EXTENDED REPORT

Childhood onset arthritis is associated with an increased risk of fracture: a population based study using the General Practice Research Database

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Background: Childhood onset arthritis is associated with low bone mass and strength.
Objective: To determine whether childhood onset arthritis is associated with greater fracture risk.
Methods: In a retrospective cohort study all subjects with onset of arthritis between 1 and 19 years of age in the United Kingdom General Practice Research Database were identified. As controls, all sex and age matched subjects from a practice that included a subject with arthritis were included. Incidence rate ratios (IRRs) for first fracture were generated using Mantel-Haenszel methods and Poisson regression.
Results: 1939 subjects with arthritis (51% female) and 207 072 controls (53% female) were identified. The median age at arthritis diagnosis was 10.9 years. A total of 129 (6.7%) first fractures were noted in subjects with arthritis compared with 6910 (3.3%) in controls over a median follow up of 3.90 and 3.95 years in the subjects with arthritis and controls, respectively. The IRR (95% confidence interval) for first fracture among subjects with arthritis, compared with controls, according to the age at the start of follow up were 1.49 (0.91 to 2.31) for age <10 years, 3.13 (2.21 to 4.33) at 10–15 years, 1.75 (1.18 to 2.51) at 15–20 years, 1.40 (0.91 to 2.08) at 20–45 years, and 3.97 (2.23 to 6.59) at >45 years.
Conclusions: Childhood onset arthritis is associated with a clinically significant increased risk of fracture in children, adolescents and, possibly, adults. Studies are urgently needed to characterise the determinants of structural bone abnormalities in childhood arthritis and devise prevention and treatment strategies.

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood.[1 2] Children with JIA have multiple risk factors for low bone mass, including delayed puberty, malnutrition, weakness, inactivity, inflammation, and glucocorticoid treatment. Throughout childhood and adolescence, bone mineral accretion results in ethnic-, sex-, and maturation-specific increases in bone dimensions and density that are critical to both short and long term skeletal integrity.[3–5] Subjects with higher peak bone mass after adolescence have a greater protective advantage when the inexorable decline in bone mass associated with increasing age occurs. Thus, the impact of childhood arthritis on bone health may be immediate, resulting in childhood fractures, or delayed, owing to suboptimal peak bone mass attainment or persistent disease activity.

Numerous studies suggest that there are significant bone deficits in JIA.[6] Roth *et al* recently examined children with active JIA using peripheral quantitative computed tomography (pQCT) of the forearm.[7] Subjects with polyarticular JIA had low trabecular volumetric density. Cortical bone strength deficits were noted in all JIA subtypes. Bianchi *et al* have recommended bisphosphonate treatment for prevention of osteoporosis in children with rheumatic diseases, such as JIA, who are receiving long term glucocorticoid treatment.[8]

Although imaging based studies of children with JIA are critical for characterising skeletal pathology precisely and for determining JIA characteristics associated with osteoporosis, bone density and strength estimates are surrogate measures of fracture risk. Case reports of fractures in JIA have been published.[9–12] Before the use of methotrexate and biological therapies, vertebral fractures were seen in up to 50% of children with JIA.[13] Lien *et al* studied changes in bone mass over 2 years in children with JIA and healthy controls.[14] Despite a similar percentage of fractures at baseline, a higher percentage of the JIA group had new fractures during the follow up period (9% of the JIA group *v* 5% of controls), but this difference was not statistically significant.

In recent years, investigators have used population based methods to examine the epidemiology of fractures during both childhood and adulthood.[15–20] In particular, the United Kingdom General Practice Research Database (GPRD) has been used to determine the risk of fracture attributable to glucocorticoid use and conditions such as inflammatory bowel disease and epilepsy. The purpose of this study was to determine whether a population based sample of subjects with childhood onset arthritis have an increased risk of fracture as children and as adults, compared with a healthy control group, using the GPRD.

METHODS

Data source

We conducted a retrospective cohort study using the GPRD, the largest longitudinal database of anonymised medical records from the primary care setting. Currently, there are 8.9 million patient records, and over 35 million patient years of observational data. Data collected include registration date, date of birth, sex, diagnostic codes for acute and chronic illnesses and injuries, and prescriptions provided by the primary care provider. GPRD contributors are rigorously trained, and data are subject to quality control audits to be considered "up to standard" (UTS).[21]

Abbreviations: CI, confidence interval; DMARDs, disease modifying antirheumatic drugs; DXA, dual x ray absorptiometry; GPRD, General Practice Research Database; IRR, incidence rate ratio; JIA, juvenile idiopathic arthritis; NSAIDs, non-steroidal anti-inflammatory drugs; OXMIS, Oxford Medical Information Systems; pQCT, peripheral quantitative computed tomography; RA, rheumatoid arthritis; UTS, up to standard

Table 1 Conditions and drug exposures excluded in study subjects

Exclusion criteria in patients with arthritis and controls			Exclusion criteria in controls only	
Conditions		**Drugs**	**Conditions**	**Drugs**
SLE	Behçet's disease	Antiepileptics	Uveitis	Prednisone
MCTD	IBD	Medroxyprogesterone acetate	Diabetes	Methylprednisolone
Sjögren's syndrome	Sickle cell disease	Lithium	Hyperthyroidism	Methotrexate
Scleroderma	Rheumatic fever	Cholestyramine	Hypothyroidism	Etanercept
Vasculitis	Rickets	Leuprolide	Lymphoedema	Infliximab
Sarcoidosis	Cerebral palsy	Antipsychotic drugs	Psoriasis	Anakinra
Inflammatory neuropathy	Cystic fibrosis			Leflunomide
Multiple sclerosis	Seizures			Hydroxychloroquine
Inflammatory myopathy	Asthma			Sulfasalazine
Non-inflammatory myopathy	Coeliac disease			Ciclosporin A
Osteogenesis imperfecta	Renal insufficiency			Thyroid active drugs
Organ transplant	Malignancy			

SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; IBD, inflammatory bowel disease.

Studies have demonstrated the completeness and accuracy of GPRD diagnostic and therapeutic data,[22–25] which have been used to identify chronic conditions and drug exposures associated with increased fracture rates. In a cohort of oral and non-systemic glucocorticoid users, van Staa *et al* found 87% and 91% confirmation of vertebral and hip fractures, respectively. No group differences in the proportion of confirmed fractures were seen, suggesting an absence of bias in fracture reporting due to underlying chronic illness.[26]

This study was approved by the Institutional Review Boards of the Children's Hospital of Philadelphia, the University of Pennsylvania School of Medicine, and the Scientific and Ethical Advisory Board of the GPRD.

Study population

The exposure of interest was entry of an Oxford Medical Information Systems (OXMIS)/READ diagnostic code consistent with arthritis between the ages of 1 and 19 years. This definition of arthritis was designed to identify subjects of all ages with a history of arthritis during childhood and adolescence and diminish the possibility of capturing infants with congenital or infectious arthropathies. Both incident and prevalent cases were identified, regardless of current age or disease activity.

The incidence of fracture varies by sex, age, race, socioeconomic status, and geographic region.[27] Accordingly, control subjects were matched by sex, year of birth, and practice. All sex and age matched subjects from a practice that included a subject with arthritis were included.

Identification of fractures

OXMIS/READ diagnostic codes consistent with fractures[18] were identified and classified according to anatomical location. For subjects with arthritis, the start of the follow up period began after the date of diagnosis of arthritis and when the participating practice's data were considered UTS, whichever was later. Control subjects were followed up from their registration date in the practice or the first UTS date, whichever was later. The follow up period was ended if the subject had a first fracture, if the practice was no longer UTS, if a subject left the participating practice or died.

Fractures occurring before the start of the follow up period were noted. For arthritic subjects, these fractures were defined as occurring at least 6 months before the first diagnosis of arthritis to avoid a common clinical situation where new onset arthritis may be misclassified as a fracture.

Identification of covariates and exclusion criteria

We identified codes consistent with conditions and drugs known to have an impact on bone health. Table 1 gives a list of these conditions drug exposures.

Table 2 Frequency of all arthritis diagnostic codes entered in 1939 subjects with arthritis

Arthritis codes	No	Frequency (%)	Exposed to DMARD* (%)
Arthritis	1284	39.09	7.1
Synovitis	731	22.25	0.6
Juvenile arthritis	348	10.59	14.5
Juvenile rheumatoid arthritis	305	9.28	9.8
Ankylosing spondylitis	253	7.70	9.3
Polyarthritis	187	5.69	4.4
Psoriatic arthropathy	117	3.56	12.2
Other†	60	1.83	6.3
Total	3285‡	100	–

*Subjects were categorised according to their last diagnosis of arthritis for the assessment of DMARD exposure; †codes in the ''Other'' category include: rheumatoid arthritis (RA) monitoring, rheumatoid disease, RA increased activity, spondylarthrosis, synovial cyst, and Reiter's syndrome; ‡note that there were multiple diagnostic code entries for individual subjects with arthritis.

Some conditions and drugs were considered criteria for exclusion in both the subjects with arthritis and controls. For example, subjects with epilepsy, including those treated with antiepileptic drugs have an increased risk of fracture.[20] Because epilepsy is not a direct cause or result of arthritis, subjects with epilepsy were excluded from both the arthritis and the control group. In contrast, JIA is associated with uveitis,[28] and may require the use of disease modifying antirheumatic drugs (DMARDs) to prevent visual loss. Subjects in the control group with uveitis, who also may require DMARD use, were excluded from the study, but arthritic subjects were not.

Statistical analysis

Analyses were conducted using Stata 8.2 (Stata Corporation, TX). Descriptive analyses included means, standard deviations, median and ranges of continuous variables, and distributions of categorical variables. Differences of means and medians were assessed using Student's t test or the Wilcoxon rank sum test, respectively. Group differences in categorical variables were assessed using the χ^2 or Fisher's exact test, where appropriate. Two sided tests of hypotheses were used and a p value <0.05 was considered to be significant.

Fracture incidence is dependent on sex and age in healthy children. Cooper *et al* described similar fracture rates in boys and girls under the age of 10. Thereafter, fracture rates continue to rise in boys until the peak incidence is reached at about 13–15 years.[27] We used Mantel-Haenszel methods to

Table 3 Characteristics of the study population and concurrent exposures

Characteristics	Arthritis group (n = 1939)	Control group (n = 207 072)	p Value
Female (%)	51.4	53.1	0.15
Age at 1st recorded diagnosis, mean (SD)	10.9 (5.2)	–	–
Age at start of follow up	17.3 (1–96)	19.7 (0–104)	0.005
Follow up duration (years)*	3.90 (0.003–14.0)	3.95 (0.003–14.0)	>0.2
Fracture before follow up (%)†	7.1	3.2	<0.001
DMARD treatment (%)‡	5.7	–	–
Glucocorticoid treatment (%)	4.9	–	–
NSAID treatment (%)	54.0	12.7	<0.001

Medians and ranges provided, unless otherwise noted.
*Follow up duration was calculated as follows: (date that the subject has first fracture, dies, leaves the eligible practice, or that the practice is no longer up to standard (UTS) − date of start of follow up)/365.25; †assessed as fractures during UTS or non-UTS periods; ‡DMARDs include methotrexate, ciclosporin, sulfasalazine, and tumour necrosis factor α inhibitors.

estimate the incidence rate ratio (IRR) for fracture with 95% confidence intervals (CIs) in the arthritis group, stratified by sex and age group at the start of follow up (<10 years, 10–15 years, 15–20 years, 20–45 years, and >45 years). If the Mantel-Haenszel test for heterogeneity strongly suggested heterogeneity ($p<0.10$), then effect modification was deemed to be present. For homogeneity across strata, the Mantel-Haenszel combined IRR estimate with 95% CIs is presented.

Models were constructed to assess the sensitivity of the fracture outcome according to restricted definitions of the arthritis exposure. Fracture rates were assessed in subjects with at least two arthritis diagnostic entries, in those with arthritis diagnosed only during a UTS period, and in patients with arthritis receiving non-steroidal anti-inflammatory drugs (NSAIDs). Multivariable Poisson regression models were used to determine IRR estimates for fracture when adjustment for multiple covariates, such as age category and sex, was required. Poisson regression models were checked for goodness of fit.

RESULTS

Study population

A total of 2792 (53.9% female) subjects with a history of arthritis and 303 711 (53.3% female) age, sex, and practice matched controls were identified. After the application of exclusion criteria (table 1), the study population included 1939 (51.4% female) subjects with arthritis and 207 072 (53.1% female) controls. Table 2 shows the most common diagnostic codes entered.

Table 3 details characteristics of the study population. The arthritic patients were slightly younger at the start of follow up (median age 17.3 *v* 19.7 years, $p = 0.005$), but the duration of follow up between groups was similar. Fractures before the start of the follow up period were significantly more common in the subjects with arthritis than in controls (7.1% *v* 3.2%, $p<0.001$). For the arthritic subjects, these fractures occurred either before or after arthritis onset, because both incident and prevalent subjects with arthritis are represented in the study population. The higher proportion of subjects in the arthritis group with documented NSAID prescriptions (54.0% *v* 12.7%, $p<0.001$) is consistent with arthritis treatment. A small percentage of subjects with arthritis received prescriptions for DMARDs (5.7%) and glucocorticoids (4.9%). There were significant differences in DMARD exposure according to arthritis group ($p<0.001$), with DMARD use being most prevalent in those with juvenile arthritis and psoriatic arthropathy codes recorded.

Incidence and determinants of fracture in patients with arthritis

The patients with arthritis and control subjects experienced 129 (6.7%) and 6910 (3.3%) first fractures during the follow up period, respectively ($p<0.001$). In female and male subjects, effect modification between the diagnosis of arthritis and the age category at the start of follow up on fracture risk was noted ($p = 0.05$ and $p = 0.04$, respectively; table 4). However, we did not observe effect modification by sex within the stratified age categories. The IRRs (95% CIs) for first fracture among female and male subjects with arthritis, compared with controls, according to age at the start of follow up, were 1.49 (0.91 to 2.31) for age <10 years, 3.13 (2.21 to 4.33) at 10–15 years, 1.75 (1.18 to 2.51) at 15–20 years, 1.40 (0.91 to 2.08) at 20–45 years, and 3.97 (2.23 to 6.59) at >45 years. There were no differences in these results when the subjects with ''Other'' arthritis codes were excluded from the analysis. In those initiating follow up at <20 years of age, the median disease duration at the time of first fracture was 3.6 (0.2–18.4) years.

In multivariable Poisson regression models in the subjects with arthritis accounting for age at the start of follow up and

Table 4 Incident rate ratio* for first fracture in the subjects with arthritis compared with healthy controls

Age category (years)	Female subjects	Male subjects	Combined†
<10	1.94 (0.96 to 3.48)	1.17 (0.54 to 2.24)	1.49 (0.91 to 2.31)
10–15	3.71 (1.96 to 6.42)	2.79 (1.80 to 4.15)	3.13 (2.21 to 4.33)
15–20	1.37 (0.50 to 3.02)	1.89 (1.21 to 2.84)	1.75 (1.18 to 2.51)
20–45	1.57 (0.63 to 3.26)	1.25 (0.74 to 1.98)	1.40 (0.91 to 2.08)
>45	4.25 (2.07 to 7.89)	3.15 (1.00 to 7.57)	3.97 (2.23 to 6.59)
Test for heterogeneity	p = 0.05	p = 0.04	p<0.001

*IRR (95% confidence interval); †when models were stratified by sex and age category at the start of follow up, we did not identify effect modification between the diagnosis of arthritis and sex on the risk of fracture in any age category.

Table 5 Sensitivity of fracture incidence rate ratio* estimates to more restrictive assessments of arthritis diagnoses

Age category (years)	During UTS† (n = 844)	Two diagnoses‡ (n = 381)	NSAIDs prescribed (n = 1047)
<10	1.84 (1.09 to 2.93)	0.98 (0.20 to 2.86)	1.34 (0.58 to 2.65)
10–15	2.86 (1.79 to 4.36)	2.29 (0.99 to 4.54)	2.54 (1.55 to 3.94)
15–20	1.86 (1.06 to 3.02)	1.32 (0.43 to 3.10)	1.66 (1.02 to 2.55)
20–45	–	1.03 (0.28 to 2.64)	1.40 (0.77 to 2.36)
>45	–	5.56 (1.79 to 13.17)	3.60 (1.63 to 6.95)
Test for heterogeneity	p>0.2	p = 0.04	p = 0.09
Combined estimate§	2.15 (1.65 to 2.80)	–	–

*IRR (95% confidence interval); †subjects ⩾20 years at the start of follow up were not analysed because of the small number of subjects with arthritis (n = 10, no fractures); ‡more than 6 weeks apart; §the Mantel-Haenszel combined estimate is provided when there is homogeneity across age category strata.

sex of the subject, there was a suggestion of a protective effect of DMARD treatment on fracture incidence (IRR 0.34; 95% CI 0.10 to 1.0; p = 0.063), but this effect was not significant. No significant associations between glucocorticoid (IRR 0.78; 95% CI 0.34 to 1.77; p>0.2) or NSAID treatment (IRR 0.81; 95% CI 0.57 to 1.17; p>0.2) were seen in similar multivariable Poisson regression models.

Analyses were performed to determine whether alterations in the diagnostic criteria for arthritis would impact fracture risk estimates (table 5). In subjects with arthritis diagnosed during UTS periods, we did not identify effect modification by age at the start of follow up. Effect modification by age at the start of follow up was present when considering subjects with two diagnostic codes consistent with arthritis at least 6 weeks apart (64% female), and subjects with arthritis who received NSAID treatment (58% female).

Assessment of fracture by skeletal location

Table 6 shows fracture sites in the arthritis and control groups. The anatomical distribution of fractures was consistent with a prior report using the GPRD,[27] with significant differences in the proportions of fracture between the subjects with arthritis and controls at the forearm and wrist (p<0.001), humerus and elbow (p = 0.003), femur (p = 0.005), lower leg (p<0.001), foot (p = 0.007), and ''other'' (p<0.001) categories.

Significance of fractures before the follow up interval

Fractures before the start of follow up occurred in 137 patients with arthritis and 6686 controls. Among those subjects, 12 (8.6%) patients with arthritis and 536 (6.5%) controls had a fracture during the follow up interval (p>0.2). In a multivariable Poisson regression model adjusting for arthritis diagnosis, sex, and age category at the start of follow up, a fracture before the start of follow up was a significant risk factor for future fracture (IRR 1.86; 95% CI 1.70 to 2.03; p<0.001). A similar model that included a prior fracture by arthritis interaction term showed no significant interaction (p>0.2), indicating that the added risk of fracture (86%) attributable to prior fractures is similar between subjects with arthritis and healthy controls.

Table 6 Incidence of first fracture by anatomical location

Fracture sites	Arthritis group No (%)	Control group No (%)	p Value
Vertebral	1 (0.05)	68 (0.03)	>0.2
Forearm* and wrist	36 (1.86)	1686 (0.81)	<0.001
Humerus and elbow	11 (0.57)	435 (0.21)	0.003
Femur	4 (0.21)	72 (0.03)	0.005
Lower leg and ankle†	18 (0.93)	778 (0.38)	<0.001
Hand/finger	11 (0.57)	1378 (0.67)	>0.2
Foot	14 (0.72)	706 (0.34)	0.007
Scapula/clavicle	7 (0.36)	397 (0.19)	0.09
Pelvis	0 (–)	32 (0.02)	>0.2
Rib	2 (0.10)	180 (0.09)	>0.2
Skull‡	9 (0.46)	524 (0.25)	0.07
Other§	16 (0.83)	654 (0.32)	<0.001
Total	129 (6.65)	6910 (3.34)	<0.001

*Radius and ulna; †tibia, fibula, ankle; ‡includes fractures of facial bones and nose; §includes recorded fractures that were not specific to individual bones, such as ''arm'' or ''leg'' fractures.

DISCUSSION

As far as we know, our study is the first to examine population based fracture risk in a large cohort of subjects with childhood arthritis. We demonstrated a significantly increased fracture risk in subjects with arthritis that was most pronounced during the adolescent years, when fractures are common occurrences, and after the age of 45 years, when bone mass begins to decline. The IRR for first fracture among children aged <10 years and adults between 20 and 45 years of age at the start of follow up suggested an increased fracture risk of 49% and 40%, respectively, but this did not achieve statistical significance. Fractures were more common in subjects with arthritis at clinically significant sites, such as the humerus, forearm, femur, and lower leg. The fracture risk estimates were robust in sensitivity analyses designed to maximise the specificity of the arthritis group. The sex distribution of subjects with arthritis in the sensitivity analyses was consistent with that seen in the tertiary care setting.[29]

The increased risks for fracture observed in this study are comparable to those seen in other high risk groups.[16–18 20 30–33] For example, van Staa *et al* found that patients with inflammatory bowel disease have a 59% increase in hip fracture risk.[16] In addition, because of the high rates of fractures among children in general, even modest relative risks translate into large risk differences.

About one third of children have a fracture. Using the GPRD, Cooper *et al* found that fractures are more common in boys, particularly around the time of puberty.[27] Peak fracture incidence occurred at 13–15 years in boys and 10–12 years in girls. Their estimates of forearm fracture incidence were similar to those in a study by Khosla *et al* in Minnesota,[15] which attests to the generalisability of our findings to populations outside the United Kingdom. Our study is strengthened by the use of the same fracture codes as those used by Cooper *et al* (van Staa TP, personal communication).

Throughout growth, increases in bone density and dimensions result in increased bone strength. The risk of fracture seems to be dependent on these structural determinants of bone integrity. Goulding and colleagues demonstrated that children with forearm fractures had lower dual *x* ray

absorptiometry (DXA) derived bone mass than controls.[34 35] In a pQCT study examining girls with forearm fractures, Skaggs *et al* found that despite similar cortical and trabecular density, the cross sectional area of the radius was 8% lower in the fracture group, consistent with diminished bone strength.[36]

Recent studies in children with JIA have demonstrated variable bone deficits,[6] possibly related to differences among arthritis groups, suboptimal control populations, and challenges in the analysis and interpretation of DXA and pQCT results. In general, studies have been limited by the confounding effect of short stature on DXA estimates of bone health. pQCT derived trabecular volumetric density is thought to be less susceptible to confounding by skeletal size, and the precise measurement of cortical dimensions allows for an assessment of bone strength. Roth *et al* examined children with active JIA and found low trabecular volumetric density in subjects with polyarticular disease, and both smaller periosteal dimensions and thinner cortices in all JIA subtypes.[7] These deficits occurred in association with low muscle mass, consistent with a bone disorder secondary to sarcopenia.[37] The authors suggested that effective arthritis treatment and physical activity promotion may be the optimal methods to enhance bone health in JIA.

Coordination and sedentariness also influence fracture susceptibility.[38–40] In JIA, flexion contractures, muscle weakness, and musculoskeletal pain may contribute to an abnormal gait, poor balance, and increased risk of injury.[41 42] Even in the absence of active arthritis, gait may be abnormal and peak impact during jumping may be increased and imbalanced.[43] Fusion or abnormal range of motion of the wrist in arthritis may unfavourably alter forces on an outstretched arm during a fall, amplifying the risk of fracture. The extent to which lower physical activity contributes to the risk of fracture in children with arthritis is unknown.[44]

There are limitations to our study that should be mentioned. Firstly, we chose a broad definition of childhood arthritis to identify our study population. The most common diagnostic codes were ''arthritis'' and ''synovitis,'' which potentially reflect a lack of familiarity among primary care providers with the classification of JIA.[45] Also, our study group may include children with brief episodes of reactive arthritis. However, the lack of specificity in the diagnostic codes used to identify subjects with arthritis would probably reduce the observed fracture risk. Secondly, adults who communicated a history of arthritis during childhood might not be representative because those with severe or persistent disease may have been more likely to report the diagnosis. This potential for recall bias does not negate the high fracture risk in adults reporting childhood onset arthritis, but the finding may not be generalisable to those with a history of mild or inactive disease. Additionally, these subjects were likely to have received chronic glucocorticoid treatment, placing them at increased risk for fracture.[46]

We were disappointed by the paucity of detail in the records documenting DMARD use. Possibly, DMARDs were more commonly prescribed by rheumatologists and not entered into the GPRD medication record, although this does not appear to be the case in adults with RA.[47] A survey recently revealed that 82% of family practitioners were more confident about managing arthritis in adults than in children.[45] The sparse documentation of DMARD use precluded a meaningful analysis of fracture incidence in subjects with arthritis exposed to drugs potentially associated with fracture risk. There was a suggestion that methotrexate use may be protective against fracture, but this effect was not statistically significant.

Three possibilities may explain our the observed lack of association between DMARD use and fractures. Firstly, DMARD and glucocorticoid use may be protective, because improved disease control may protect against poor bone accrual or frank bone loss. Recent studies in adults with RA support this hypothesis.[48 49] Haugeberg and colleagues recently reported that hand bone loss in RA was associated with mean C reactive protein and rheumatoid factor status, but not with age, Health Assessment Questionnaire score, or glucocorticoid use.[48] In a randomised clinical trial, Haugeberg *et al* found that glucocorticoid use was protective against bone loss in the hand.[49] In the glucocorticoid treated group, the relation between C reactive protein levels and bone loss was reduced. Secondly, some subjects with a history of severe but inactive disease may be represented in the database. These subjects were likely to remain at high risk for fracture owing to a history of poor bone accrual or low peak bone mass. Thirdly, differential misclassification of DMARD or glucocorticoid treated subjects as non-treated would potentially bias results toward the null hypothesis if these subjects were, in fact, at higher risk for fracture.

If the documentation of DMARD and glucocorticoid use in our study was accurate, the cohort presented would represent one with mild and inactive disease, presumably at lower risk of osteoporosis than more severely affected subjects with JIA. Alternatively, infrequent DMARD and glucocorticoid use in active disease would probably contribute to poor bone accrual and heightened fracture risk. Each of these two possibilities may affect the generalisability of our study. Additionally, the lack of anthropometric data in the subject records, as has been noted in a prior paediatric GPRD study,[50] precluded an analysis of body mass index as a predictor of fracture risk.

Our study sample includes the period between 1987 and 2002. Therefore, adults and the majority of children did not benefit from biological therapies. Recent improvements in disease control associated with the availability of effective drugs may protect against bone loss, augmenting peak bone mass in afflicted children. However, recent studies demonstrate a continued threat to skeletal integrity, even in the era of biological treatment.[7 14]

In conclusion, childhood arthritis is associated with a substantially increased risk of fracture that is most marked during adolescence and over the age of 45 years. Although studies of bone health in JIA have been limited by suboptimal imaging techniques and analytical challenges, this study demonstrates a significant clinical problem requiring further study. The immediate goal should be to identify children with JIA at high risk for fracture to target for clinical trials.

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