ORIGINAL ARTICLE

Elevated risk of clinical fractures and associated risk factors in patients with systemic lupus erythematosus versus matched controls: a population-based study in the United Kingdom

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Abstract

Summary The incidence of clinical fractures and the associated factors were assessed in patients with systemic lupus erythematosus (SLE) versus matched controls. We found an increased fracture risk in SLE patients compared to controls. Glucocorticoid use, longer disease duration, neuropsychiatric disease complications and previous osteoporotic fractures were identified as associated factors.

Introduction The aims of this study were to estimate the risk of clinical fractures in patients with SLE versus matched controls and to evaluate the risk factors associated with clinical fractures in SLE.

Methods This is a population-based cohort study using the Clinical Practice Research Datalink (from 1987–2012). Each SLE patient ($n = 4{,}343$) was matched with up to six controls ($n = 21{,}780$) by age and sex. Clinical fracture type was stratified according to the WHO definitions into osteoporotic and non-osteoporotic fracture. Cox proportional hazards calculated relative rates (RR) of clinical fracture and time interaction terms to evaluate the timing patterns of fracture. Clinical fracture rates in SLE patients, stratified by age, gender, type of fracture, disease duration and therapy variables, were compared with those rates in controls.

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Results Follow-up durations were 6.4 years in SLE patients and 6.6 years in controls. SLE patients had a 1.2-fold increased clinical fracture risk compared to controls (adjusted RR=1.22, 95% CI=1.05–1.42), and the risk further increased with a longer disease duration. Glucocorticoid (GC) use in the previous 6 months raised the risk of clinical fracture (adjusted RR=1.27, 95% CI=1.02–1.58). Cerebrovascular events, seizures and previous osteoporotic fractures were identified as predictors of clinical fractures.

Conclusions We found an increased risk of clinical fracture in SLE patients compared to controls. GC use in the previous 6 months and longer disease duration are associated with the increased fracture risk in SLE. Patients with neuropsychiatric organ damage or previous osteoporotic fractures are also at increased risk of the occurrence of clinical fractures.

Keywords Bone fractures · Glucocorticoids · Hydroxychloroquine · Osteoporosis · Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disorder that usually affects women and may involve every organ system in the body. Because the survival of patients with SLE has improved dramatically over recent decades [1], attention is now focused on disease complications leading to increased morbidity. Osteoporosis-related fractures damage one of the most frequently involved organ systems in patients with SLE: the musculoskeletal system. Osteopenia has been reported in 25–74 % [2, 3] and osteoporosis, defined as T-score less than −2.5, is reported in 1.4–68 % [4, 5] of SLE patients, depending on the population studied. The etiology of bone loss and the occurrence of clinical fractures in SLE are likely to be multifactorial, involving both non-disease-related and disease-related factors [6]. A study among Dutch SLE patients reported prevalent morphometric vertebral fractures in 20 % of the patients, which is remarkable since the mean age of the patients was only 41 years [7]. In that study, it was noteworthy that osteoporosis (defined as a T-score less than -2.5) was found in only 4 %, whilst vertebral fractures were found in 20 % and (previous) non-vertebral fractures in 11 % of the patients. These findings are consistent with the notion that SLE might influence clinical fracture risk through an effect on bone strength, at least partly independent of any effect on bone mineral density (BMD). In addition, risk of clinical fracture was related to the use of methylprednisolone, suggesting that disease severity and potential therapeutic strategies may play a role. The relatively high frequency of vertebral fractures in patients with SLE has been confirmed by three other studies, demonstrating prevalent vertebral fractures in 20–26.1 % of the patients [8–10]. Symptomatic (both

peripheral and vertebral) fractures since lupus diagnosis have been reported in 9.1–18.8 % of patients [7, 11–14], and older age [11, 13, 15, 16], postmenopausal status [12], non-African-American ethnicity [12], obesity [12], smoking [12], disease duration [14], glucocorticoid (GC) treatment [11, 12, 15–17], renal insufficiency [12], Raynaud's syndrome [12], lupus anticoagulant [12] and reduced BMD [13] have been reported as risk factors of symptomatic fractures in SLE.

However, there is limited evidence pertaining to the relative risk of fractures in SLE patients, and the impact of the duration or severity of disease has not been studied. Three population-based studies showed 1.8- to 4.7-fold increased risk of fracture in female SLE patients compared with healthy controls [11, 15, 18]. Patients were selected from specialized lupus cohorts in tertiary university hospitals. They may have overestimated fracture risk due to the predominance of patients with a severe disease course. In addition, the numbers of patients were small and treatment severity was not evaluated. Two nationwide case–control studies reported an increased risk of fracture in both female and male patients with SLE [16, 19], but these studies were restricted to patients who had been hospitalized for hip fractures [16, 19] or vertebral fractures [19] and no evaluation of the influence of disease duration and body mass index on fracture risk was performed.

Therefore, the aims of this study were, in a population-based cohort, (1) to estimate the incidence rates of clinical fractures in a very large number of patients with SLE and relative risks compared with matched controls and (2) to evaluate the role of cumulative GC exposure and other possible risk factors on risk of clinical fracture in SLE.

Methods

Source population

Information for this retrospective cohort study was obtained from the UK Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database. CPRD comprises the computerized medical records of 10 million patients under the care of general practitioners. These data include the patient's demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and hospital discharge summaries. This database is representative of the total UK population. It has been the source for numerous epidemiological studies in recent years, and the accuracy and completeness of these data have been well documented and validated [20, 21]. Previous studies of CPRD data have shown a high level of data validity with respect to the reporting of clinical fractures (>90 % of clinical fractures were confirmed) [22].

Study population

The study population consisted of all patients with a record of SLE (as recorded in CPRD; first record) during the period of valid CPRD data collection (from January 1987 through December 2012).

Selection of control subjects

Each SLE patient was matched by year of birth (in increments of 1 year, to a maximum of 5 years), sex and practice to up to six control patients (without a history of SLE, including nonspecific codes for SLE, cutaneous lupus erythematosus and antiphospholipid syndrome). The index date of the patients with SLE was defined as the date of the first record of SLE after data collection started. The index date of an SLE patient defined the index date of his or her matched control(s).

Outcomes

Patients were followed up from the index date to either the end of data collection, the date of transfer of the patient out of the practice area, the patient's death or fracture (READ codes), whichever came first. Fracture type was stratified according to the World Health Organization definitions into osteoporotic fracture (spine, hip, forearm or humerus) and non-osteoporotic fracture [23].

Potential confounders

The following risk factors were assessed at baseline: sex, smoking status, body mass index and a history of clinical fractures. For time-dependent covariates, the total follow-up period was divided into 6-month intervals. For these time-dependent risk factors, the presence of these covariates was assessed by reviewing the computerized medical records for any record of risk factors prior to the start of an interval. These included age; a record of falls in the previous 6–12 months; a history of a chronic disease (cerebrovascular disease [24], heart failure, renal disease, diabetes, malignancy, inflammatory bowel disease, asthma/chronic obstructive pulmonary disease [25], anaemia and dementia); and a prescription in the previous 6 months for GCs [26], hydroxychloroquine, immunosuppressive agents, antiobesity drugs, calcium/vitamin D supplements, antihypertensive drugs, loop diuretics, hypnotics/anxiolytics, antipsychotics [27], antidepressants, proton pump inhibitors, or antiepileptic agents, as well as drugs for the treatment of Parkinson's disease [28]. These covariates were handled differently according to whether they were present at baseline and were real-time reversible (for example, current medications) or real-time irreversible (for example, diagnoses of chronic diseases such as diabetes, where, once diagnosed, the condition will be present for the individual's remaining time in the study). These classifications are itemised for each covariate in Table 1.

For current systemic GC and hydroxychloroquine use (i.e. at least one prescription in the previous 6 months), cumulative amounts of daily defined dosages (DDDs) were calculated (prior to the start of each period), allowing a maximum non-use gap of 6 months.

SLE patients were stratified according to their 'treatment intensity' in the previous 6 months, which was primarily based on the revised British Isles Lupus Assessment Group (BILAG) index [29]. This stratification includes the following categories:

- High intensity: daily GC exposure of >20 mg oral prednisolone equivalents which is equal to 2 DDDs [30] (assessed by reviewing the latest prescribed daily dose) or use of immunosuppressive drugs
- Medium intensity: daily GC exposure of ≤2 DDDs or use of antimalarials/antiepileptics/antidepressants in combination with non-steroidal anti-inflammatory drugs (NSAIDs) or topical steroids
- Low intensity: symptomatic treatment only, i.e. use of analgesics/NSAIDs
- No drug use: none of the aforementioned drugs

In addition, we stratified the results for risk factors of fracture included in the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (SDI) [31]. These risk factors include a history of seizures, cerebrovascular accident, chronic renal disease, osteoporotic fracture or vertebral collapse, use of blood glucose-lowering agents (proxy for diabetes mellitus), malignancies and cognitive impairment. Because cognitive impairment is not routinely measured by GPs, we used a recording of dementia as a proxy.

Statistical analysis

In the first analysis, the rates of clinical fracture in patients with SLE were compared with control subjects using Cox proportional hazards models to derive adjusted relative risks (RRs; SAS 9.2, PHREG procedure). Potential confounders were entered into the final model if they independently changed the beta coefficient for SLE by at least 5 %. These are summarized in the legend to Table 2. Within SLE patients, we evaluated the influence of 'treatment intensity', systemic GC use, hydroxychloroquine use and fracture risk factors included in the SDI on clinical fracture risk, adjusted for the general risk factors. The timing of clinical fracture occurrence was examined by including time interaction terms (time period×SLE) into the model for the following time intervals: <3 months, 3–12 months, 1–2 years, 2–5 years and ≥5 years. Using smoothing spline regression [32], we visualized the time trend for risk

Table 1 Baseline characteristics of SLE patients and matched controls

Characteristics	SLE patients		Matched controls	
	$N=4{,}343$	%	$N=21{,}780$	%
Follow-up (years, mean, SD)	6.4 (5.1)		6.6 (5.1)	
Females	3.865	89.0	19.398	89.1
Age, real time (years, mean, SD)	46.7 (16.3)		46.7 (16.3)	
BMI, baseline (kg/m^2, mean, SD)	26.1 (5.8)		26.4 (5.8)	
<20.0 kg/m^2	365	8.4	1.605	7.3
20.0–24.9 kg/m^2	1.578	36.3	7.405	34.0
25.0–29.9 kg/m^2	1.136	26.1	5.695	26.1
≥30.0 kg/m^2	828	19.1	4.197	19.3
Unknown	437	10.1	2.877	13.2
Smoking status (baseline)				
Never	2.348	54.1	12.385	56.9
Current	1.162	26.7	5.278	24.2
Ex	712	16.4	3.063	14.1
Unknown	122	2.8	1.054	4.8
Ethnicity (baseline)				
Caucasian	1.346	31.0	6.235	28.6
Asian	125	2.9	531	2.4
Other/unknown	2.872	66.1	15.013	68.9
Falls (6–12 months before, real-time reversible)	259	6.0	1.010	4.6
Fracture ever before (baseline)	631	14.5	2.964	13.6
History of diseases (real-time irreversible)				
Heart failure	67	1.5	165	0.8
Ischaemic heart disease	238	5.5	720	3.3
Cerebrovascular event	201	4.6	343	1.6
Dementia	6	0.1	72	0.3
Seizures	175	4.0	451	2.1
Renal disease	142	3.3	277	1.3
Malignancy	224	5.2	1.023	4.7
Drug use 6 months before (real-time reversible)				
Systemic glucocorticoids	1.001	23.0	430	2.0
Ever before the index date	1.537	35.4	1.851	8.5
Topical glucocorticoids	745	17.1	1.484	6.8
Antimalarials	878	20.2	35	0.2
Any time during data collection	2.373	54.6	142	0.7
Azathioprine	254	5.9	25	0.1
Anticonvulsants	189	4.4	372	1.7
Antidiabetics	107	2.5	557	2.6
Antidepressants	800	18.4	2.238	10.3
Anxiolytics/hypnotics	393	9.0	1.122	5.1
Bisphosphonates	258	5.9	256	1.2
Calcium/vitamin D	420	9.7	427	2.0

BMI body mass index, *SD* standard deviation, *SLE* systemic lupus erythematosus

of fracture for these given time intervals. In the second analysis, we calculated the incidence rate of clinical fracture for SLE patients and matched controls separately. The incidence rates among SLE patients were stratified by age, sex, type of fracture, SLE duration, 'treatment intensity', systemic GC use, hydroxychloroquine use and SDI risk factors. Sensitivity analyses were performed to check assumptions regarding adjustments, models based on adjustment for age and sex only; baseline covariates; time-dependent covariates excluding vitamin D/calcium supplements and the history of fracture; or

Table 2 Risk of clinical fracture in SLE patients compared with matched controls, stratified by age, sex and type of fracture

	Person-years	Fractures	Age/sex adj RR (95% CI)	Baseline adj RR (95% CI)[a]	Adj RR (95% CI)[a]
No SLE[b]	137.403	1.477	Reference	Reference	Reference
SLE					
Any fracture	26.343	409	1.58 (1.41–1.76)	1.45 (1.27–1.66)	1.22 (1.05–1.42)
By age (years)					
18–39	6.609	49	1.39 (1.01–1.92)	1.47 (1.01–2.14)	0.95 (0.60–1.51)
40–59	12.045	167	1.66 (1.39–1.99)	1.40 (1.12–1.76)	1.19 (0.91–1.55)
60–79	6.817	168	1.67 (1.40–2.00)	1.56 (1.26–1.94)	1.34 (1.07–1.69)
80+	871	25	1.08 (0.68–1.71)	1.10 (0.65–1.85)	1.08 (0.62–1.91)
By sex[c]					
Males	2.954	37	1.55 (1.06–2.25)	1.92 (1.18-3–10)	1.91 (1.14–3.20)
Females	23.389	372	1.58 (1.40–1.78)	1.42 (1.23–1.63)	1.18 (1.01–1.39)
Osteoporotic fracture	27.094	207	1.60 (1.37–1.88)	1.43 (1.18–1.74)	1.19 (0.97–1.47)
Hip fracture	27.807	33	1.58 (1.06–2.35)	1.49 (0.93–2.39)	1.09 (0.65–1.82)
Non-osteoporotic fracture	26.880	256	1.58 (1.37–1.83)	1.48 (1.25–1.76)	1.27 (1.05–1.54)

Adj adjusted, *CI* confidence interval, *RR* relative risk, *SLE* systemic lupus erythematosus

[a] Adjusted for previous fracture, use of systemic glucocorticoids, hydroxychloroquine, calcium/vitamin D supplements, benzodiazepines and proton pump inhibitors in the previous 6 months

[b] Results display effect modification, e.g. male SLE patients were compared with male control patients

[c] Not adjusted for sex

time-dependent covariates including vitamin D/calcium supplements and history of fracture at baseline only.

Study approval

Patient consent

Not applicable (see "Study approval").

Results

Characteristics of SLE patients and matched controls

A total of 4,343 eligible SLE patients and 21,780 age- and sex-matched controls were identified (Table 1). On average, we had 6.4 years of follow-up for SLE patients and 6.6 years for matched controls. Due to matching, the age and sex distribution was similar between the two patient groups (mean age, 46.7 years; 89 % females). SLE patients were more likely than controls to have used GCs, antimalarials, antidepressants, benzodiazepines and calcium/vitamin D supplements in the previous 6 months.

Fracture risk in SLE patients and matched controls

SLE patients were at increased risk of clinical fracture, and this risk remained significantly elevated after statistical adjustment [adjusted (adj) RR=1.22, 95% CI=1.05–1.42] (Table 2).

Figure 1 shows that, compared with controls, the risk further increased with a longer disease duration: individuals with an SLE duration of more than 10 years had a twofold increased risk of clinical fracture (adj RR=2.00, 95 % CI=1.50–2.67), whereas no significant elevated risk was found in individuals with an SLE duration of 6 months–10 years (adj RR=1.14, 95% CI= 0.96–1.34) or <6 months (adj RR=1.10, 95% CI=0.77–1.57). No significant interaction was found with age, sex or type of fracture, although the association tended to be stronger for males (adj RR=1.91, 95% CI=1.14–3.20) compared with females (adj RR=1.18, 95% CI=1.01–1.39). In sensitivity analyses, testing assumptions relating to time dependency of covariates, inclusion of vitamin D/calcium supplements and fracture history, the relative risk of fracture amongst SLE patients remained statistically significant, ranging from 1.22 to 1.58, with the results adjusted for baseline covariates presented in Table 2.
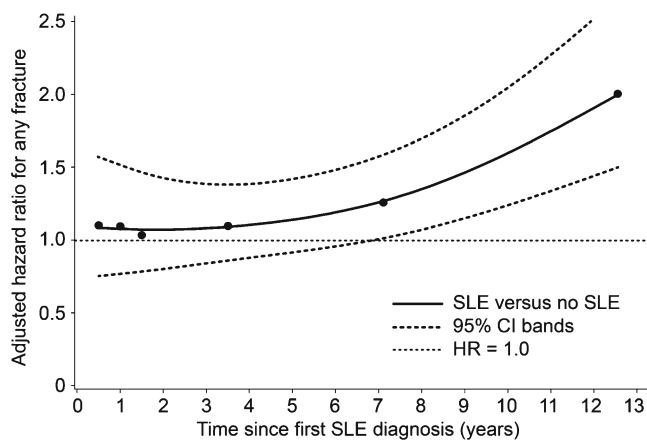
Fig. 1 Spline regression plot of time since first SLE record and risk of any fracture in SLE patients versus matched controls. Adjusted for confounders as shown in Table 2 (time-dependent model)

factors included in the SDI. Thus, prior GC treatment, cerebrovascular disease, seizures and prior fracture were all associated with increased fracture risk.

Discussion

We observed an increased rate of clinical fractures in patients with SLE in this large population-based cohort study. The risk increased with increasing duration of SLE and with systemic GC use in the previous 6 months. Moreover, clinical fracture risk was increased in SLE patients in whom the disease course had been complicated by seizures or a cerebrovascular event and in patients who had suffered previous osteoporotic fractures.

Our main finding of a 1.2-fold increased risk of clinical fracture in SLE patients versus population-based controls is in line with other studies drawing participants from the general community [16,19]. However, it is lower than the relative risks (1.8- to 4.7-fold) which have been previously reported [11, 15, 18] in studies focused on specialist care settings. The lower relative fracture risk observed in our study might thus be explained by several factors. First, the SLE patients in our

Influence of treatment intensity and comorbidities on clinical fracture risk

Table 3 shows the risk of clinical fracture within SLE patients, stratified by SLE treatment intensity, the use of systemic GCs/hydroxychloroquine in the previous 6 months and the risk

Table 3 Determinants of risk of clinical fracture within SLE patients

	Any fracture			Osteoporotic fracture		
	Events	IR[a]	Adj RR (95% CI)[b]	Events	IR[a]	Adj RR (95% CI)[b]
SLE patients	15.5			7.7		
By SLE treatment intensity (reference=no associated drug use)						
Low	78	19.4	1.25 (0.92–1.69)	46	11.1	1.54 (1.01–2.34)
Medium	136	17.3	0.75 (0.52–1.06)	71	8.8	0.89 (0.54–1.47)
High	92	18.3	0.81 (0.55–1.20)	45	8.7	0.93 (0.53–1.63)
By cumulative DDD of systemic glucocorticoid exposure ever before among current users (reference=no current use)						
1–181	19	16.5	1.20 (0.75–1.92)	6	5.1	0.78 (0.34–1.78)
182–730	40	17.8	1.17 (0.83–1.66)	21	9.1	1.25 (0.78–2.02)
>730	114	24.0	1.33 (1.03–1.70)	60	12.1	1.32 (0.94–1.86)
By cumulative DDD of hydroxychloroquine exposure ever before among current users (reference=no current use)						
1–181	21	12.3	0.91 (0.58–1.42)	11	6.4	1.07 (0.57–1.98)
182–730	52	15.6	1.07 (0.79–1.45)	27	8.0	1.22 (0.81–1.86)
>730	69	21.0	1.14 (0.87–1.49)	32	9.3	1.02 (0.69–1.52)
By a history of risk factors included in the SDI (reference=no risk factor)						
Dementia	5	49.8	1.67 (0.68–4.08)	4	38.1	2.25 (0.82–6.16)
Seizures	34	27.8	2.01 (1.41–2.86)	22	17.5	2.81 (1.80–4.40)
Cerebrovascular events	55	33.3	1.49 (1.12–2.00)	35	20.5	1.77 (1.22–2.57)
Renal disease	54	31.4	1.30 (0.96–1.75)	32	17.5	1.35 (0.91–2.00)
Osteoporotic fracture	172	48.6	4.26 (3.49–5.18)	95	22.1	3.85 (2.92–5.07)
Use of antidiabetics	21	24.3	1.39 (0.89–2.17)	11	12.1	1.33 (0.72–2.45)
Malignancy	50	27.4	1.23 (0.91–1.68)	28	14.7	1.22 (0.81–1.84)

Adj adjusted, *CI* confidence interval, *DDD* daily defined dosage, *RR* relative risk, *SDI* System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, *IR* incidence rate, *SLE* systemic lupus erythematosus

[a] Incidence rate per 1,000 person-years

[b] Adjusted for confounders as shown in Table 2 (time-dependent model)

study were selected from the CPRD, which comprises the medical records of patients under the care of general practitioners, in contrast to the studies from the Pittsburgh Lupus Registry [11], the Chicago Lupus Database [18] and the Helsinki University Central Hospital [15] in which patients were recruited from specialized lupus cohorts in university hospitals providing tertiary care for SLE patients. Obviously, a general practitioners database comprises relatively more SLE patients with a mild disease course and less organ damage, including musculoskeletal damage. This argument is supported by the lower percentage of patients who ever used systemic GCs in our study population compared to the studies from Helsinki and Pittsburgh (61 % versus 75 % and 87 %, respectively) [11, 15]. Second, the mean disease duration in our study (mean±SD=6.4±5.1 years) was considerably lower than the disease duration in the study from Pittsburgh (mean±SD=11.0±7.1 years) and the Helsinki study (mean±SD=13.1±9.8 years); indeed, the present study (Fig. 1) and a cross-sectional study from the combined lupus cohorts in Pittsburgh and Chicago [14] demonstrated that disease duration is an independent risk factor of fractures in SLE, especially in patients with a disease duration of 10 years or more. With regard to hip fracture, our finding of no association with SLE contrasts with that from a study from Taiwan [16], a disparity that is likely to be explained by ethnic differences between the populations.

The association found between GC use in the previous 6 months and an increased risk of clinical fracture in the present study is in line with findings in GC-treated individuals with other underlying diseases [33] and is consistent with previous studies in SLE patients reporting longer use of GCs [11, 15, 18], ever use of GCs [15–17] and current GC use [16, 18] as risk factors of fractures in SLE. Consistent with results from the population-based study of the Pittsburgh Lupus Registry, we did not observe a further increase in clinical fracture rate with higher cumulative GC exposure, after adjustment for confounders. This finding is in contrast to the results of a study from the Hopkins Lupus Cohort [17] and the population-based study on hip fractures from Taiwan [16], which both reported an increasing fracture risk with increasing cumulative GC dose. This discrepancy might be explained by differences in the assessment of cumulative GC use between studies: In the present study and the study from Pittsburgh, only oral GCs were taken into account, whilst in the studies from the Hopkins Lupus Cohort and from Taiwan, oral GCs plus intravenously administered methylprednisolone pulses were assessed to calculate cumulative GC dose.

Hydroxychloroquine therapy did not influence the risk of clinical fracture in our study. This finding is important in light of the increasing therapeutic use of antimalarials (which are currently regarded as 'anchor drugs' for the treatment of SLE) [34], whilst studies on the effect of hydroxychloroquine use on BMD in SLE showed conflicting results. In contrast to retrospective studies reporting a protective effect of hydroxychloroquine use on BMD in SLE [3, 35], another retrospective study [36] and

a prospective 6-year follow-up study [37] demonstrated significant bone loss in patients using antimalarials.

The present study identified SLE patients with seizures and patients with a history of a cerebrovascular event to have a particularly high risk of clinical fracture. This finding might be explained by the increased fall risk associated with these neuropsychiatric disease complications of SLE and by the adverse effects of antiepileptic agents on bone mass [38].

This study had several strengths. As far as we know, this is the largest study and it was conducted in the general population. Its external validity and generalizability is high because CPRD is representative of the total UK population. We had a substantial duration of follow-up and the opportunity to evaluate a wide range of potential confounders including BMI and smoking status. We attempted to control for comorbid conditions and risk factors by handling confounding factors in a time-dependent manner (i.e. baseline, real-time reversible, or real-time irreversible). The proportionality assumption of the model was checked by performing proportionality tests of the model, which demonstrated a normal distribution of the residuals. Furthermore, assumptions relating to the treatment of covariates were explored in sensitivity analyses, in which the increased risk of fracture associated with SLE remained broadly similar and statistically significant.

This study also has limitations. The study population consisted of patients with a CPRD READ code for SLE, comprising the medical records of SLE patients under the care of general practitioners. We did not have the opportunity to verify the diagnosis of SLE and the clinical fractures documented in the study population. However, previous studies using this database have demonstrated a high degree of validity and completeness of diagnoses [20, 21] and a high level of data validity with respect to the reporting of clinical fractures (>90 % of clinical fractures were confirmed) [22]. Somers and colleagues [39] studied the annual incidence of SLE in the UK using the CPRD and demonstrated results remarkably similar to those reported from active surveillance studies, a finding which provides evidence that the CPRD can be utilized for studying SLE. In addition, in our study, we estimated the relative risks of fractures rather than absolute numbers, and therefore, non-differential misclassification of SLE exposure would have masked the true effect of the diagnosis of SLE on fracture risk rather than erroneously inflating it.

We did not have data on BMD measurements in the SLE patients and matched controls. Therefore, we were not able to draw conclusions on the contribution of low BMD to fracture risk in lupus patients in the present study. In addition, information on intravenously administered methylprednisolone pulse therapy was not available for the present study. Furthermore, we did not have data on disease activity and organ damage index (SDI) in the SLE patients and therefore were not able to study the associations between disease activity and fracture risk and between cumulative organ damage

and fracture occurrence. However, we investigated the influence of disease severity on fracture risk by stratifying SLE patients according to their 'treatment severity' (based on the revised BILAG criteria) in the previous 6 months, which might be regarded as a surrogate marker of disease severity in SLE. It should be noted, though, that this stratification also included systemic steroid medication, and so it is not possible to definitely differentiate between effects of disease severity and those resulting from treatment.

In summary, this is probably the largest population-based study of all clinical fractures and the associated risk factors in patients with SLE. The results of the present study demonstrate that SLE patients in the UK have an increased rate of clinical fractures compared to age- and sex-matched controls, and the risk further increases with systemic GC use in the previous 6 months and with longer disease duration. Moreover, special attention should be paid to lupus patients with specific neuropsychiatric complications or a history of osteoporotic fractures since these subgroups of patients are at high risk of the occurrence of fractures.

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