Original Article

Atopic Eczema–Associated Fracture Risk and Oral Corticosteroids: A Population-Based Cohort Study

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What is already known about this topic? Adults with atopic eczema, especially those with severe atopic eczema, are at increased risk of major osteoporotic fracture; however, it is unclear what drives this association.

What does this article add to our knowledge? The association between atopic eczema and major osteoporotic fractures cannot be explained by oral corticosteroid use.

How does this study impact current management guidelines? Atopic eczema, especially severe atopic eczema, should be considered for inclusion in fracture-risk screening guidelines.

BACKGROUND: Evidence suggests adults with atopic eczema have increased fracture risk. However, it is unclear whether oral corticosteroids explain the association.

OBJECTIVE: To assess to what extent oral corticosteroids mediate the relationship between atopic eczema and fractures.

METHODS: We conducted a cohort study using English primary care (Clinical Practice Research Datalink) and hospital admissions (Hospital Episode Statistics) records (1998–2016) including adults (18 years old and older) with atopic eczema matched (age, sex, and general practice) with up to 5 adults without atopic eczema. We used Cox regression to estimate hazard ratios (HRs) for specific major osteoporotic fractures (hip, spine, pelvis, or wrist) and for any-site fracture comparing individuals with atopic eczema with those without, adjusting for 6 different definitions of time-updated oral corticosteroid use (ever any prescription, ever high-dose, and recent, cumulative, current, or peak dose).

RESULTS: We identified 526,808 individuals with atopic eczema and 2,569,030 without. We saw evidence of an association between atopic eczema and major osteoporotic fractures (eg, spine HR 1.15, 99% CI 1.08–1.22; hip HR 1.11, 99% CI 1.08–1.15) that remained after additionally adjusting for oral corticosteroids (eg, cumulative corticosteroid dose: spine HR 1.09, 99% CI 1.03–1.16; hip HR 1.09, 99% CI 1.06–1.12). Fracture rates were higher in people with severe atopic eczema than in people without even after adjusting for oral corticosteroids (eg, spine HR [99% CI]: confounder-adjusted 2.31 [1.91–2.81]; additionally adjusted for cumulative dose 1.71 [1.40–2.09]).

CONCLUSIONS: Our findings suggest that little of the association between atopic eczema and major osteoporotic fractures is explained by oral corticosteroid use. © 2021 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open

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Abbreviations used
BMI- Body mass index
CPRD- Clinical Practice Research Datalink
GP- General practice
HES- Hospital Episode Statistics
HR- Hazard ratio
ICD- International Classification of Diseases
IMD- Index of Multiple Deprivation
PED- Prednisolone equivalent dose
QOF- Quality and Outcomes Framework

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Key words: *Atopic eczema; Atopic dermatitis; Fracture; Osteoporotic fracture; Oral corticosteroids*

INTRODUCTION

Atopic eczema, also referred to as atopic dermatitis, is common (affecting up to 10% of adults)[1] and characterized by rash and itching. Evidence indicates people with atopic eczema have increased fracture risk.[2-5] Our previous study showed that people with atopic eczema have 10% higher fracture risk than those without, and risk increases substantially in people with severe atopic eczema (eg, the spinal fracture risk in people with severe atopic eczema was more than twice that in people without).[6] Understanding the mechanisms behind the association between atopic eczema and fracture is important given the high morbidity and mortality associated with fractures.[7] It is possible that oral corticosteroid use may explain fracture risk in people with atopic eczema. Although current guidelines for the treatment of atopic eczema generally discourage oral corticosteroid use,[8-10] there is evidence of their frequent use in practice.[11-14] Thus, some of the effect of atopic eczema on fracture risk could be mediated through oral corticosteroids, especially in those with more severe atopic eczema, who may be treated more frequently with oral corticosteroids. Asthma, a common comorbidity in people with atopic eczema, is also commonly treated with oral steroids,[15,16] and consequently, may confound the relationship between atopic eczema and fractures.

In our previous study of atopic eczema and fracture,[6] we adjusted for both asthma and oral corticosteroid use (defined as never or ever having received a prescription for a high-dose oral corticosteroid, ie, ≥20 mg prednisolone equivalent dose [PED]/d). However, oral corticosteroids are often prescribed dynamically in relapsing and remitting diseases such as atopic eczema and asthma, with changing doses and prescription lengths,[17] so it is possible we did not adequately capture the mediating effect of oral corticosteroid use in our previous study. Further, recent evidence highlights the importance of incorporating more detailed definitions of exposure to oral corticosteroids when assessing fracture risks.[17] Understanding the role of oral corticosteroid use is clinically relevant to clarify whether atopic eczema, in the absence of oral corticosteroid use, should be considered a risk factor in bone density–screening guidelines.

Therefore, we aimed to explore the role of oral corticosteroid use in the relationship between atopic eczema and major osteoporotic fractures, including its role as a mediator using different definitions of oral corticosteroid use.

METHODS

Study design and setting

We conducted a cohort study using primary care electronic health record data from the Clinical Practice Research Datalink (CPRD) and linked hospital admissions data from Hospital Episode Statistics (HES).

Data sources

The CPRD includes over 11 million people from 674 practices in the United Kingdom.[18] The HES database contains information for all National Health Service (NHS)–funded hospital admissions in England.[19]

Study population

Our study population included adults (18 years old and older) with at least 1 year of registration with a CPRD practice between January 2, 1998, and March 31, 2016, who were eligible for HES linkage (England only). Individuals entered the atopic eczema cohort on the latest of the following: date atopic eczema diagnosis algorithm met, 18th birthday, study start date (January 2, 1998), date their practice met CPRD quality-control standards, or practice registration date plus 1 year (to allow for the accurate capture of comorbidities and lifestyle factors). We included individuals with both prevalent and incident atopic eczema (dynamic cohort approach) (Figure 1).[20]

We matched individuals with atopic eczema (without replacement) with up to 5 randomly selected individuals without atopic eczema on age, sex, general practice (GP), and date of cohort entry. Matched individuals without atopic eczema entered the cohort on the same date as the individual with atopic eczema they were matched to. People without atopic eczema with a subsequent morbidity code for atopic eczema contributed follow-up time to the cohort without atopic eczema until their first record of an atopic eczema diagnosis. Participants were followed until the earliest of: fracture diagnosis (specific fracture of interest or any fracture site depending on the outcome analyzed), death, departure from their practice, or practice no longer contributing to CPRD.

Exposures, outcomes, and covariates

We defined atopic eczema (exposure) and atopic eczema severity (secondary exposure), fractures (outcome) and covariates using primary-care (Read codes) and secondary-care (International Classification of Diseases, 10th revision) morbidity coding, and primary care prescriptions.[21] Code lists for all study variables are available for download (https://doi.org/10.17037/DATA.00001156), and variable definitions were described in detail for our previous study.[6]

Atopic eczema. We identified people with atopic eczema, based on a validated algorithm, if they had at least 1 diagnostic code for atopic eczema and at least 2 records for atopic eczema treatment on separate days (ie, topical corticosteroids, calcineurin inhibitors, cyclosporine, azathioprine, mycophenolate, or methotrexate; or phototherapy).[21,22]

Participants with atopic eczema were assumed to have mild disease by default. They were identified as having moderate atopic eczema on the date they were prescribed either potent topical corticosteroids or topical calcineurin inhibitors and severe atopic eczema when they were referred to a dermatologist, prescribed a systemic drug for the treatment of atopic eczema (ie, azathioprine, cyclosporine, methotrexate, or mycophenolate mofetil, but not including oral corticosteroids), or had a record for phototherapy.[23,24]

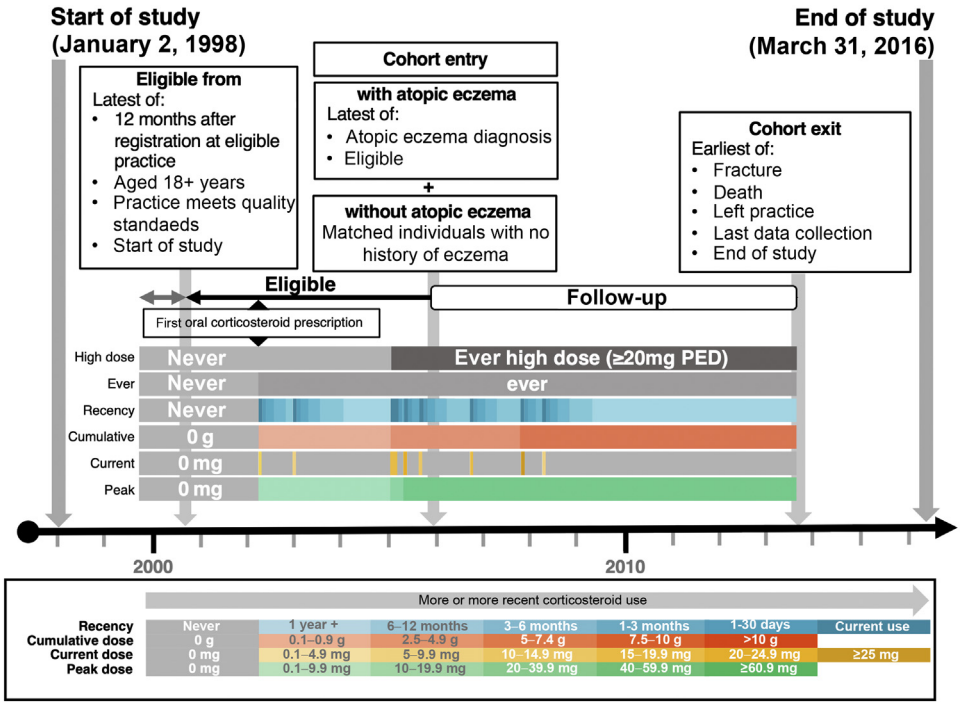

FIGURE 1. Illustration of the study cohort includes an example of how corticosteroid use was captured over time, with lighter gradients representing less or less recent and darker gradients representing more or more recent corticosteroid use.

Fracture. Our outcomes were specific major osteoporotic fractures: spine, hip (proximal femur), wrist and pelvis. Our any-fracture outcome included any fracture site, but specifically excluded surgical, allograft, autograft, neoplasm-related, and stress fractures because these were considered to be unlikely to be related to atopic eczema.[6]

Participants were followed until they first experienced a fracture at the site under analysis. We excluded participants if they had a record for a previous fracture at the same site at any time point before the start of follow-up (eg, in analyses of hip fractures, individuals were excluded if they had a hip fracture before cohort entry) because previous fractures greatly increase the risk of subsequent fracture at the same site.[25]

Covariates. We used quintiles of Index of Multiple Deprivation (IMD) to assess deprivation.[26] We used individual-level IMD data and supplemented with practice-level IMD data if individual-level data were unavailable. We identified asthma (presence/absence) using primary-care morbidity coding updating asthma status on the first date of a relevant diagnostic code. We defined body mass index (BMI) and smoking status (never/ever) using primary-care records close to cohort entry, as described in detail for our previous study.[6,27] We identified participants as harmful alcohol users from their first record for a morbidity code suggesting harmful alcohol use or if they had a prescription for drugs used to maintain abstinence. Justifications for the inclusion of covariates, and the basis of their categorization, are provided in the online repository (Appendix 1; available in this article's Online Repository at www.jaci-inpractice.org).

We identified primary-care prescriptions for oral corticosteroids with glucocorticoid activity (prednisolone, betamethasone, deflazacort, dexamethasone, hydrocortisone, methylprednisolone, prednisone, triamcinolone, and cortisone) and calculated the PED in milligrams (mg)/d. In addition to the definition of high-dose oral corticosteroid use we used in our previous study (ie, ≥20 mg PED/d),[6] we identified 5 different time-updated measures of oral corticosteroid use: ever-prescribed an oral corticosteroid, recent dose, cumulative dose, current prescription, and peak dose (Table I).[17]

Modelling strategy. We used a directed acyclic graph to visualize our *a priori* assumptions about the potential mechanisms explaining any link between atopic eczema and fractures and to guide selection of confounders and mediators for use in adjusted regression models (Figure E1; available in this article's Online Repository at www.jaci-inpractice.org). We drew paths using prior knowledge and existing literature.[1,28-34]

Statistical analyses

Main analyses. We used Cox proportional hazards regression, stratifying on matched set, to estimate hazard ratios (HRs) for the effect of atopic eczema on fractures. Our analyses implicitly adjusted for age, sex, practice, and date of cohort entry through matching and underlying timescale (age), and additionally adjusted (confounder-adjusted model) for calendar time (1997−2001, 2002−2006, 2007−2011, and 2012−2016), asthma and IMD quintiles. To estimate the effect of atopic eczema that was not mediated through oral corticosteroid use, we additionally adjusted for 6 different definitions of corticosteroid use (1, ever vs never; 2, high-dose [>20 mg PED/d] vs never; 3, recent prescription; 4, cumulative dose; 5, current dose; and 6, peak dose) in 6 separate models.[17]

Sensitivity analyses

We undertook sensitivity analyses to examine whether a different cumulative dose definition or the addition of ethnicity as a covariate affected our results (Tables E1 and E2 and "Sensitivity analysis:

TABLE I. Different oral corticosteroid use definitions

Definition	Description	Categories
Original high-dose oral corticosteroid definition[6]	Ever or never having received a prescription for ≥ 20 mg/d PED Updated on the date of the first recorded high-dose oral corticosteroid prescription	Never, ever
Ever vs never	Ever or never having received any prescription for oral corticosteroids Updated on the date of the first recorded prescription	Never, ever
Recency	Has a current active prescription (ie, between start and end of prescription date), or time since the last prescription end date	Never 1 y+ (>365 d) 6−12 mo (181−365 d) 3−6 mo (91−180 d) 1−3 mo (31−90 d) 1−30 d Current
Cumulative dose	Sum of all corticosteroid doses prescribed, based on prescription length and daily PED Updated at the start of prescriptions, adding the entirety of the prescription dose to the cumulative dose at once	0 g 0.1−0.9 g 1−2.4 g 2.5−4.9 g 5−7.4 g 7.5−9.9 g ≥10 g
Current dose	Prescribed daily PED, categorized at start of an oral corticosteroid prescription, and then set back to 0 at the end of the prescription	0 mg (ie, no current prescription) 0.1−4.9 mg 5−9.9 mg 10−14.9 mg 15−19.9 mg 20−24.9 mg ≥25 mg
Peak dose	Highest daily PED recorded Category updated if a prescription with a higher dose than any previous prescription was recorded	0 mg 0.1−9.9 mg 10−19.9 mg 20−39.9 mg 40−59.9 mg ≥60 mg

PED, Prednisolone equivalent dose.

inclusion of ethnicity as a covariate"; available in this article's Online Repository at www.jaci-inpractice.org).

Secondary analyses

Atopic eczema severity. To explore the effect of atopic eczema severity on fracture risk, we compared people with time-updated mild, moderate, or severe atopic eczema with people with no atopic eczema.

Rate differences

We calculated rate differences from fracture incidence rates for different fractures in those with and without atopic eczema. The incidence rate of specific fractures in participants without atopic eczema was estimated as the incidence rate of those with atopic eczema multiplied by the inverse of the HR of the confounder-adjusted model with cumulative dose (r*(1/HR)) (Table E3; available in this article's Online Repository at www.jaci-inpractice.org).

We used 99% CIs throughout the study to minimize the risk of type I error. We used Stata version 15 (StataCorp) for initial data management, and R version 3.5.2 for further data management and statistical analyses.[35,36]

The study was approved by CPRD's Independent Scientific Advisory Committee (ISAC Protocol Number: 16_100RA).

RESULTS

We identified 525,923 individuals with atopic eczema and 2,562,334 matched participants without (Figure 2). Individuals with and without atopic eczema were broadly similar in terms of age, sex, BMI, smoking status, and IMD (Table II). Those with atopic eczema were more likely to have asthma (27.7% vs 15.0%) and at least 1 prescription for oral corticosteroids (27.8% vs 14.1%).

Main analysis

In minimally adjusted (implicitly adjusted for age, sex, GP, and date of cohort entry) Cox models, those with atopic eczema compared with those without atopic eczema had higher risk of fracture (eg, spine HR 1.19, 99% CI 1.12−1.26; hip HR 1.13, 99% CI 1.05−1.21). After additionally adjusting for calendar time, IMD, and asthma, the effect of atopic eczema on fracture risk somewhat attenuated (eg, spine HR 1.15, 99% CI 1.08−1.22; hip HR 1.11 99% CI 1.08−1.15) (Table E4; available in this article's Online Repository at www.jaci-inpractice.org). After further adjusting for oral corticosteroid use, there was still evidence of increased fracture risk in people with atopic eczema compared with those without (eg, adjusted for never vs ever use: spine HR 1.09, 99% CI 1.03−1.16; hip HR 1.09, 99% CI 1.06−1.12) (Figure 3). Across all fracture sites, adjustment for high versus never and current dose

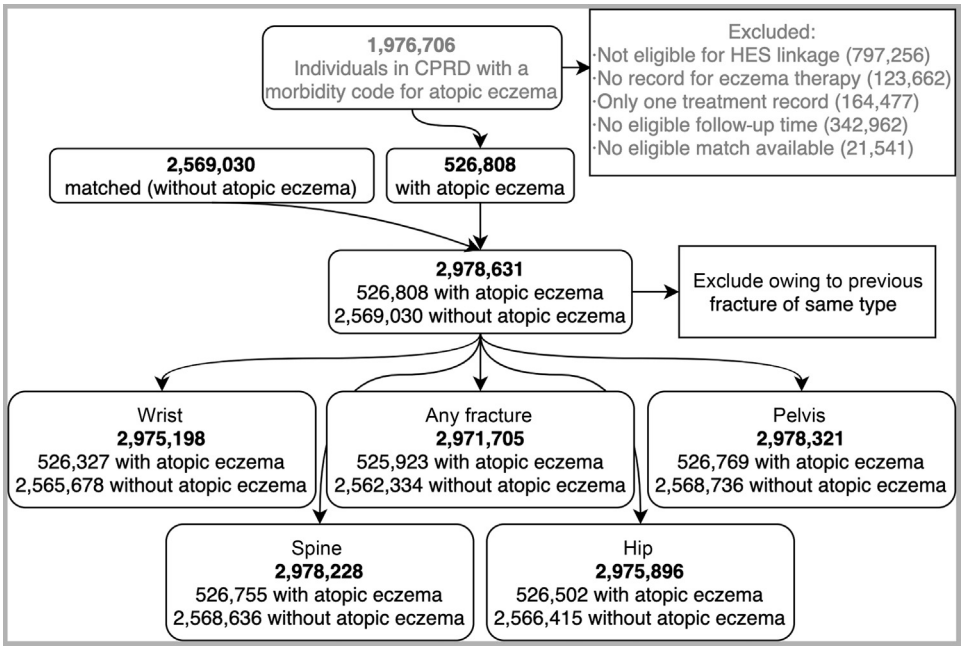

FIGURE 2. Study flow diagram. The dataset used for this study contained the 526,808 individuals with atopic eczema and matched 2,569,030 individuals without atopic eczema that remained after exclusions. Participants with a previous fracture at the same site were excluded. For the analysis of specific fractures, only those that had a previous fracture of the fracture type of interest were excluded.

corresponded to lower levels of attenuation whereas adjustment for the remaining definitions corresponded to greater levels of attenuation, although the extent of between-definition variability in attenuation differed by site and CIs for different definitions overlapped.

Sensitivity analyses

Results from analyses using a different definition for cumulative corticosteroid dose were similar to those in the main analysis (Table E1). After additionally adjusting for ethnicity and restricting to individuals entering the cohort from 2006, effect estimates for the association between atopic eczema and pelvis, hip, spine, and wrist fractures were attenuated and CIs crossed the null, in both confounder-adjusted models and models additionally adjusting for cumulative oral corticosteroid dose (Table E2 and Appendix 2; available in this article's Online Repository at www.jaci-inpractice.org). The restricted study population (with cohort entry dates from 2006) differed from the main study cohort, with individuals being on average younger (Table E5; available in this article's Online Repository at www.jaci-inpractice.org).

Secondary analyses

Atopic eczema severity. Fracture risk increased with increasing atopic eczema severity (eg, confounder-adjusted HRs [99% CIs] for spinal fractures compared with no atopic eczema: mild 1.03 [0.95−1.12], moderate 1.14 [1.04−1.25], severe 2.31 [1.91−2.81]) (Figure 4 and Table E6; available in this article's Online Repository at www.jaci-inpractice.org). Additionally adjusting for oral corticosteroid use somewhat attenuated effect estimates (eg, HRs [99% CIs] for spine fractures additionally adjusting for cumulative oral corticosteroid dose compared with no atopic eczema: mild 1.00 [0.92−1.08], moderate 1.11 [1.01−1.22], severe 1.71 [1.40−2.09]). Regardless of the definition used for oral corticosteroid use, we saw a link between increasing severity of atopic eczema and increasing fracture risk.

Rate differences. After adjusting for confounders and oral corticosteroid use, we estimated that among those with atopic eczema between 0.07 (wrist) and 0.35 (hip) site-specific fractures per 1,000 person years were attributable to atopic eczema (Table E3).

DISCUSSION

We found evidence of an association between atopic eczema and major osteoporotic fractures that persisted after adjusting for oral corticosteroids regardless of how oral corticosteroid use was defined. The link between atopic eczema and fractures was greater in more severe atopic eczema and varied by fracture site, with spinal fractures being more than twice as common in those with severe atopic eczema compared with people without atopic eczema. Evidence of an association between atopic eczema and fracture risk remained after adjusting for oral corticosteroid use, indicating that only some of the association between atopic eczema and fracture risk could be explained by oral corticosteroid use. After adjusting for oral corticosteroids, the attenuation of the association between atopic eczema and fractures was greater in people with severe atopic eczema (ie, when additionally adjusting for oral corticosteroids the effect estimate decreased more in people with severe atopic eczema than for those with moderate or mild atopic eczema), potentially owing to more frequent use of oral corticosteroids in severe atopic eczema.

Results in context

Our results offer insight into the role of oral corticosteroids in the association between atopic eczema and fracture. Whereas a

TABLE II. Characteristics of participants*

Characteristic	Without atopic eczema (n = 2,569,030)	With atopic eczema (n = 526,808)
Age, y		
18–39	1,217,722 (47.4)	246,596 (46.8)
40–49	351,927 (13.7)	69,696 (13.2)
50–59	329,007 (12.8)	63,943 (12.1)
60–69	303,790 (11.8)	61,902 (11.8)
≥70	366,584 (14.3)	84,671 (16.1)
Sex female	1,489,261 (58.0)	308,071 (58.5)
IMD†		
1 (least deprived)	611,904 (23.8)	126,806 (24.1)
2	589,313 (22.9)	120,946 (23.0)
3	508,469 (19.8)	103,646 (19.7)
4	489,144 (19.0)	100,430 (19.1)
5 (most deprived)	370,200 (14.4)	74,980 (14.2)
Total follow-up, p-y (%)	14,118,405 (100)	3,102,202 (100)
Median follow-up, y (IQR)	4.41 (1.70–8.90)	5.02 (2.00–9.64)
Asthma, p-y (%)	1,872,813 (12.5)	780,567 (23.6)
Any oral steroids, p-y (%)	1,585,726 (10.6%)	723,365 (21.9)
High-dose oral steroids,‡ p-y (%)	849,832 (5.7%)	396,332 (12.0)
Cumulative dose, p-y (%)		
0 g	12,535,009 (83.9)	2,379,540 (71.9)
0.1–0.9 g	1,108,362 (7.4)	503,272 (15.2)
1–2.4 g	204,979 (1.4)	102,161 (3.1)
2.5–4.9 g	110,409 (0.7)	50,918 (1.5)
5–7.4 g	50,360 (0.3)	22,065 (0.7)
7.5–10 g	29,600 (0.2)	12,731 (0.4)
>10 g	79,687 (0.5)	31,515 (1.0)
Peak dose, p-y (%)		
0 mg	12,535,610 (83.9)	2,379,748 (71.9)
0.1–9.9 mg	368,976 (2.5)	150,459 (4.5)
10–19.9 mg	159,699 (1.1)	68,647 (2.1)
20–39.9 mg	747,918 (5.0)	349,456 (10.6)
40–59.9 mg	294,671 (2.0)	148,464 (4.5)
>60 mg	11,532 (0.1)	5,428 (0.2)

IMD, Index of Multiple Deprivation; p-y, person-years.
*Data are n (%) unless otherwise specified. Age, sex, and IMD were assessed at the beginning of follow-up. Person-years throughout follow-up are displayed for time-updated variables.
†Quintiles of the IMD.
‡High-dose oral corticosteroids are defined as ever having been prescribed a PED of > 20 mg/d.

number of other studies describe an association between atopic eczema and worse bone health, insight into the impact of oral corticosteroids on the relationship, until now, has been limited, as described in a recent systematic review.[5] Of the studies included in the review, only our previous study[6] and 1 other population-based cohort study from Taiwan[2] adjusted analyses for oral corticosteroid use, both using definitions that classified steroid use into categories of never or ever.

Results from a recent Danish study suggest that the use of high cumulative doses of potent topical corticosteroids could be associated with increased risk of major osteoporotic fractures, albeit with small effect sizes (3% relative risk increase per doubling of cumulative topical corticosteroid dose).[37] The Danish study's observed role of topical steroids in the association between atopic eczema and fractures could be explained by confounding by indication (ie, those receiving the highest cumulative doses of topical steroids are also those with the most severe disease) or residual confounding through oral corticosteroids, BMI, or other covariates that were not accounted for in the study. However, topical corticosteroids may still explain some of the association between atopic eczema and fracture risk that we found. Our definition of atopic eczema severity included prescriptions for topical corticosteroids and may, therefore, to some extent have captured the effect of topical corticosteroids on the association between atopic eczema and fracture.

Strengths and limitations

Our study uses a large population-based cohort from a data source that contains information on key variables. Using detailed definitions of oral corticosteroid use allowed us to address to what degree oral corticosteroid use might explain the previously observed relationship between atopic eczema and fracture risk.[5]

The results of our study are likely to be generalizable to the general population of England because CPRD covers a

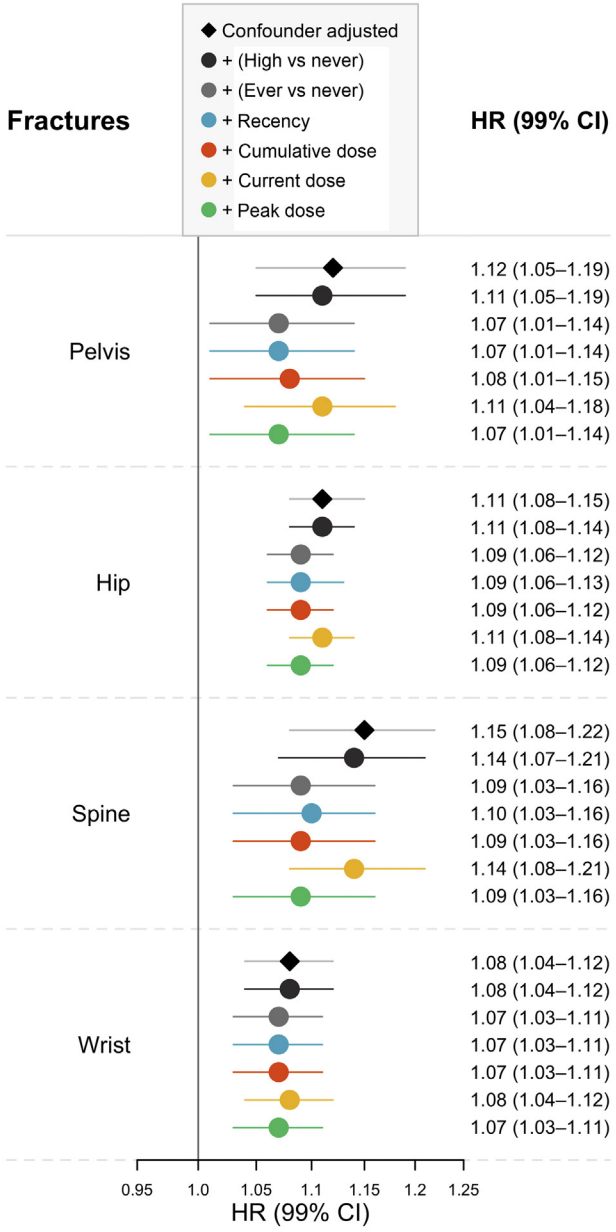

FIGURE 3. Hazard ratios (HR) with 99% CI for risk of fracture in people with atopic eczema compared with people without in confounder-adjusted models additionally adjusted for different definitions of oral corticosteroid use. HRs estimated using Cox regression implicitly adjusted for age, sex, GP, and date of cohort entry (owing to matching and underlying timescale), and explicitly adjusted for calendar period, IMD, and asthma (confounder-adjusted). Number of fracture events recorded in those with atopic eczema: spine 3,327; hip 13,709; pelvis: 3,151; wrist 7,737.

population that is broadly representative of the English general population in terms of age, sex, and ethnicity.[18]

The association we saw between atopic eczema and fracture could be explained by mediation through other potential observed (ie, harmful alcohol use, smoking, BMI) and unobserved mediators (Figure 2), potentially including physical activity, osteoporosis, sleep impairment, and fatigue or daytime sleepiness (owing to nighttime itching or the use of sedating antihistamines to manage the sleep problems associated with the itch of atopic eczema).[38] Our study did not directly account for topical corticosteroid use. Accurate capture of topical steroid use using health record data is complex because it depends on prescribed dose, treatment adherence, and skin integrity. However, we were able to partially account for the effect of topical corticosteroids in our atopic eczema severity analyses because our moderate atopic eczema definition included potent topical corticosteroid prescriptions.

Atopic eczema is a relapsing and remitting condition; therefore, our severity definition may not have adequately captured changing disease severity over time (because our definition did not allow individuals to return to a lower severity status). In not allowing individuals with more severe atopic eczema to be returned to a lower severity status, we may have wrongly classified individuals with milder atopic eczema as having more severe disease. However, this would only bias our results to the null, meaning that the findings of our severity analyses are likely to be underestimates of the true effect of atopic eczema severity on fracture risk.

We used routinely collected health records to define atopic eczema severity based on prescribed drugs and therapies, rather than a standardized clinical severity score (because these definitions are not available in routine data).[39] Our severity definition has been used in previous electronic health record studies and demonstrates a similar distribution of mild, moderate, or severe atopic eczema to those seen using clinical severity definitions.[6,40,41] Therefore, we believe our severity definition is appropriate in this context but encourage efforts to standardize severity definitions for electronic health records research.

However, there is some potential for misclassification of atopic eczema severity in our severity definition, possibly biasing effect estimates. Individuals can only step up in severity, but not step down (ie, once an individual is classified as having moderate or severe atopic eczema, they cannot be reclassified as having a milder form of atopic eczema). Therefore, individuals with remitted disease may be misclassified as having more severe disease. Conversely, individuals with more severe atopic eczema may be misclassified as having milder disease if they do not regularly consult their doctor for help with their condition.

We identified time-updated cumulative oral corticosteroid dose at the beginning of each prescription, adding the dose of the entirety of the respective prescription duration on the date of prescription (so cumulative dose status changed at the beginning of the prescription that initiated the increase in cumulative dose). It is likely that time-updating cumulative dose status more frequently (eg, daily) would have little impact on our estimates because most prescription lengths are not long enough to lead to multiple changes in categories (median prescription duration: 28 days). However, results were similar in sensitivity analyses using the alternative approach of updating cumulative dose at the end of each prescription (Table E1).

There is potential for wrongly identifying individuals as taking corticosteroid drugs owing to them not adhering to prescribed corticosteroid treatment; we were unable to assess adherence. Most participants receiving oral corticosteroid prescriptions received more than 1 prescription (60.8%), implying that previous prescriptions were used. There remains some potential for misclassification in those with the most infrequent prescriptions; however, we attempted to mitigate this by using detailed time-updated definitions of oral corticosteroid use (recency, cumulative, current, and peak dose), which limits the potential periods of misclassification to the length of the prescription.

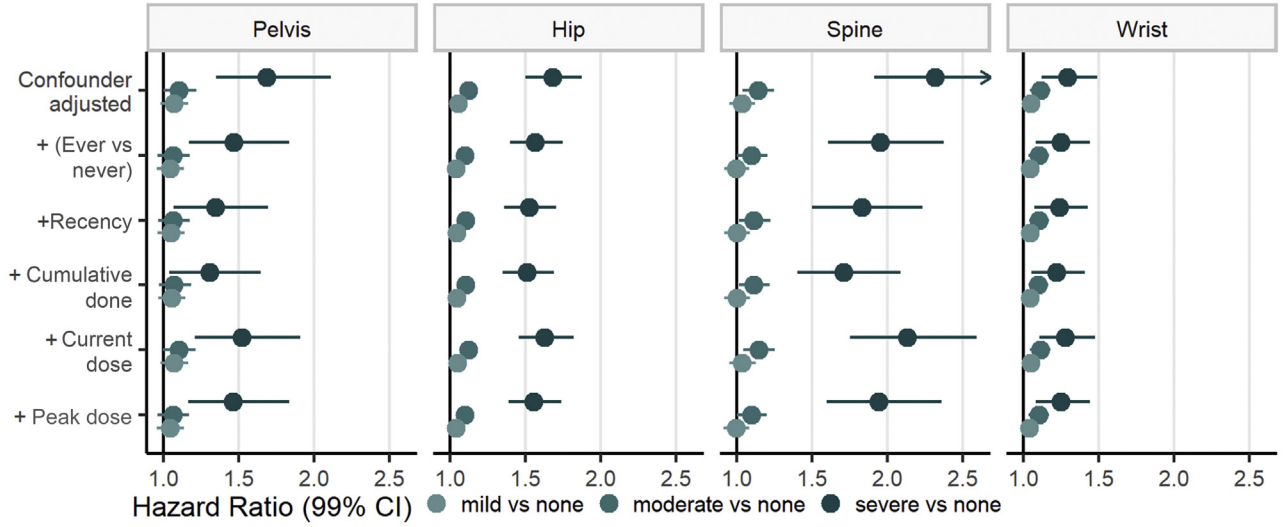

FIGURE 4. Hazard ratios with 99% CIs comparing fracture risk for different fracture types in people with mild/moderate/severe atopic eczema with people without atopic eczema. Points with error bars are colored by atopic eczema severity. Estimates from the confounder-adjusted models (implicitly adjusted for age, sex, GP, and date of cohort entry, and explicitly adjusted for calendar period, IMD, and asthma) and additionally adjusted for different definitions of oral corticosteroid use are shown. All estimates including estimates for any fracture site can be found in Table E6.

Participants with atopic eczema were identified based on an algorithm, with a positive predictive value of 82%.[6,22] It is possible that a small number of individuals without atopic eczema may have been wrongly identified as having atopic eczema. However, it is unlikely any misclassification of atopic eczema status is related to fracture recording, so our estimates will only be biased toward the null. Further, a sensitivity analysis in our previous study using a broader atopic eczema definition showed similar results.[6] Fractures are seldom missed in primary or secondary care. However, spinal fractures can go undiagnosed.[42,43] Spinal fractures are more likely to be detected for participants with more frequent GP consultations, which is likely to be the case for those with atopic eczema, and especially for those with severe atopic eczema. Some of the effect of atopic eczema on spinal fractures might, therefore, be explained by more frequent GP attendance. However, a sensitivity analysis in our previous study, restricting to participants who had attended their GP practice in the year before cohort entry, found only minimal differences in results.[6]

We did not explore the relationship between atopic eczema and osteoporosis because osteoporosis diagnoses and results from bone mineral density measurements are not robustly and systematically captured in routine health data, with higher-risk individuals more likely to have a record for either. There is potential for residual confounding in this study. Data from CPRD do not provide robust information on vitamin D level, food allergy or intolerance, malnourishment, or eating disorders.[6]

Clinical interpretation

Our results indicate that the increased fracture risk in people with atopic eczema cannot be explained by oral corticosteroid use alone. Explanations for the link we saw between atopic eczema and fracture include chronic inflammation associated with atopic eczema, changed diet linked to food intolerances, or avoidance of physical activity because sweating can exacerbate atopic eczema symptoms, leading to osteoporosis and, in turn, to fractures.[44] Other possible explanations for increased fracture risk are increased rates of harmful alcohol use or the use of sedating antihistamines leading to falls. The fracture outcomes used in this study are considered to be commonly associated with osteoporosis.[45] Major osteoporotic fractures are associated with high morbidity and mortality, leading to, among other things, immobility, restriction of activities of daily living, and thromboembolic disease. If atopic eczema increases the risk of these fractures, then considering including atopic eczema in guidelines for fracture prevention and encouraging the appropriate preventive care could substantially reduce fracture-related morbidity and mortality in people with atopic eczema. Given that atopic eczema is common, preventing associated fractures would represent an important public health intervention.

Importantly, our results do not suggest that oral corticosteroids do not contribute to at least some of the association between atopic eczema and fracture or that oral corticosteroids for atopic eczema management is unproblematic. In line with current atopic eczema management guidelines, which reserve the use of oral corticosteroids for exceptional circumstances, clinicians should continue to avoid oral corticosteroids for atopic eczema.[10]

In sensitivity analyses additionally adjusting for ethnicity and restricting to those entering the study population from 2006 onward (when ethnicity data was more likely to be complete[46]), our effect estimates were attenuated. This attenuation of effect after adjusting for ethnicity may be explained by the younger population in the restricted sample (see "Sensitivity analysis: inclusion of ethnicity as a covariate" and Table E5).

Policy implications and future research

Current guidance recommends fracture-risk screening in people taking oral corticosteroids but does not specifically reference atopic eczema.[47-49] Our results indicate that atopic eczema, especially severe atopic eczema, should be considered for

inclusion in fracture-risk screening guidelines. Further research should explore why there is a link between atopic eczema and fracture, including the role of topical corticosteroids.

In summary, we found that the association between atopic eczema and major osteoporotic fractures was not explained by oral corticosteroid use. Consideration should be given to adding atopic eczema to fracture-risk screening guidance.

Acknowledgments

This study is based on data from the CPRD obtained under license from the U.K. Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the National Health Service (NHS) as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. The study was approved by the Independent Scientific Advisory Committee (ISAC Protocol Number 16_100RA). The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funders.

J. Matthewman, K. E. Mansfield, and S. M. Langan were responsible for the conception and design of the study. K. E. Mansfield and J. Matthewman were responsible for acquisition of data. J. Matthewman, K. E. Mansfield, D. Pietro-Alhambra, A. R. Mulick, L. Smeeth, R. J. Silverwood, and S. M. Langan were responsible for analysis and interpretation of data. J. Matthewman, K. E. Mansfield, and S. M. Langan were responsible for drafting the article. J. Matthewman, K. E. Mansfield, D. Pietro-Alhambra, A. R. Mulick, L. Smeeth, K. E. Lowe, R. J. Silverwood, and S. M, Langan revised the article. J. Matthewman, K. E. Mansfield, D. Pietro-Alhambra, A. R. Mulick, L. Smeeth, K. E. Lowe, R. J. Silverwood, and S. M. Langan had final approval.

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ONLINE REPOSITORY

Appendix 1

Justifications for the inclusion of covariates and the basis of their categorization

Deprivation. Deprivation (conceptually related to lower socioeconomic status) has been found to be associated with higher risk of low bone density and a lower risk of atopic eczema.[E1-E5] We have, therefore, assumed that deprivation is a confounder, affecting multiple other variables. We used quintiles on the index of multiple deprivation (IMD), which aims to measure the relative deprivation between small geographic areas in England. The IMD is based on income, employment, education, health, crime, barriers to health and services, and living environment.[E6] We used individual level IMD data, with practice-level IMD data used only when individual-level data were not available.

Calendar time. We addressed changes over time in treatment, diagnostic and coding practices, and environmental exposures by considering calendar time as a confounder. We split calendar time into the following time bands: 1997−2001, 2002−2006, 2007−2011, and 2012−2016. We included a deliberate split at 2012 as indicators of secondary fragility fracture prevention (related to osteoporosis) were added to the Quality and Outcomes Framework (QOF) that year.[E7] Inclusion of indicators in the QOF (which is responsible for incentivizing the recording of specific codes in U.K. primary care[E8]) could have led to changes in recording and screening practices.[E9]

Asthma. Asthma is a common comorbidity in people with atopic eczema, being related to atopic eczema through a common ancestor (atopy or genetics).[E10,E11] Inhaled corticosteroids are often used to treat asthma, which might lead to increased fracture risk and lower bone density at high doses[E12,E13]; however, there is no clear evidence of this effect at lower doses, even when used long term.[E13-E17] Asthma serves as a proxy for inhaled corticosteroid use because records of prescriptions only poorly reflect the actual use of inhaled corticosteroids because these are often prescribed "to be taken as needed." As with atopic eczema, owing to the adverse effects linked to oral steroids, oral (or other systemic) steroids for the treatment of asthma should be reserved for scenarios in which other treatments, including inhaled steroids, fail. Nevertheless, oral steroids were used extensively in the past for the treatment of asthma, especially before the advent of inhaled steroids, and are still used in many cases today.[E18,E19] Therefore, we considered asthma to be a confounder, with oral steroid use likely accounting for most of its confounding effect, and inhaled steroid use and the effect of asthma on body mass index (BMI)[E20] playing smaller roles. Adjusting for asthma blocks these confounding paths (however, a mediating path via oral steroids prescribed for atopic eczema remains open). We included asthma as a time-updated covariate. Asthma is an indicator in the QOF and should, therefore, be well captured in Clinical Practice Research Datalink (CPRD).[E7]

Body mass index. The BMI is associated with osteoporosis, with underweight individuals at a higher risk. The protective effect of increasing weight is likely due to the strengthening effect on bones over time owing to increased impact forces.[E21,E22]

The BMI is likely to mediate some of the effect of atopic eczema on fractures. There are multiple plausible mechanisms through which BMI may mediate the effect of atopic eczema on fractures, including diet, oral corticosteroids, and physical activity.[E21,E23-E25] We therefore considered BMI as a mediator in this study and included it as a covariate in models estimating the direct effect of atopic eczema.

Participants were categorized according to World Health organization (WHO) guidelines into group of underweight (BMI < 18.5 kg/m^2), normal weight (18.5−25 kg/m^2), overweight (25−30 kg/m2), and obese (>30 kg/m^2). The BMI was defined based on the record closest to index date with records within the year before to 1 month after index date preferred, then records from 1 month to 1 year after index date, then the most recent record prior to 12 months before index date, and then records within a year from index date.

Smoking. Smoking is associated with reduced bone density and, therefore, increased fracture risk.[E26] Individuals with atopic eczema are also more likely to be smokers.[E27] We, therefore, consider smoking to be a mediator in our analyses. Participants were categorized as either never-smokers or ever-smokers (current or former smokers), based on the closest record of smoking status to cohort entry. Smoking status was defined based on the record closest to index date with records within the year before to 1 month after index date preferred, then records from 1 month to 1 year after index date, then the most recent record prior to 12 months before index date, and then records within a year from index date.

Harmful alcohol use. Harmful alcohol use is associated with fracture risk,[E28-E30] and people with atopic eczema have also been found to be at higher risk of harmful alcohol use,[E31] making it a potential mediator. We used primary-care records for relevant morbidity and prescription codes (for drugs used to deter people from alcohol use) that suggested harmful alcohol use and categorized individuals as harmful alcohol users from their first primary-care record suggesting harmful alcohol use. We considered that harmful alcohol use was likely to mediate the effect of atopic eczema on fracture through increased rates of accidents and not via osteoporosis.

Appendix 2

Sensitivity analysis: inclusion of ethnicity as a covariate

We identified ethnicity (White, South Asian, Black, and other or mixed) from primary care (CPRD) and hospital admissions (Hospital Episode Statistics [HES]) data using a previously developed algorithm.[E32] To explore whether including ethnicity in models had an impact on the effect estimates, we performed sensitivity analyses including ethnicity and restricting to individuals entering the cohort from 2006 (when ethnicity data was more likely to be complete, owing to its recording being incentivized in the QOF).[E32] Effect estimates from confounder-adjusted and additionally corticosteroid-adjusted models for the association between atopic eczema and pelvis, hip, spine, and wrist fractures were attenuated and CIs crossed the null when ethnicity was added to the models (Table E2). However, effect estimates from confounder-adjusted and additionally corticosteroids-adjusted models using the restricted population also showed attenuated effect estimates without the addition of ethnicity as a

covariate. Therefore, the results of the sensitivity analysis could be explained through differences in population structure rather than through an effect of ethnicity. We found that, in the population with follow-up from 2006 onward, individuals were on average younger at baseline compared with the main analysis (Table E5).

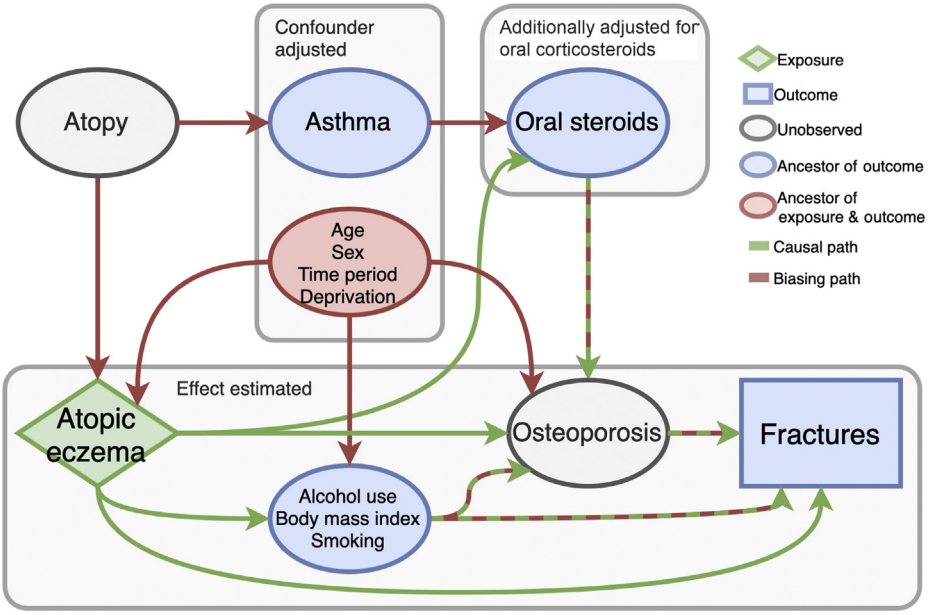

FIGURE E1. Directed acyclic graph shows the hypothesized relationships between exposure (eczema), outcome (fractures), and measured and unmeasured covariates. The variables that are included in the main study models are marked, as is the effect estimated when adjusting for these variables.

TABLE E1. Sensitivity analysis using a different definition of cumulative dose

		HR (99% CI) for fracture risk comparing those with atopic eczema with those without, adjusted for confounders* and additionally adjusted for cumulative oral steroid dose				
Analysis	**Justification**	**Pelvis**	**Hip**	**Spine**	**Wrist**	**Any site**
Main analysis	Included for comparison with results of sensitivity analysis	1.08 (1.01−1.15)	1.09 (1.06−1.12)	1.09 (1.03−1.16)	1.07 (1.03−1.11)	1.09 (1.08−1.11)
Analysis in which cumulative dose for oral corticosteroid exposure was updated at the end of each respective prescription instead of at the beginning.	To explore whether changing the definition has any major impact on the effect estimates	1.07 (1.01−1.14)	1.09 (1.06−1.12)	1.09 (1.03−1.16)	1.07 (1.03−1.11)	1.09 (1.08−1.10)

*Implicitly adjusted for age, sex, GP, and date of cohort entry and additionally adjusted for time period (1997−2001, 2002−2006, 2007−2011, and 2012−2016), quintiles of IMD, and asthma.

TABLE E2. Sensitivity analysis additionally adjusting for ethnicity

		HR (99% CI) for fracture risk comparing those with atopic eczema with those without									
		Adjusted for confounders*					Adjusted for confounders* and additionally adjusted for cumulative oral steroid dose				
Analysis	Justification	Pelvis	Hip	Spine	Wrist	Any site	Pelvis	Hip	Spine	Wrist	Any site
Main analysis	Included for comparison with results of sensitivity analysis	1.12 (1.05−1.19)	1.11 (1.08−1.15)	1.15 (1.08−1.22)	1.08 (1.04−1.12)	1.11 (1.09−1.13)	1.08 (1.01−1.15)	1.09 (1.06−1.12)	1.09 (1.03−1.16)	1.07 (1.03−1.11)	1.09 (1.08−1.11)
Main analysis restricting participants to those recruited from 2006 onward	Included for comparison with results of sensitivity analysis	0.96 (0.84−1.10)	1.06 (1.00−1.13)	1.05 (0.94−1.18)	1.06 (0.98−1.14)	1.10 (1.07−1.12)	0.94 (0.82−1.08)	1.04 (0.98−1.11)	1.00 (0.89−1.12)	1.04 (0.97−1.12)	1.08 (1.05−1.10)
Analysis additionally adjusting for ethnicity and restricting participants to those recruited from 2006 onward	To explore whether including ethnicity in models has an impact on the effect estimates.†	0.90 (0.79−1.03)	1.03 (0.97−1.10)	1.02 (0.91−1.15)	1.03 (0.95−1.11)	1.07 (1.05−1.10)	0.89 (0.77−1.02)	1.01 (0.95−1.08)	0.98 (0.87−1.10)	1.01 (0.94−1.10)	1.06 (1.03−1.08)

*Implicitly adjusted for age, sex, GP, and date of cohort entry and additionally adjusted for time period (1997−2001, 2002−2006, 2007−2011, and 2012−2016), quintiles of IMD, and asthma.
†Only included as a sensitivity analysis because data on ethnicity was frequently missing Renumeration for the recording of ethnicity was introduced in 2006 in the QOF, leading to more complete data on ethnicity from 2006 onward.[E32]

TABLE E3. Incidence rates for different types of fractures for people with atopic eczema, confounder- and cumulative steroid dose−adjusted HRs for fracture comparing those with atopic eczema with those without, and absolute rate differences (compared with people without atopic eczema)

Fracture	Incidence rate (per 1,000 p-y) in participants with atopic eczema	HR* comparing risk of fracture in people with atopic eczema to people without (99% CI)†	Rate difference (per 1,000 p-y) (99% CI)‡
Pelvis	0.95	1.08 (1.01−1.15)	0.07 (0.01−0.12)
Hip	4.14	1.09 (1.06−1.12)	0.35 (0.23−0.46)
Spine	1.01	1.09 (1.03−1.16)	0.08 (0.02−0.13)
Wrist	2.34	1.07 (1.03−1.11)	0.16 (0.07−0.23)
Any fracture	14.49	1.10 (1.08−1.12)	1.31 (1.11−1.52)

p-y, Person-years.*For the risk of fracture comparing those with atopic eczema with those without atopic eczema.†From models implicitly adjusted for age sex, GP, and date of cohort and additionally adjusted for time period (1997 −2001, 2002−2006, 2007−2011, and 2012−2016), quintiles of IMD, asthma and cumulative oral corticosteroid dose.‡The incidence rate in participants without atopic eczema used to calculate the rate difference is estimated as the incidence rate of those with atopic eczema multiplied by the inverse of the HR of the confounder-adjusted model with cumulative dose (r*(1/HR)).

TABLE E4. HRs (99% CIs) for the for risk of fracture comparing people with atopic eczema with people without atopic eczema in minimally adjusted models, confounder-adjusted models, and additionally adjusted for different steroid definitions*

Fracture	Person-y	Fractures (in those with atopic eczema)	Fracture rate per 1,000 p-y	Minimally adjusted	Confounder-adjusted†	+ Simple steroid definition (ever vs never)	+ Recency of oral steroid prescription	+ Cumulative dose of oral steroids	+ Current dose of oral steroids	+ Peak dose of oral steroids
Pelvis	3,309,099	3,151	0.95	1.14 (1.07−1.21)	1.12 (1.05−1.19)	1.07 (1.01−1.14)	1.07 (1.01−1.14)	1.08 (1.01−1.15)	1.11 (1.04−1.18)	1.07 (1.01−1.14)
Hip	3,307,483	13,709	4.14	1.13 (1.10−1.16)	1.11 (1.08−1.15)	1.09 (1.06−1.12)	1.09 (1.06−1.13)	1.09 (1.06−1.12)	1.11 (1.08−1.14)	1.09 (1.06−1.12)
Spine	3,308,947	3,327	1.01	1.19 (1.12−1.26)	1.15 (1.08−1.22)	1.09 (1.03−1.16)	1.10 (1.03−1.16)	1.09 (1.03−1.16)	1.14 (1.08−1.21)	1.09 (1.03−1.16)
Wrist	3,300,886	7,737	2.34	1.11 (1.07−1.15)	1.08 (1.04−1.12)	1.07 (1.03−1.11)	1.07 (1.03−1.11)	1.07 (1.03−1.11)	1.08 (1.04−1.12)	1.07 (1.03−1.11)
Any site	3,102,202	44,959	14.49	1.14 (1.12−1.16)	1.11 (1.09−1.13)	1.09 (1.07−1.11)	1.09 (1.08−1.11)	1.09 (1.08−1.11)	1.11 (1.09−1.13)	1.09 (1.07−1.11)

p-y, Person-years.
*Total person-y and number of fractures and crude rates per 1,000 p-y are shown.
†Implicitly adjusted for age, sex, GP, and date of cohort entry, and additionally adjusted for calendar period (1997 −2001, 2002−2006, 2007−2011, and 2012−2016), quintiles of IMD, and asthma.

TABLE E5. Characteristics of participants from the study population used for the main analysis and from the study population restricted to those recruited from 2006 onward, which was used for the sensitivity analysis additionally adjusting for ethnicity

	Main analysis sample (n =3,095,838)		Restricted to those recruited from 2006 onward (n = 1,634,818)	
Characteristic	Without atopic eczema (n = 2,569,030)	With atopic eczema (n = 526,808)	Without atopic eczema (n = 1,353,624)	With atopic eczema (n = 281,194)
Follow-up time, p-y	14,932,553	3,309,366	4,568,393	1,012,408
Median follow- up time, y (IQR)	4.41 (2.00−9.64)	5.02 (2.00−9.64)	2.75 (1.14−5.16)	3.03 (1.28−5.54)
Sex female, n (%)	1,489,261 (58.0)	308,071 (58.5)	762,689 (56.3)	160,753 (57.2)
Age (y), n (%)				
18−39	1,217,722 (47.4)	246,596 (46.8)	715,467 (52.9)	145,762 (51.8)
40−49	351,927 (13.7)	69,696 (13.2)	180,172 (13.3)	35,480 (12.6)
50−59	329,007 (12.8)	63,943 (12.1)	158,152 (11.7)	30,897 (11.0)
60−69	303,790 (11.8)	61,902 (11.8)	147,092 (10.9)	30,709 (10.9)
≥70	366,584 (14.3)	84,671 (16.1)	152,741 (11.3)	38,346 (13.6)
BMI (kg/m^2), n (%)				
Normal (18.5−25)	828,367 (32.2)	172,446 (32.7)	413,000 (30.5)	84,772 (30.1)
Underweight (<18.5)	185,784 (7.2)	37,756 (7.2)	101,069 (7.5)	20,498 (7.3)
Overweight (25−30)	667,277 (26.0)	143,919 (27.3)	338,930 (25.0)	73,334 (26.1)
Obese (>30 kg)	393,529 (15.3)	92,507 (17.6)	224,251 (16.6)	53,622 (19.1)
Missing	494,073 (19.2)	80,180 (15.2)	276,374 (20.4)	48,968 (17.4)
Smoking, n (%)				
Never	1,293,983 (50.4)	266,134 (50.5)	662,868 (49.0)	136,691 (48.6)
Ever	1,125,627 (43.8)	246,782 (46.8)	633,388 (46.8)	139,152 (49.5)
Missing	149,420 (5.8)	13,892 (2.6)	57,368 (4.2)	5,351 (1.9)
IMD,* n (%)				
1 (least deprived)	611,904 (23.8)	126,806 (24.1)	311,069 (23.0)	66,174 (23.5)
2	589,313 (22.9)	120,946 (23.0)	306,271 (22.6)	64,133 (22.8)
3	508,469 (19.8)	103,646 (19.7)	266,234 (19.7)	55,080 (19.6)
4	489,144 (19.0)	100,430 (19.1)	267,687 (19.8)	54,947 (19.5)
5 (most deprived)	370,200 (14.4)	74,980 (14.2)	202,363 (14.9)	40,860 (14.5)

IQR, Interquartile range; *p-y,* person-years.
*Quintiles of IMD.

TABLE E6. HRs (99% CIs) for the for risk of fracture comparing people with mild, moderate, or severe atopic eczema with people without atopic eczema in minimally adjusted models, confounder-adjusted models, and additionally adjusted for different steroid definitions*

Term	Person-y	Fractures (in those with atopic eczema)	Fracture rate per 1,000 p-y	Minimally adjusted	Confounder-adjusted†	+ Simple steroid definition (ever vs never)	+ Recency of oral steroid prescription	+ Cumulative dose of oral steroids	+ Current dose of oral steroids	+ Peak dose of oral steroids
Pelvis										
Mild	2,000,441	1,636	0.82	1.08 (0.99−1.18)	1.07 (0.98−1.16)	1.04 (0.95−1.13)	1.05 (0.96−1.14)	1.05 (0.96−1.15)	1.07 (0.98−1.16)	1.04 (0.95−1.13)
Moderate	1,140,433	1,244	1.09	1.12 (1.02−1.24)	1.10 (1.00−1.22)	1.06 (0.96−1.17)	1.06 (0.96−1.18)	1.07 (0.97−1.18)	1.10 (1.00−1.21)	1.06 (0.96−1.17)
Severe	168,225	271	1.61	1.75 (1.40−2.19)	1.69 (1.35−2.11)	1.46 (1.17−1.83)	1.34 (1.07−1.69)	1.31 (1.04−1.64)	1.52 (1.21−1.91)	1.46 (1.16−1.83)
Hip										
Mild	1,999,680	6,825	3.41	1.06 (1.02−1.11)	1.05 (1.01−1.10)	1.04 (1.00−1.08)	1.04 (1.00−1.08)	1.04 (1.00−1.08)	1.05 (1.01−1.09)	1.04 (1.00−1.08)
Moderate	1,139,706	5,771	5.06	1.14 (1.09−1.19)	1.12 (1.07−1.17)	1.10 (1.05−1.15)	1.10 (1.05−1.15)	1.10 (1.05−1.15)	1.12 (1.07−1.17)	1.10 (1.05−1.15)
Severe	168,098	1,113	6.62	1.71 (1.53−1.92)	1.68 (1.50−1.87)	1.56 (1.40−1.75)	1.52 (1.36−1.70)	1.51 (1.35−1.69)	1.63 (1.45−1.82)	1.55 (1.39−1.74)
Spine										
Mild	2,000,332	1,601	0.80	1.06 (0.97−1.15)	1.03 (0.95−1.12)	1.00 (0.92−1.08)	1.00 (0.92−1.08)	1.00 (0.92−1.08)	1.03 (0.95−1.12)	0.99 (0.91−1.08)
Moderate	1,140,376	1,349	1.18	1.18 (1.08−1.30)	1.14 (1.04−1.25)	1.10 (1.00−1.20)	1.11 (1.01−1.22)	1.11 (1.01−1.22)	1.14 (1.04−1.25)	1.09 (1.00−1.20)
Severe	168,238	377	2.24	2.45 (2.02−2.96)	2.31 (1.91−2.81)	1.95 (1.60−2.37)	1.83 (1.50−2.23)	1.71 (1.40−2.09)	2.13 (1.75−2.59)	1.94 (1.59−2.36)
Wrist										
Mild	1,995,547	4,295	2.15	1.07 (1.02−1.12)	1.05 (1.00−1.10)	1.04 (0.99−1.09)	1.04 (0.99−1.09)	1.04 (0.99−1.09)	1.05 (1.00−1.10)	1.04 (0.99−1.09)
Moderate	1,137,548	2,920	2.57	1.13 (1.06−1.20)	1.11 (1.04−1.18)	1.10 (1.03−1.17)	1.10 (1.04−1.17)	1.10 (1.03−1.16)	1.11 (1.04−1.18)	1.10 (1.03−1.17)
Severe	167,791	522	3.11	1.35 (1.17−1.55)	1.29 (1.12−1.49)	1.25 (1.08−1.44)	1.24 (1.07−1.43)	1.22 (1.05−1.40)	1.28 (1.10−1.47)	1.25 (1.08−1.44)
Any site										
Mild	1,888,348	25,932	13.73	1.10 (1.07−1.12)	1.07 (1.05−1.09)	1.06 (1.04−1.08)	1.06 (1.04−1.08)	1.06 (1.04−1.08)	1.07 (1.05−1.09)	1.06 (1.04−1.08)
Moderate	1,061,083	16,293	15.36	1.18 (1.15−1.21)	1.15 (1.12−1.18)	1.13 (1.10−1.16)	1.13 (1.10−1.16)	1.13 (1.10−1.16)	1.15 (1.12−1.18)	1.13 (1.10−1.16)
Severe	152,771	2,734	17.90	1.37 (1.29−1.47)	1.33 (1.25−1.42)	1.24 (1.16−1.33)	1.21 (1.13−1.29)	1.19 (1.11−1.27)	1.29 (1.21−1.38)	1.24 (1.16−1.32)

p-y, Person-years.
*Total p-y and number of fractures and crude rates per 1,000 p-y are shown.
†Implicitly adjusted for age, sex, GP, and date of cohort entry and additionally adjusted for time period (1997 −2001, 2002−2006, 2007−2011, and 2012−2016), quintiles of IMD, and asthma.

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