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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: Inhaled corticosteroids (ICS) may increase risk of fracture in chronic obstructive pulmonary disease, but it is unclear whether such adverse effects also occur in 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 RCTs and controlled observational studies of any ICS (duration at least 52 weeks) compared to non-ICS use in patients with asthma. We conducted meta-analysis of odds ratios for fractures, and mean differences in bone mineral density. Heterogeneity was assessed using the I^2 statistic.

Results: We included 18 studies (seven RCTs and 11 observational studies) in the systematic review. There was no significant association between ICS and fractures in children in one RCT, or in a pooled analysis of two observational studies, (OR 1.02, 95% CI 0.94-1.10). No significant fracture risk in adults was reported in 4 observational studies (pooled OR 1.09, 95% CI 0.45 – 2.62). Meta-analysis of bone mineral density at the lumbar spine did not show significant reductions with ICS use in children (three RCTs and three observational studies), or in adults (three RCTs and four observational studies). Similarly, meta-analysis of bone mineral density at the femur in adults did not demonstrate significant reductions compared to control (three RCTs and four observational studies).

Conclusion: ICS Use for >12 months in adults or children with asthma was not significantly associated with harmful effects on bone mineral density or fractures.

Article Summary

'Strengths and limitations of this study

- Comprehensive search of two databases with independent study selection and data extraction
- Included both observational and randomized studies in adults and/or children with asthma
- Heterogenous nature of studies and the outcome measures which were available for analysis
- Inability to properly assess differences between drugs, type of inhaler device or dose-responsiveness

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Competing Interests Statement

"All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from Asthma UK for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

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. [1] They are therefore considered the gold standard first line preventative therapy and are widely recommended in national and international guidelines. [2 3]

However, long-term ICS use may be associated with adverse effects such as cataract, osteoporosis, fractures, and reduction in growth velocity in children. [4] 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. [4] 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) [5-7]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 COPD patient because of differences in risk factors such as cigarette consumption, multimorbdity, and nutritional problems that are prevalent in COPD patients. [8 9] 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 asthma patients alone.

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

Methods

Study selection criteria

We aimed to focus in 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 52 weeks duration.

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

We also evaluated controlled observational studies (case control, prospective cohort or retrospective cohort) reporting on bone mineral density or risk of fractures 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, and we subsequently updated this through a more focused PubMed search in December 2014 (see eAppendix 1 for search terms and restrictions). We also checked the bibliographies of included studies and 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. 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 pre-formatted 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 pre-specified fracture risk of primary interest, and bone mineral density as secondary. 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, 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. [10]

We aimed to use a funnel plot to assess publication bias provided that there were more than 10 studies in the meta-analysis, and the absence of significant heterogeneity. [11]

Statistical Analysis

We pooled trial data using Review Manager (RevMan) version 5.3.2 (Nordic Cochrane Center, Copenhagen, Denmark). We used the inverse variance method to pool odds ratios for fracture events, and mean differences for bone mineral density (gram per cm squared). In accordance with the recommendations of the Cochrane Handbook, we imputed any

standard deviations from 95% confidence intervals or p-values. [12] We assessed statistical heterogeneity using the I^2 statistic with I^2> 50% indicating a substantial level of heterogeneity.

If a trial had more than one group of non-ICS users, we analysed data from the placebo arm (wherever possible) in preference to data from active comparators such as nedocromil or montelukast. If a trial had several arms involving different ICS doses, we combined all the ICS arms together as recommended by the Cochrane Handbook. [13]

We did not have a pre-registered protocol.

Results

We screened 1886 potentially relevant articles, and finally included 18 studies in our systematic review (comprising seven RCTs, [14-20]and 11 observational studies). [21-31] The process of study selection is shown in Figure 1.

Tables 1 a) and b) show the characteristics of the included RCTs, and the observational studies respectively. Tables 2 a) and b) report on study validity and outcomes in adult and children.

Four of the RCTs focused solely on children, [14 15 19 20] while the remaining three were in adults. [16-18] Treatment duration was up to four years in one study, [15] while the remaining six trials had ICS therapy for between 52-104 weeks. Intervention arms of the trials included fluticasone (5 trials), budesonide (3 trials) and mometasone (one trial).

Five of the observational studies focused solely on children, [21-23 25 29] whilst 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, flunisolone and triamcinolone users.

Study validity

Randomized Controlled Trials (n=7)

Validity assessment of the included RCTs is reported in Table 2. Overall, four of the RCTs reported an appropriate method of sequence generation, whilst 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 done through 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. [26 27 29 30]. Assessment of compliance or adherence to ICS use was reported in 4 studies. [21 22 30 31] 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 4 studies possibly of slightly better

methodological quality because of adequate outcome ascertainment and adjustment for confounders. [26 27 29 30]

Lumbar spine BMD

Three RCTs and three observational studies reported on comparative change at the lumbar spine in children. [15 19 20 22 23 25] (Figure 2) ICS use was not associated with significant reductions in BMD as compared to controls in RCTs (Mean difference -0.0018 g cm-^{2}; 95% CI -0.0051 – 0.0016 g cm-^{2}; I^2=45%) or observational studies (Mean difference -0.0021 g cm-^{2}; 95% CI -0.058 – 0.016 g cm-^{2}; I^2=56%). There was no clear signal of dose responsiveness in one observational study that separated participants into different dose levels, [25] whereas one RCT found that persistent longer-term use of budesonide had significant reduction in BMD compared to non-users. [20]

Three RCTs and four observational studies reported on comparative change in bone mineral density at the lumbar spine in adults (Figure 3). [16-18 24 28 30 31] ICS use was not associated with significant reductions in BMD as compared to controls in RCTs (Mean difference -0.0019 g cm-^{2}; 95% CI -0.0075 – 0.0038 g cm-^{2}; I^2=0%) or observational studies (Mean difference -0.0055 g cm-^{2}; 95% CI -0.047 – 0.058 g cm-^{2}; I^2=45%).

Femur/hip BMD for adults

There were three RCTs and four observational studies reporting comparative change in bone mineral density at the femur or hip in adults (Figure 3). [16-18 24 28 30 31] ICS use was not associated with significant reductions in BMD as compared to controls in RCTs (Mean difference 0.0020 g cm-^{2}; 95% CI -0.0030 – 0.0070 g cm-^{2}; I^2=0%) or observational studies (Mean difference 0.0070 g cm-^{2}; 95% CI -0.045 – 0.059 g cm-^{2}; I^2=73%).

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). [32] 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 0.94-1.10, I^2=0%)[27 29] as shown in figure 4. The point estimates of fracture risk had a trend towards elevation at higher dose levels, with one study demonstrating an OR of 1.15 (0.89 – 1.48) for children with ≥20 prescriptions[27], and the other study reporting an OR of 1.17 (0.93 – 1.45) for children using a daily dose of >400 µg BDP equivalents. [29]

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 – 2.62) (Figure 4). [26 28 30 31] There was substantial heterogeneity in this meta-analysis (I^2=76%), with Sosa's study reporting significantly increased fracture risk, [28] whilst 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. [28] In this dataset, 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. [26]

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 randomized to Fluticasone propionate 100 µg twice daily as compared to Budesonide, mean difference 0.0075 g cm-^{2} (95% CI -0.033 to 0.048 g cm-^{2}). [14] 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. [18]

Owing to heterogeneity, we did not proceed to constructing a funnel plot for detection of publication bias.

Discussion

We focused our systematic review of RCTs and observational studies on skeletal adverse effects of ICS in patients with asthma. There was no consistent evidence of any significant detrimental relationship between ICS use and bone mineral density at the lumbar spine (in adults and children) or femur (in adults). Equally, we did not find convincing evidence of increased fracture risk with ICS use in adults or children. There was insufficient data for us to detect any dose-response relationship, or to judge any potential differences between the available ICS molecules.

Our findings should be contrasted with those of other recent published reviews. There have been at least 4 systematic reviews evaluating fractures or bone mineral density in ICS users, with two earlier reviews demonstrating a significant reduction in bone mineral density but no definite impact on fractures. [5 33] 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 chronic obstructive pulmonary disease (COPD). [6 7] 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 bone mineral density seen in previous meta-analyses could be explained in part by the higher prevalence of smoking in COPD patients as previous studies have shown that smoking has a harmful effect on bone mineral density, and increasing fracture risk. [8] In addition, as a group, patients with asthma are likely to be younger and to have fewer co-morbidities than those with COPD which may impact on bone mineral density and fracture risk. Recent research indicates that multi-morbidity (including cachexia and low-grade systemic inflammation) is often seen in patients with COPD, [9] 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 corticosteroids 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 bone mineral density. 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), [1] 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. Although, studies have attempted to assess skeletal adverse effects in many different ways, we have limited our review to clinically meaningful outcomes such as bone mineral density in g cm^{-2} 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 recognize that there is potential for risk of bias (stemming from substantial loss to follow-up for bone mineral density measurements) within this dataset. 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 evidence, 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. Nevertheless, prescribers of ICS should continue to focus on using the lowest effective dose to minimize unexpected adverse consequences of ICS therapy.

References

1. Ricciardolo FLM. The treatment of asthma in children: Inhaled corticosteroids. Pulmonary Pharmacology & Therapeutics 2007;**20**(5):473-82.
2. British-Thoracic-Society/Scottish-Intercollegiate-Guidelines-Network. British Guideline on the Management of Asthma. Thorax 2008;**63 Suppl 4**:iv1-121.
3. National-Asthma-Education-and-Prevention-Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol 2007;**120**(5 Suppl):S94-138.
4. Rossi GA, Cerasoli F, Cazzola M. Safety of inhaled corticosteroids: Room for improvement. Pulmonary Pharmacology & Therapeutics 2007;**20**(1):23-35.
5. Jones A, Fay JK, Burr M, et al. Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease. The Cochrane database of systematic reviews 2002(1):Cd003537.
6. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. Thorax 2011;**66**(8):699-708.
7. Weatherall M, James K, Clay J, et al. Dose-response relationship for risk of non-vertebral fracture with inhaled corticosteroids. Clin Exp Allergy 2008;**38**(9):1451-8.
8. Law MR, Hackshaw AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. BMJ 1997;**315**(7112):841-6.
9. Vanfleteren LE, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;**187**(7):728-35.
10. Loke YK, Golder SP, Vandenbroucke JP. Comprehensive evaluations of the adverse effects of drugs: importance of appropriate study selection and data sources. Ther Adv Drug Saf 2011;**2**(2):59-68.
11. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. CMAJ 2007;**176**(8):1091-6.
12. Higgins JPT, Deeks JJ, Altman DG. Chapter 16. Special topics in statistics. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2008.
13. Higgins JPT, Deeks JJ, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2008.
14. Ferguson AC, Van Bever HP, Teper AM, et al. A comparison of the relative growth velocities with budesonide and fluticasone propionate in children with asthma. Respiratory Medicine 2007;**101 (1)**:118-29.
15. Kelly HW, Van Natta ML, Covar RA, et al. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. Pediatrics 2008;**122 (1)**:e53-61.
16. Kemp JP, Osur S, Shrewsbury SB, et al. Potential Effects of Fluticasone Propionate on Bone Mineral Density in Patients with Asthma: A 2-Year Randomized, Double-Blind, Placebo-Controlled Trial. Mayo Clinic Proceedings 2004;**79 (4)**:458-66.
17. Li JTC, Ford LB, Chervinsky P, et al. Fluticasone propionate powder and lack of clinically significant effects on hypothalamic-pituitary-adrenal axis and bone mineral density over 2 years in adults with mild asthma. Journal of Allergy and Clinical Immunology 1999;**103 (6)**:1062-68.

18. Maspero J, Backer V, Yao R, et al. Effects of mometasone, fluticasone, and montelukast on bone mineral density in adults with asthma. The journal of allergy and clinical immunology In practice 2013;**1**(6):649-55.e1.
19. Roux C, Kolta S, Desfougeres JL, et al. Long-term safety of fluticasone propionate and nedocromil sodium on bone in children with asthma. Pediatrics 2003;**111 (6 Pt 1)**:e706-13.
20. Turpeinen M, Pelkonen AS, Nikander K, et al. Bone mineral density in children treated with daily or periodical inhaled budesonide: The Helsinki early intervention childhood asthma study. Pediatric Research 2010;**68 (2)**:169-73.
21. Agertoft L, Pedersen S. Bone mineral density in children with asthma receiving long-term treatment with inhaled budesonide. American Journal of Respiratory and Critical Care Medicine 1998;**157 (1)**:178-83.
22. Allen HDW, Thong IG, Clifton-Bligh P, et al. Effects of high-dose inhaled corticosteroids on bone metabolism in prepubertal children with asthma. Pediatric Pulmonology 2000;**29 (3)**:188-93.
23. Bahceciler NN, Sezgin G, Nursoy MA, et al. Inhaled corticosteroids and bone density of children with asthma. Journal of Asthma 2002;**39 (2)**:151-57.
24. El O, Gulbahar S, Ceylan E, et al. Bone mineral density in asthmatic patients using low dose inhaled glucocorticosteroids. Journal of Investigational Allergology and Clinical Immunology 2005;**15 (1)**:57-62.
25. Harris M, Hauser S, Nguyen TV, et al. Bone mineral density in prepubertal asthmatics receiving corticosteroid treatment. Journal of Paediatrics and Child Health 2001;**37 (1)**:67-71.
26. Johannes CB, Schneider GA, Dube TJ, et al. The risk of nonvertebral fracture related to inhaled corticosteroid exposure among adults with chronic respiratory disease. Chest 2005;**127 (1)**:89-97.
27. Schlienger RG, Jick SS, Meier CR. Inhaled corticosteroids and the risk of fractures in children and adolescents. Pediatrics 2004;**114 (2 I)**:469-73.
28. Sosa M, Saavedra P, Valero C, et al. Inhaled Steroids Do Not Decrease Bone Mineral Density But Increase Risk of Fractures: Data from the GIUMO Study Group. Journal of Clinical Densitometry 2006;**9 (2)**:154-58.
29. Van Staa TP, Bishop N, Leufkens HGM, et al. Are inhaled corticosteroids associated with an increased risk of fracture in children? Osteoporosis International 2004;**15 (10)**:785-91.
30. Wisniewski AF, Lewis SA, Green DJ, et al. Cross sectional investigation of the effects of inhaled corticosteroids on bone density and bone metabolism in patients with asthma. Thorax 1997;**52 (10)**:853-60.
31. Yanik B, Ayrim A, Ozol D, et al. Influence of obesity on bone mineral density in postmenopausal asthma patients undergoing treatment with inhaled corticosteroids. Clinics 2009;**64 (4)**:313-18.
32. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. . The New England journal of medicine 2000;**343**(15):1054-63.
33. Richy F, Bousquet J, Ehrlich GE, et al. Inhaled corticosteroids effects on bone in asthmatic and COPD patients: a quantitative systematic review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2003;**14**(3):179-90.

Tables

Table 1(a) and (b): Characteristics of Included Trials and Observational Studies

(a) Randomized Controlled Trials

Source	Location	Treatment Duration,	Asthma Criteria	Drug and Inhaler Device	Male, %	Mean Age, (Years)	Mean % Predicted FEV1	Prior ICS use (%)
CAMP 2000/Kelly 2008 [15 32]	Multicentre, 7 centres in U, 1993 - 1999	>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 mcg bd (n=311)	58.2	9.0	93.6	40.5
				Nedocromil 8 mg daily (n=312)	66.0	8.8	93.4	36.5
				Placebo (n=412)	56.0	9.0	94.2	35.9
Ferguson 2006 [14]	Multicentre – 35 centres in 11 countries, 1999-2001	52 weeks	Age 6-9 years persistent asthma ≥ 6 months; FEV1 ≥ 60% predicted; ↑PEFR 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 ± 1.0 years.	90.2 ± 15.6	25% oral steroids past 6 months
				BUD 200 µg bd (n=119) *Turbuhaler*	70	7.4 ± 1.0 years	92.3 ± 17.9	21% oral steroids past 6 months
Kemp 2004 [16]	Multicentre, San Diego, California, United States	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	60	31.6 (18 to 49)	83	0
				FP 440 µg bd (n=51) Metered dose inhaler	59	29.0 (18 to 50)	82	0
				Placebo (n=54)	59	28.4 (18 to 44)	85	0

Li 1999 [17]	7 clinical sites in the United States	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	91	28.0 ± 1.2 (18 – 41)	91 ± 2.9	Not reported
				Placebo bd (n=32) Diskhaler	81	31.1 ± 1.3 (18 – 49)	91 ± 3.0	Not reported
Maspero 2013 [18]	50 centres worldwide	52 weeks	Adults with >3 months history of asthma, and not using ICS past 3 months. FEV1 between 60-90% predicted. Must have DEXA scan, and no evidence of low Vitamin D.	Mometasone 400 mcg daily (n=137)	34	30	76.5	7
				Mometasone 200 mcg daily (n=140)	35	30	74.7	7
				FP 250 mcg bd (n=147)	39	28	75.3	6
				Montelukast 10 mg (n=142)	38	28	76.9	10
Roux 2003 [19]	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 100µg bd (n=87) Diskus/Accuhaler dry powder inhaler	64	9.1 ± 2.5	88.9 ± 12.4	Not reported
				Nedocromil sodium 4mg bd (n=87) MDI	66	9.4 ± 2.4	88.5 ± 14.1	Not reported
Turpeinen 2010 [20]	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 enrollment.	Continuous BUD (n=50) Turbuhaler BUD 400 µg bd for 1 month, then 200 µg bd for 2nd – 6th months, then 100 µg bd for 7th – 18th months	60	6.9	Not reported	Not reported

				BUD/Placebo (n=44) Turbuhaler BUD 400 µg bd for 1st month, then 200 µg bd for 2nd to 6th months, then placebo for 7th – 18th months	66	6.7	Not reported	Not reported
				Sodium cromoglicate – 10mg tds for 1st to 18th months (unblinded) (n=42) Inhaler device: MDI	50	7.0	Not reported	Not reported

BDP: beclometasone diproprionate; BUD: budesonide; FP: fluticasone propionate; MDI: Metered dose inhaler; DPI: Dry powder inhaler

(b) Observational studies

Study	Design	Adverse Effects Measured	Data source and Number of Patients	Selection of patients: Asthma definition & Patient Characteristics (or Selection of Cases and Controls)	Type of ICS
Agertoft and Pedersen 1998 [21]	Cross-sectional study	Bone Mineral Density	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 2000 [22]	Prospective	Bone Mineral Density	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 (SD): 7.8 ± 2.4 years, Male 63% *Selection of controls*: children not using corticosteroids. Mean age (SD): 8.4 ± 1.7 years, Male 78%	BDP, BUD
Bahceciler 2002 [23]	Cross-sectional study	Bone mineral density	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 ≥ six months. Male 42%, Mean age (SD): 6.4 ± 2.2 years *Characteristics of high dose ICS group:* Mean age: 3 years (range: 3 to 10.5 years) Mean duration of disease: 50.4 months (range: 18 to 108 months) *Characteristics of low dose ICS group:*	BUD

				Mean age: 5.8 years (range: 1.5 to 10.5 years) Mean duration of disease: 38.3 months (range: 6 to 84 months) *Selection of controls:* Age-matched asthmatic children who have never received ICS. Male 45% , Mean age (SD): 6.8 ± 2.2 years	
El 2005 [24]	Observational	Bone mineral density	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 regular ICS use.: Male 0% l Mean age (SD) (years): 44.04 ± 8.67, %FEV1: 89.71 ± 17.13 *Controls :* Male 0%; Mean age (SD) (years): 44.43 ± 8.68	Not specified.
Harris 2001 [25]	Cross-sectional study	Bone mineral density	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 4 groups according to corticosteroid treatment received in the last 6 months. 1) no inhaled corticosteroid Male 70%, Mean age (SD): 8.2 ± 1.5 years 2) moderate dose inhaled corticosteroid (400 – 800µg/day), Male 56%, Mean age (SD): 7.4 ± 1.3 years 3) high dose inhaled corticosteroid (>800µg/day), Male 75%, Mean age (SD): 8.9 ± 1.8 years	BDP, BUD, FP
Johannes 2005 [26]	Nested case-control study	Risk of nonvertebral fracture	Ingenix Epidemiology – Research database of United Healthcare members, 17 states	*Selection of cases:* Adults ≥ 40 yrs age, in health plan for ≥ 12 continuous months Jan 1997 to Jun 2001, with ≥ 2 claims for doctor visit in outpatient setting or ≥1 claim in inpatient setting with ICD-9	BDP, BUD, FP flunisolone, triamcinolone

			in the United States. 1722 cases, 17220 controls.	code for asthma, or COPD. Selection of cases from cohort: Nonvertebral fractures by ICD-9 codes, with claim for treatment.(including inpatient hip fractures) Male 29.4%. Mean age 52.9 years *Selection of controls:* Sampled from person-time of respiratory cohort by two-tiered random sampling with replacement. Male 41.1%. Mean age 52.2 years	
Schlienger 2004 [27]	Retrospective Population-based nested case-control analysis	Fracture risk	United Kingdom General Practice Research Database. 3744 cases, 21757 controls.	*Selection of cohort:* Aged 5 to 79 years with ICD code for asthma or COPD with ≥1 prescription for ICS and/or OCS; or with no exposure to corticosteroids. (3) random sample 50 000 individuals aged 5 to 79 years ; no respiratory disease or corticosteroids. From there 65 779 individuals aged 5 to 17 years identified to form base population for study. *Selection of cases:* Patients with 1st-time diagnosis ICD-8 bone fracture; 65.6% male. *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; 64.9% male	76.2 % BDP 21.7% BUD 2.1% FP
Sosa 2006 [28]	Cross-sectional study	Bone mineral density; Fracture risk	Canary Islands, Spain. 105 cases; 133	*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 (SD): 53.0 ± 13.7 years, Number of menopausal subjects *n* (%): 65 (61.9)	ICS formulations not specified

			controls	*Selection of controls:* Weight-matched women, no asthma and no steroids. Controls were usually friends or neighbours of the patients. Mean age (SD): 49.7 ± 11.2 years, Number of menopausal subjects *n* (%): 74 (57.8)	
Van Staa 2004 [29]	Population-based cohort study/ nested case-control analysis.	Fracture risk	UK General Practice Research Database (GPRD). Cohort: ICS users: 97387 Bronchodilators only: 70984 Controls: 345758 Fracture cases: 23984; Controls: 23984	*Selection of cohort:* Children aged 4 – 17 years old, on ICS. 3 study groups: *Selection of cases:* Non-vertebral fracture. Male 61.0%, 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 61.0%, 8861 (36.9%) aged 4-9 years, 8497 (35.4%) aged 10-13 years, 6626 (27.6%) aged 14-17 years	BDP, BUD, FP
Wisniewski 1997 [30]	Cross-sectional study	Bone mineral density	Asthma register and local general practices in Nottingham, United Kingdom 47 cases; 34 controls	*Selection of cases:* Aged 20 – 40 years with documented history of asthma: Group 1: asthmatics using inhaled β_2-agonist only. Males 56%, Mean age (years) (SD): men: 30.3 (6.4); women: 25.6 (5.5), Mean FEV1 (litres) (SD): men: 3.87 (0.59); women: 3.13 (0.45) Group 2: ICS use ≥ 5 years with no systemic steroids in the past 6 months. Males 40%, Mean age (years) (SD): men: 32.3 (6.2); women: 32.0 (5.9) Mean FEV1 (litres) (SD): men: 3.40 (0.85); women: 2.83 (0.50)	BDP, BUD

Yanik 2009 [31]	Observational	Bone mineral density	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. Male 0%, Mean age (SD): 62.5 ± 10.6 years, Mean FEV1 (% predicted) (SD): 83.1 ± 17.8, All cases were postmenopausal *Selection of controls:* Healthy postmenopausal females. Mean age (SD): 63.0 ± 6.1 years.	BDP, BUD, FP,

Abbreviations: Beclomethasone dipropionate (BDP); fluticasone propionate (FP); budesonide (BUD); FEV1 (Forced Expiratory Volume in 1 second)

Table 2 (a) RCTs and (b) Observational studies: Study Validity and Outcomes (Bone Mineral Density and Fractures) in Children

(a) **Risk of bias assessment and Bone mineral density outcomes in RCTs of inhaled corticosteroids- Children**

Source	Sequence generation	Allocation Concealment	Blinding	AE monitoring	Adverse Events	Dis-continued, No. (%)	Loss to follow-up, No (%)
CAMP 2000/ Kelly 2008 [15 32]	Permuted blocks, stratified	Adequate	Double-blind	Height recorded at every visit; BMD once every year.	Fracture rate (adjusted for age at randomization, race or ethnic group, sex, clinic, base line duration, skin-test reactivity and severity of asthma): Budesonide: 5.7 per 100 person-years Placebo: 5.1 per 100 person-years P=0.59 Mean difference in BMD (ICS vs. placebo): Females: -0.001 (imputed SE 0.0016) Male:-0.003 (imputed SE 0.0014)	11%	5%
Ferguson 2006 [14]	Not reported	Remote computerized allocation	Double-blind	Lumbar-spine bone mineral density (BMD) assessed at beginning and end of treatment with DEXA scan.	Mean difference in lumbar spine BMD for FP vs Budesonide: 0.0075 (95% CI -0.033 to 0.048)	90% patients received > 40 weeks	26% did not reach 51 weeks
Roux 2003 [19]	Unclear	Central Block randomization with gender stratification.	Largely Open. Analysis of DEXA scans blinded	Lumber spine and femoral neck BMD (DEXA) during run-in and 6, 12 and 24 months. Adjusted for age, height, weight, baseline BMD, gender & measuring device.	Mean difference in lumbar spine BMD for FP vs control: 0.012 (SE 0.0073); values calculated from % change in manuscript.	23%	4%

Turpeine n 2010 [20]	Block	Unclear	Partial Blinding	Bone mineral density of L1 - 4 measured by 1 radiologist using DEXA at baseline and at 18 months.	Mean change in lumbar spine BMD: All budesonide patients: 0.026 (SD 0.022) DSCG: 0.034 (SD 0.022) Longer term budesonide 0.023 (SD 0.022) Shorter term budesonide 0.029 (SD 0.022)	20%	3%

BDP: beclometasone diproprionate; BUD: budesonide; FP: fluticasone propionate; MDI: Metered dose inhaler

DSCG, Disodium cromoglicate;

(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^{-2})
Agertoft and Pedersen 1998 [21]	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:* pMDI; Turbuhaler *Type of Steroid:* BUD	Log of accumulated dose of budesonide; gender; age.	Mean ICS Budesonide dose 504 µg (daily)	Mean BMD: Budesonide group: 0.92 Control group: 0.92
Allen 2000 [22]	DEXA scan at baseline and again at 9 – 20 months later. Value for 12-month time point calculated with all outcomes	Compliance checked: Adequate Duration of follow-up: 9-20 months	*Type of Inhalor:* Spacer, Turbohaler *Type of Steroid:* BDP, BUD	Age; height; weight; dose of inhaled corticosteroid	Mean ICS Dose 0.67 ± 0.48 mg/m^2/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 2002 [23]	Anteroposterior (AP) spine (L2-4) by DEXA scan	Compliance: Not reported Follow-up: 13.0 ± 9.8 months	Use of BUD as MDI ≥ 6 months.	None	ICS Mean daily dose (SD): 419 ±154 µg	Mean Lumbar spine BMD: ICS group: 0.593 (SD 0.122)
					Control	Mean Lumbar spine BMD: 0.579 (SD 0.156)
Harris 2001 [25]	Lumbar spine by DEXA.	Compliance checked: Not reported Duration of follow up: 3.5 ± 2.4 years	Stratified by treatment in last 6 months *Type of inhaler:* Spacer device *Type of Steroid: BDP,* BUD, FP	Weight	0 µg/day	Mean lumbar spine BMD (SD) 0.68 (0.07)
					400 - 800µg/day	Mean lumbar spine BMD (SD) 0.70 (0.08)
					>800µg/day	Mean lumbar spine BMD (SD) 0.67 (0.08)

Studies reporting on Fracture risk						**Fracture Outcomes**
Schlienger et al 2004 [27]	Identified by ICD-8 codes 800.x – 829.x, from computerised records Cases = 1st-time diagnosis of bone fracture Controls – no fracture	Compliance checked: Not reported Duration: Median number of prescriptions: 26, corresponds to >7 years of continuous exposure	ICS use in United Kingdom General Practice Research Database. *Type of inhaler:* not reported *Type of Steroid:* BDP, BUD, FP	Age, gender, general practice, calendar time, years in GPRD controlled by matching. Comorbidities: chronic renal failure, hyperthyroidism, hyperparathyroidism, inflammatory bowel disease, malnutrition, malabsorption. Medications: asthma drugs, psychotropic drugs, antihypertensives, calcium, fluoride, vitamin D.	1-9 prescriptions Cases: n = 332 Controls: n = 2017	Adjusted OR: 0.97 (0.85 – 1.11)
					10 to 19 prescriptions Cases: n = 124 Controls: n = 682	Adjusted OR: 1.08 (0.87 – 1.33)
					≥20 prescriptions Cases: n = 88 Controls: n = 422	Adjusted OR: 1.15 (0.89 – 1.48)
					All ICS users combined	Adjusted OR: 1.01 (0.90-1.13)
Van Staa 2004 [29]	Ascertained from diagnoses within computer records	Compliance not reported Duration: Children followed (1987 onwards) or from age 4 years until (December 1997) or age 18 years.	Current users of ICS *Type of Inhaler:* not reported *Type of inhaled Steroid:* BDP, BUD, FP	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.	200 µg	Adjusted OR : 0.96 (0.83 – 1.12)
					201 – 400 µg	Adjusted OR: 1.07 (0.93 – 1.24)
					>400 µg	Adjusted OR: 1.17 (0.93 – 1.45)
					All ICS users	Adjusted OR 1.03 (0.93 – 1.15)

BDP: beclometasone diproprionate; BUD: budesonide; FP: fluticasone propionate; MDI: Metered dose inhaler

Table 3 (a) RCTs and (b) Observational Studies Study Validity and Outcomes (Bone Mineral Density and Fractures) in Adults

Risk of bias assessment and Bone mineral density outcomes in RCTs of inhaled corticosteroids - Adults

Source	Sequence generation	Allocation Concealment	Blinding	AE monitoring	Drug (n)	Mean change in BMD g/cm^2	Dis-continued, No. (%)	Loss to follow-up, No (%)
Kemp 2004 [16]	Adequate	Adequate	Double-blinding Adequate	DEXA scan every 6 months at lumbar spine (L1-L4). Analyzed 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 1999 [17]	Unclear	Unclear	Double-blinding 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 2013 [18]	Adequate	Adequate	Double blinding adequat	DEXA at L1-L4 of lumbar spine. Follow-up at 26	Mometasone 400 µg	*1) Lumbar spine:* 0.009 *2) Femur:* 0.004	34 (25)	5 (3)

			e	and 52 weeks.	Mometasone 200 µg daily	*1) Lumbar spine:* 0.008 *2) Proximal femur:* 0.004	35 (25)	7 (4)
					FP 250 µg bd	*1) Lumbar spine:* 0.012 *2) Femur:* -0.005	38 (26)	4 (3)
					All ICS	*1) Lumbar spine:* 0.009 *2) Femur:* 0.0008	107 (25)	16 (4)
					Montelukast 10 mg daily	*1) Lumbar spine:* 0.013 *2) Femur:* -0.002	31 (22)	3 (3)

AE, adverse event; BDP, beclometasone diproprionate; BUD, budesonide; DEXA dual-energy X-ray absorptiometry; DSCG, Disodium cromoglycate; FP: fluticasone propionate; NA, not available; RCT, randomized controlled trial; SAE, serious AE

(a) 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 2005 [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 daily ICS dose 326.43 µg	*Mean* Lumbar*:* 0.925, SD 0.211 Mean Femoral neck: 0.746, SD 0.127
					Controls (No exposure)	*Mean* Lumbar: *BMD*: 0.927, SD 0.229 Mean Femoral neck: 0.792, SD 0.097
Johannes 2005 [26]	Nonvertebral identified by ICD-9 diagnosis codes in association with insurance claim for fracture treatment within 2 weeks of diagnosis.	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. Co-morbidities – wide range of cardiovascular, endocrine, metabolic and musculoskeletal conditions. Medications - oral corticosteroids, bisphosphonates, statins, anticonvulsants, oestrogen, raloxifene, calcitonin. Health-care utilisation for underlying respiratory disease	1 – 167µg	OR 1.00 95% CI: 0.84 – 1.18
					168 – 504µg	OR: 1.02 95% CI: 0.83 – 1.26
					505 – 840µg	OR: 1.14 95% CI: 0.80 – 1.62
					> 840µg	0.99 95% CI: 0.66 – 1.50
Sosa 2006 [28]	DEXA lumbar spine (L2–L4) and proximal femur	Compliance: Not reported Duration of Follow up: Median treatment with ICS: 10 years	ICS for > 1year. *Type of inhaler:* Not reported *Type of ICS:* Not reported	Age	Cases (dose not reported)	Lumbar spine: 0.960; 95% CI: 0.925 – 0.995 Femoral neck: 0.776; 95% CI: 0.750 – 0.802 Fractures: 22/105 (21.0%)
					Controls	Lumbar spine: 0.991; 95% CI: 0.960 – 1.022 Femoral neck: 0.780; 95% CI: 0.758

						–0.803 Fractures: 9/133 (7.0%)
Wisniewski 1997 [30]	Posterior-anterior spine (L2-4), lateral spine (body of L3) measured by DEXA once. All scans by same radiographer (blinded).	Compliance checked: Adequate Duration: Median duration of use of ICS (years) Men: 9.00 Women: 6.29	ICS for > 5 years *Type of inhaler:* Metered dose inhaler – 36 patients; dry powder inhaler – 11 patients. *Type of ICS:* BDP, BUD	age; weight; smoking; alcohol; activity grade; asthma severity; age at menarche; lifetime total dose of oestrogen and progesterone; prednisolone use.	Cases	*Lumbar spine* ± *SD* Men : 1.28± 0.13; Women: 1.04 ±0.14 Femoral neck ± *SD*: Men : 1.17± 0.18; Women: 1.09 ±0.14 Vertebral fractures overall: 2/47
					Controls (No exposure)	*Lumbar spine* *Men:*1.21±0.17*;* *Women:* 1.25 ±0.12 Femoral neck ± *SD*: Men : 1.04± 0.14; Women: 1.10 ±0.14 Vertebral fractures overall: 6/34
Yanik 2009 [31]	DEXA lumbar spine and hip (femoral neck and trochanter). Patient-reported history of fractures.	Compliance checked: Adequate Duration of Follow up: 4.3 ±2.6 years	Regular ICS > 12 months *Type of inhaler:* Not reported *Type of ICS:* BDP, BUD, FP	None	Cases (total) Mean daily ICS dose (µg) (SD): 324.9 ± 121.8	Lumbar spine ± *SD* 0.95 ± 0.29 Femoral neck ± *SD* 0.83 ± 0.12 Atraumatic vertebral fractures: 4 (8.6%)
					Controls	Lumbar spine ± *SD* 0.88 ± 0.14 Femoral neck ± *SD* 0.74 ± 0.23 Atraumatic vertebral fracture: 6 (10%)

BDP, beclometasone diproprionate; BUD, budesonide; FP: fluticasone propionate

Figure 1. Flow Diagram of Study Selection

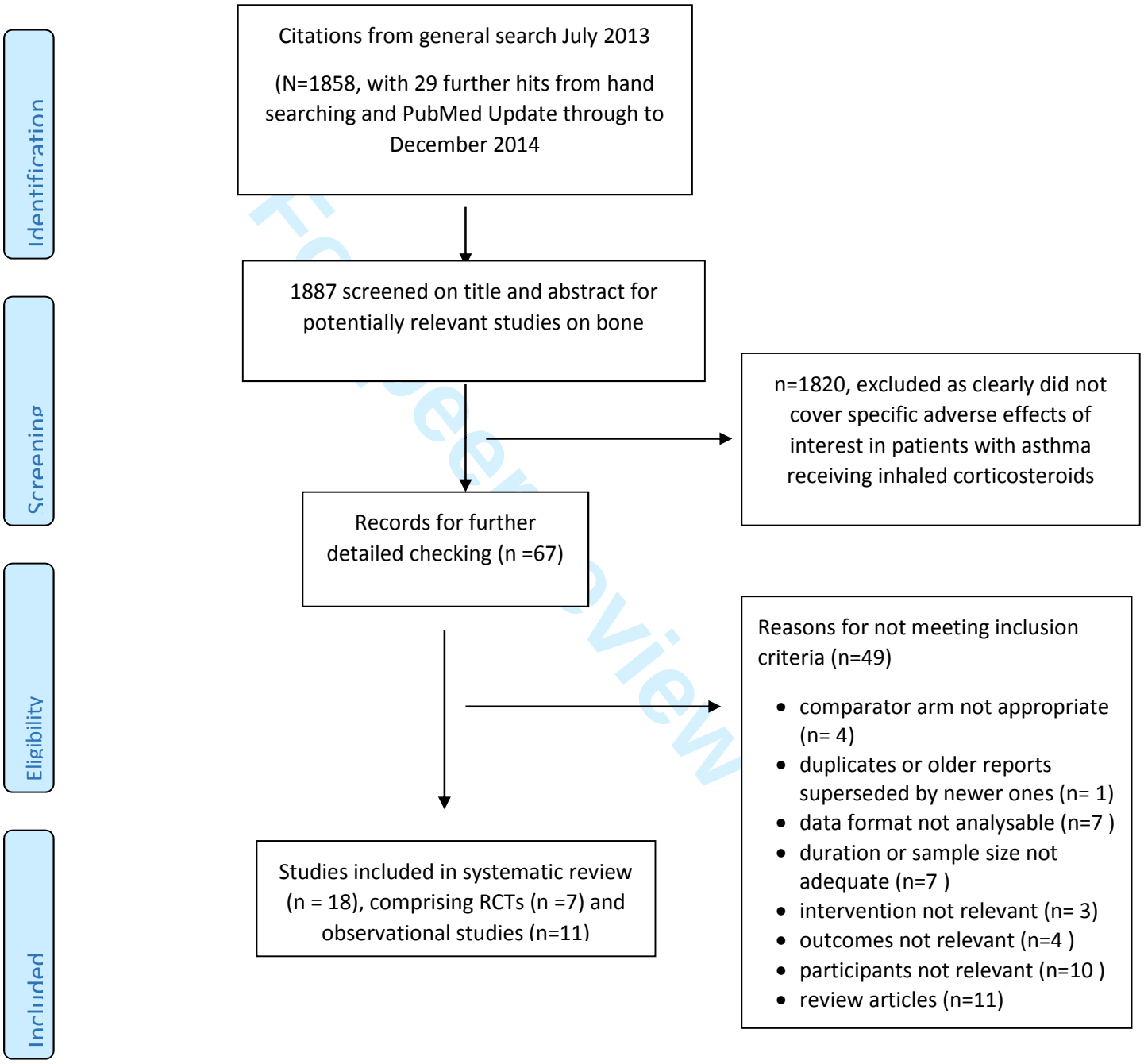


Figure 2. BMD in Lumbar Spine Children, ICS use vs. Non-use

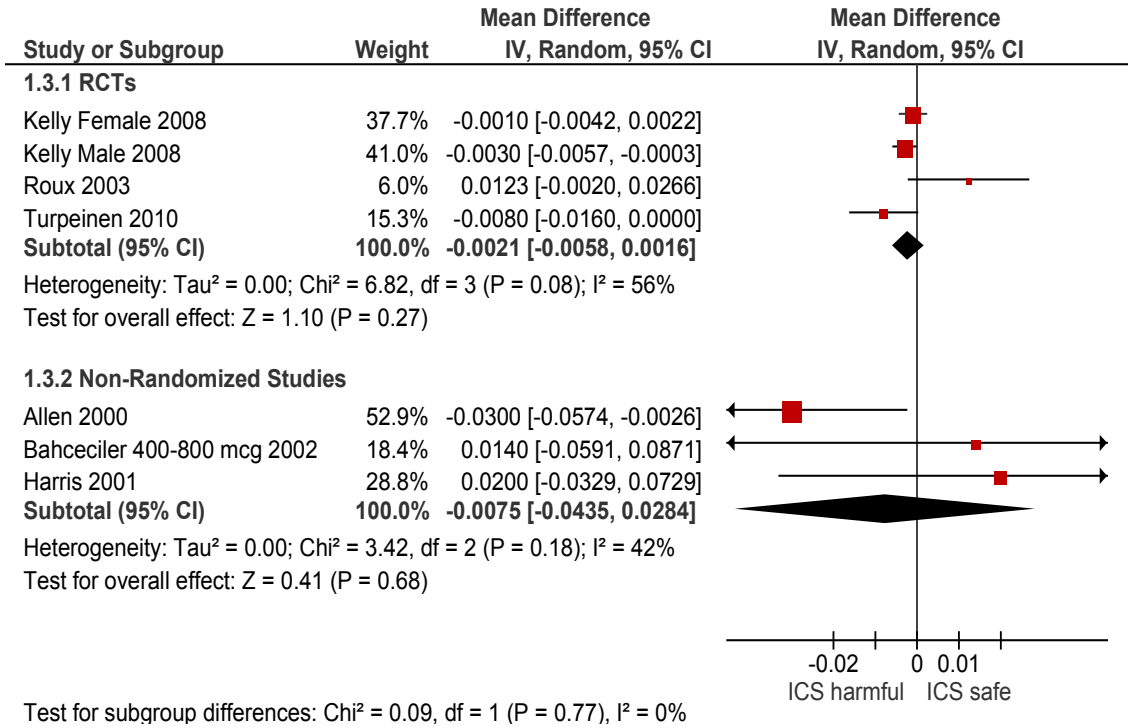


Figure 3. BMD in Adults Lumbar Spine and Femur, ICS use vs. Non-use

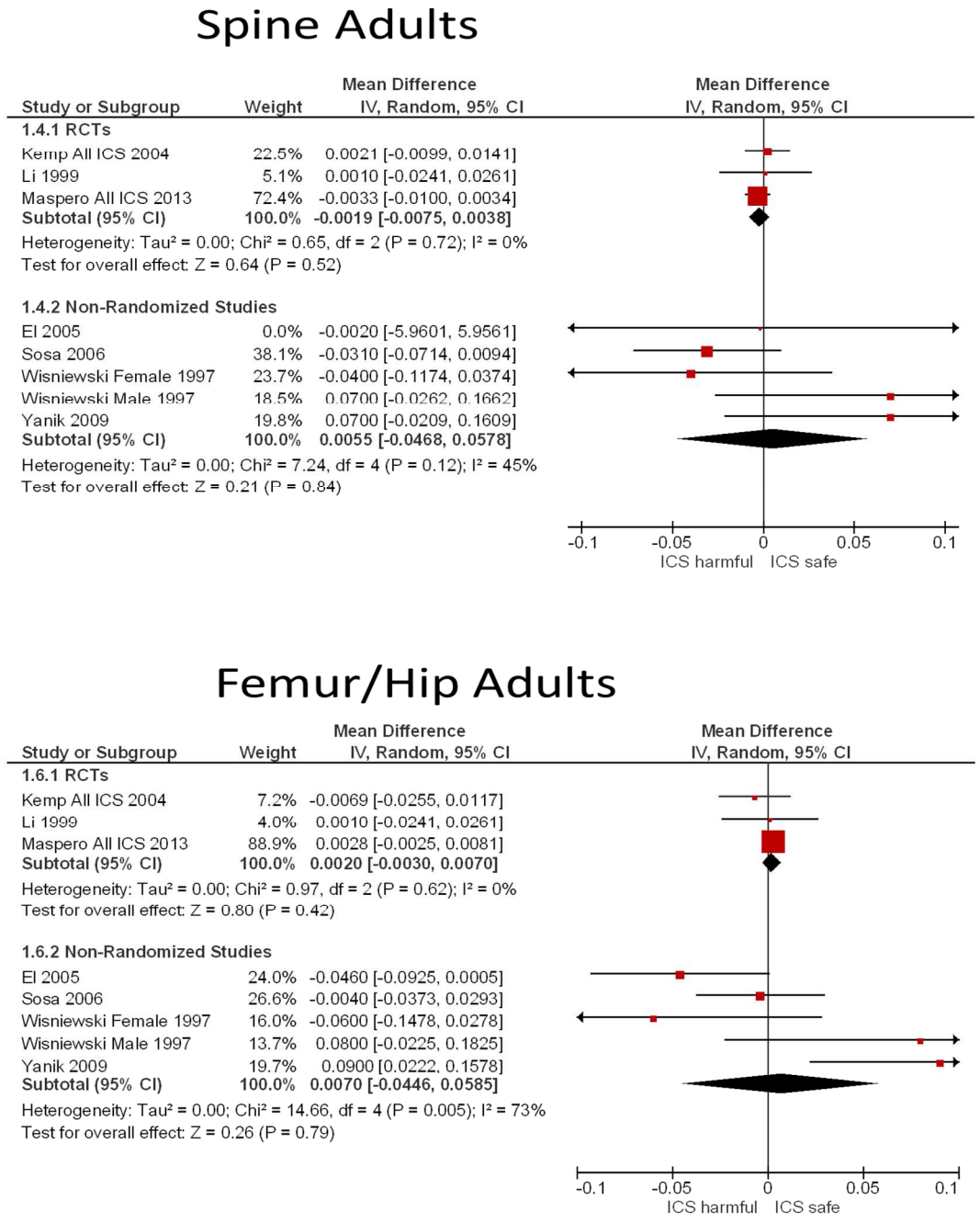
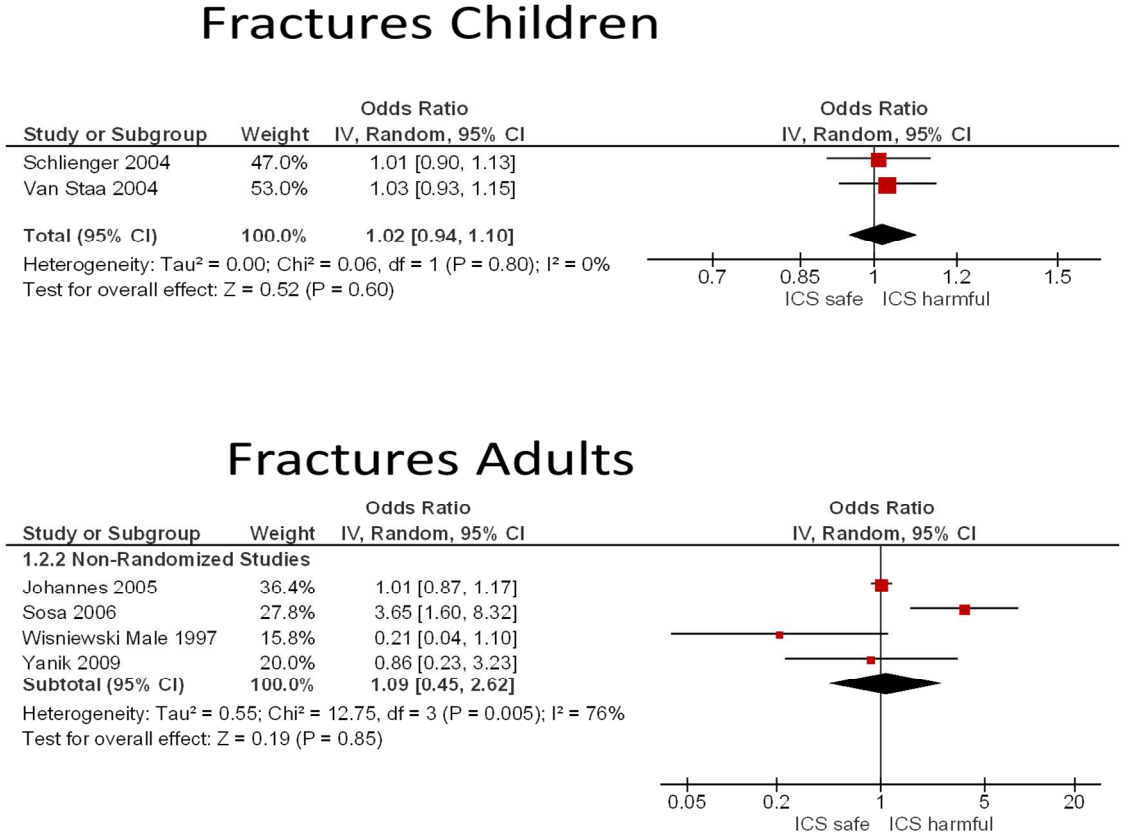


Figure 4. Fracture Risk Children and Adults, ICS use vs. Non-use



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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PubMed Update June and Dec 2014

("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 and bones"[All Fields] OR "bone"[All Fields]) OR ("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields])) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields])

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, Table 2-3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig. 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig. 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

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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Manuscript ID	bmjopen-2015-008554.R1
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Date Submitted by the Author:	22-Sep-2015
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Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Respiratory medicine
Keywords:	Adverse events < THERAPEUTICS, Asthma < THORACIC MEDICINE, CLINICAL PHARMACOLOGY

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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Word count: 2822

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 randomized controlled trials (RCTs) and controlled observational studies of any ICS (duration at least one year) compared to non-ICS use in patients with asthma. We conducted meta-analysis of odds ratios (OR) for fractures, and mean differences in bone mineral density. Heterogeneity was assessed using the I^2 statistic.

Results: We included 18 studies (seven 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 0.94-1.10, two studies), or adults (pooled OR 1.09, 95% CI 0.45 – 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.

Conclusion: ICS use for ≥one year in adults or children with asthma was not significantly associated with harmful effects on bone mineral density or fractures.

Article Summary

‘Strengths and limitations of this study

- Comprehensive search of two databases with independent study selection and data extraction
- Included both observational and randomized studies in adults and/or children with asthma
- Heterogenous nature of studies and the outcome measures which were available for analysis
- Inability to properly assess differences between drugs, type of inhaler device or dose-responsiveness

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. [1] They are therefore considered the gold standard first line preventative therapy and are widely recommended in national and international guidelines. [2 3]

However, long-term ICS use may be associated with adverse effects such as cataract, osteoporosis, fractures, and reduction in growth velocity in children. [4] 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. [4] 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) [5-7]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 COPD patient because of differences in risk factors such as cigarette consumption, multimorbidity, and nutritional problems that are prevalent in COPD patients. [8 9] 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 asthma patients alone.

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

Methods

Study selection criteria

We aimed to focus in 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 one year in duration.

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

We also evaluated controlled observational studies (case control, prospective cohort or retrospective cohort) reporting on bone mineral density or risk of fractures 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 pre-formatted 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 pre-specified fracture risk of primary interest, and bone mineral density at the lumbar spine or the femur as secondary endpoints. 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,randomization 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. [10]

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. [11]

Statistical Analysis

We pooled trial data using Review Manager (RevMan) version 5.3.2 (Nordic Cochrane Center, Copenhagen, Denmark). We used the inverse variance method to pool odds ratios for fracture events, and mean differences for bone mineral density (gram cm^{-2}). In accordance with the recommendations of the Cochrane Handbook, we derived any standard deviations from 95% confidence intervals or p-values. [12] We assessed statistical heterogeneity using the I^2 statistic with I^2> 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. [13]

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 seven RCTs, [14-20]and 11 observational studies). [21-31] The process of study selection is shown in Figure 1.

Tables 1 a) and 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, [14 15 19 20] while the remaining three were in adults. [16-18] Treatment duration was up to four years in one study, [15] while the remaining six trials had ICS therapy for between 52-104 weeks. Intervention arms of the trials included fluticasone (5 trials), budesonide (3 trials) and mometasone (one trial).

Five of the observational studies focused solely on children, [21-23 25 29] whilst 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.

Randomized Controlled Trials (n=7)

Overall, four of the RCTs reported an appropriate method of sequence generation, whilst 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 done through 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. [26 27 29 30]. Assessment of compliance or adherence to ICS use was reported in 4 studies. [21 22 30 31] 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 4 studies possibly of slightly better

methodological quality because of adequate outcome ascertainment and adjustment for confounders. [26 27 29 30]

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). [32] 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 0.94-1.10, I^2=0%)[27 29] as shown in figure 2. The point estimates of fracture risk was not significantly elevated at higher dose levels, with one study demonstrating an OR of 1.15 (0.89 – 1.48) for children with ≥20 prescriptions[27], and the other study reporting an OR of 1.17 (0.93 – 1.45) for children using a daily dose of >400 µg BDP equivalents. [29]

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 – 2.62) (Figure 2). [26 28 30 31] There was substantial heterogeneity in this meta-analysis (I^2=76%), with Sosa's study reporting significantly increased fracture risk, [28] whilst 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. [28] In this dataset, 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. [26]

Lumbar spine BMD

Three RCTs and three observational studies reported on comparative change at the lumbar spine in children. [15 19 20 22 23 25] (Figure 3) ICS use was not associated with significant reductions in BMD as compared to controls in RCTs (Mean difference -0.0018 g cm-^{2}; 95% CI -0.0051 – 0.0015 g cm-^{2}; I^2=46%) or observational studies (Mean difference -0.0075 g cm-^{2}; 95% CI -0.044 – 0.028 g cm-^{2}; I^2=42%). There was no clear signal of dose responsiveness in one observational study that separated participants into different dose levels, [25] 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. [20]

Three RCTs and four observational studies reported on comparative change in bone mineral density at the lumbar spine in adults (Figure 4). [16-18 24 28 30 31] ICS use was not associated with significant reductions in BMD as compared to controls in RCTs (Mean difference -0.0019 g cm-^{2}; 95% CI -0.0075 – 0.0038 g cm-^{2}; I^2=0%) or observational studies (Mean difference -0.0055 g cm-^{2}; 95% CI -0.047 – 0.058 g cm-^{2}; I^2=45%).

Femur/hip BMD for adults

There were three RCTs and four observational studies reporting comparative change in bone mineral density at the femur or hip in adults (Figure 4). [16-18 24 28 30 31] ICS use was not associated with significant reductions in BMD as compared to controls in RCTs (Mean difference 0.0020 g cm-^{2}; 95% CI -0.0030 – 0.0070 g cm-^{2}; I^2=0%) or observational studies (Mean difference 0.0070 g cm-^{2}; 95% CI -0.045 – 0.059 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 randomized to Fluticasone propionate 100 µg twice daily as compared to Budesonide, mean difference 0.0075 g cm-^{2} (95% CI -0.033 to 0.048 g cm-^{2}). [14] 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. [18]

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 observational studies on skeletal adverse effects of ICS in patients with asthma. There was no consistent evidence of any significant detrimental relationship between ICS use and bone mineral density at the lumbar spine (in adults and children) or femur (in adults). Equally, we did not find convincing evidence of increased fracture risk with ICS use in adults or children. There was insufficient data for us to detect any dose-response relationship, or to judge any potential differences between the available ICS molecules.

Our findings should be contrasted with those of other recent published reviews. There have been at least 4 systematic reviews evaluating fractures or bone mineral density in ICS users, with two earlier reviews demonstrating a significant reduction in bone mineral density but no definite impact on fractures. [5 33] 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 chronic obstructive pulmonary disease (COPD). [6 7] 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 bone mineral density seen in previous meta-analyses could be explained in part by the higher prevalence of smoking in COPD patients as previous studies have shown that smoking has a harmful effect on bone mineral density, and increasing fracture risk. [8] In addition, as a group, patients with asthma are likely to be younger and to have fewer co-morbidities than those with COPD which may impact on bone mineral density and fracture risk. Recent research indicates that multi-morbidity (including cachexia and low-grade systemic inflammation) is often seen in patients with COPD, [9] 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 corticosteroids 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 bone mineral density. 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), [1] 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 skeletal adverse effects in many different ways, we have limited our review to clinically meaningful outcomes such as bone mineral density in g cm^{-2} 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 recognize that there is potential for risk of bias (stemming from substantial loss to follow-up for bone mineral density measurements) within this dataset. 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 evidence, 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.

Contributors: YKL and AMW conceptualized the review and obtained funding. 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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Competing Interests Statement

"All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from Asthma UK for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Data sharing

There are no additional unpublished data.

References

1. Ricciardolo FLM. The treatment of asthma in children: Inhaled corticosteroids. Pulmonary Pharmacology & Therapeutics 2007;**20**(5):473-82.
2. British-Thoracic-Society/Scottish-Intercollegiate-Guidelines-Network. British Guideline on the Management of Asthma. Thorax 2008;**63 Suppl 4**:iv1-121.
3. National-Asthma-Education-and-Prevention-Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol 2007;**120**(5 Suppl):S94-138.
4. Rossi GA, Cerasoli F, Cazzola M. Safety of inhaled corticosteroids: Room for improvement. Pulmonary Pharmacology & Therapeutics 2007;**20**(1):23-35.
5. Jones A, Fay JK, Burr M, et al. Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease. The Cochrane database of systematic reviews 2002(1):Cd003537.
6. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. Thorax 2011;**66**(8):699-708.
7. Weatherall M, James K, Clay J, et al. Dose-response relationship for risk of non-vertebral fracture with inhaled corticosteroids. Clin Exp Allergy 2008;**38**(9):1451-8.
8. Law MR, Hackshaw AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. BMJ 1997;**315**(7112):841-6.
9. Vanfleteren LE, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;**187**(7):728-35.
10. Loke YK, Golder SP, Vandenbroucke JP. Comprehensive evaluations of the adverse effects of drugs: importance of appropriate study selection and data sources. Ther Adv Drug Saf 2011;**2**(2):59-68.
11. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. CMAJ 2007;**176**(8):1091-6.
12. Higgins JPT, Deeks JJ, Altman DG. Chapter 16. Special topics in statistics. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2008.
13. Higgins JPT, Deeks JJ, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2008.
14. Ferguson AC, Van Bever HP, Teper AM, et al. A comparison of the relative growth velocities with budesonide and fluticasone propionate in children with asthma. Respiratory Medicine 2007;**101 (1)**:118-29.
15. Kelly HW, Van Natta ML, Covar RA, et al. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. Pediatrics 2008;**122 (1)**:e53-61.
16. Kemp JP, Osur S, Shrewsbury SB, et al. Potential Effects of Fluticasone Propionate on Bone Mineral Density in Patients with Asthma: A 2-Year Randomized, Double-Blind, Placebo-Controlled Trial. Mayo Clinic Proceedings 2004;**79 (4)**:458-66.
17. Li JTC, Ford LB, Chervinsky P, et al. Fluticasone propionate powder and lack of clinically significant effects on hypothalamic-pituitary-adrenal axis and bone mineral density over 2 years in adults with mild asthma. Journal of Allergy and Clinical Immunology 1999;**103 (6)**:1062-68.

18. Maspero J, Backer V, Yao R, et al. Effects of mometasone, fluticasone, and montelukast on bone mineral density in adults with asthma. The journal of allergy and clinical immunology In practice 2013;**1**(6):649-55.e1.
19. Roux C, Kolta S, Desfougeres JL, et al. Long-term safety of fluticasone propionate and nedocromil sodium on bone in children with asthma. Pediatrics 2003;**111 (6 Pt 1)**:e706-13.
20. Turpeinen M, Pelkonen AS, Nikander K, et al. Bone mineral density in children treated with daily or periodical inhaled budesonide: The Helsinki early intervention childhood asthma study. Pediatric Research 2010;**68 (2)**:169-73.
21. Agertoft L, Pedersen S. Bone mineral density in children with asthma receiving long-term treatment with inhaled budesonide. American Journal of Respiratory and Critical Care Medicine 1998;**157 (1)**:178-83.
22. Allen HDW, Thong IG, Clifton-Bligh P, et al. Effects of high-dose inhaled corticosteroids on bone metabolism in prepubertal children with asthma. Pediatric Pulmonology 2000;**29 (3)**:188-93.
23. Bahceciler NN, Sezgin G, Nursoy MA, et al. Inhaled corticosteroids and bone density of children with asthma. Journal of Asthma 2002;**39 (2)**:151-57.
24. El O, Gulbahar S, Ceylan E, et al. Bone mineral density in asthmatic patients using low dose inhaled glucocorticosteroids. Journal of Investigational Allergology and Clinical Immunology 2005;**15 (1)**:57-62.
25. Harris M, Hauser S, Nguyen TV, et al. Bone mineral density in prepubertal asthmatics receiving corticosteroid treatment. Journal of Paediatrics and Child Health 2001;**37 (1)**:67-71.
26. Johannes CB, Schneider GA, Dube TJ, et al. The risk of nonvertebral fracture related to inhaled corticosteroid exposure among adults with chronic respiratory disease. Chest 2005;**127 (1)**:89-97.
27. Schlienger RG, Jick SS, Meier CR. Inhaled corticosteroids and the risk of fractures in children and adolescents. Pediatrics 2004;**114 (2 I)**:469-73.
28. Sosa M, Saavedra P, Valero C, et al. Inhaled Steroids Do Not Decrease Bone Mineral Density But Increase Risk of Fractures: Data from the GIUMO Study Group. Journal of Clinical Densitometry 2006;**9 (2)**:154-58.
29. Van Staa TP, Bishop N, Leufkens HGM, et al. Are inhaled corticosteroids associated with an increased risk of fracture in children? Osteoporosis International 2004;**15 (10)**:785-91.
30. Wisniewski AF, Lewis SA, Green DJ, et al. Cross sectional investigation of the effects of inhaled corticosteroids on bone density and bone metabolism in patients with asthma. Thorax 1997;**52 (10)**:853-60.
31. Yanik B, Ayrim A, Ozol D, et al. Influence of obesity on bone mineral density in postmenopausal asthma patients undergoing treatment with inhaled corticosteroids. Clinics 2009;**64 (4)**:313-18.
32. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. . The New England journal of medicine 2000;**343**(15):1054-63.
33. Richy F, Bousquet J, Ehrlich GE, et al. Inhaled corticosteroids effects on bone in asthmatic and COPD patients: a quantitative systematic review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2003;**14**(3):179-90.

Tables

Table 1(a) and (b): Characteristics of Included Trials and Observational Studies

(a) Randomized Controlled Trials

Source	Location	Treatment Duration	Asthma Criteria	Drug and Inhaler Device	Male %	Mean Age (Years)	Mean % Predicted FEV1	Prior ICS use (%)
CAMP 2000/Kelly 2008 [15 32]	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)	58.2	9.0	93.6	40.5
				Nedocromil 8 mg daily (n=312)	66.0	8.8	93.4	36.5
				Placebo (n=412)	56.0	9.0	94.2	35.9
Ferguson 2006 [14]	Multicentre - 35 centres in 11 countries	52 weeks	Age 6-9 years persistent asthma ≥ 6 months; FEV1 ≥ 60% predicted; ↑PEFR 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
				BUD 200 µg bd (n=119) Turbuhaler	70	7.4	92.3	21% oral steroids past 6 months
Kemp 2004 [16]	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	60	31.6	83	0
				FP 440 µg bd (n=51) Metered dose inhaler	59	29.0	82	0
				Placebo (n=54)	59	28.4	85	0
Li 1999 [17]	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	91	28.0	91	Not reported
				Placebo bd (n=32) Diskhaler	81	31.1	91	Not

								reported
Maspero 2013 [18]	50 centres worldwide	52 weeks	Adults with > 3 months history of asthma, and not using ICS past 3 months. FEV1 between 60-90% predicted. Must have DEXA scan, and no evidence of low Vitamin D.	Mometasone 400 µg daily (n=137)	34	30	76.5	7
				Mometasone 200 µg daily (n=140)	35	30	74.7	7
				FP 250 µg bd (n=147)	39	28	75.3	6
				Montelukast 10 mg (n=142)	38	28	76.9	10
Roux 2003 [19]	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 100 µg bd (n=87) Diskus/Accuhaler dry powder inhaler	64	9.1	88.9	Not reported
				Nedocromil 4 mg bd (n=87) MDI	66	9.4	88.5	Not reported
Turpeinen 2010 [20]	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 2nd - 6th months, then 100 µg bd for final 12 months.	60	6.9	Not reported	Not reported
				BUD/Placebo (n=44) Turbuhaler BUD 400 µg bd for 1st month, then 200 µg bd for 2nd to 6th months, then placebo for final 12 months	66	6.7	Not reported	Not reported
				Sodium cromoglicate - 10mg tds for 18 months (unblinded)	50	7.0	Not	Not

				(n=42) MDI			reported	reported

bd: twice daily; BUD: Budesonide; DEXA: Dual-energy X-ray absorptiometry; FEV1: Forced Expiratory Volume in 1 second; FP: Fluticasone propionate; 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 & Patient Characteristics (or Selection of Cases and Controls)	Type of ICS
Agertoft and Pedersen 1998 [21]	Cross-sectional study	Bone Mineral Density	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 2000 [22]	Prospective	Bone Mineral Density	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
Bahceciler 2002 [23]	Cross-sectional study	Bone mineral density	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 2005 [24]	Observational	Bone mineral density	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%, %FEV1: 89.71 Controls : Mean age: 44.43 years, Male 0%	Not specified.
Harris 2001 [25]	Cross-sectional study	Bone mineral density	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 last 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 2005 [26]	Nested case-control study	Risk of nonvertebral fracture	Ingenix Epidemiology - Research database of United Healthcare members, 17 states in the United States. 1722 cases, 17220 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: Nonvertebral fractures by ICD-9 codes, with claim for treatment (including inpatient hip fractures) Mean age 52.9 years, Male 29.4% 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%	BDP, BUD, FP flunisolone, triamcinolone
Schlienger 2004 [27]	Retrospective Population-based nested case-control analysis	Fracture risk	United Kingdom General Practice Research Database. 3744 cases, 21757 controls.	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	76.2 % BDP 21.7% BUD 2.1% FP

				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%	
Sosa 2006 [28]	Cross-sectional study	Bone mineral density; 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 2004 [29]	Population-based cohort study / nested case-control analysis.	Fracture risk	UK General Practice Research Database (GPRD). Cohort: ICS users: 97387 Bronchodilators only: 70984 Controls: 345758 Fracture cases: 23984; Controls: 23984	Children aged 4 - 17 years old, on ICS. 3 study groups: Selection of cases: Non-vertebral fracture. Male 61.0%, 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 61.0%, 8861 (36.9%) aged 4 - 9 years, 8497 (35.4%) aged 10 - 13 years, 6626 (27.6%) aged 14 - 17 years	BDP, BUD, FP
Wisniewski 1997 [30]	Cross-sectional study	Bone mineral density	Asthma register and local general practices in Nottingham, United Kingdom 47 cases; 34 controls	Selection of cases: Aged 20 - 40 years with documented history of asthma: Group 1: asthmatics using inhaled β_2-agonist only. Males 56%, Mean age: men 30.3 years; women 25.6 years, Mean FEV1 (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 32.0 years, Mean FEV1 (litres): men 3.40; women 2.83	BDP, BUD

Yanik 2009 [31]	Observational	Bone mineral density	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%, %FEV1 predicted: 83.1, All cases were postmenopausal Selection of controls: Healthy postmenopausal females. Mean age: 63.0 years.	BDP, BUD, FP,

BDP: Beclomethasone dipropionate; BUD: Budesonide; FEV1: Forced Expiratory Volume in 1 second; FP: Fluticasone propionate

Table 2 Study Validity and Outcomes (Bone Mineral Density and Fractures) in Children

(a) **RCTs of inhaled corticosteroids- Children**

Source	Sequence generation	Allocation Concealment	Blinding of participants and personnel	AE monitoring	Adverse Events	Dis-continued, No. (%)	Loss to follow-up, No (%)
CAMP 2000/ Kelly 2008 [15 32]	Permuted blocks, stratified	Adequate	Adequate	Height recorded at every visit; BMD once every year.	Fracture rate (adjusted for age, ethnic group, sex, clinic, base line duration, skin-test reactivity and asthma severity): BUD: 5.7 per 100 person-years Placebo: 5.1 per 100 person-years P=0.59 Mean difference in BMD (ICS vs. placebo): Females: -0.001 (derived SE 0.0016) Male:-0.003 (derived SE 0.0014)	11%	5%
Ferguson 2006 [14]	Not reported	Remote computerized allocation	Adequate	Lumbar-spine BMD assessed at beginning and end of treatment with DEXA scan.	Mean difference in lumbar spine BMD for FP vs BUD: 0.0075 (95% CI - 0.033 to 0.048)	90% patients received > 40 weeks	26% did not reach 51 weeks
Roux 2003 [19]	Central Block randomization with gender stratification	.	Largely Open. Analysis of DEXA scans blinded	Lumber spine and femoral neck BMD (DEXA) during run-in and 6, 12 and 24 months. Adjusted for age, height, weight, baseline BMD, gender & measuring device.	Mean difference in lumbar spine BMD for FP vs control: 0.012 (SE 0.0073); values calculated from % change in manuscript.	23%	4%

Turpeine n 2010 [20]	Block	Unclear	Blinded for budesonide and placebo arms	BMD of L1-4 measured by radiologist using DEXA at baseline and at 18 months.	Mean change in lumbar spine BMD: Budesonide for 12 months 0.023 (SD 0.022) Placebo for 12 months 0.029 (SD 0.022) DSCG: 0.034 (SD 0.022)	20%	3%

BUD: Budesonide; DEXA: Dual-energy X-ray absorptiometry; DSCG: Disodium cromoglicate; FP: Fluticasone propionate

(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^{-2})
Agertoft and Pedersen 1998 [21]	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 2000 [22]	DEXA scan at baseline and again at 9 - 20 months later. Value for 12-month time point calculated with all outcomes	Compliance checked: Adequate Duration of follow-up: 9 - 20 months	Type of Inhaler: Spacer, Turbohaler Type of Steroid: BDP, BUD	Age; height; weight; dose of inhaled corticosteroid	Mean ICS Dose 0.67 ± 0.48 mg m^{-2}/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 2002 [23]	Anteroposterior (AP) spine (L2-4) by DEXA scan	Compliance: Not reported Follow-up: 13.0 ± 9.8 months	Use of BUD as MDI ≥ 6 months.	None	ICS Mean daily dose (SD): 419 ± 154 µg	Mean Lumbar spine BMD: ICS group: 0.593 (SD 0.122)
					Control	Mean Lumbar spine BMD: 0.579 (SD 0.156)
Harris 2001 [25]	Lumbar spine by DEXA.	Compliance checked: Not reported Duration of follow up: 3.5 ± 2.4 years	Stratified by treatment in last 6 months Type of inhaler: Spacer device Type of Steroid: BDP,BUD, FP	Weight	0 µg/day	Mean lumbar spine BMD (SD) 0.68 (0.07)
					400 - 800 µg/day	Mean lumbar spine BMD (SD) 0.70 (0.08)
					> 800 µg/day	Mean lumbar spine BMD (SD) 0.67 (0.08)

Studies reporting on Fracture risk						Fracture Outcomes
Schlienger et al 2004 [27]	Identified by ICD-8 codes 800.x - 829.x, from computerised records Cases = 1st-time diagnosis of bone fracture Controls - no fracture	Compliance checked: Not reported Duration: Median number of prescriptions: 26, corresponds to > 7 years of continuous exposure	ICS use in United Kingdom General Practice Research Database. Type of inhaler: not reported Type of Steroid: BDP, BUD, FP	Matched for age, gender, general practice, calendar time, years in GPRD Adjusted for comorbidities: chronic renal failure, hyperthyroidism, hyperparathyroidism, inflammatory bowel disease, malnutrition, malabsorption. Medications: asthma drugs, psychotropic drugs, antihypertensives, calcium, fluoride, vitamin D.	1 - 9 prescriptions Cases: n = 332 Controls: n = 2017	Adjusted OR: 0.97 (0.85 - 1.11)
					10 - 19 prescriptions Cases: n = 124 Controls: n = 682	Adjusted OR: 1.08 (0.87 - 1.33)
					≥ 20 prescriptions Cases: n = 88 Controls: n = 422	Adjusted OR: 1.15 (0.89 - 1.48)
					All ICS users combined	Adjusted OR: 1.01 (0.90 - 1.13)
Van Staa 2004 [29]	Ascertained from diagnoses within computer records	Compliance not reported Start of follow-up:1987 onwards or from age 4 years End: December 1997 or age 18 years.	Current users of ICS Type of Inhaler: not reported Type of inhaled Steroid: BDP, BUD, FP	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.	200 µg	Adjusted OR : 0.96 (0.83 - 1.12)
					201 – 400 µg	Adjusted OR: 1.07 (0.93 - 1.24)
					> 400 µg	Adjusted OR: 1.17 (0.93 - 1.45)
					All ICS users	Adjusted OR 1.03 (0.93 - 1.15)

BDP: Beclometasone diproprionate; BUD: Budesonide; DEXA: Dual-energy X-ray absorptiometry; FP: Fluticasone propionate; ICD: International Classification of Disease; MDI: Metered dose inhaler

Table 3 Study Validity and Outcomes (Bone Mineral Density and Fractures) in Adults

(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/cm^2	Dis-continued, No. (%)	Loss to follow-up, No (%)
Kemp 2004 [16]	Random code with blinded labels	Adequate	Adequate	DEXA scan every 6 months at lumbar spine (L1-L4). Analyzed 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 1999 [17]	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 2013 [18]	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: 0.009 2) Femur: 0.004	34 (25)	5 (3)
					Mometasone 200 µg daily	1) Lumbar spine: 0.008 2) Proximal femur: 0.004	35 (25)	7 (4)
					FP 250 µg bd	1) Lumbar spine: 0.012 2) Femur: -0.005	38 (26)	4 (3)
					All ICS	1) Lumbar spine: 0.009	107 (25)	16 (4)

						2) Femur: 0.0008		
					Montelukast 10 mg daily	1) Lumbar spine: 0.013 2) Femur: -0.002	31 (22)	3 (3)

AE: Adverse event; bd: twice daily; DEXA: Dual-energy X-ray absorptiometry; FP: Fluticasone propionate; RCT: Randomized controlled trial

(a) 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/cm^2) and fractures
El 2005 [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 daily ICS dose 326.43 µg	Mean Lumbar: 0.925, SD 0.211 Mean Femoral neck: 0.746, SD 0.127
					Controls (No exposure)	Mean Lumbar: BMD: 0.927, SD 0.229 Mean Femoral neck: 0.792, SD 0.097
Johannes 2005 [26]	Nonvertebral 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. Co-morbidities - wide range of cardiovascular, endocrine, metabolic and musculoskeletal conditions. Medications - oral corticosteroids, bisphosphonates, statins, anticonvulsants, oestrogen, raloxifene, calcitonin. Health-care utilisation for underlying respiratory disease	1 - 167 µg	OR 1.00 95% CI: 0.84 - 1.18
					168 - 504 µg	OR: 1.02 95% CI: 0.83 - 1.26
					505 - 840 µg	OR: 1.14 95% CI: 0.80 - 1.62
					> 840 µg	0.99 95% CI: 0.66 - 1.50
Sosa 2006 [28]	DEXA lumbar spine (L2-L4) and proximal femur	Compliance: Not reported Duration of Follow up: Median treatment with ICS: 10 years	ICS for > 1year. Type of inhaler: Not reported Type of ICS: Not reported	Age	Cases (dose not reported)	Lumbar spine: 0.960; 95% CI: 0.925 - 0.995 Femoral neck: 0.776; 95% CI: 0.750 - 0.802 Fractures: 22/105 (21.0%)
					Controls	Lumbar spine: 0.991; 95% CI: 0.960 - 1.022 Femoral neck:

						0.780; 95% CI: 0.758 - 0.803 Fractures: 9/133 (7.0%)
Wisniewski 1997 [30]	Posterior-anterior spine (L2-4), lateral spine (body of L3) measured by DEXA once. All scans by same radiographer (blinded).	Compliance checked: Adequate Duration: Median duration of use of ICS (years) Men: 9.00 Women: 6.29	ICS for > 5 years Type of inhaler: Metered dose inhaler - 36 patients; dry powder inhaler - 11 patients. Type of ICS: BDP, BUD	age; weight; smoking; alcohol; activity grade; asthma severity; age at menarche; lifetime total dose of oestrogen and progesterone; prednisolone use.	Cases	Lumbar spine ± SD Men : 1.28 ± 0.13; Women: 1.04 ± 0.14 Femoral neck ± SD: Men : 1.17± 0.18; Women: 1.09 ± 0.14 Vertebral 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 Vertebral fractures overall: 6/34
Yanik 2009 [31]	DEXA lumbar spine and hip (femoral neck and trochanter). Patient-reported history of fractures.	Compliance checked: Adequate Duration of Follow up: 4.3 ± 2.6 years	Regular ICS > 12 Months Type of inhaler: Not reported Type of ICS: BDP, BUD, FP	None	Cases (total) Mean daily ICS dose (µg) (SD): 324.9 ± 121.8	Lumbar spine ± SD 0.95 ± 0.29 Femoral neck ± SD 0.83 ± 0.12 Atraumatic vertebral fractures: 4 (8.6%)
					Controls	Lumbar spine ± SD 0.88 ± 0.14 Femoral neck ± SD 0.74 ± 0.23 Atraumatic vertebral fracture: 6 (10%)

BDP: Beclometasone diproprionate; BUD: Budesonide; DEXA: Dual-energy X-ray absorptiometry; FP: Fluticasone propionate; ICD: International Classification of Disease

Figure 1. Flow Diagram of Study Selection

Figure 2. Fracture Risk, ICS use vs. Non-use

Figure 3. BMD in Lumbar Spine Children, ICS use vs. Non-use

Figure 4. BMD in Adults, ICS use vs. Non-use

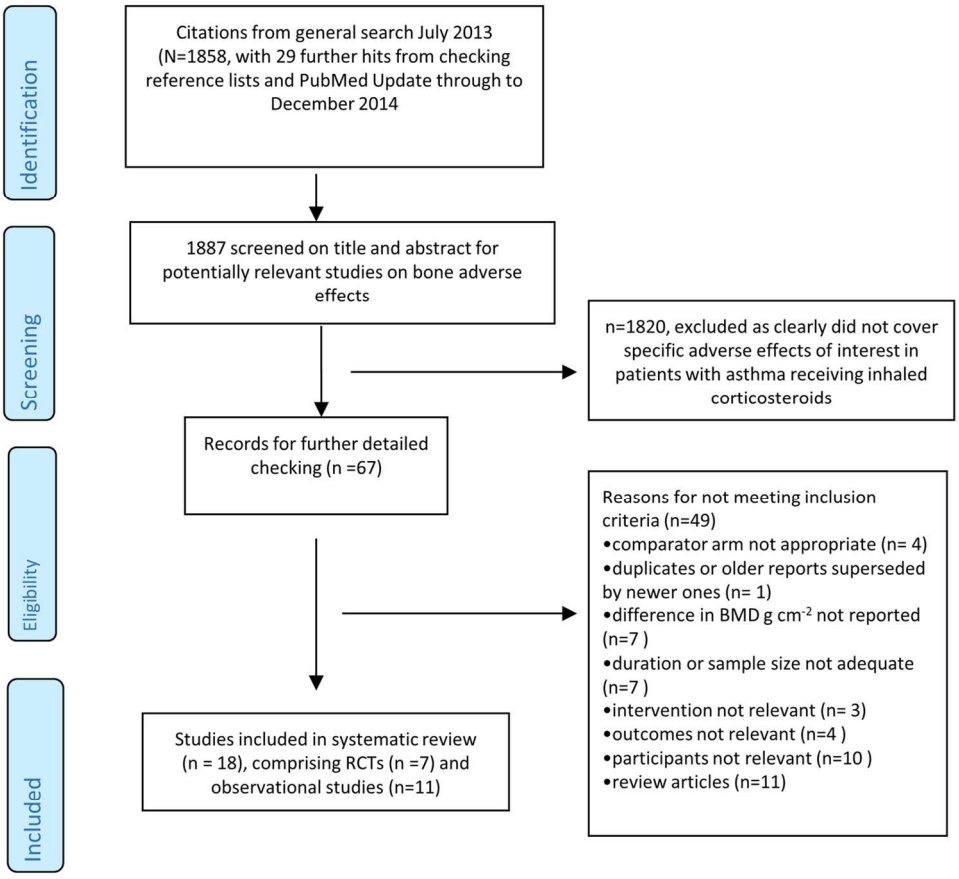

Figure 1. Flow Diagram of Study Selection
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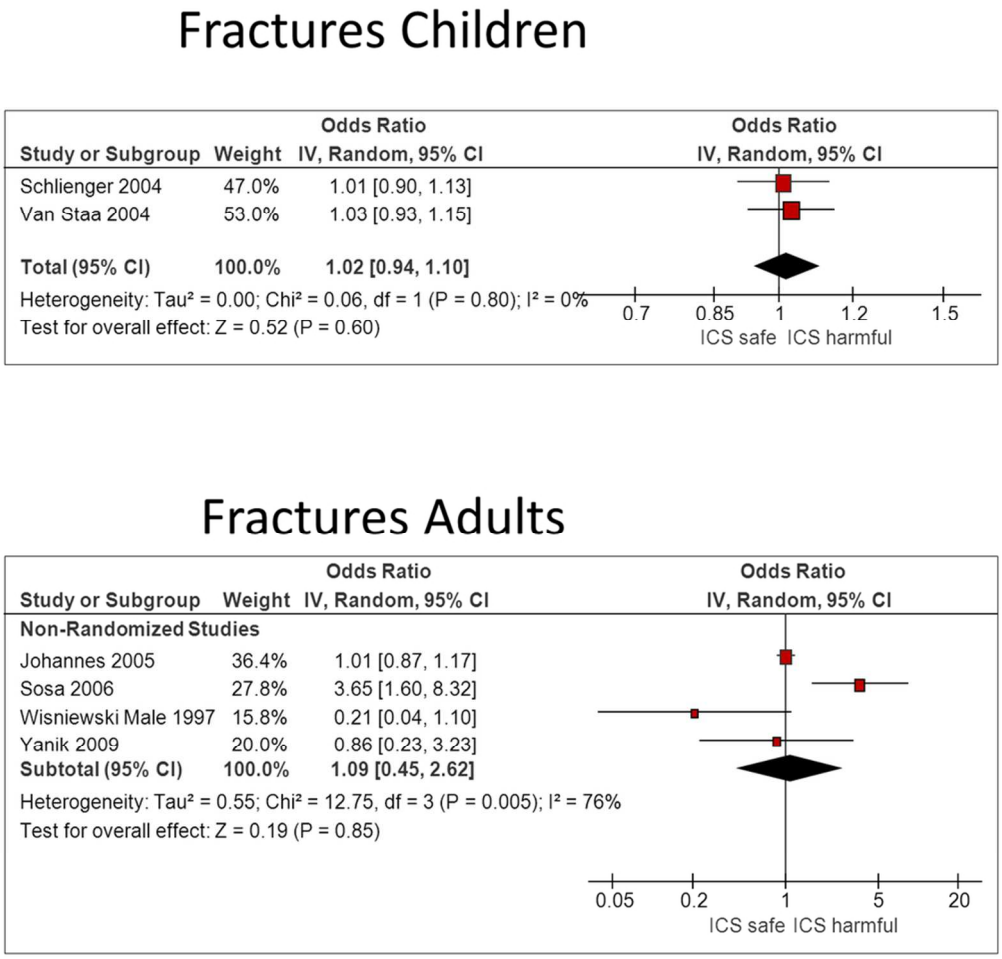

Figure 2. Fracture Risk, ICS use vs. Non-use
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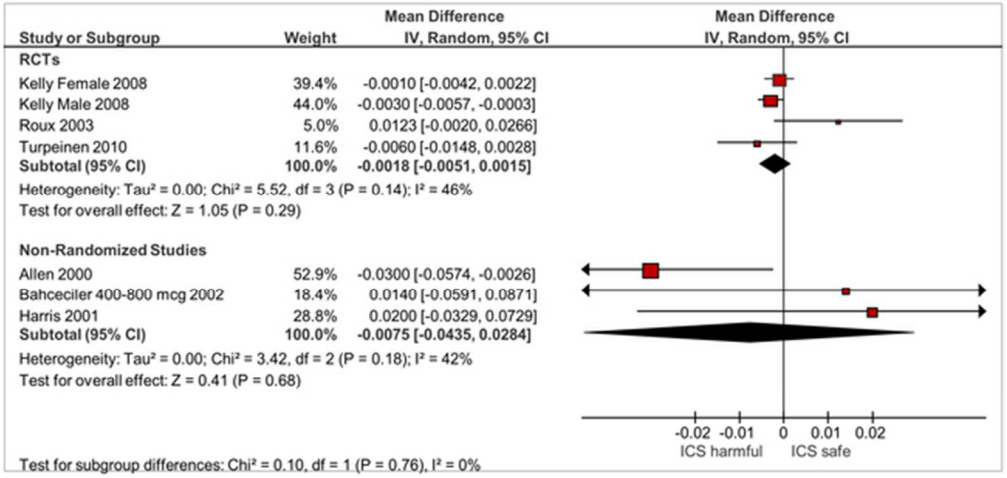

Figure 3. BMD in Lumbar Spine Children, ICS use vs. Non-use
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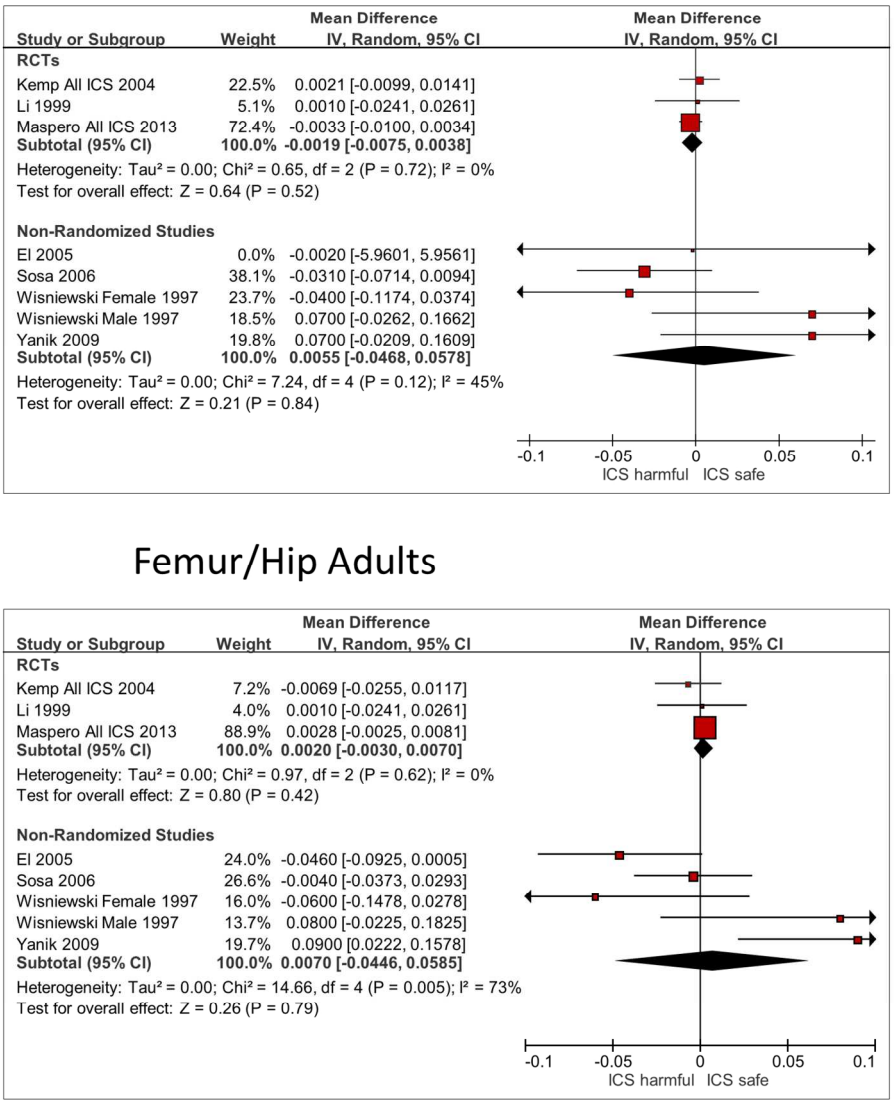

Figure 4. BMD in Adults, ICS use vs. Non-use
180x236mm (300 x 300 DPI)

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

PubMed Update June and Dec 2014

("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 and bones"[All Fields] OR "bone"[All Fields]) OR ("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields])) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields])

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, Table 2-3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig. 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig. 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

Bone Mineral Density and Fracture Risk with Long-term use of Inhaled Corticosteroids in Patients with Asthma: Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-008554.R2
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Date Submitted by the Author:	22-Oct-2015
Complete List of Authors:	Loke, Yoon; University of East Anglia, Norwich Medical School Gilbert, Daniel; University of East Anglia, Norwich Medical School Thavarajah, Menaka; University of East Anglia, Norwich Medical School Blanco, Patricia; University of East Anglia, Norwich Medical School Wilson, Andrew; University of East Anglia, Norwich Medical School
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Respiratory medicine
Keywords:	Adverse events < THERAPEUTICS, Asthma < THORACIC MEDICINE, CLINICAL PHARMACOLOGY

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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Word count: 2822

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 randomized 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 odds ratios (OR) for fractures, and mean differences in bone mineral density. Heterogeneity was assessed using the I^2 statistic.

Results: We included 18 studies (seven 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 0.94-1.10, two studies), or adults (pooled OR 1.09, 95% CI 0.45 – 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.

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

Article Summary

‘Strengths and limitations of this study

- Comprehensive search of two databases with independent study selection and data extraction
- Included both observational and randomized studies in adults and/or children with asthma
- Heterogenous nature of studies and the outcome measures which were available for analysis
- Inability to properly assess differences between drugs, type of inhaler device or dose-responsiveness

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. [1] They are therefore considered the gold standard first line preventative therapy and are widely recommended in national and international guidelines. [2 3]

However, long-term ICS use may be associated with adverse effects such as cataract, osteoporosis, fractures, and reduction in growth velocity in children. [4] 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. [4] 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) [5-7]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 COPD patient because of differences in risk factors such as cigarette consumption, multimorbidity, and nutritional problems that are prevalent in COPD patients. [8 9] 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 asthma patients 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 in 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 vs a control treatment, where the comparison groups consisted of ICS vs other asthma therapy (or placebo), or ICS in combination with long-acting beta-agonist (LABA) vs a LABA alone; and (4) stated aim to evaluate fractures or bone mineral density .

We also evaluated controlled observational studies (case control, prospective cohort or retrospective cohort) reporting on risk of fractures or change in bone mineral density 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 pre-formatted 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 pre-specified fracture risk of primary interest, and bone mineral density at the lumbar spine or the femur as secondary endpoints. 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,randomization 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. [10]

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. [11]

Statistical Analysis

We pooled trial data using Review Manager (RevMan) version 5.3.2 (Nordic Cochrane Center, Copenhagen, Denmark). We used the inverse variance method to pool odds ratios for fracture events, and mean differences for bone mineral density (gram cm^{-2}). In accordance with the recommendations of the Cochrane Handbook, we derived any standard deviations from 95% confidence intervals or p-values. [12] We assessed statistical heterogeneity using the I^2 statistic with I^2> 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. [13]

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 seven RCTs, [14-20]and 11 observational studies). [21-31] The process of study selection is shown in Figure 1.

Tables 1 a) and 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, [14 15 19 20] while the remaining three were in adults. [16-18] Treatment duration was up to four years in one study, [15] while the remaining six trials had ICS therapy for between 52-104 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. [18]

Five of the observational studies focused solely on children, [21-23 25 29] whilst 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.

Randomized Controlled Trials (n=7)

Overall, four of the RCTs reported an appropriate method of sequence generation, whilst 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 done through 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. [26 27 29 30]. Assessment of compliance or adherence to ICS use was reported in 4 studies. [21 22 30 31] 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 4 studies possibly of slightly better methodological quality because of adequate outcome ascertainment and adjustment for confounders. [26 27 29 30]

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). [32] 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 0.94-1.10, I^2=0%)[27 29] as shown in figure 2. The point estimates of fracture risk was not significantly elevated at higher dose levels, with one study demonstrating an OR of 1.15 (0.89 – 1.48) for children with ≥20 prescriptions[27], and the other study reporting an OR of 1.17 (0.93 – 1.45) for children using a daily dose of >400 µg BDP equivalents. [29]

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 – 2.62) (Figure 2). [26 28 30 31] There was substantial heterogeneity in this meta-analysis (I^2=76%), with Sosa's study reporting significantly increased fracture risk, [28] whilst 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. [28] In this dataset, 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. [26]

Lumbar spine BMD

Three RCTs and three observational studies reported on comparative change at the lumbar spine in children. [15 19 20 22 23 25] (Figure 3) ICS use was not associated with significant reductions in BMD as compared to controls in RCTs (Mean difference -0.0018 g cm-^{2}; 95% CI -0.0051 – 0.0015 g cm-^{2}; I^2=46%) or observational studies (Mean difference -0.0075 g cm-^{2}; 95% CI -0.044 – 0.028 g cm-^{2}; I^2=42%). There was no clear signal of dose responsiveness in one observational study that separated participants into different dose levels, [25] 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. [20]

Three RCTs and four observational studies reported on comparative change in bone mineral density at the lumbar spine in adults (Figure 4). [16-18 24 28 30 31] ICS use was not associated with significant reductions in BMD as compared to controls in RCTs (Mean difference -0.0019 g cm-^{2}; 95% CI -0.0075 – 0.0038 g cm-^{2}; I^2=0%) or observational studies (Mean difference -0.0055 g cm-^{2}; 95% CI -0.047 – 0.058 g cm-^{2}; I^2=45%).

Femur/hip BMD for adults

There were three RCTs and four observational studies reporting comparative change in bone mineral density at the femur or hip in adults (Figure 4). [16-18 24 28 30 31] ICS use was not associated with significant reductions in BMD as compared to controls in RCTs (Mean difference 0.0020 g cm-^{2}; 95% CI -0.0030 – 0.0070 g cm-^{2}; I^2=0%) or observational studies (Mean difference 0.0070 g cm-^{2}; 95% CI -0.045 – 0.059 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 randomized to Fluticasone propionate 100 µg twice daily as compared to Budesonide, mean difference 0.0075 g cm-^{2} (95% CI -0.033 to 0.048 g cm-^{2}). [14] 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. [18]

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 observational 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 significant detrimental relationship between ICS use and bone mineral density 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 differences between the available ICS molecules.

Our findings should be contrasted with those of other recent published reviews. There have been at least 4 systematic reviews evaluating fractures or bone mineral density in ICS users, with two earlier reviews demonstrating a significant reduction in bone mineral density but no definite impact on fractures. [5 33] 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 chronic obstructive pulmonary disease (COPD). [6 7] 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 bone mineral density seen in previous meta-analyses could be explained in part by the higher prevalence of smoking in COPD patients as previous studies have shown that smoking has a harmful effect on bone mineral density, and increasing fracture risk. [8] In addition, as a group, patients with asthma are likely to be younger and to have fewer co-morbidities than those with COPD which may impact on bone mineral density and fracture risk. Recent research indicates that multi-morbidity (including cachexia and low-grade systemic inflammation) is often seen in patients with COPD, [9] 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 corticosteroids 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 bone mineral density. 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), [1] 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 skeletal adverse effects in many different ways, we have limited our review to clinically meaningful outcomes such as bone mineral density in g cm^{-2} 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 recognize that there is potential for risk of bias (stemming from substantial loss to follow-up for bone mineral density measurements) within this dataset. 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 evidence, 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.

Contributors: YKL and AMW conceptualized the review and obtained funding. 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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Competing Interests Statement

"All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from Asthma UK for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Data Sharing Statement

There are no additional unpublished data.

References

1. Ricciardolo FLM. The treatment of asthma in children: Inhaled corticosteroids. Pulmonary Pharmacology & Therapeutics 2007;**20**(5):473-82.
2. British-Thoracic-Society/Scottish-Intercollegiate-Guidelines-Network. British Guideline on the Management of Asthma. Thorax 2008;**63 Suppl 4**:iv1-121.
3. National-Asthma-Education-and-Prevention-Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol 2007;**120**(5 Suppl):S94-138.
4. Rossi GA, Cerasoli F, Cazzola M. Safety of inhaled corticosteroids: Room for improvement. Pulmonary Pharmacology & Therapeutics 2007;**20**(1):23-35.
5. Jones A, Fay JK, Burr M, et al. Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease. The Cochrane database of systematic reviews 2002(1):Cd003537.
6. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. Thorax 2011;**66**(8):699-708.
7. Weatherall M, James K, Clay J, et al. Dose-response relationship for risk of non-vertebral fracture with inhaled corticosteroids. Clin Exp Allergy 2008;**38**(9):1451-8.
8. Law MR, Hackshaw AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. BMJ 1997;**315**(7112):841-6.
9. Vanfleteren LE, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;**187**(7):728-35.
10. Loke YK, Golder SP, Vandenbroucke JP. Comprehensive evaluations of the adverse effects of drugs: importance of appropriate study selection and data sources. Ther Adv Drug Saf 2011;**2**(2):59-68.
11. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. CMAJ 2007;**176**(8):1091-6.
12. Higgins JPT, Deeks JJ, Altman DG. Chapter 16. Special topics in statistics. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2008.
13. Higgins JPT, Deeks JJ, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2008.
14. Ferguson AC, Van Bever HP, Teper AM, et al. A comparison of the relative growth velocities with budesonide and fluticasone propionate in children with asthma. Respiratory Medicine 2007;**101 (1)**:118-29.
15. Kelly HW, Van Natta ML, Covar RA, et al. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. Pediatrics 2008;**122 (1)**:e53-61.
16. Kemp JP, Osur S, Shrewsbury SB, et al. Potential Effects of Fluticasone Propionate on Bone Mineral Density in Patients with Asthma: A 2-Year Randomized, Double-Blind, Placebo-Controlled Trial. Mayo Clinic Proceedings 2004;**79 (4)**:458-66.
17. Li JTC, Ford LB, Chervinsky P, et al. Fluticasone propionate powder and lack of clinically significant effects on hypothalamic-pituitary-adrenal axis and bone mineral density over 2 years in adults with mild asthma. Journal of Allergy and Clinical Immunology 1999;**103 (6)**:1062-68.

18. Maspero J, Backer V, Yao R, et al. Effects of mometasone, fluticasone, and montelukast on bone mineral density in adults with asthma. The journal of allergy and clinical immunology In practice 2013;**1**(6):649-55.e1.
19. Roux C, Kolta S, Desfougeres JL, et al. Long-term safety of fluticasone propionate and nedocromil sodium on bone in children with asthma. Pediatrics 2003;**111 (6 Pt 1)**:e706-13.
20. Turpeinen M, Pelkonen AS, Nikander K, et al. Bone mineral density in children treated with daily or periodical inhaled budesonide: The Helsinki early intervention childhood asthma study. Pediatric Research 2010;**68 (2)**:169-73.
21. Agertoft L, Pedersen S. Bone mineral density in children with asthma receiving long-term treatment with inhaled budesonide. American Journal of Respiratory and Critical Care Medicine 1998;**157 (1)**:178-83.
22. Allen HDW, Thong IG, Clifton-Bligh P, et al. Effects of high-dose inhaled corticosteroids on bone metabolism in prepubertal children with asthma. Pediatric Pulmonology 2000;**29 (3)**:188-93.
23. Bahceciler NN, Sezgin G, Nursoy MA, et al. Inhaled corticosteroids and bone density of children with asthma. Journal of Asthma 2002;**39 (2)**:151-57.
24. El O, Gulbahar S, Ceylan E, et al. Bone mineral density in asthmatic patients using low dose inhaled glucocorticosteroids. Journal of Investigational Allergology and Clinical Immunology 2005;**15 (1)**:57-62.
25. Harris M, Hauser S, Nguyen TV, et al. Bone mineral density in prepubertal asthmatics receiving corticosteroid treatment. Journal of Paediatrics and Child Health 2001;**37 (1)**:67-71.
26. Johannes CB, Schneider GA, Dube TJ, et al. The risk of nonvertebral fracture related to inhaled corticosteroid exposure among adults with chronic respiratory disease. Chest 2005;**127 (1)**:89-97.
27. Schlienger RG, Jick SS, Meier CR. Inhaled corticosteroids and the risk of fractures in children and adolescents. Pediatrics 2004;**114 (2 I)**:469-73.
28. Sosa M, Saavedra P, Valero C, et al. Inhaled Steroids Do Not Decrease Bone Mineral Density But Increase Risk of Fractures: Data from the GIUMO Study Group. Journal of Clinical Densitometry 2006;**9 (2)**:154-58.
29. Van Staa TP, Bishop N, Leufkens HGM, et al. Are inhaled corticosteroids associated with an increased risk of fracture in children? Osteoporosis International 2004;**15 (10)**:785-91.
30. Wisniewski AF, Lewis SA, Green DJ, et al. Cross sectional investigation of the effects of inhaled corticosteroids on bone density and bone metabolism in patients with asthma. Thorax 1997;**52 (10)**:853-60.
31. Yanik B, Ayrim A, Ozol D, et al. Influence of obesity on bone mineral density in postmenopausal asthma patients undergoing treatment with inhaled corticosteroids. Clinics 2009;**64 (4)**:313-18.
32. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. . The New England journal of medicine 2000;**343**(15):1054-63.
33. Richy F, Bousquet J, Ehrlich GE, et al. Inhaled corticosteroids effects on bone in asthmatic and COPD patients: a quantitative systematic review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2003;**14**(3):179-90.

Tables

Table 1(a) and (b): Characteristics of Included Trials and Observational Studies

(a) Randomized Controlled Trials

Source	Location	Treatment Duration	Asthma Criteria	Drug and Inhaler Device	Male %	Mean Age (Years)	Mean % Predicted FEV1	Prior ICS use (%)
CAMP 2000/Kelly 2008 [15 32]	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)	58.2	9.0	93.6	40.5
				Nedocromil 8 mg daily (n=312)	66.0	8.8	93.4	36.5
				Placebo (n=412)	56.0	9.0	94.2	35.9
Ferguson 2006 [14]	Multicentre - 35 centres in 11 countries	52 weeks	Age 6-9 years persistent asthma ≥ 6 months; FEV1 ≥ 60% predicted; ↑PEFR 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
				BUD 200 µg bd (n=119) Turbuhaler	70	7.4	92.3	21% oral steroids past 6 months
Kemp 2004 [16]	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	60	31.6	83	0
				FP 440 µg bd (n=51) Metered dose inhaler	59	29.0	82	0
				Placebo (n=54)	59	28.4	85	0
Li 1999 [17]	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	91	28.0	91	Not reported
				Placebo bd (n=32) Diskhaler	81	31.1	91	Not

								reported
Maspero 2013 [18]	50 centres worldwide	52 weeks	Adults with > 3 months history of asthma, and not using ICS past 3 months. FEV1 between 60-90% predicted. Must have DEXA scan, and no evidence of low Vitamin D.	Mometasone 400 µg daily (n=137)	34	30	76.5	7
				Mometasone 200 µg daily (n=140)	35	30	74.7	7
				FP 250 µg bd (n=147)	39	28	75.3	6
				Montelukast 10 mg (n=142)	38	28	76.9	10
Roux 2003 [19]	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 100 µg bd (n=87) Diskus/Accuhaler dry powder inhaler	64	9.1	88.9	Not reported
				Nedocromil 4 mg bd (n=87) MDI	66	9.4	88.5	Not reported
Turpeinen 2010 [20]	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 2nd - 6th months, then 100 µg bd for final 12 months.	60	6.9	Not reported	Not reported
				BUD/Placebo (n=44) Turbuhaler BUD 400 µg bd for 1st month, then 200 µg bd for 2nd to 6th months, then placebo for final 12 months	66	6.7	Not reported	Not reported
				Sodium cromoglicate - 10mg tds for 18 months (unblinded)	50	7.0	Not	Not

				(n=42) MDI			reported	reported

bd: twice daily; BUD: Budesonide; DEXA: Dual-energy X-ray absorptiometry; FEV1: Forced Expiratory Volume in 1 second; FP: Fluticasone propionate; 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 & Patient Characteristics (or Selection of Cases and Controls)	Type of ICS
Agertoft and Pedersen 1998 [21]	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 2000 [22]	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
Bahceciler 2002 [23]	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 2005 [24]	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%, %FEV1: 89.71 Controls : Mean age: 44.43 years, Male 0%	Not specified.
Harris 2001 [25]	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 last 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 2005 [26]	Nested case-control study	Risk of nonvertebral fracture	Ingenix Epidemiology - Research database of United Healthcare members, 17 states in the United States. 1722 cases, 17220 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: Nonvertebral fractures by ICD-9 codes, with claim for treatment (including inpatient hip fractures) Mean age 52.9 years, Male 29.4% 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%	BDP, BUD, FP flunisolone, triamcinolone
Schlienger 2004 [27]	Retrospective Population-based nested case-control analysis	Fracture risk	United Kingdom General Practice Research Database. 3744 cases, 21757 controls.	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	76.2 % BDP 21.7% BUD 2.1% FP

				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%	
Sosa 2006 [28]	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 2004 [29]	Population-based cohort study / nested case-control analysis.	Fracture risk	UK General Practice Research Database (GPRD). Cohort: ICS users: 97387 Bronchodilators only: 70984 Controls: 345758 Fracture cases: 23984; Controls: 23984.	Children aged 4 - 17 years old, on ICS. 3 study groups: Selection of cases: Non-vertebral fracture. Male 61.0%, 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 61.0%, 8861 (36.9%) aged 4 - 9 years, 8497 (35.4%) aged 10 - 13 years, 6626 (27.6%) aged 14 - 17 years	BDP, BUD, FP
Wisniewski 1997 [30]	Cross-sectional study	BMD	Asthma register and local general practices in Nottingham, United Kingdom 47 cases; 34 controls.	Selection of cases: Aged 20 - 40 years with documented history of asthma: Group 1: asthmatics using inhaled β_2-agonist only. Males 56%, Mean age: men 30.3 years; women 25.6 years, Mean FEV1 (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 32.0 years, Mean FEV1 (litres): men 3.40; women 2.83	BDP, BUD

Yanik 2009 [31]	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%, %FEV1 predicted: 83.1, All cases were postmenopausal Selection of controls: Healthy postmenopausal females. Mean age: 63.0 years.	BDP, BUD, FP,

BDP: Beclomethasone dipropionate; BUD: Budesonide; FEV1: Forced Expiratory Volume in 1 second; FP: Fluticasone propionate

Table 2 Study Validity and Outcomes (Bone Mineral Density and Fractures) in Children

(a) **RCTs of inhaled corticosteroids- Children**

Source	Sequence generation	Allocation Concealment	Blinding of participants and personnel	AE monitoring	Adverse Events	Dis-continued, No. (%)	Loss to follow-up, No (%)
CAMP 2000/ Kelly 2008 [15 32]	Permuted blocks, stratified	Adequate	Adequate	Height recorded at every visit; BMD once every year.	Fracture rate (adjusted for age, ethnic group, sex, clinic, base line duration, skin-test reactivity and asthma severity): BUD: 5.7 per 100 person-years Placebo: 5.1 per 100 person-years P=0.59 Mean difference in BMD (ICS vs. placebo): Females: -0.001 (derived SE 0.0016) Male:-0.003 (derived SE 0.0014)	11%	5%
Ferguson 2006 [14]	Not reported	Remote computerized allocation	Adequate	Lumbar-spine BMD assessed at beginning and end of treatment with DEXA scan.	Mean difference in lumbar spine BMD for FP vs BUD: 0.0075 (95% CI - 0.033 to 0.048)	90% patients received > 40 weeks	26% did not reach 51 weeks
Roux 2003 [19]	Central Block randomization with gender stratification	.	Largely Open. Analysis of DEXA scans blinded	Lumber spine and femoral neck BMD (DEXA) during run-in and 6, 12 and 24 months. Adjusted for age, height, weight, baseline BMD, gender & measuring device.	Mean difference in lumbar spine BMD for FP vs control: 0.012 (SE 0.0073); values calculated from % change in manuscript.	23%	4%

Turpeine n 2010 [20]	Block	Unclear	Blinded for budesonide and placebo arms	BMD of L1-4 measured by radiologist using DEXA at baseline and at 18 months.	Mean change in lumbar spine BMD: Budesonide for 12 months 0.023 (SD 0.022) Placebo for 12 months 0.029 (SD 0.022) DSCG: 0.034 (SD 0.022)	20%	3%

BUD: Budesonide; DEXA: Dual-energy X-ray absorptiometry; DSCG: Disodium cromoglicate; FP: Fluticasone propionate

(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^{-2})
Agertoft and Pedersen 1998 [21]	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 2000 [22]	DEXA scan at baseline and again at 9 - 20 months later. Value for 12-month time point calculated with all outcomes	Compliance checked: Adequate Duration of follow-up: 9 - 20 months	Type of Inhaler: Spacer, Turbohaler Type of Steroid: BDP, BUD	Age; height; weight; dose of inhaled corticosteroid	Mean ICS Dose 0.67 ± 0.48 mg m^{-2}/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 2002 [23]	Anteroposterior (AP) spine (L2-4) by DEXA scan	Compliance: Not reported Follow-up: 13.0 ± 9.8 months	Use of BUD as MDI ≥ 6 months.	None	ICS Mean daily dose (SD): 419 ± 154 µg	Mean Lumbar spine BMD: ICS group: 0.593 (SD 0.122)
					Control	Mean Lumbar spine BMD: 0.579 (SD 0.156)
Harris 2001 [25]	Lumbar spine by DEXA.	Compliance checked: Not reported Duration of follow up: 3.5 ± 2.4 years	Stratified by treatment in last 6 months Type of inhaler: Spacer device Type of Steroid: BDP,BUD, FP	Weight	0 µg/day	Mean lumbar spine BMD (SD) 0.68 (0.07)
					400 - 800 µg/day	Mean lumbar spine BMD (SD) 0.70 (0.08)
					> 800 µg/day	Mean lumbar spine BMD (SD) 0.67 (0.08)

Studies reporting on Fracture risk						Fracture Outcomes
Schlienger et al 2004 [27]	Identified by ICD-8 codes 800.x - 829.x, from computerised records Cases = 1st-time diagnosis of bone fracture Controls - no fracture	Compliance checked: Not reported Duration: Median number of prescriptions: 26, corresponds to > 7 years of continuous exposure	ICS use in United Kingdom General Practice Research Database. Type of inhaler: not reported Type of Steroid: BDP, BUD, FP	Matched for age, gender, general practice, calendar time, years in GPRD Adjusted for comorbidities: chronic renal failure, hyperthyroidism, hyperparathyroidism, inflammatory bowel disease, malnutrition, malabsorption. Medications: asthma drugs, psychotropic drugs, antihypertensives, calcium, fluoride, vitamin D.	1 - 9 prescriptions Cases: n = 332 Controls: n = 2017	Adjusted OR: 0.97 (0.85 - 1.11)
					10 - 19 prescriptions Cases: n = 124 Controls: n = 682	Adjusted OR: 1.08 (0.87 - 1.33)
					≥ 20 prescriptions Cases: n = 88 Controls: n = 422	Adjusted OR: 1.15 (0.89 - 1.48)
					All ICS users combined	Adjusted OR: 1.01 (0.90 - 1.13)
Van Staa 2004 [29]	Ascertained from diagnoses within computer records	Compliance not reported Start of follow-up:1987 onwards or from age 4 years End: December 1997 or age 18 years.	Current users of ICS Type of Inhaler: not reported Type of inhaled Steroid: BDP, BUD, FP	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.	200 µg	Adjusted OR : 0.96 (0.83 - 1.12)
					201 – 400 µg	Adjusted OR: 1.07 (0.93 - 1.24)
					> 400 µg	Adjusted OR: 1.17 (0.93 - 1.45)
					All ICS users	Adjusted OR 1.03 (0.93 - 1.15)

BDP: Beclometasone diproprionate; BUD: Budesonide; DEXA: Dual-energy X-ray absorptiometry; FP: Fluticasone propionate; ICD: International Classification of Disease; MDI: Metered dose inhaler

Table 3 Study Validity and Outcomes (Bone Mineral Density and Fractures) in Adults

(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/cm^2	Dis-continued, No. (%)	Loss to follow-up, No (%)
Kemp 2004 [16]	Random code with blinded labels	Adequate	Adequate	DEXA scan every 6 months at lumbar spine (L1-L4). Analyzed 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 1999 [17]	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 2013 [18]	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: 0.009 2) Femur: 0.004	34 (25)	5 (3)
					Mometasone 200 µg daily	1) Lumbar spine: 0.008 2) Proximal femur: 0.004	35 (25)	7 (4)
					FP 250 µg bd	1) Lumbar spine: 0.012 2) Femur: -0.005	38 (26)	4 (3)
					Combined	1) Lumbar spine: 0.009	107 (25)	16 (4)

					estimate for all ICS users	2) Femur: 0.0008		
					Montelukast 10 mg daily	1) Lumbar spine: 0.013 2) Femur: -0.002	31 (22)	3 (3)

AE: Adverse event; bd: twice daily; DEXA: Dual-energy X-ray absorptiometry; FP: Fluticasone propionate; RCT: Randomized controlled trial

(a) 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/cm^2) and fractures
El 2005 [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 daily ICS dose 326.43 µg	Mean Lumbar: 0.925, SD 0.211 Mean Femoral neck: 0.746, SD 0.127
					Controls (No exposure)	Mean Lumbar: BMD: 0.927, SD 0.229 Mean Femoral neck: 0.792, SD 0.097
Johannes 2005 [26]	Nonvertebral 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. Co-morbidities - wide range of cardiovascular, endocrine, metabolic and musculoskeletal conditions. Medications - oral corticosteroids, bisphosphonates, statins, anticonvulsants, oestrogen, raloxifene, calcitonin. Health-care utilisation for underlying respiratory disease	1 - 167 µg	OR 1.00 95% CI: 0.84 - 1.18
					168 - 504 µg	OR: 1.02 95% CI: 0.83 - 1.26
					505 - 840 µg	OR: 1.14 95% CI: 0.80 - 1.62
					> 840 µg	0.99 95% CI: 0.66 - 1.50
Sosa 2006 [28]	DEXA lumbar spine (L2-L4) and proximal femur	Compliance: Not reported Duration of Follow up: Median treatment with ICS: 10 years	ICS for > 1year. Type of inhaler: Not reported Type of ICS: Not reported	Age	Cases (dose not reported)	Lumbar spine: 0.960; 95% CI: 0.925 - 0.995 Femoral neck: 0.776; 95% CI: 0.750 - 0.802 Fractures: 22/105 (21.0%)
					Controls	Lumbar spine: 0.991; 95% CI: 0.960 - 1.022 Femoral neck:

						0.780; 95% CI: 0.758 - 0.803 Fractures: 9/133 (7.0%)
Wisniewski 1997 [30]	Posterior-anterior spine (L2-4), lateral spine (body of L3) measured by DEXA once. All scans by same radiographer (blinded).	Compliance checked: Adequate Duration: Median duration of use of ICS (years) Men: 9.00 Women: 6.29	ICS for > 5 years Type of inhaler: Metered dose inhaler - 36 patients; dry powder inhaler - 11 patients. Type of ICS: BDP, BUD	age; weight; smoking; alcohol; activity grade; asthma severity; age at menarche; lifetime total dose of oestrogen and progesterone; prednisolone use.	Cases	Lumbar spine ± SD Men : 1.28 ± 0.13; Women: 1.04 ± 0.14 Femoral neck ± SD: Men : 1.17± 0.18; Women: 1.09 ± 0.14 Vertebral 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 Vertebral fractures overall: 6/34
Yanik 2009 [31]	DEXA lumbar spine and hip (femoral neck and trochanter). Patient-reported history of fractures.	Compliance checked: Adequate Duration of Follow up: 4.3 ± 2.6 years	Regular ICS > 12 Months Type of inhaler: Not reported Type of ICS: BDP, BUD, FP	None	Cases (total) Mean daily ICS dose (µg) (SD): 324.9 ± 121.8	Lumbar spine ± SD 0.95 ± 0.29 Femoral neck ± SD 0.83 ± 0.12 Atraumatic vertebral fractures: 4 (8.6%)
					Controls	Lumbar spine ± SD 0.88 ± 0.14 Femoral neck ± SD 0.74 ± 0.23 Atraumatic vertebral fracture: 6 (10%)

BDP: Beclometasone diproprionate; BUD: Budesonide; DEXA: Dual-energy X-ray absorptiometry; FP: Fluticasone propionate; ICD: International Classification of Disease

Figure 1. Flow Diagram of Study Selection

Figure 2. Fracture Risk, ICS use vs. Non-use

Figure 3. BMD in Lumbar Spine Children, ICS use vs. Non-use

Figure 4. BMD in Adults, ICS use vs. Non-use

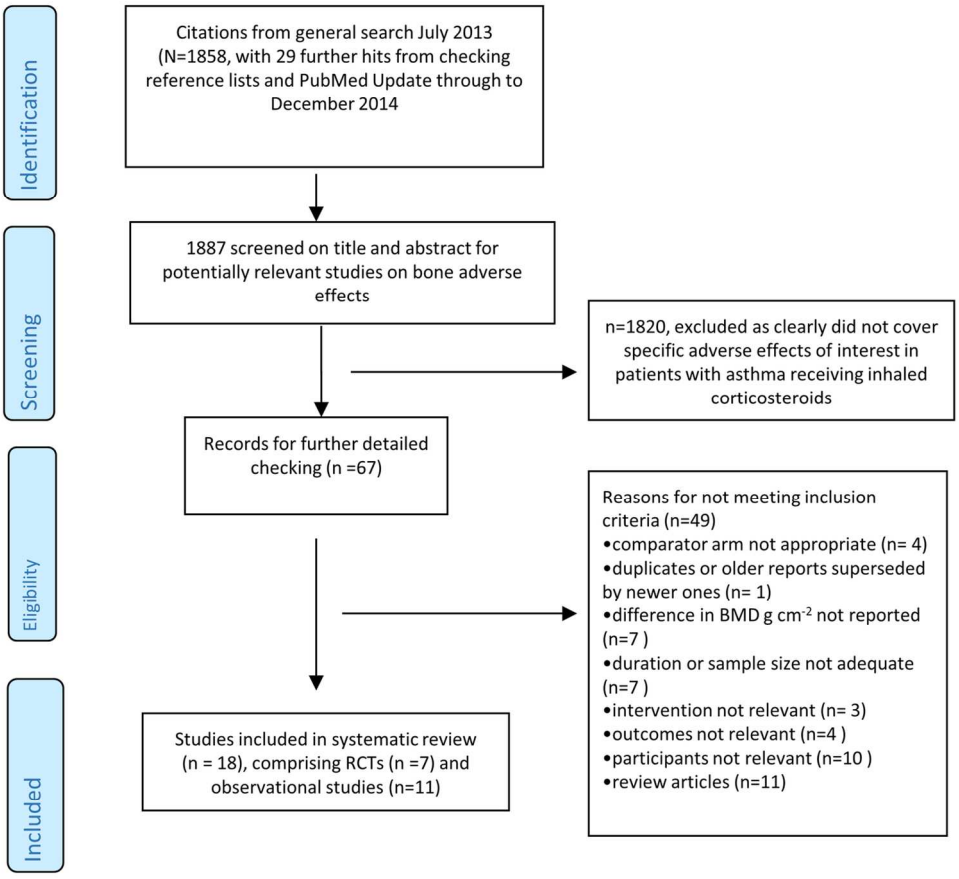

Figure 1. Flow Diagram of Study Selection
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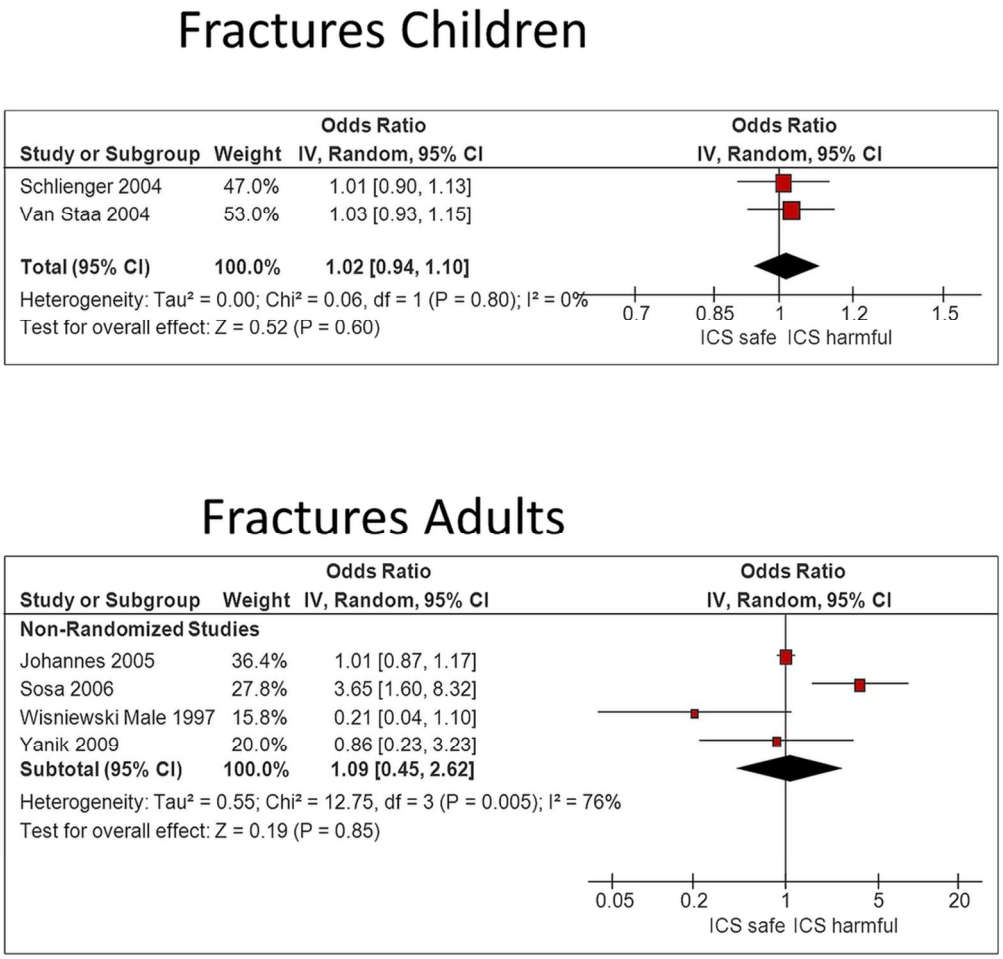

Figure 2. Fracture Risk, ICS use vs. Non-use
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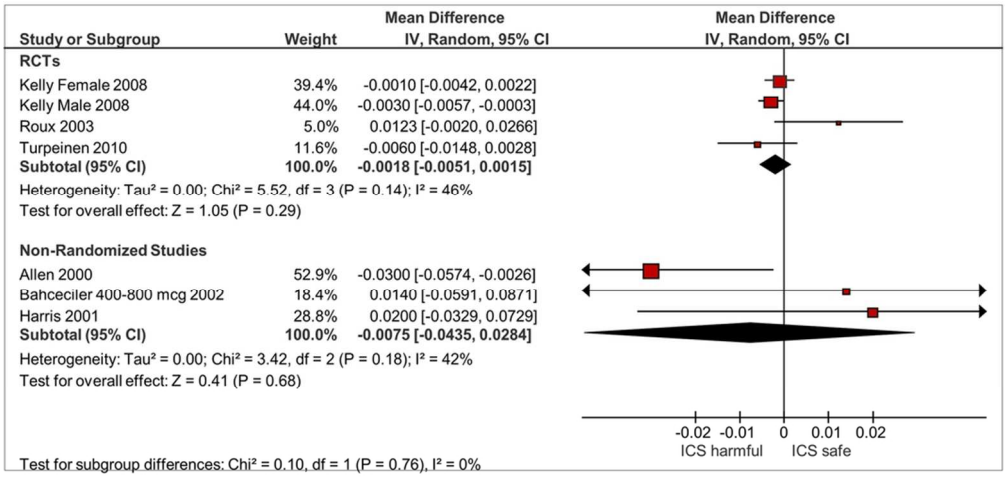

Figure 3. BMD in Lumbar Spine Children, ICS use vs. Non-use
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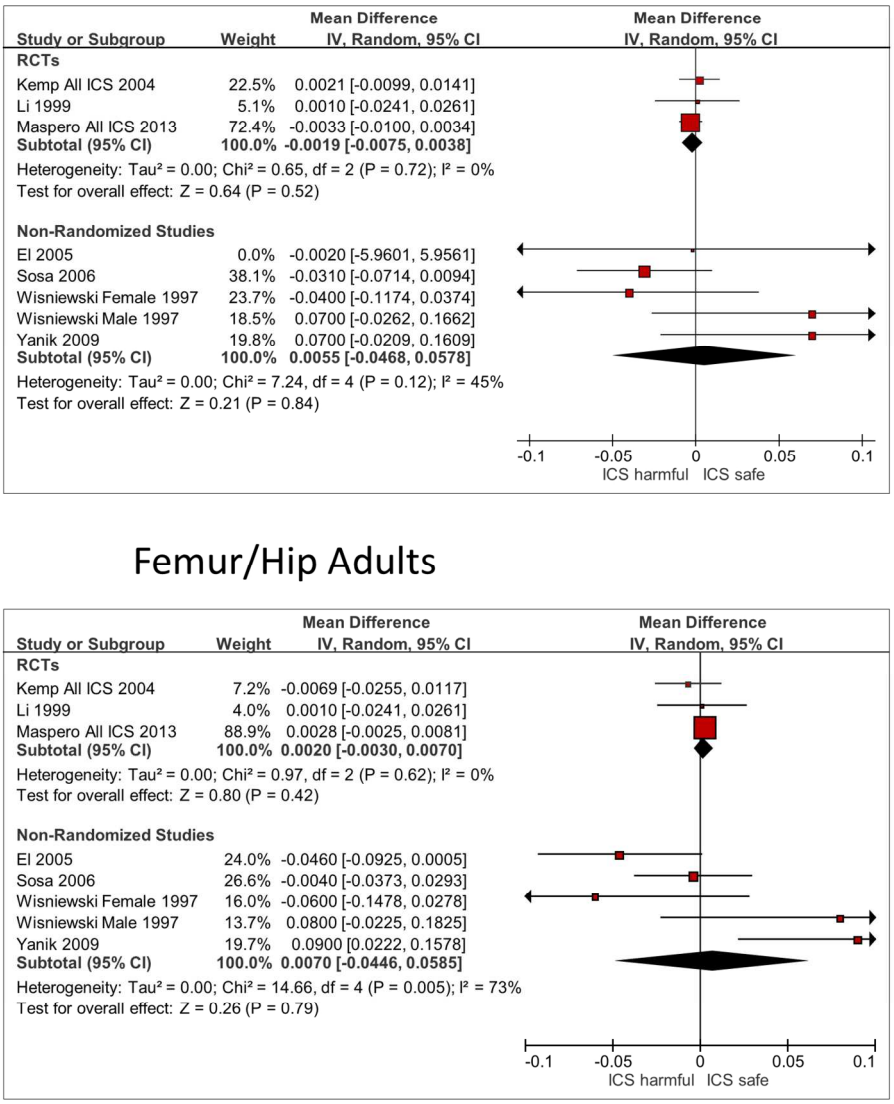

Figure 4. BMD in Adults, ICS use vs. Non-use
180x236mm (300 x 300 DPI)

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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PubMed Update June and Dec 2014

("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 and bones"[All Fields] OR "bone"[All Fields]) OR ("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields])) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields])

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, Table 2-3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig. 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig. 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist