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ORIGINAL ARTICLE

Are inhaled corticosteroids associated with an increased risk of fracture in children?

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Abstract Inhaled corticosteroids are widely used in the long-term management of asthma in children. Data on the relationship between inhaled corticosteroid therapy and osteoporotic fracture are inconsistent. We address this issue in a large population-based cohort of children aged 4–17 years in the UK (the General Practice Research Database). The incidence rates of fracture among children aged 4–17 years taking inhaled corticosteroids ($n = 97{,}387$), taking bronchodilators only ($n = 70\ 984$) and a reference group ($n = 345{,}758$) were estimated. Each child with a non-vertebral fracture ($n = 23{,}984$) was subsequently matched by age, sex, practice, and calendar time to one child without a fracture. Fracture incidence was increased in children using inhaled corticosteroids, as well as in those receiving bronchodilators alone. With an average daily beclomethasone dose of 200 μg or less, the crude fracture risk relative to nonusers was 1.10 [95% confidence interval (CI), 0.96–1.26]; with dosage of 201–400 μg, it was 1.23 (95% CI, 1.08–1.39); and with dosages over 400 μg, it was 1.36 (95% CI, 1.11–1.67). This excess risk disappeared after adjustment for indicators of asthma severity. The increased risk of fracture associated with use of inhaled corticosteroids is likely to be the result of the underlying illness, rather than being directly attributable to inhaled corticosteroid therapy.

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Introduction

Asthma is a common childhood illness. Inhaled corticosteroids are frequently used in the long-term management of asthma in children. Treatment guidelines in the United Kingdom (UK) advise regular use of inhaled corticosteroids following insufficient symptomatic relief with beta$_2$-adrenoceptor stimulants [1]. The use of inhaled corticosteroids in children has consequently increased sharply over the last decade.

Oral corticosteroid therapy is associated with osteoporosis and an increased fracture risk [2]. Inhaled corticosteroid treatment may be associated with normal or reduced bone mass in children [3, 4, 5, 6, 7, 8, 9, 10, 11, 12]. Suppression of bone turnover has been demonstrated only for some markers of formation and resorption in children receiving inhaled steroids [13, 14, 15, 16]. Skeletal growth is suppressed by high doses of inhaled steroids [17]. However, growth failure can complicate poorly treated chronic asthma [18]. These data are difficult to interpret in respect of the effects of inhaled corticosteroids on skeletal integrity and fracture risk. There are as yet no data on fracture risk thresholds in relation to bone mineral density or turnover for children. Fracture, despite its frequency in childhood, has not been assessed as an outcome in children receiving inhaled corticosteroids. We postulated that inhaled corticosteroid prescription would be associated with an increased risk of fractures in children.

Materials and methods

Data source

In the UK, health care delivery is centred on general practitioners (GPs), whose responsibilities include primary health care and

specialist referrals. The information for this study was obtained from the General Practice Research Database (GPRD) that contains computerised medical records of 683 general practices across the UK [19]. Approximately 6% of the total registered population of England and Wales are represented in the database. The age and sex distribution of patients enrolled is representative of the general English and Welsh populations. The data accrued in the GPRD include demographic information (including patient's sex and year of birth), prescription details, clinical events, preventive care, referrals to specialist care, and hospital admissions and their major outcomes [19]. The data quality of each entry into the GPRD is measured against specific targets, developed by comparisons with external statistics, to ensure that research standards are met. Several independent validation studies have ascertained the high level of completeness and validity of the GPRD, and, more specifically, the recording of fractures [20, 21]. The GPRD is owned by the UK Department of Health and managed by the Medicines Control Agency.

Study population

We screened the GPRD for all permanently registered children aged 4–17 years who were prescribed a corticosteroid (oral, injections, suppositories, inhaled, skin creams, ear, eye or nose drops). Out of this population, three study groups were formed.

Group 1 cohort of users of inhaled corticosteroids comprised of children prescribed one or more courses of inhaled corticosteroids. Some of these children also received inhaled bronchodilators or oral corticosteroids or both.

Group 2 general reference cohort comprised of children prescribed non-systemic corticosteroids (topical, aural, ophthalmic or nasal) but not oral, inhaled, injectable or suppository corticosteroids. The most frequently used non-systemic corticosteroids in group 2 were skin creams (79.1% of the children).

Group 3 asthma reference cohort comprised of children prescribed bronchodilators but not inhaled corticosteroids. Some also received oral corticosteroids.

Selecting a study population based on corticosteroid prescription records ensured active registration of the children at the general practice. Children were followed from the start of data collection (1987 onwards) or from age four years (whichever date came last) until the end of data collection (December 1997) or to age 18 years (whichever date came first).

General practitioners were requested to confirm the diagnosis of fracture and to provide discharge summaries or diagnostic reports. Children who had left the practice were excluded, as their medical notes were no longer held there. We analysed returned questionnaires from 100 randomly selected children (50 from group 1 and 50 from group 2). The diagnosis of fracture was confirmed by the GP in 95.0% of the cases. Of the five other children, three had a suspected fracture that was not confirmed after further investigation. There was no ascertainment bias between groups.

Incidence analysis

We estimated the incidence rate of fracture during exposure to inhaled corticosteroid treatment. The period of exposure was taken as the time-period from start of inhaled corticosteroid treatment up to 91 days after the last prescription for group 1. A similar definition of exposure was used for group 3 (children using only bronchodilators). For group 2, the incidence rate of fracture was based on the total follow-up period.

Nested case-control analysis

We used a nested case-control analysis to evaluate any effect of corticosteroid dose on fracture risk. We compared users of inhaled corticosteroids with non-users from the two reference cohorts (groups 2 and 3). Using this design, corticosteroid exposure was measured relative to a single point in time—the date of first fracture during follow-up (index date). For each fracture case, one control patient was randomly selected, matched by age (same birth year), sex, GP practice, and calendar time (by using the same index date as for cases). If no control patient was found, the age criterion was expanded by 1 year to match patients and controls within the same practice; otherwise, children of the same age were randomly selected as controls from other practices. 99.2% of the cases were matched by practice, sex, calendar time and year of birth. Cases and controls with prior use of oral corticosteroids were excluded. The analysis was restricted to children with a non-vertebral fracture, given the very small number of children with a vertebral fracture.

The exposure to inhaled corticosteroids was based on the prescription information prior to the index date. Current users were children who had received their last inhaled corticosteroid prescription in the 3 months preceding the index date; recent users, within 3–12 months; and past users, more than 12 months prior to the index date. The daily dose of inhaled corticosteroid was obtained from the written dosage instructions for the last inhaled corticosteroid prescription prior to the index date and the strength of the metered dose inhalation or capsules. Beclomethasone dipropionate and budesonide were considered dose-equivalent. Fluticasone propionate was considered to be twice as potent as beclomethasone [22]. Three dose categories were assigned: low dose (200 μg/day or less), medium (201–400 μg/day), and high dose (more than 400 μg/day).

Statistical analysis

Incidence rates of fractures were calculated by dividing the number of cases by the total number of person-years of follow-up [23]. The adjusted relative rate (RR) was estimated using a Poisson regression model that included age and sex. In the case-control analysis, the odds ratio (OR) of fracture was calculated comparing children with and without fracture. Conditional logistic regression models included current, recent and past use of inhaled corticosteroids. The analysis was controlled for clinical variables and drug use that have been associated in adults with risk of fracture [2]. Variables that occurred at least in 1% of the study population were included [i.e. history of seizures and use in the 6 months prior to the index date of non-steroidal anti-inflammatory drugs (NSAIDs)]. Current, recent and past use of bronchodilators, hospitalisation for asthma during the 2 years preceding the index date, and number of prescriptions issued by the GP in the preceding year were also included in the regression models as indicators of asthma severity.

Bronchodilator usage was included as a measure of asthma severity. This might seem inappropriate, given the strong likelihood of co-prescribing of the two modes of therapy. However, the timing of bronchodilator prescribing was not co-linear with that of inhaled corticosteroid prescribing, thus enabling its use in adjusting for the severity of asthma in the study population.

Results

Between January 1987 and December 1997, 97,387 children (44.6% girls, mean age 9 years) were prescribed an inhaled corticosteroid preparation. The children were followed for an average of 2.5 years and median of 2.1 years after commencing inhaled corticosteroid treatment. During the follow-up period, they received an average of 7.3 inhaled corticosteroid prescriptions; 23.2% received only one inhaled corticosteroid prescription; 52.6% received four or more prescriptions. Of the children using inhaled corticosteroids, 92.9% also received prescriptions for bronchodilators and 25.9% for oral corticosteroids. 70,984 children (48.5% girls; mean average 8 years) were prescribed bronchodilators but not inhaled

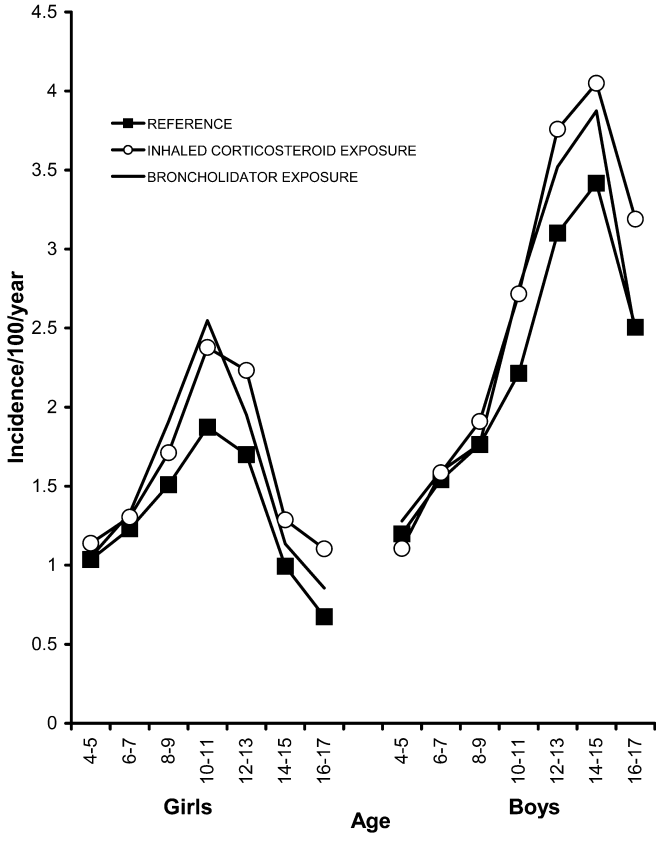

Fig. 1 Incidence of fractures during inhaled corticosteroid or bronchodilator exposure and in the reference cohort stratified by age (years) and sex

corticosteroids. The general reference cohort consisted of 345,758 children (52.9% girls, mean age 8 years). They were followed for an average and median of 3.7 and 3.5 years, respectively.

In the inhaled corticosteroid cohort, 3754 children suffered a fracture during the treatment period (rate of 2.2 fractures per 100 person-years). Figure 1 shows the fracture incidence in the reference and inhaled therapy cohorts during exposure. The incidence of fractures rises before puberty, reaches a peak around puberty, and falls thereafter. The risk of fractures for boys was generally higher than that for girls. The age- and sex-adjusted RR of fracture in the inhaled corticosteroid cohort was 1.18 [95% confidence interval (CI) 1.14–1.23] compared to the cohort of children who only used non-systemic corticosteroids. The excess fracture incidence in the inhaled corticosteroid group was apparent in both boys and girls and at most ages. Children taking inhaled corticosteroids or bronchodilators had comparable risks of fracture. The age- and sex-adjusted RR of fracture during inhaled corticosteroid exposure was 1.03 (95% CI 0.97–1.10) compared to bronchodilator exposure.

The case-control analysis included 23,984 children with a non-vertebral fracture and 23,984 controls with a similar age and sex distribution (Table 1). In all, 6271 children were prescribed inhaled corticosteroid prior to the index date. Table 2 shows the OR of non-vertebral

Table 1 Characteristics of fracture cases and controls

	Cases ($n = 23,984$)	Controls ($n = 23,984$)
Age, years		
4–9	8856 (36.9%)	8861 (36.9%)
10–13	8496 (35.4%)	8497 (35.4%)
14–17	6632 (27.7%)	6626 (27.6%)
Sex		
Girls	9344 (39.0%)	9344 (39.0%)
Boys	14,640 (61.0%)	14,640 (61.0%)
Medical history		
Seizures	647 (2.7%)	601 (2.5%)
Asthma hospitalisation in the 2 years before	69 (0.3%)	43 (0.2%)
Drug use in the 6 months before		
Bronchodilators	3063 (12.8%)	2549 (10.6%)
NSAIDs	543 (2.3%)	382 (1.6%)

fracture according to inhaled corticosteroid use. There was a small but statistically significant increase in the crude risk of non-vertebral fractures in children using inhaled corticosteroids. The crude OR for non-vertebral fracture within 3 months of inhaled corticosteroid use was 1.19 (95% CI 1.10–1.29). This excess risk disappeared after adjustment for indicators of asthma severity (adjusted OR of 1.03, 95% CI 0.93–1.15).

Children using the higher daily doses of inhaled corticosteroids and with a frequent history of past use did not have an increased risk of non-vertebral fracture (Table 3): the adjusted OR of non-vertebral fracture in these children was 1.12 (95% CI 0.84–1.48). Similarly, the ORs for children using daily doses of 800 μg beclomethasone or more were comparable to non-users (crude OR 1.43, 95% CI 1.13–1.82; adjusted OR 1.23, 95% CI 0.96–1.59) as were those for children using more than 14 inhaled corticosteroid prescriptions prior to the reference date (crude OR 1.10, 95% CI 0.93–1.30; adjusted OR 0.91, 95% CI 0.76–1.10).

Similar results were found for children using bronchodilators. There was a small but statistically significant increase in the risk of non-vertebral fracture in current users of bronchodilators (crude OR 1.19, 95% CI 1.11–1.28). This excess risk disappeared after adjustment (adjusted OR 1.10, 95% CI 1.00–1.21). The risk of past users of bronchodilators was comparable to non-users (crude OR 1.05, 95% CI 0.99–1.11; adjusted OR 1.03, 95% CI 0.97–1.09). Children using a higher dose of salbutamol (800 μg/day) also did not have an increased risk of non-vertebral fracture after adjustment (crude OR 1.22, 95% CI 1.00–1.48; adjusted OR 1.13, 95% CI 0.92–1.38).

The most frequent types of fractures were radius/ulna (8377 children), followed by carpal (4903), humerus (2318), and foot (1907). As shown in Table 4, current use of inhaled corticosteroids was associated with an increased risk of various types of fractures, such as radius/ulna, carpal, humerus, and foot. After adjustment for underlying disease and severity, no specific fracture site was associated with inhaled corticosteroid treatment.

Table 2 Use of inhaled corticosteroids and risk of fracture

Use of inhaled corticosteroids	No. of cases	No. of controls	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Non-use	20,646	21,051	Reference	Reference
Current use	1464	1266	1.19 (1.10–1.29)	1.03 (0.93–1.15)
Number of prior prescriptions				
1	211	154	1.40 (1.14–1.73)	1.27 (1.02–1.58)
2–5	527	430	1.26 (1.11–1.43)	1.10 (0.95–1.27)
6	726	682	1.10 (0.98–1.22)	0.93 (0.81–1.06)
Daily dose (beclomethasone dipropionate or equivalent), μg/day				
200	444	413	1.10 (0.96–1.26)	0.96 (0.83–1.12)
201–400	552	462	1.23 (1.08–1.39)	1.07 (0.93–1.24)
>400	216	165	1.36 (1.11–1.67)	1.17 (0.93–1.45)
Recent use	1131	972	1.20 (1.10–1.31)	1.07 (0.96–1.18)
Past use	743	695	1.11 (0.99–1.24)	1.06 (0.95–1.19)

[a]Adjusted ORs are based on multivariate conditional logistic regression models including current, recent, and past use of bronchodilators, previous asthma hospitalisation, past use of NSAIDs, history of seizures and number of prescriptions issued by the GP in the preceding year

Table 3 Current use of inhaled corticosteroids and risk of fracture stratified by daily dose and number of prior prescriptions

Daily dose (μg/day)	No. of prior prescriptions	No. of cases	No. of controls	Crude OR (95% CI)	Adjusted OR (95% CI)
200	1	77	51	1.55 (1.09–2.22)	1.43 (1.00–2.07)
	2–5	167	150	1.14 (0.91–1.42)	1.00 (0.79–1.26)
	6	200	212	0.96 (0.79–1.17)	0.82 (0.67–1.01)
201–400	1	84	70	1.22 (0.89–1.67)	1.09 (0.79–1.51)
	2–5	202	148	1.40 (1.13–1.74)	1.22 (0.97–1.54)
	6	266	244	1.12 (0.94–1.34)	0.97 (0.80–1.18)
>400	1	21	10	2.14 (1.01–4.56)	1.97 (0.93–4.20)
	2–5	73	61	1.24 (0.88–1.75)	1.09 (0.77–1.55)
	6	122	94	1.35 (1.03–1.77)	1.12 (0.84–1.48)

Table 4 Use of inhaled corticosteroids and risk of fractures at different skeletal sites

Fracture	No. of cases	No. of controls	Crude OR (95% CI)	Adjusted OR (95% CI)
Radius/ulna				
Non-use	7274	7375	Reference	Reference
Current use	479	407	1.20 (1.04–1.37)	1.06 (0.88–1.27)
Carpal				
Non-use	4104	4224	Reference	Reference
Current use	333	289	1.21 (1.02–1.42)	1.03 (0.81–1.31)
Humerus				
Non-use	2018	2070	Reference	Reference
Current use	140	112	1.31 (1.01–1.71)	1.42 (1.00–2.02)
Foot				
Non-use	1622	1677	Reference	Reference
Current use	130	100	1.37 (1.04–1.80)	0.85 (0.58–1.25)

Discussion

This study has demonstrated an increased risk of fracture in children prescribed inhaled treatment for asthma. The increased risk occurred in children receiving inhaled steroids, either alone or in combination with bronchodilators, or receiving bronchodilators alone. The increased risk of fractures also remained after removing from the analysis children treated with oral corticosteroids. Rates of fracture increased with increasing intake of inhaled corticosteroids, but the relationship disappeared after controlling for the severity of the underlying disease. Exclusion of children with a short period of time between start of data collection and index date did not change the results. The fractures were generally peripheral rather than axial as seen in classical corticosteroid-induced osteoporosis. The children who had discontinued inhaled corticosteroid treatment had fracture risks comparable to those of non-users.

Our study suggests that children with more severe disease are more likely to fracture. Mechanisms underlying the disease process, or the consequences of the disease for the body as a whole, could produce this association. Children with asthma are more likely to be overweight than are healthy children [24]. Increased weight for height is associated with reduced bone mineral density in childhood, and overweight children are over-represented in the population of children with fractures [25, 26, 27]. Obese children have a relative loss of muscle mass, so mechanical stimuli to bone mineral density accretion may be reduced. Alternatively, adipocytic rather than osteoblastic differentiation of mesenchymal precursors could limit the capacity for bone formation.

Physical activity is strongly associated with bone size, mineral density and strength in children [28, 29, 30]. Asthmatic children have lower anaerobic fitness and suboptimal cardiorespiratory performance characteristics compared with healthy children [31, 32, 33]. Although asthmatic children may participate in physical

activities as often as their peers [34], exercise limitation and lower levels of physical fitness will reduce the stimulus to increase bone size, mineral density and strength. It is tempting to speculate that children with asthma have weaker bones because of reduced physical activity in association with increased weight for height. Since neither height nor physical activity was recorded in the GPRD, we cannot directly infer from our data that these are the primary mechanisms by which fracture rates in asthmatic children are elevated. Children with exercise-induced asthma do not show a long-term increase in airway reactivity [35]. It seems logical to provide prophylactic treatment that will facilitate participation in normal childhood games and activities.

We could not obtain measurements of bone mineral density in this study. Several studies have reported that children using inhaled corticosteroids have bone mineral density comparable to that of controls [3, 4, 5, 6, 7, 8, 9, 10, 11]. A randomised clinical study of 1000 children with mild to moderate asthma found similar changes in bone mineral density in the children on budesonide and placebo [11]. In addition to concerns about the effects of inhaled corticosteroids on bone mineral density, there have been reports of growth impairment [18]. Two recent studies reported a reduction in growth velocity of some 20% during the first year of inhaled corticosteroid treatment [36, 37]; growth velocity subsequently increased, however, and the children were expected to attain a normal adult height [37].

The majority of children in this study used a daily dose of 400 μg or less of beclomethasone (or equivalent). The possibility of adverse skeletal effects of inhaled corticosteroids at much higher doses cannot be excluded. However, our data are not supportive of a clinically large fracture effect of high dose inhaled corticosteroids. In the 7.4% of children using high doses of inhaled corticosteroids (over 400 μg per day) and with a frequent history of use, the risk of fracture was comparable, after adjustment for underlying disease, to that of non-users.

In adults, we also found that inhaled corticosteroid users had a dose-related increase in risk of fracture [38]. A Cochrane meta-analysis of a small number of randomised trials in adults reported that there was no evidence of an increased risk of loss of bone mineral density or fractures [39]. However, this analysis only included patients with mild respiratory disease using inhaled corticosteroids for a short period of time. It thus did not address the possible long-term effects in elderly patients with more severe respiratory disease. Reduced bone mineral density was observed among users of inhaled corticosteroids in a large meta-analysis of clinical and also observational studies [40]. However, this meta-analysis did not adjust for severity of the underlying lung disease. The possible role of underlying disease in the aetiology of fractures is suggested by our findings in children and also adults [38] that patients using bronchodilator drugs also had increased risks of fracture compared to controls. Two recent cross-sectional studies found patients with airflow obstruction were more likely to have osteoporosis [41, 42]. This was independent of recent use of oral or inhaled GCs [41] and the results were similar after excluding patients with a past history of respiratory disease [42]. These data support the hypothesis that the underlying respiratory disease may influence the risk of fracture.

Control for confounding in this study was restricted to age, sex, and a variety of medical diagnoses and treatments. An important limitation of this study was that there were no data on the nutritional status of the children, their height, growth velocity or their physical activity. No detailed information was available on the severity of the underlying disease and the statistical adjustment was limited to presence or absence of disease or drug use. Cases and controls were not matched for disease severity, and children using inhaled corticosteroids may have had more severe disease activity. The most plausible effect of these limitations was that we were more likely to observe an increased risk of fracture in children using inhaled corticosteroids. Also, the relationship between severity on the basis of bronchodilator use and fracture risk may be a reflection of more use of bronchodilators for protection of exercise-induced asthma. Children who are more involved in physical exercise may be more likely to have fractures. Alternatively, children who are more sedentary, who might be expected to have weaker bones, might be more likely to fracture. Another possible limitation of the study is that lifetime data on oral corticosteroid use were not available. Information was restricted to the period of GPRD data collection. The fracture estimates in children using inhaled corticosteroids were adjusted for past use of oral corticosteroids as recorded in GPRD. Also, the reference group in our study consisted of children prescribed non-systemic corticosteroids. Documented prescription was a means for ensuring active registration at the practice. Users of non-systemic corticosteroids were selected because this would conservatively (downwards) bias any estimate of risk associated with inhaled corticosteroids. Exclusion of children with frequent use of non-systemic corticosteroids prior to the reference date did not modify the results. Finally, the cytokines TNFα and IL-1, elevated in the serum of asthmatics [43], promote generation of bone-resorbing osteoclasts. However, serum IL-1 and TNFα are also increased in atopic dermatitis [43]. The majority (79%) of the reference cohort were prescribed skin cream for atopic conditions such as eczema. The use of this reference cohort may have blunted associations between inflammatory processes and fracture outcome.

In conclusion, our data suggest that children using inhaled corticosteroids are at increased risk for fracture. This increased risk is more likely to be the result of the underlying illness rather than the usage of inhaled corticosteroids.

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