0
30–49	122	439	1.0 (0.75–1.4)	30	108	0.89 (0.44–1.8)	31	76	1.8 (0.68–4.8)
50–64	110	365	0.99 (0.69–1.4)	25	98	0.71 (0.35–1.5)	16	56	1.2 (0.41–3.6)
65–79	88	445	0.69 (0.46–1.0)	24	113	0.64 (0.30–1.4)	6	64	0.38 (0.10–1.4)
BMI category [c]									
< 18.5	8	32	0.95 (0.42–2.2)	1	8	0.44 (0.05–3.9)	2	9	1.0 (0.18–6.1)
18.5–24	137	502	1.0	33	120	1.0	15	80	1.0
25–30	99	327	1.1 (0.81–1.5)	25	90	1.0 (0.56–2.0)	18	58	1.8 (0.74–4.1)
> 30	42	164	0.80 (0.54–1.2)	14	36	1.4 (0.61–3.2)	12	27	2.0 (0.76–5.4)
Unknown	115	579	0.72 (0.53–0.98)	28	150	0.57 (0.30–1.1)	14	70	1.1 (0.45–2.7)
Smoking status									
Never	158	680	1.0	50	178	1.0	30	95	1.0
Former	65	174	1.7 (1.2–2.4)	12	37	1.1 (0.52–2.4)	7	42	0.66 (0.25–1.7)
Current	108	391	1.1 (0.86–1.5)	27	97	0.89 (0.51–1.6)	18	68	0.84 (0.41–1.7)
Unknown	70	359	0.76 (0.53–1.1)	12	92	0.36 (0.17–0.78)	6	39	0.49 (0.17–1.4)
Drinking status [c]									
Never	51	182	1.0	11	54	1.0	8	20	1.0
Former	4	14	0.65 (0.20–2.1)	2	5	2.6 (0.44–16)	0	1	Too few cases
Current	223	850	0.89 (0.62–1.3)	69	205	1.7 (0.78–3.6)	45	161	0.87 (0.33–2.3)
Unknown	123	558	0.79 (0.52–1.2)	19	140	0.51 (0.21–1.3)	8	62	0.38 (0.11–1.4)
Comorbidities									
Any malignant cancer	23	100	1.0 (0.62–1.6)	6	19	1.4 (0.50–3.8)	1	17	0.29 (0.04–2.4)
Type-I diabetes	18	31	2.4 (1.3–4.3)	4	8	2.1 (0.58–7.2)	1	3	1.3 (0.12–15)
Type-II diabetes	17	32	2.2 (1.2–4.0)	4	11	1.5 (0.46–4.7)	4	5	5.8 (1.2–29)
Osteoporosis	15	60	1.1 (0.61–2.0)	1	11	0.41 (0.05–3.3)	2	16	0.72 (0.14–3.6)
Hypothyroidism	16	60	1.1 (0.64–2.0)	3	19	0.68 (0.18–2.6)	2	6	1.5 (0.26–8.7)
Rheumatoid arthritis [c]	18	31	2.1 (1.1–3.9)	1	9	0.35 (0.04–2.8)	0	3	Too few cases
Peripheral vascular disease	3	14	Too few cases	1	2	2.6 (0.22–31)	0	2	Too few cases
Medication use									
Any steroids [c]	44	143	1.3 (0.87–1.8)	8	33	0.79 (0.34–1.8)	6	26	0.85 (0.30–2.4)
Any NSAIDs [d]	164	350	2.5 (2.0–3.2)	38	87	2.7 (1.6–4.6)	25	46	2.9 (1.5–5.8)
Anticonvulsants	11	45	0.94 (0.48–1.8)	4	17	0.89 (0.28–2.8)	1	13	0.27 (0.03–2.1)
Hormone therapy	22	56	1.6 (0.92–2.7)	4	16	1.0 (0.32–3.4)	2	8	0.76 (0.14–4.0)
Thyroid hormone therapy	17	66	1.1 (0.63–1.9)	4	19	0.95 (0.29–3.1)	2	5	2.2 (0.35–14)
Bone-loss therapy	18	61	1.4 (0.79–2.5)	3	16	0.84 (0.22–3.1)	3	15	1.0 (0.23–4.6)
Anticoagulants [c]	4	28	0.82 (0.28–2.4)	2	7	1.2 (0.24–6.4)	2	4	2.8 (0.31–25)
Antibiotics [c]	157	605	0.96 (0.76–1.2)	46	147	1.4 (0.87–2.2)	21	82	0.77 (0.41–1.5)
Chemotherapy									
Falls	20	72	1.2 (0.72–2.1)	5	15	1.4 (0.46–4.1)	2	16	0.74 (0.15–3.6)
Motor vehicle accident	8	14	2.3 (0.96–5.7)	0	2	Too few cases	4	3	7.4 (1.4–39)

[a] All odds ratios were adjusted for age and sex.
[b] Also adjusted for smoking and NSAIDs.
[c] Also adjusted for NSAIDs.
[d] Also adjusted for steroids.

Discussion

The results of this study indicate that patients with certain comorbidities, specifically type-I and type-II diabetes, were more likely to have a fracture-healing complication. Patients using certain medications in the 12 months prior to their fracture, specifically NSAIDs and estrogen-containing hormone therapy, were also more likely to have a fracture-healing complication (although use of estrogen-containing hormone therapy could be a proxy for osteoporosis). Patients who had had a motor vehicle accident 1 month or less before their fracture were at increased risk of these outcomes, suggesting that major trauma increases the risk of healing complications. While there was some variation depending on the fracture site and the specific type of fracture-healing complication, these same factors were consistently associated with increased risks of the outcome in the various analyses. Specifically, although the reasons for malunion are multifactorial (including surgeon technique and patient non-compliance) and not necessarily related to fracture healing per se, the results in the malunion

group were similar to those in patients with nonunion and delayed union.

One of the most consistent findings in the present study was the positive association between diabetes and fracture-healing complications. The existing evidence supporting this association comes mainly from basic science experiments, which suggest that inadequate insulin production leads to reduced production of collagen by osteoblasts (Spanheimer et al. 1988, Lu et al. 2003). Subsequently, mechanical defects (e.g. reduced tensile strength or stiffness) can result in the callus that forms at a fracture site, which can impair healing (Macey et al. 1989). Few clinical studies have quantified the risk of fracture-healing complications in diabetics. Loder (1988) found that patients with diabetes who had a closed fracture of the lower extremity had a time to union that was approximately two-thirds longer on average than what would be expected for those fractures. Micro- and macrovascular disease associated with diabetes and/or treatment for diabetes may also put these patients at a higher risk of fracture-healing complications; for example, thiazolidinidiones have been shown to be associated with an increased risk of fracture (Dormuth et al. 2009). As noted in a recent review related to this topic, there have been few well-designed, large-scale, epidemiological studies on the prevalence and incidence of fracture-healing complications in a population of diabetic patients (Retzepi and Donos 2010).

Another consistent finding in the present study was the positive association between the use of NSAIDs and fracture-healing complications, which adds to existing evidence from other clinical studies. However, because previous studies evaluated the use of NSAIDs after the initial fracture occurrence, it is difficult to determine whether NSAID use in those studies was a result of pain associated with an undiagnosed healing complication or whether it was a risk factor for the healing complication (Giannoudis et al. 2000, Bhandari et al. 2003, Bhattacharyya et al. 2005). For example, Bhattacharyya et al. (2005) reported that while exposure to NSAIDs 61–90 days after a humeral shaft fracture was associated with nonunion (RR = 3.9, 95% CI: 2.0–6.2), the association was more likely to reflect the use of analgesics for pain related to non-healing fractures rather than a causal relationship between NSAIDs and the increased risk of nonunion. Because we evaluated NSAID use recorded before the initial fracture diagnosis, we could more clearly establish a temporal relationship between NSAID use and fracture-healing complications, with patients taking NSAIDs 1 year or less before the initial fracture diagnosis having an approximately 2- to 3-fold higher risk of experiencing a fracture-healing complication than patients who were not treated with NSAIDs during the same period. Because the intent in our study was not specifically to investigate the relationship between NSAID use and fracture-healing complications, we did not look at how recency, duration, and dosage might have affected our results.

While the data for our study were based on information recorded by GPs, information related to hospital discharges and communications from specialists is required by the UK National Health Service to be sent to GPs and entered into the database as part of the complete medical history of each patient (Gelfand et al. 2005). Providing evidence that this information is captured in the GPRD in a valid way, Jick et al. (1991) showed that GPs entered approximately 90% of diagnoses from specialist and hospital letters. However, while the GPRD contained diagnoses for fractures, more detailed information on fracture characteristics (e.g. open/closed, simple/comminuted) was generally not available; nor were soft-tissue injuries described. Thus, we were unable to evaluate how aspects of these characteristics were associated with fracture-healing complications. For example, severe fractures probably include extensive damage to the soft tissue surrounding the fracture site, which disrupts the local vasculature, thereby affecting formation of the fracture hematoma and delaying formation of repair tissue—all of which increases the likelihood of a fracture-healing complication occurring (Rodriguez-Merchan and Forriol 2004). It is likely that our consistent finding of higher odds of having a fracture-healing complication for patients involved in a motor vehicle accident 1 month or less before their fracture reflects some measure of fracture severity or major trauma (since GPs are probably more inclined to record only serious accidents), despite our exclusion of patients with fractures at multiple sites. Karladani et al. (2001) found that patients with tibial shaft fractures due to high-energy trauma (i.e. a traffic accident or a fall from a height of at least 3 m) were at increased risk of developing a nonunion (RR = 2.9). While having data on fracture-related risk factors would be informative, the goal of our study was to evaluate patient-related risk factors, including comorbidities and medication use. Future studies should elucidate the role of fracture-related risk factors, including the role of postoperative infection in the incidence of fracture-healing complications.

Some aspects of our study should be considered. First, while we validated the case diagnosis for a random sample of cases, we did not validate any of the controls. Thus, it is possible that some controls had an unrecorded fracture-healing complication, which could lead to a small degree of misclassification in our results. Second, we combined fracture sites into groups because the sample size restricted our ability to look at individual fracture sites. While the groups were based on the premise that the healing process was similar for the various fracture sites (e.g. all long bones), we recognize that there are differences in the healing process even within a particular bone (e.g. metaphysis and diaphysis of the tibia). Combining fracture sites and not specifying particular regions within a bone, however, probably resulted in our estimates being lower than what they would have been had we been able to study fracture sites and regions separately. We lacked data on smoking, alcohol use, and BMI for 16–28% of the patients in our study, and therefore could not fully evaluate these risk factors; nor could we evaluate socioeconomic-related factors due to our matching on GP. However, a variety of individual

diagnoses (including diabetes) have been validated by direct questioning of the GPs, indicating that the GPRD is a useful source of morbidity data (Hollowell 1997). Finally, due to the small number of exposed cases for certain risk factors of interest, some odds ratios were estimated with less precision in the stratified analyses, as reflected in the wider confidence intervals.

In conclusion, we quantified the association between a variety of patient characteristics and fracture-healing complications in a population-based, heterogeneous cohort representative of most patients with fractures. Our results are consistent with the literature, indicating that diabetes and NSAID use are strongly associated with the development of fracture-healing complications. Future research should be aimed at elucidating which aspects of NSAID use (e.g. dosage, duration, type) are associated with the highest risk of fracture-healing complication, and also whether well-controlled diabetes might reduce the risk of fracture-healing complications. Additional research should also be aimed at investigating whether fracture-specific and treatment-specific characteristics (e.g. fracture severity, immobilization) are associated with increased risk of specific fracture-healing complications, as the mechanism of action is more likely to be influenced by these characteristics than by patient-related factors.

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