Bone mineral density and fracture risk with long-term use of inhaled corticosteroids in patients with asthma: systematic review and meta-analysis

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ABSTRACT

Objectives: We aimed to assess the association between long-term use of inhaled corticosteroids (ICS) and bone adverse effects in patients with asthma.

Design: Systematic review and meta-analysis of fracture risk and changes in bone mineral density with long-term ICS use in asthma.

Methods: We initially searched MEDLINE and EMBASE in July 2013, and performed an updated PubMed search in December 2014. We selected randomised controlled trials (RCTs) and controlled observational studies of any ICS (duration at least 12 months) compared to non-ICS use in patients with asthma. We conducted meta-analysis of ORs for fractures, and mean differences in bone mineral density. Heterogeneity was assessed using the I² statistic.

Results: We included 18 studies (7 RCTs and 11 observational studies) in the systematic review. Meta-analysis of observational studies did not demonstrate any significant association between ICS and fractures in children (pooled OR 1.02, 95% CI 0.94 to 1.10, two studies), or adults (pooled OR 1.09, 95% CI 0.45 to 2.62, four studies). Three RCTs and three observational studies in children reported on bone mineral density at the lumbar spine, and our meta-analysis did not show significant reductions with ICS use. Three RCTs and four observational studies in adults reported on ICS use and bone mineral density at the lumbar spine and femur, with no significant reductions found in the meta-analysis compared to control.

Conclusions: ICS use for ≥12 months in adults or children with asthma was not significantly associated with harmful effects on fractures or bone mineral density.

INTRODUCTION

Asthma is a chronic inflammatory condition that affects both adults and children. There is a substantial body of evidence that suggest inhaled corticosteroids (ICS) are effective at controlling symptoms, improving lung function and reducing acute exacerbations. They are therefore considered the gold standard first-line preventative therapy and are widely recommended in national and international guidelines.

However, long-term ICS use may be associated with adverse effects such as cataract, osteoporosis, fractures and reduction in growth velocity in children. Concerns surrounding these potential harms may have a negative effect on ICS adherence, thus exposing patients to poorer asthma control and a potentially higher risk of needing oral corticosteroids for acute exacerbations. Certain age groups, such as children or postmenopausal women may be particularly susceptible to adverse effects on bone metabolism and formation, and this therefore remains an area of concern for these patients.

The existing meta-analyses of ICS and bone adverse effects have usually included data from participants with chronic obstructive pulmonary disease (COPD) and to date, there has been less focus on the effects in asthma alone. Patients with asthma may not share the same susceptibilities to osteoporosis as the patient with COPD because of differences in risk factors such as cigarette consumption, multimorbidity and nutritional problems that are prevalent in patients with COPD. It
therefore remains unclear whether patients with asthma have a greater or lesser risk of bone adverse effects than those with COPD and a further review is necessary to clarify these risks for patients with asthma alone.

Hence we aimed to analyse the effects of long-term (≥12 months) ICS use in patients with asthma alone, concentrating on fracture and bone mineral density (BMD) outcomes.

METHODS
Study selection criteria
We aimed to focus on long-term, important but infrequent adverse effects on bone and as such, eligible studies had to have >20 users of each ICS formulation, with follow-up of at least 12 months in duration.

Our inclusion criteria for RCTs were (1) parallel-group RCT; (2) participants with asthma of any severity; (3) ICS as the intervention versus a control treatment, where the comparison groups consisted of ICS versus other asthma therapy (or placebo), or ICS in combination with long-acting β-agonist (LABA) versus a LABA alone; and (4) stated aim to evaluate fractures or BMD.

We also evaluated controlled observational studies (case control, prospective cohort or retrospective cohort) reporting on risk of fractures or change in BMD with any ICS exposure compared to those without ICS exposure.

Exclusion criteria
We excluded studies that recruited mixed groups of participants (asthma/COPD) if the outcomes were not separately reported according to specific disease condition. We excluded crossover trials and studies that considered only oral corticosteroid use without reporting the effects of inhaled corticosteroids.

Search strategy
We initially searched MEDLINE and EMBASE in June 2013 using a broad strategy for a wide range of adverse effects potentially associated with ICS use, and we subsequently updated this through a more focused PubMed search in December 2014 (see eAppendix 1 for search terms and restrictions). We also manually looked through the bibliographies of included studies as well as existing systematic reviews for any other articles that may be potentially suitable.

Study selection
Two reviewers (MT and PB) independently, and in duplicate scanned all titles and abstracts and excluded articles that clearly were not RCTs or observational studies of ICS in patients with asthma. We proceeded to assess full-text versions of potentially relevant articles and conducted more detailed checks against our eligibility criteria, focusing on bone and fracture adverse effects. A third researcher (YKL or AMW) evaluated the decision on inclusion or exclusion in discussion with the two reviewers.

Study characteristics and data extraction
We used preformatted tables to record study design and participant characteristics, definition of asthma, pharmacological agent (dose, device and frequency), and duration of follow-up. Two reviewers independently extracted data (MT and PB) on relevant outcomes, where we prespecified fracture risk of primary interest, and BMD at the lumbar spine or the femur as secondary end points. Any discrepancies were resolved through the involvement of a third reviewer (DG or YKL or AMW) after rechecking the source papers.

Risk of bias assessment
Two reviewers independently assessed the reporting of blinding of participants and personnel, randomisation sequence, allocation concealment, withdrawals and the loss to follow-up in RCTs. In order to assess validity of the associations between adverse effects and ICS use, we extracted information on participant selection, ascertainment of exposure and outcomes, and methods of addressing confounding in observational studies.

We aimed to use a funnel plot and asymmetry testing to assess publication bias provided that there were more than 10 studies in the meta-analysis, and the absence of significant heterogeneity.

Statistical analysis
We pooled trial data using Review Manager (RevMan) V.5.3.2 (Nordic Cochrane Center, Copenhagen, Denmark). We used the inverse variance method to pool ORs for fracture events, and mean differences for BMD (g/cm²). In accordance with the recommendations of the Cochrane Handbook, we derived any SDs from 95% CIs or p values. We assessed statistical heterogeneity using the I² statistic with I²>50% indicating a substantial level of heterogeneity.

If a trial had more than one group of non-ICS users as controls, we analysed data for ICS versus placebo (if available) in preference to data from active comparators such as ICS versus nedocromil, montelukast or disodium cromoglycate. If combination formulations were evaluated in the trial, we chose unconfounded comparisons based on ICS used together with the other drug versus other drug alone.

If a trial had several arms involving different ICS doses, we combined all the ICS arms together as recommended by the Cochrane Handbook.

We did not have a pre-registered protocol.

RESULTS
We screened 1887 potentially relevant articles, and finally included 18 studies in our systematic review (comprising 7 RCTs and 11 observational studies). The process of study selection is shown in figure 1.

Table 1A, B show the characteristics of the included RCTs, and the observational studies, respectively.
Tables 2 and 3 report on study validity and outcomes in adult and children, respectively.

Four of the RCTs focused solely on children, while the remaining three were in adults. Treatment duration was up to 4 years in one study, while the remaining six trials had ICS therapy for between 52 and 104 weeks. Intervention arms of the trials included fluticasone (5 trials), budesonide (3 trials) and mometasone (one trial). Fluticasone and mometasone were the ICS used in the intervention arms of one trial, and in this trial, we evaluated the results of all ICS users combined against montelukast.

Five of the observational studies focused solely on children, while the remainder looked at adults or a mixture of age groups. The observational studies looked at wider range of ICS than the RCTs, with the inclusion of beclometasone, flunisolide and triamcinolone users.

Study validity
Validity assessment of the included studies is reported in tables 2 and 3.

Randomised controlled trials (n=7)
Overall, four of the RCTs reported an appropriate method of sequence generation, while five provided details on how concealment of allocation was achieved. With regards to blinding, five trials reported the use of double-blinding. Ascertainment of BMD was consistently performed through dual-energy X-ray absorptiometry (DEXA) scans, but the trials did not state how and when fracture diagnoses were confirmed. One major limitation that affected all the trials stemmed from discontinuations and substantial losses to follow-up for measurement of BMD outcomes at final time-points.

Observational studies (n=11)
We felt that only four studies took account of a good range of variables when tackling baseline confounding. Assessment of compliance or adherence to ICS use was reported in four studies. Fracture events were typically recorded through administrative codes while one study relied on patient self-report. Ascertainment of BMD was through DEXA scans. Overall, we felt that most of the studies were at moderate to high risk of bias due to the above limitations, with four studies possibly of slightly better methodological quality because of adequate outcome ascertainment and adjustment for confounders.

Fractures with ICS
We identified one large long-term RCT in children that reported adjusted fracture rate of 5.7 per 100 patient years with budesonide as compared to 5.1 per 100 patient years with placebo (p=0.53). Similarly, there was no significant increase in likelihood of fracture in a meta-analysis of two observational studies in children, (OR 1.02, 95% CI 0.94 to 1.10, I²=0%) as shown in figure 2. The point estimates of fracture risk was not

Figure 1 Flow diagram of study selection. BMD, bone mineral density; RCT, randomised controlled trial.
Table 1 Characteristics of included trials and observational studies

(A) Randomised controlled trials

| Source                  | Location                  | Treatment duration | Asthma criteria                                                                 | Drug and inhaler device                          | Male % | Mean age (years) | Mean % predicted FEV₁ | Prior ICS use (%) |
|-------------------------|---------------------------|--------------------|--------------------------------------------------------------------------------|--------------------------------------------------|--------|------------------|-----------------------|-------------------|
| CAMP/Kelly et al 2006   | Multicentre US            | >208 weeks         | Mild-to-moderate asthma defined by symptoms or by use of inhaled bronchodilator ≥ twice weekly or daily medication for asthma. Airway methacholine challenge test. | BUD 200 µg bd (n=311) Nedocromil 8 mg daily (n=312) Placebo (n=412) | 58.2   | 9.0              | 93.6                  | 40.5              |
| Ferguson et al 2007     | Multicentre—35 centres in 11 countries | 52 weeks        | Age 6–9 years persistent asthma ≥6 months; FEV₁ ≥60% predicted; 1PEFR of ≥15% after salbutamol. Exclusions: oral corticosteroids on >2 occasions or >12 days or >210 mg prednisolone past 6 months; known growth disorder or glaucoma/cataracts | FP 100 µg bd (n=114) Diskus (dry powder inhaler) | 68     | 7.2              | 90.2                  | 25% oral steroids past 6 months |
| Kemp et al 2007         | Multicentre US            | 104 weeks         | 6-month history of mild asthma (FEV₁ 82–85% predicted) able to be managed without steroids for 2 years | FP 88 µg bd (n=55) Metered dose inhaler FP 440 µg bd (n=51) Metered dose inhaler Placebo (n=54) | 60     | 31.6             | 83                    | 0                 |
| Li et al 2017           | Multicentre US            | 104 weeks         | At least 6-month history with diagnosis using American Thoracic Society definition. FEV₁ of ≥60% predicted, and limited previous corticosteroid therapy | FP 500 µg bd (n=32) Diskhaler Placebo bd (n=32) Diskhaler | 91     | 28.0             | 91                    | Not reported |
| Maspero et al 2018      | 50 centres worldwide      | 52 weeks          | Adults with >3 months history of asthma, and not using ICS past 3 months. FEV₁ between 60 and 90% predicted. Must have DEXA scan, and no evidence of low vitamin D | Mometasone 400 µg daily (n=137) Mometasone 200 µg daily (n=140) | 34     | 30               | 76.5                  | 7                 |
| Roux et al 2019         | 52 respiratory specialist clinics in France | 104 weeks | Exacerbations ≥1x/week but <1x daily; or chronic symptoms requiring daily treatment. Fulfilling: (1) FEV₁ or PEFR ≥80% predicted; (2) reversibility ≥15%; (3) daily variability PEFR 20%–30% ≥2 days, or salbutamol use >3 times previous week, or nocturnal symptoms ≥2x during run-in | FP 250 µg bd (n=147) Montelukast 10 mg (n=142) FP 100 µg bd (n=87) Diskus/Accuhaler dry powder inhaler Nedocromil 4 mg bd (n=87) MDI | 39     | 28               | 75.3                  | 6                 |
| Turpeinen et al 2020    | Helsinki University Hospital, Finland | 72 weeks          | ‘Newly detected mild asthma’ Excluded if history of inhaled, nasal or oral corticosteroid use in the previous 2 months before enrolment | Continuous BUD (n=50) Turbuhaler BUD 400 µg bd for 1 month, then 200 µg bd for | 60     | 6.9              | Not reported            | Not reported |
### (A) Randomised controlled trials

| Source | Location | Treatment duration | Asthma criteria | Drug and inhaler device | Male % | Mean age (years) | Mean % predicted FEV₁ | Prior ICS use (%) |
|--------|----------|--------------------|-----------------|-------------------------|--------|-----------------|----------------------|------------------|
|        |          |                    |                 |                         |        |                 |                      |                  |
|        |          | 2nd–6th months, then 100 μg bd for final 12 months. BUD/placebo (n=44) Turbuhaler         | 66 6.7 Not reported Not reported |        |
|        |          | BUD 400 μg bd for 1st month, then 200 μg bd for 2nd to 6th months, then placebo for final 12 months Sodium cromoglicate—10 mg tds for 18 months (unblinded) (n=42) MDI | 50 7.0 Not reported Not reported |        |

Bd, two times a day; BUD, budesonide; DEXA, dual-energy X-ray absorptiometry; FEV₁, forced expiratory volume in 1 s; FP, fluticasone propionate; ICS, inhaled corticosteroids; MDI, metered dose inhaler; PEFR, peak expiratory flow rate.

### (B) Observational studies

| Study | Design | Adverse effects measured | Data source and number of patients | Selection of patients: asthma definition and patient characteristics (or selection of cases and controls) | Type of ICS |
|-------|--------|--------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------|-------------|
| Agertoft and Pedersen²¹ | Cross-sectional study | BMD | Outpatient paediatric clinic, Kolding Hospital, Denmark 157 cases, 111 controls | Selection of cases: Children with persistent asthma and no other chronic disease, on ICS continuously for ≥3 years. Mean age: 10.3 years, male 69%, %FEV₁ predicted: 97 Selection of controls: asthmatic children, who have never taken inhaled/systemic corticosteroids for ≥2 weeks per year. Mean age: 9.9 years, male 55%, %FEV₁ predicted: 81 | BUD |
| Allen et al²² | Prospective | BMD | Department of Paediatrics, Royal North Shore Hospital, Sydney, Australia 48 cases, 9 controls | Selection of cases: prepubertal asthmatic children requiring ≥3 courses oral corticosteroids within study period Mean age: 7.8 years, male 63% Selection of controls: children not using corticosteroids. Mean age: 8.4 years, male 78% | BDP, BUD |

Continued
| Study                  | Design            | Adverse effects measured | Data source and number of patients | Selection of patients: asthma definition and patient characteristics (or selection of cases and controls)                                                                 | Type of ICS |
|------------------------|-------------------|--------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Bahceciler et al<sup>23</sup> | Cross-sectional study | BMD                      | Outpatient Allergy Clinic of Marmara University Hospital, Istanbul, Turkey 52 cases, 22 controls | Asthma definition: mild intermittent plus persistent mild to moderate asthma. Selection of cases: Children treated for ≥6 months. Mean age: 6.4 years, male 42%. Characteristics of high-dose ICS group: Mean age: 3 years. Mean duration of disease: 50.4 months. Characteristics of low dose ICS group: Mean age: 5.8 years. Mean duration of disease: 38.3 months. Selection of controls: Age-matched asthmatic children who have never received ICS Mean age: 6.8 years, male 45%. | BUD         |
| El et al<sup>24</sup>    | Observational     | BMD                      | Outpatients, Dokuz Eylul University, Balcova, Izmir, Turkey 45 cases, 46 controls | Asthma severity defined according to Global Initiative for Asthma guideline. Selection of cases: patients with mild or moderate asthma and regular ICS use. Mean age: 44.04 years, male 0%. %FEV<sub>1</sub>: 89.71. Controls: Mean age: 44.43 years, male 0%. | Not specified |
| Harris et al<sup>25</sup> | Cross-sectional study | BMD                      | Outpatient clinics of Sydney Children’s Hospital, Randwick, New South Wales and Monash Medical Centre, Clayton, Victoria, Australia. 76 subjects | Selection of subjects: Prepubertal asthmatic children stratified into groups according to corticosteroid treatment received in the past 6 months 1) no inhaled corticosteroid, mean age: 8.2 years, male 70%. 2) moderate dose inhaled corticosteroid (400–800 μg/day), mean age: 7.4 years, male 56%. 3) high-dose inhaled corticosteroid (>800 μg/day), mean age: 8.9 years, male 75%. | BDP, BUD, FP |
| Johannes et al<sup>26</sup> | Nested case-control study | Risk of non-vertebral fracture | Ingenix Epidemiology—Research database of United Healthcare members, 17 states in the USA. 1722 cases, 17 220 controls | Adults ≥40 years age, in health plan for ≥12 continuous months Jan 1997 to Jun 2001, with ICD-9 code for asthma, or COPD. Selection of cases: Non-vertebral fractures by ICD-9 codes, with claim for treatment (including inpatient hip fractures). Mean age 52.9 years, male 29.4%. | BDP, BUD, FP flunisolone, triamcinolone |
### (B) Observational studies

| Study             | Design                        | Adverse effects measured | Data source and number of patients | Selection of patients: asthma definition and patient characteristics (or selection of cases and controls) | Type of ICS |
|-------------------|-------------------------------|--------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------|-------------|
| Schlienger et al  | Retrospective Population-based nested case-control analysis | Fracture risk            | UK General Practice Research Database 3744 cases, 21 757 controls | Selection of controls: Sampled from person-time of respiratory cohort by two-tiered random sampling with replacement. Mean age 52.2 years, male 41.1%. Aged 5–79 years with ICD code for asthma or COPD with ≥1 prescription for ICS and/or OCS, or with no exposure to corticosteroids. From there 65 779 individuals aged 5–17 years identified to form base population for study. Selection of cases: Patients with 1st-time diagnosis ICD-8 bone fracture; male 65.6%. Selection of controls: Up to 6 control subjects selected per case, matched on age, gender, general practice attended, calendar time and years of history in GPRD; male 64.9%. | BDP (76.2%), BUD (21.7%), FP (2.1%) |
| Sosa et al        | Cross-sectional study         | BMD; Fracture risk       | Canary Islands, Spain 105 cases, 133 controls | Selection of cases: Women suffering from stable bronchial asthma, treated with ICS ≥1 year, and who did not receive oral or parenteral steroids. Mean age: 53.0 years, number of menopausal subjects n (%): 65 (61.9%). Selection of controls: weight-matched women, no asthma and no steroids. Controls were usually friends or neighbours of the patients. Mean age: 49.7 years, number of menopausal subjects n (%): 74 (57.8%) | ICS formulations not specified |
| Van Staa et al    | Population-based cohort study/nested case-control analysis | Fracture risk            | UK General Practice Research Database (GPRD) Cohort: ICS users: 97 387 Bronchodilators only: 70 984 Controls: 345 758 Fracture cases: 23 984; Controls: 23 984 | Children aged 4–17 years old, on ICS. 3 study groups: selection of cases: non-vertebral fracture. Male 61%, 8856 (36.9%) aged 4–9 years, 8496 (35.4%) aged 10–13 years, 6632 (27.7%) aged 14–17 years. Selection of controls: for each fracture case, one control patient randomly selected, matched by age, sex, GP practice and calendar time. Male 61%, 8861 (36.9%) aged | BDP, BUD, FP |
### (B) Observational studies

| Study                  | Design          | Adverse effects measured | Data source and number of patients | Selection of patients: asthma definition and patient characteristics (or selection of cases and controls) | Type of ICS |
|------------------------|-----------------|--------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------|-------------|
| Wisniewski *et al*     | Cross-sectional study | BMD                      | Asthma register and local general practices in Nottingham, UK 47 cases; 34 controls | 4–9 years, 8497 (35.4%) aged 10–13 years, 6626 (27.6%) aged 14–17 years Selection of cases: aged 20–40 years with documented history of asthma: Group 1: asthmatics using inhaled β<sub>2</sub>-agonist only. Males 56%, mean age: men 30.3 years; women 25.6 years, mean FEV<sub>1</sub> (litres): men 3.87; women 3.13 Group 2: ICS use ≥5 years with no systemic steroids in the past 6 months. Males 40%, mean age: men 32.3 years; women 32 years, mean FEV<sub>1</sub> (litres): men 3.40; women 2.83 | BDP, BUD    |
| Yanik *et al*          | Observational   | BMD                      | Pulmonology outpatient clinic at Fatih University Faculty of Medicine, Ankara, Turkey 46 cases, 60 controls | Selection of cases: Regular ICS use ≥12 months) as defined by The Global Initiative for Asthma (GINA) criteria Mean age: 62.5 years, male 0%, %FEV<sub>1</sub> predicted: 83.1. All cases were postmenopausal Selection of controls: healthy postmenopausal females. Mean age: 63 years | BDP, BUD, FP |

BDP, beclomethasone dipropionate; BUD, budesonide; COPD, chronic obstructive pulmonary diseases; FEV<sub>1</sub>, forced expiratory volume in 1 s; FP, fluticasone propionate; GP, general practitioner; ICD, International Classification of Diseases; ICS, inhaled corticosteroids.
| Study Validity and Outcomes (Bone Mineral Density and Fractures) in Children |
|-----------------------------|-----------------------------|-----------------------------|
| **Source**                  | **Sequence generation**     | **Allocation concealment**   |
| Roux et al 2011             | Central Block randomisation | Adequate                    |
| Ferguson et al 2014         | Block randomisation with gender stratification | Adequate                    |
| Roux et al 2011             | Block randomisation         | Adequate                    |
| Ferguson et al 2014         | Block randomisation         | Adequate                    |

| **Blinding of participants and personnel** |
|---------------------------------------------|
| Ferguson et al 2014                         | Adequate                    |
| Roux et al 2011                             | Adequate                    |
| Ferguson et al 2014                         | Adequate                    |
| Roux et al 2011                             | Adequate                    |

| **AE monitoring** |
|-------------------|
| Ferguson et al 2014| Adequate                    |
| Roux et al 2011    | Adequate                    |
| Ferguson et al 2014| Adequate                    |
| Roux et al 2011    | Adequate                    |

| **Adverse events** |
|--------------------|
| Ferguson et al 2014 | BMD recorded at every visit: BUD 3.5 per 100 person-years, placebo 2.8 per 100 person-years, p = 0.002 |
| Roux et al 2011     | BMD recorded at every visit: BUD 3.5 per 100 person-years, placebo 2.8 per 100 person-years, p = 0.002 |
| Ferguson et al 2014 | BMD recorded at every visit: BUD 3.5 per 100 person-years, placebo 2.8 per 100 person-years, p = 0.002 |
| Roux et al 2011     | BMD recorded at every visit: BUD 3.5 per 100 person-years, placebo 2.8 per 100 person-years, p = 0.002 |

| **Table 2** Study Validity and Outcomes (Bone Mineral Density and Fractures) in Children |
|---------------------------------------------|-----------------------------|-----------------------------|
| **Source**                  | **Sequence generation**     | **Allocation concealment**   |
| Ferguson et al 2014         | Remotely generated          | Adequate                    |
| Roux et al 2011             | Central Block randomisation | Adequate                    |
| Ferguson et al 2014         | Block randomisation         | Adequate                    |
| Roux et al 2011             | Block randomisation         | Adequate                    |

**BUD, budesonide; DEXA, dual-energy X-ray absorptiometry; DSCG, disodium cromoglicate; FP, fluticasone propionate.**

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### Table 2 Continued

**B) Observational studies of bone mineral density and fractures—children**

| Study                  | Ascertainment of BMD                                                                 | Ascertainment of exposure | Definition of ICS use                                                                 | Adjustments               | ICS exposure       | BMD (g/cm) |
|------------------------|---------------------------------------------------------------------------------------|----------------------------|--------------------------------------------------------------------------------------|---------------------------|-------------------|-------------|
| Agertoft and Pedersen  | DEXA scan at one visit, performed by same investigator blinded to treatment group    | Compliance checked: Good Duration: Mean 1603 days | Asthmatic children with ICS use continuously for ≥3 years Type of inhaler: MDI; Turbuhaler Type of steroid: BUD | Log of accumulated dose of BUD; gender; age | Mean ICS BUD dose 504 μg (daily) | Mean BMD: BUD group: 0.92 Control group: 0.92 |
| Allen et al            | DEXA scan at baseline and again at 9–20 months later. Value for 12-month average time point calculated with all outcomes | Compliance checked: Adequate Duration of follow-up: 9–20 months | Type of inhaler: MDI; Turbuhaler Type of steroid: BUD | Age; height; weight; dose of inhaled corticosteroid | Mean ICS dose 0.67±0.48 mg/m²/day | Change in mean vertebral BMD (SD) over 12 months: ICS group (n=47): 0.03±0.03 Control group (n=9): 0.06±0.04 p<0.025 |
| Bahceciler et al       | Anteroposterior (AP) spine (L2–4) by DEXA scan                                      | Compliance: Mean daily dose (SD): 419 μg | Use of BUD as MDI ≥6 months | None | Mean lumbar spine BMD: ICS group (SD 0.156) | |
| Harris et al           | Lumbar spine by DEXA                                                                | Compliance checked: not reported Follow-up: 13.0 ±9.8 months | Stratified by treatment in past 6 months Type of inhaler:Spacer device Type of steroid: BDP, BUD, FP | Weight | Mean lumbar spine BMD (SD) 0.68 (0.07) | |

Mean lumbar spine BMD (SD) 0.67 ±0.08
### Table 2 Continued

| Studies reporting on fracture risk | Fracture outcomes |
|----------------------------------|-------------------|
| **Schlienger et al**<sup>27</sup> | **Identified by ICD-8 codes 800.x –829.x, from computerised records**<br>**Cases=1st-time diagnosis of bone fracture**<br>**Controls—no fracture**<br>**Compliance checked: not reported**<br>**Duration:** Median number of prescriptions: 26, corresponds to >7 years of continuous exposure<br>**ICS use in UK General Practice Research Database**<br>**Type of inhaler:** not reported<br>**Type of steroid:** BDP, BUD, FP<br>**Matched for age, gender, general practice, calendar time, years in GPRD**<br>**Adjusted for comorbidities:** chronic renal failure, hyperthyroidism, hyperparathyroidism, inflammatory bowel disease, malnutrition, malabsorption<br>**Medications:** asthma drugs, psychotropic drugs, antihypertensives, calcium, fluoride, vitamin D<br>**1–9 prescriptions**<br>**Cases: n=332**<br>**Controls: n=2017**<br>**10–19 prescriptions**<br>**Cases: n=124**<br>**Controls: n=682**<br>**≥20 prescriptions**<br>**Cases: n=88**<br>**Controls: n=422**<br>**Adjusted OR: 0.97 (0.85 to 1.11)**<br>**Adjusted OR: 1.08 (0.87 to 1.33)**<br>**Adjusted OR: 1.15 (0.89 to 1.48)**<br>**Adjusted OR: 1.01 (0.90 to 1.13)**<br>**Adjusted OR: 0.96 (0.83 to 1.12)**<br>**Adjusted OR: 1.07 (0.93 to 1.24)**<br>**Adjusted OR: 1.17 (0.93 to 1.45)**<br>**Adjusted OR: 1.03 (0.93 to 1.15)**<br>**Type of inhaler:** not reported<br>**Type of steroid:** BDP, BUD, FP<br>**Matched for age, gender, general practice, calendar time, years in GPRD**<br>**Adjusted for comorbidities:** chronic renal failure, hyperthyroidism, hyperparathyroidism, inflammatory bowel disease, malnutrition, malabsorption<br>**Medications:** asthma drugs, psychotropic drugs, antihypertensives, calcium, fluoride, vitamin D<br>**1–9 prescriptions**<br>**Cases: n=332**<br>**Controls: n=2017**<br>**10–19 prescriptions**<br>**Cases: n=124**<br>**Controls: n=682**<br>**≥20 prescriptions**<br>**Cases: n=88**<br>**Controls: n=422**<br>**Adjusted OR: 0.97 (0.85 to 1.11)**<br>**Adjusted OR: 1.08 (0.87 to 1.33)**<br>**Adjusted OR: 1.15 (0.89 to 1.48)**<br>**Adjusted OR: 1.01 (0.90 to 1.13)**<br>**Adjusted OR: 0.96 (0.83 to 1.12)**<br>**Adjusted OR: 1.07 (0.93 to 1.24)**<br>**Adjusted OR: 1.17 (0.93 to 1.45)**<br>**Adjusted OR: 1.03 (0.93 to 1.15)**<br>**BDP, beclometasone dipropionate; BUD, budesonide; DEXA, dual-energy X-ray absorptiometry; FP, fluticasone propionate; ICD, International Classification of Disease; ICS, inhaled corticosteroids; MDI, metered dose inhaler.**

**Van Staa et al**<sup>29</sup> | **Ascertained from diagnoses within computer records**<br>**Compliance not reported**<br>**Start of follow-up:** 1987 onwards or from age 4 years<br>**End:** December 1997 or age 18 years<br>**Current users of ICS**<br>**Type of inhaler:** not reported<br>**Type of inhaled steroid:** BDP, BUD, FP<br>**History of seizures; use of non-steroidal anti-inflammatory drugs or bronchodilators; hospitalisation for asthma past 2 years; number of prescriptions in past year. Age; sex**<br>**200 μg**<br>**201–400 μg**<br>**>400 μg**<br>**All ICS users combined**<br>**Adjusted OR: 1.01 (0.90 to 1.13)**<br>**Adjusted OR: 0.96 (0.83 to 1.12)**<br>**Adjusted OR: 1.07 (0.93 to 1.24)**<br>**Adjusted OR: 1.17 (0.93 to 1.45)**<br>**Adjusted OR: 1.03 (0.93 to 1.15)**<br>**Type of inhaler:** not reported<br>**Type of steroid:** BDP, BUD, FP<br>**Matched for age, gender, general practice, calendar time, years in GPRD**<br>**Adjusted for comorbidities:** chronic renal failure, hyperthyroidism, hyperparathyroidism, inflammatory bowel disease, malnutrition, malabsorption<br>**Medications:** asthma drugs, psychotropic drugs, antihypertensives, calcium, fluoride, vitamin D<br>**1–9 prescriptions**<br>**Cases: n=332**<br>**Controls: n=2017**<br>**10–19 prescriptions**<br>**Cases: n=124**<br>**Controls: n=682**<br>**≥20 prescriptions**<br>**Cases: n=88**<br>**Controls: n=422**<br>**Adjusted OR: 0.97 (0.85 to 1.11)**<br>**Adjusted OR: 1.08 (0.87 to 1.33)**<br>**Adjusted OR: 1.15 (0.89 to 1.48)**<br>**Adjusted OR: 1.01 (0.90 to 1.13)**<br>**Adjusted OR: 0.96 (0.83 to 1.12)**<br>**Adjusted OR: 1.07 (0.93 to 1.24)**<br>**Adjusted OR: 1.17 (0.93 to 1.45)**<br>**Adjusted OR: 1.03 (0.93 to 1.15)**<br>**BDP, beclometasone dipropionate; BUD, budesonide; DEXA, dual-energy X-ray absorptiometry; FP, fluticasone propionate; ICD, International Classification of Disease; ICS, inhaled corticosteroids; MDI, metered dose inhaler.**
| Source         | Sequence generation | Allocation concealment | Blinding of participants and personnel | AE monitoring | Drug (n) | Mean change in BMD g/cm² | Dis-continued, number (%) | Loss to follow-up, number (%) |
|---------------|---------------------|------------------------|----------------------------------------|--------------|----------|--------------------------|----------------------------|------------------------------|
| Kemp et al     | Random code with blinded labels | Adequate              | Adequate                               | DEXA scan every 6 months at lumbar spine (L1-L4), analysed by central osteoporosis research facility for quality assurance Adjusted for baseline value, investigator, sex, age | FP 88 µg bd | At week 104 1) Lumbar spine: 0.008, SE 0.006 2) Proximal femur: −0.009, SE 0.009 | 17 (31) | 6 (11) |
|               |                     |                       |                                        |              | FP 440 µg bd | At week 104 1) Lumbar spine: −0.003, SE 0.008 2) Proximal femur: −0.020, SE 0.009 | 18 (35) | 7 (14) |
|               |                     |                       |                                        |              | Placebo bd | At week 104 1) Lumbar spine: 0.001, SE 0.005 2) Proximal femur: −0.007, SE 0.007 | 10 (19) | 4 (7) |
| Li et al       | Unclear             | Unclear               | Adequate                               | DEXA at L1-L4 of lumbar spine. Measured at screening and 6-month intervals | FP | At week 104, lumbar spine: −0.006, SE 0.008 | 9 (28) | 2 (6) |
|               |                     |                       |                                        |              | Placebo | At week 104, lumbar spine: −0.007, SE 0.010 | 8 (25) | 7 (22) |
| Maspero et al  | Centrally administered through interactive voice response system | Adequate              | Adequate                               | DEXA at L1-L4 of lumbar spine. Follow-up at 26 and 52 weeks | Mometasone 400 µg | 1) Lumbar spine: 0.0092, Femur: 0.004 | 34 (25) | 5 (3) |
|               |                     |                       |                                        |              | Mometasone 200 µg daily | 1) Lumbar spine: 0.0082, Proximal femur: 0.004 | 35 (25) | 7 (4) |
|               |                     |                       |                                        |              | FP 250 µg bd | 1) Lumbar spine: 0.0122, Femur: −0.005 | 38 (26) | 4 (3) |

Continued
### Table 3  Continued

**(a) RCTs of inhaled corticosteroids—adults**

| Source | Sequence generation | Allocation concealment | Blinding of participants and personnel | AE monitoring | Drug (n) | Mean change in BMD g/cm² | Dis-continued, number (%) | Loss to follow-up, number (%) |
|--------|---------------------|------------------------|----------------------------------------|---------------|----------|--------------------------|----------------------------|----------------------------|
|        |                     |                        |                                        |               | Combined estimate for all ICS users |                          |                            |                            |
|        |                     |                        |                                        |               | Montelukast 10 mg daily |                          |                            |                            |
|        |                     |                        |                                        |               | 1) Lumbar spine: 0.0092 | Femur: 0.0008 | 107 (25) | 16 (4) |
|        |                     |                        |                                        |               | 1) Lumbar spine: 0.0132 | Femur: −0.002 | 31 (22) | 3 (3) |

AE, adverse event; bd, two times a day; DEXA, dual-energy X-ray absorptiometry; FP, fluticasone propionate; ICS, inhaled corticosteroids; RCT, randomised controlled trial.

### Observational studies of bone mineral density and fractures—adults

| Study | Ascertainment of BMD/fracture | Ascertainment of ICS exposure | Definition of ICS use | Adjustments | ICS exposure | Results of BMD (g/cm²) and fractures |
|-------|-------------------------------|-------------------------------|-----------------------|-------------|--------------|-------------------------------------|
| El et al [24] | DEXA lumbar spine (L1–4) and femoral neck | Compliance checked: poor Duration: mean duration (SD) (years): 2.79±1.77 | Regular ICS >6 months Type of inhaler: not reported Type of ICS: not reported | Age | Cases | Mean lumbar: 0.925, SD 0.211 | Mean femoral neck: 0.746, SD 0.127 |
| Johannes et al [26] | Non-vertebral identified by ICD-9 codes and insurance claim for fracture treatment within 2 weeks | Compliance checked: not reported Duration: 1 Year ICS exposure | ICS use from pharmacy claims in the 365 days before index date. Type of inhaler: not reported Type of steroid: BDP, BUD, FP, flunisolone, triamcinolone | Demographics—age, sex, region, time and season Comorbidities—wide range of cardiovascular, endocrine, metabolic and musculoskeletal conditions Medications—oral corticosteroids, bisphosphonates, statins, anticonvulsants, oestrogen, raloxifene, calcitonin Healthcare utilisation for underlying respiratory disease | Cases | Mean daily ICS dose 326.43 µg Controls (no exposure) | 1–167 µg 168–504 µg 505–840 µg >840 µg | 0.99 1.00 95% CI 0.84 to 1.18 OR 1.02 95% CI 0.83 to 1.26 OR 1.14 95% CI 0.80 to 1.62 0.99 95% CI 0.66 to 1.50 |
| Sosa et al [28] | DEXA lumbar spine (L2-L4) and proximal femur | Compliance: not reported Duration of follow up: | ICS for >1 year Type of inhaler: not reported | Age | Cases (dose not reported) | Lumbar spine: 0.960; 95% CI 0.925 to 0.995 Femoral neck: 0.776; 95% CI 0.725 to 0.827 |
### Table 2 Continued

**Observational studies of bone mineral density and fractures—adults**

| Study                        | Ascertainment of BMD/fracture | Ascertainment of ICS exposure | Definition of ICS use | Adjustments | ICS exposure | Results of BMD (g/cm²) and fractures |
|------------------------------|-------------------------------|-------------------------------|-----------------------|-------------|--------------|--------------------------------------|
| Wisniewski et al<sup>30</sup> | Posterior-anterior spine (L2–4), lateral spine (body of L3) measured by DEXA once. All scans by same radiographer (blinded) | Compliance checked: Adequate | ICS for > 5 years | None | 95% CI 0.750 to 0.802 | Fractures: 22/105 (21.0%) |
|                              | Median duration of use of ICS (years) | Duration: | Type of inhaler: Metered dose inhaler—36 patients; dry powder inhaler—11 patients | | Controls | Lumbar spine: 0.991; 95% CI 0.960 to 1.022 |
|                              | Men: 9.00 | Median duration of use of ICS (years) | | | Femoral neck: 0.780; 95% CI 0.758 to 0.803 | |
|                              | Women: 6.29 | | | | Fractures: 9/133 (7.0%) | |
| Yanik et al<sup>31</sup>     | DEXA lumbar spine and hip (femoral neck and trochanter). Patient-reported history of fractures | Compliance checked: Adequate | Regular ICS | None | Controls | Lumbar spine±SD |
|                              | Duration of Follow-up: 4.3±2.6 years | Duration: | >12 months | | Men: 1.28±0.13; Women: 1.04±0.14 | |
|                              | | Median duration of use of ICS (years) | | | Femoral neck±SD: Men: 1.17±0.18; Women: 1.09±0.14 | |
|                              | | | | | Vertebra fractures overall: 2/47 | |
|                              | | | | | Controls (No exposure) | Lumbar spine±SD |
|                              | | | | | Men: 1.21±0.17; Women: 1.25±0.12 | |
|                              | | | | | Femoral neck±SD: Men: 1.04±0.14; Women: 1.10±0.14 | |
|                              | | | | | Vertebra fractures overall: 6/34 | |
|                              | | | | | Cases (total) | Lumbar spine± SD |
|                              | | | | | Mean daily ICS dose (μg) (SD): | 0.95±0.29 |
|                              | | | | | BDP, BUD, FP | 0.83±0.12 |
|                              | | | | | Atraumatic vertebral fractures: 4 (8.6%) | |
|                              | | | | | Lumbar spine±SD | 0.88±0.14 |
|                              | | | | | Femoral neck±SD | 0.74±0.23 |
|                              | | | | | Controls | Atraumatic vertebral fracture: 6 (10%) |

BDP, beclometasone dipropionate; BUD, budesonide; DEXA, dual-energy X-ray absorptiometry; FP, fluticasone propionate; ICD, International Classification of Disease; ICS, inhaled corticosteroids.
significantly elevated at higher dose levels, with one study demonstrating an OR of 1.15 (0.89 to 1.48) for children with ≥20 prescriptions, and the other study reporting an OR of 1.17 (0.93 to 1.45) for children using a daily dose of >400 μg beclomethasone dipropionate equivalents.

No consistent association between ICS use and fracture risk in adults was seen in the pooled estimate from four observational studies (overall OR 1.09, 95% CI 0.45 to 2.62; figure 2). There was substantial heterogeneity in this meta-analysis (I²=76%), with Sosa’s study reporting significantly increased fracture risk, while the others did not.

However, we judged a study by Sosa et al. to be at high risk of bias because the control group consisted of relatives and neighbours of patients, the type of ICS was not reported and there were no statistical adjustments for confounders. In this data set, Johannes et al. was the only study reporting fractures according to dose, but this did not demonstrate any consistent trend towards elevated risk at higher doses.

Lumbar spine BMD

Three RCTs and three observational studies reported on comparative change at the lumbar spine in children. ICS use was not associated with significant reductions in BMD as compared to controls in RCTs (mean difference −0.0018 g/cm²; 95% CI −0.0051 to 0.0015 g/cm²; I²=46%) or observational studies (mean difference −0.0075 g/cm²; 95% CI −0.044 to 0.028 g/cm²; I²=42%). There was no clear signal of dose responsiveness in one observational study that separated...
participants into different dose levels, whereas one RCT suggested that longer term users of budesonide with greater cumulative doses had lower BMD compared to those who received lower cumulative doses.

Three RCTs and four observational studies reported on comparative change in BMD at the lumbar spine in adults (figure 4). ICS use was not associated with significant reductions in BMD as compared to controls in RCTs (mean difference $-0.0020 \text{ g/cm}^2$; 95% CI $-0.0030$ to $0.0070 \text{ g/cm}^2$; $I^2=0\%$) or observational studies (mean difference $0.0070 \text{ g/cm}^2$; 95% CI $-0.0450$ to $0.0590 \text{ g/cm}^2$; $I^2=73\%$).

There was sparse data comparing different ICS molecules head to head. Ferguson et al measured lumbar spine BMD and reported a non-significant finding between children randomised to fluticasone propionate $100 \mu\text{g}$ twice daily as compared to budesonide, mean difference $0.0075 \text{ g/cm}^2$ (95% CI $-0.0330$ to $0.0480 \text{ g/cm}^2$).

Maspero conducted a five arm trial that included mometasone and fluticasone propionate in adults. There were no significant differences in lumbar spine and femur BMD between the two compounds at the end of the trial.

Figure 4  BMD in adults, ICS use versus non-use. BMD, bone mineral density; ICS, inhaled corticosteroids; RCT, randomised controlled trial.

Femur/hip BMD for adults
There were three RCTs and four observational studies reporting comparative change in BMD at the femur or hip in adults (figure 4). ICS use was not associated with significant reductions in BMD as compared to controls in RCTs (mean difference $0.0020 \text{ g/cm}^2$; 95% CI $-0.0030$ to $0.0070 \text{ g/cm}^2$; $I^2=0\%$) or observational studies (mean difference $0.0070 \text{ g/cm}^2$; 95% CI $-0.0450$ to $0.0590 \text{ g/cm}^2$; $I^2=73\%$).

There was sparse data comparing different ICS molecules head to head. Ferguson et al measured lumbar spine BMD and reported a non-significant finding between children randomised to fluticasone propionate $100 \mu\text{g}$ twice daily as compared to budesonide, mean difference $0.0075 \text{ g/cm}^2$ (95% CI $-0.0330$ to $0.0480 \text{ g/cm}^2$).

Maspero conducted a five arm trial that included mometasone and fluticasone propionate in adults. There were no significant differences in lumbar spine and femur BMD between the two compounds at the end of the trial.
We did not proceed to constructing a funnel plot for
detection of publication bias because we had less than
10 studies in the meta-analysis of each outcome, and
there was substantial heterogeneity.

DISCUSSION
We focused our systematic review of RCTs and observa-
tional studies on skeletal adverse effects of ICS in patients
with asthma. We did not find convincing evidence of
increased fracture risk with ICS use in adults or children.
Equally, there was no consistent evidence of any signifi-
cant detrimental relationship between ICS use and BMD
at the lumbar spine (in adults and children) or femur (in
adults). There was insufficient data for us to detect any
dose–response relationship, or to judge any potential dif-
fferences between the available ICS molecules.

Our findings should be contrasted with those of other
recent published reviews. There have been at least four
systematic reviews evaluating fractures or BMD in ICS
users, with two earlier reviews demonstrating a signifi-
cant reduction in BMD but no definite impact on frac-
tures. The most recent meta-analyses have identified
a small but statistically significant dose-related increase
in risk of fracture associated with ICS use in patients
with COPD. Our findings differ from these other
reviews as we have specifically focused on ICS use in
patients with asthma. Here, we used very rigid selection
criteria in an attempt to exclude patients with COPD
from our meta-analysis.

The deleterious effects of ICS on BMD seen in previous
meta-analyses could be explained in part by the higher
prevalence of smoking in patients with COPD as previous
studies have shown that smoking has a harmful effect on
BMD, and increasing fracture risk. In addition, as a
group, patients with asthma are likely to be younger and
to have fewer comorbidities than those with COPD which
may impact on BMD and fracture risk. Recent research
indicates that multimorbidity (including cachexia and
low-grade systemic inflammation) is often seen in patients
with COPD, and it is conceivable that these factors may
have a further negative impact on bone formation that
accentuate the risks of ICS in COPD.

ICS therapy may have a positive impact on bone
density through reduction of chronic inflammation and
avoidance of need for acute short courses of oral corti-
costeroids during exacerbations. In addition, ICS may
allow better control of asthma in patients such that they
become more active, thereby slowing or preventing
steroid-induced osteoporosis through the beneficial
effects of physical activity on BMD. Bone mass can also
be influenced by a wide range of other factors (such as
nutrition, genetic make-up, endocrine status and
amount of physical exercise), and ICS may therefore
not be the most important influence on bone density in
patients with asthma.

There are a number of limitations to our systematic
review. Our search was limited to English language
articles. Although, studies have attempted to assess skel-
etal adverse effects in many different ways, we have
limited our review to clinically meaningful outcomes
such as BMD in g/cm² at lumbar spine and femur, and
fractures. We did not have sufficient data from the
primary studies for us to conduct meaningful analyses
on different combinations of drug compounds, inhaler
devices and dosage regimens. Some of the included
studies were published more than a decade ago, and
advances in asthma care may have made their findings
less applicable to current-day patients. We recognise
that there is potential for risk of bias (stemming from
substantial loss to follow-up for BMD measurements) within
this data set. Hence, we are unable to interpret the
effects of ICS in very long-term use of ICS over a decade
or more.

Our systematic review demonstrates that there is no
consistent evidence of serious skeletal harm from use of
ICS. Although there are intrinsic limitations to the evi-
dence, we believe that our systematic review provides
some reassurance to patients and prescribers of ICS.
Our findings enables ICS users to judge the benefits
and harms of their medication in a more accurate
manner and helps to address concerns and uncertainty
surrounding the exact risk of skeletal adverse effects.

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YKL, DG, MT, PB and AMW selected studies and abstracted the data. YKL carried
out the synthesis of the data and wrote the manuscript with critical input from all authors. YKL acts as guarantor for the paper.

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Appendix 1: Search strategy

Ovid SP search of EMBASE and MEDLINE

Database inception to July 2013

Limited to English, Human, with Abstract

Based on combination of Disease terms, Intervention terms, and Adverse Effects known to be associated with the intervention

| Disease term: asthma |
|----------------------|
| AND |
| Intervention term: (beclometasone OR beclomethasone OR fluticasone OR budesonide OR mometasone OR triamcinolone OR inhaled-corticosteroid OR inhaled-corticosteroids OR ciclesonide OR inhaled-steroid or inhaled-glucocorticoid).mp |
| AND |
| Adverse effect terms such as: (fracture$ OR cataract$ or glaucoma$ OR growth OR height OR stature OR pituitary OR hypothalamic OR diabetes OR glucose).mp |

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("Anti-Asthmatic Agents/adverse effects"[MeSH Terms] OR "Administration, Inhalation"[MeSH Terms] OR inhaled-corticosteroid[All Fields] OR inhaled-glucocorticoid[All Fields]) AND ( "bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields])