BMJ Open Respiratory Research

Systemic adverse effects from inhaled corticosteroid use in asthma: a systematic review

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To cite: Patel R, Naqvi SA, Griffiths C, *et al*. Systemic adverse effects from inhaled corticosteroid use in asthma: a systematic review. *BMJ Open Resp Res* 2020;**7**:e000756. doi:10.1136/bmjresp-2020-000756

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjres-2017-000756).

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Received 27 August 2020
Revised 8 October 2020
Accepted 19 October 2020

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ABSTRACT

Background Oral corticosteroid use increases the risk of systemic adverse effects including osteoporosis, bone fractures, diabetes, ocular disorders and respiratory infections. We sought to understand if inhaled corticosteroid (ICS) use in asthma is also associated with increased risk of systemic effects.

Methods MEDLINE and Embase databases were searched to identify studies that were designed to investigate ICS-related systemic adverse effects in people with asthma. Studies were grouped by outcome: bone mineral density (BMD), respiratory infection (pneumonia or mycobacterial infection), diabetes and ocular disorder (glaucoma or cataracts). Study information was extracted using the PICO checklist. Risk of bias was assessed using the Cochrane Risk of Bias tool (randomised controlled trials) and Risk of Bias In Non-randomised Studies of Interventions-I tool (observational studies). A narrative synthesis was carried out due to the low number of studies reporting each outcome.

Results Thirteen studies met the inclusion criteria, 2 trials and 11 observational studies. Study numbers by outcome were: six BMD, six respiratory infections (four pneumonia, one tuberculosis (TB), one non-TB mycobacteria), one ocular disorder (cataracts) and no diabetes. BMD studies found conflicting results (three found loss of BMD and three found no loss), but were limited by study size, short follow-up and lack of generalisability. Studies addressing infection risk generally found positive associations but suffered from a lack of power, misclassification and selection bias. The one study which assessed ocular disorders found an increased risk of cataracts. Most studies were not able to fully adjust for known confounders, including oral corticosteroids.

Conclusion There is a paucity of studies assessing systemic adverse effects associated with ICS use in asthma. Those studies that have been carried out present conflicting findings and are limited by multiple biases and residual confounding. Further appropriately designed studies are needed to quantify the magnitude of the risk for ICS-related systemic effects in people with asthma.

Key messages

What is the key question?

► Do inhaled corticosteroids in people with asthma increase the risk of systemic adverse effects that are known to occur with oral corticosteroid use?

What is the bottom line?

► There are few studies addressing this question, and those studies are limited by multiple biases, but they suggest an increased risk of bone mineral density loss, respiratory infections and cataracts.

Why read on?

► This review reports on the few studies that have been carried out on this topic, and highlights current evidence gaps.

INTRODUCTION

Asthma is a highly prevalent global disease; for example, around 8% of adults in the UK and the USA have active asthma.[1 2] Since the 1970s, inhaled corticosteroids (ICS) have been the mainstay of treatment—significantly reducing morbidity and mortality, thus they are recommended as first-line preventer treatment in national and international guidelines.[3–5] For most people, maximal clinical benefit can be achieved with low-dose ICS.[6–8] Yet in the UK, the number of adults with asthma that are prescribed medium-dose or high-dose ICS has increased considerably over the past decade (to around 70% in 2017).[9] Oral corticosteroid use in people with asthma has been found to increase the risk of conditions including osteoporosis, bone fractures, cataracts, pneumonia, opportunistic lung infections, diabetes and obesity.[10] Studies evaluating the dose equivalence of oral corticosteroids to ICS, in terms of systemic effects, found most of the oral corticosteroid-sparing effect that occurs with high-dose ICS is ascribed to their systemic absorption; suggesting high-dose ICS requires similar consideration as starting maintenance low-dose oral corticosteroids.[11] But patients at higher risk of systemic side effects (those that are already diagnosed with osteopenia, osteoporosis, diabetes and cataracts) are not preferentially started on low-dose ICS or stepped down from higher ICS doses,[9] even though people with asthma do consider potential side effects a priority when choosing treatment.[12]

The benefits of an ICS undoubtedly outweigh the risks when used in clinically effective doses, however, long-term ICS use may cause systemic side effects.[13] There has only been one previous systematic review (published in 1999) of all major potential adverse systemic effects associated with ICS, including people with asthma. Due to a dearth of studies the author was unable to perform a meta-analysis, except for the numerous studies evaluating adrenal insufficiency.[14] The aim of this present systematic review was to review the latest scientific evidence of adverse systemic effects associated with ICS use in asthma (excluding adrenal insufficiency which was recently reviewed elsewhere).[15]

METHODS

The systematic review protocol was registered with the International Prospective Register of Systematic Reviews, registration number: CRD42020187770 and we followed the guidelines published by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Consortium (PRISMA).[16]

Study objectives

Our objective was to quantify, in adults with asthma, any association between adverse systematic effects (known to occur with oral corticosteroids) and ICS use. We sought to assess the following effects: bone mineral loss (bone density or fractures), respiratory infections (pneumonia, tuberculosis (TB), or non-TB mycobacteria), ophthalmic effects (cataracts/glaucoma) and diabetes.

Literature search

We systematically searched MEDLINE and Embase (from 10 June 1999 through 10 June 2020) using both Medical Subject Headings terms and free-text searching to identify literature related to asthma, ICS-containing medication and the systemic adverse effects listed in the objectives (online supplemental table 1). These three concepts were combined using the Boolean operator 'AND'. The database search was supplemented by a manual scan of the reference lists of included studies.

Selection of studies

We selected randomised controlled trials (RCTs) and observational studies that included adults with asthma (≥18 years), or that included at most 20% of the study population aged 12–18 years. We considered observational studies where at least one of our outcomes of interest was measured as the primary outcome, and primary or secondary analyses of RCTs. The exposure considered for this review were ICS-containing inhalers (single component or dual component with a long-acting β agonist); those not exposed were using a placebo or non-ICS-containing medication. For observational studies only, we included studies where the control group could contain people without asthma. We only included studies that were designed to evaluate at least one of our outcomes of interest: bone density loss (measure by ultrasound or X-ray absorptiometry), pneumonia, TB, non-TB mycobacteria, cataracts, glaucoma and diabetes (new diagnosis or hyperglycaemia). Articles were excluded if they contained <100 patients that met the inclusion criteria, mixed-study population encompassing more than 10% of people with COPD (chronic obstructive pulmonary disease) or were a study of pregnant women. Abstracts, case histories, reviews/pooled analysis, guidelines, commentaries, animal/in vitro studies and articles not written in English language were also excluded.

Data extraction, quality assessment and data synthesis

Data were extracted following predetermined criteria based on the PICO (Patient Information Comparison Outcome) checklist (online supplemental table 2). Study details included: study name; patient number; length of follow-up; study inclusion and exclusion criteria; population characteristics including how asthma was defined, gender and age range; primary and secondary outcomes; non-ICS comparison; ICS type where reported; confounding factors; crude and adjusted effect estimates; statistical analysis; and any additional notes. Two reviewers extracted relevant data, which were compared, and inconsistencies discussed.

Quality of RCTs were assessed using the Cochrane Risk of Bias tool. Quality of studies was reported as high, moderate, low bias or unclear. Quality of observational studies was assessed using Risk of Bias In Non-randomised Studies of Interventions. Quality of studies was reported as critical, serious, moderate or low bias. Studies were grouped according to study design (RCT or observational), outcome (including by measurement tool, for example, bone density was measured using ultrasound, single or dual energy X-ray absorptiometry) and effect estimate (HR or OR). There were no more than two studies in each group, therefore it was deemed inappropriate to calculate pooled effect estimates, and a narrative synthesis was conducted.

Patient and public involvement statement

Six patients, from a community asthma clinic and a large UK asthma charity, were consulted in a focus group as to their perceived need of this review and the study design, specifically regarding the inclusion and exclusion criteria to be used. Two patients subsequently critically reviewed the manuscript.

RESULTS

Study selection and characteristics

Following our database searches, we identified a total of 5102 studies. After screening for criteria outlined in the methods and illustrated in the PRISMA flow chart, 5089 papers were excluded, leaving a total of 13 articles to be included in this systematic review (online supplemental figure 1 and tables 1–3).

Inclusion and exclusion criteria within papers

A common inclusion criterion was for patients to have a minimum number of months (for example, some studies had a minum of 6 months) since their asthma was first diagnosed, although many papers failed to provide a definition for the diagnosis of asthma (online supplemental table 3a-d). Two studies specified that patients should have mild asthma (according to forcedexpiratory volume in 1 s or peak flow readings prebronchodilator) but no study specified moderate or severe asthma. Common exclusion criteria that many, but not all, studies included: COPD diagnosis/hospital admission for COPD exacerbations, use of oral/parenteral steroids in a specified time prestudy commencement and medical conditions known to affect the outcomes being measured.

Bone density studies

Six studies specified the measurement of bone mineral density (BMD) as the primary outcome[17–22] (table 1). The studies (four observational, two RCT) each included under 250 participants, except one observational study which included 8624 participants.[21] BMD was measured using ultrasound or X-ray absorptiometry (single or dual), or a combination of both, and in different bones (wrist, femur, hip and spine); therefore, findings could not be directly compared between more than two trials. Three of the studies found a decrease in BMD,[18 19 21] while three found no change in BMD;[17 20 22] one found an increased risk of fractures but no loss of BMD. Study follow-up varied between 6 months to several years and the total time of ICS exposure was not reported. In addition, previous OCS (oral corticosteroids) use was not accounted for in two of the four observational studies.[20 22]

Respiratory infection studies: pneumonia

Four observational studies identified pneumonia, diagnosed by a general practitioner, hospital admission or insurance codes, as a primary outcome (table 2). All four studies found an increased risk of pneumonia,[23–26] although one study found the risk was only increased with fluticasone, not budesonide;[25] however, it was likely the subanalysis was underpowered due to the low event rates. Another study due to its cross-sectional design had a high risk of reverse causality,[26] one study had a high risk of misclassification as it did not include hospitalised pneumonia,[23] and the fourth study only included people aged 12–35 years old.[24]

Respiratory infection studies: mycobacterial infection

Two case-control studies measured the odds of mycobacterial infection in patients with asthma on ICS to people without asthma and not on ICS (table 2). One study used a South Korean database (n=2779 patients aged over 20 years) to measure the odds of TB,[27] the other study used a Canadian administrative database (n=1091 patients aged over 66 years) to measure the risk of TB and non-tuberculous mycobacterial pulmonary disease (NTM-PD);[28] both studies found approximately 50% increase in the odds of TB, although this was not statistically significant in the study by Brode *et al*. However, there was a statistically significant increase in the odds of NTM-PD associated with fluticasone, but not budesonide.

Ocular disorder studies

One case-control study analysed the impact of ICS on the development of cataracts in a primary care population of over 30000 patients aged above 40 years (table 3). Controls had no previous use of ICS and findings were adjusted for OCS use.[29] Exposed patients had to have at least one ICS prescription in a 180-day period, but accumulative ICS use was not accounted for. Adjusted results found a 5% significant increase in the odds of developing cataract in patients using an ICS.

Risk of bias

With regards to the RCTs, both successfully demonstrated low levels of selection bias,[17 19] but one showed a potentially high risk of performance bias by keeping the study 'open' and unblinded to participants and personnel[19] (table 4). We found varying levels of bias in terms of observational studies (table 5). Six of the 11 studies had at least a moderate risk of bias due to confounding, including not accounting for any confounders,[22] or only one to three confounders,[20 25 29] or not including oral corticosteroids—potentially the largest confounder.[20 22 24–26] Seven studies had at least a moderate risk of selection bias,[18 20–25] for example, by only selecting a limited young age range at lower risk of BMD loss.[17–19] Seven studies showed at least moderate bias in intervention classification;[18 22–24 26 27 29] many did not take any account of how long participants were on ICS for.[18 21–23 25 26 28 29] Only three studies had low bias of missing data,[19 24 29] most did not report on missing data[20–22 25–28] and one had serious bias risk.[23] Three studies had at least moderate risk of bias in measurement of outcomes[20 23 26] and three studies did not report if the investigators were aware of the intervention status.[21 22 28] All studies had low risk of bias in reporting results.[17–29]

DISCUSSION

This systematic review investigated the potential risk of adverse systemic effects, known to occur with OCS, in people with asthma using ICS. We found 2 RCTs and 11 observational studies meeting the inclusion criteria.

Table 1 Description of studies with bone density as an outcome

Primary author	Sasagawa[22]	Sosa[20]	Langhammer[21]	Israel[18]	Tattersfield[19]	Kemp[17]
Year	2011	2006	2004	2001	2001	2004
Study design	Case-control	Cross-sectional	Cross-sectional	Cohort	RCT	Double blind RCT
Length of study/follow-up	Follow-up was 6 months	ICS >1 year before study entry	Variable	3 years	2 years	104 weeks
Population	Japan	Canary Islands, Spain	Norway	Premenopausal women	19 centres across France, New Zealand, Spain and the UK	Not reported
Sample size	198 ICS users; 93 controls	105 cases; 133 controls	8624	109	239	160
Age range	16 years +	18 years +	20 years +	18–45 years	20–60 years	18–50 years for men, 18–40 years for women
Asthma diagnosis definition	Physician diagnosed, no details	Physician diagnosed, no details	Self-reported	Physician diagnosed, no details	Relatively mild asthma and prebronchodilator FEV_1 of 65% predicted or above	Mean FEV_1 82%–85% of predicted
ICS type (drug/name)	Fluticasone propionate, budesonide, beclomethasone	Not specified	Beclometasone dipropionate, budesonide, fluticasone propionate	Triamcinolone acetonide	Budesonide, beclomethasone	Fluticasone propionate
Control/comparison group	Volunteers or other diseases—not using ICS	Friends and neighbours of the patients, not on ICS or have asthma	Never used corticosteroids and not used β2-agonists in the last month; asthma or randomly selected general population	Premenopausal asthmatic women taking no ICS	Non-ICS for example, LABA, sodium cromoglycate, nedocromil sodium, ipratropium bromide or theophylline	Placebo
Bone tested	Calcaneus	Calcaneus and lumbar and femur	Wrist	Lumbar and femur and trochanter	Femur and lumbar	Lumbar and femur
Density measure	Ultrasound	Ultrasound and DEXA	Single energy X-ray absorptiometry	DEXA	DEXA	DEXA
Secondary outcome of study	N/A	N/A	N/A	N/A	▶ Lung function ▶ Relation between change in bone density and inhaled steroid dose ▶ Change in biochemical markers of bone metabolism	AEs
Statistical analysis	χ^2	Logistic regression	Linear regression	Proc Mixed programme of the SAS software package	ANOVA	ANCOVA

Continued

Table 1 Continued

Primary author	Sasagawa[22]	Sosa[20]	Langhammer[21]	Israel[18]	Tattersfield[19]	Kemp[17]
Adjusted covariates	N/A	Age	Age, square age, height, BMI, number of pack years cigarettes, physical activity, work physical load, family history of osteoporosis, years since menopause, HRT	Age, use of oral contraceptives, use of oral glucocorticoids, use of topical nasal glucocorticoid preparations	Baseline BMD, age (group), sex and country. Change was related to dose of ICS, mean lung function and change in markers of bone metabolism	Baseline value, investigator, sex and age effect
Crude results	First %OSI controls=100.7; cases=102.8 (p=0.12) second %OSI controls=100.5; cases=102.1 (p=0.12)		N/A	In all women, yearly change (g/cm^2/puff)—total hip: −0.00044±0.00017; trochanter: −0.00044±0.00016; femoral neck: −0.00005±0.00028; spine: −0.00008±0.00019 In women who received no oral or parenteral glucocorticoid therapy—total hip: −0.00041±0.00019; trochanter: −0.00048±0.00019; femoral neck: −0.00015±0.00030; spine: −0.00001±0.00020	Mean % change in BMD from baseline in subjects completing the study at month 24 (budesonide): lumbar=0.1%, neck of femur=−0.9%, total body=0.6% Mean % change in BMD from baseline in subjects completing the study at month 24 (beclomethasone): lumbar=−0.4%, neck of femur=−0.9%, total body=0.4%	N/A

Continued

Table 1 Continued

Primary author	Sasagawa[22]	Sosa[20]	Langhammer[21]	Israel[18]	Tattersfield[19]	Kemp[17]
Adjusted results	N/A	Age-adjusted OR=2.79 (95% CI 1.19 to 6.54)	Adjusted mean difference in distal BMD (x10ˆ−3): control versus ICS only ▶ Women: −11.5 (p<0.01). 95% CI −17.1 to −6.0 ▶ Men: −12.4 (p<0.01). 95% CI −18.2 to −6.5	In all women, yearly change (g/cmˆ2/puff)—total hip: −0.00048±0.00018*; trochanter: −0.00042±0.00017*; femoral neck: −0.00017±0.00028; spine: −0.00012±0.00018. In women who received no oral or parenteral glucocorticoid therapy—total hip: −0.00041±0.00020*; trochanter: −0.00047±0.00019*; femoral neck: −0.00015±0.00031; spine: −0.00015±0.00019	Estimated difference between treatments in % change in BMD over 2 years after adjusting (budesonide vs reference): lumbar=−0.35%, neck of femur=−0.70%, total body=−0.42% Estimated difference between treatments in % change in BMD over 2 years after adjusting (beclomethasone vs reference): lumbar=−0.83%, neck of femur=−0.52%, total body=−0.55%	Change in total BMD in placebo=0.008 (0.004) (mean (SE)). Change in FP 88 mcg=0.008 (0.003). Change in FP 440 mcg=0.002 (0.003)

AE, adverse events; ANOVA, analysis of variance; BMD, bone mineral density; BMI, body mass index; DEXA, dual energy X-ray absorptiometry; FEV_1, forced expiratory volume in 1 s; FP, fluticasone proprionate; HRT, hormone replace test; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; %OSI, osteo sono assessment index; RCT, randomised controlled trial; SAS, statistical analysis software.

Table 2 Description of observational studies with respiratory infection as an outcome

Primary author	McKeever[23]	Qian[24]	Ekbom[25]	Kim[26]	Lee[27]	Brode[28]
Year	2013	2017	2019	2019	2013	2017
Study design	Case-control	Cohort	Cohort	Cross-section	Case-control	Case-control
Length of study/follow-up	90 days	Average of 4.8 years	Length of study: 2005–2010	In several places mentions 'study period' but nowhere does it describe what that period was	Up to 3 years	1 January 2001 to 31 December 2013
Population	UK primary care patients in THIN (The Health Improvement Network) database	Pharmacy claims databases from 40% Quebec population and health databases of RAMQ (>7 million people)	Longitudinal Respiratory Health in Northern Europe (RHINE) Study	Total of 16 804 sites (43 tertiary general hospitals, 280 secondary general hospitals and 14 745 primary clinics)	HIRA database (Seoul, South Korea)	Registered residents of Ontario, Canada
Sample size	6857 patients with asthma and pneumonia/LRTI, 36 312 control subjects	152 412 subjects	7284 in total, 587 with asthma	831 613	427 cases have asthma and 2352 controls	219 asthma cases and 872 controls
Age range	18–80 years	12–35 years	28–54 years	15 years +	20 years+	>66 years
Asthma diagnosis definition	GP records via NIH database	>1 prescription for a respiratory medication	Self-reported diagnosis or asthma-related symptoms	Treated with asthma medications or received inpatient care for asthma using insurance asthma codes	ICD-10 codes	Validated algorithms
ICS type (drug/name)	Beclomethasone, budesonide, fluticasone propionate, ciclesonide/mometasone	Budesonide, fluticasone 'and others'	Fluticasone propionate, budesonide	No mention	Beclomethasone, budesonide, fluticasone, triamcinocline, ciclesonide, flunisolide	Beclomethasone, budesonide, ciclesonide, fluticasone propionate or momethasone
Control/comparison group	Asthma with no ICS in 90 days before index	No ICS ever in population using respiratory medication at least once	ICS not used, both people with and without asthma	Not using ICS during undefined study period	Asthma, no ICS	Asthma, no ICS
Primary outcome of study—LRTI or pneumonia	Pneumonia/LRTI recorded in GP database	Hospitalised pneumonia using hospital records	Hospitalised pneumonia from hospital records	Pneumonia using insurance pneumonia codes—not told where pneumonia was treated (primary or secondary care)	TB	NTM-PD
Secondary outcomes of study	N/A	N/A	N/A	N/A	N/A	TB
Statistical analysis	Conditional logistic regression	Quasi-cohort methodology	Poisson regression	Logistic regression	Conditional logistic regression	Conditional logistic regression

Continued

Table 2 Continued

Primary author	McKeever[23]	Qian[24]	Ekbom[25]	Kim[26]	Lee[27]	Brode[28]
Adjusted covariates	Priori confounders, number of relievers in the past year, Charlson Comorbidity Index Score, smoking, social class and use of oral steroids in the past year	Age (matched by design), gender, severity of disease and other comorbidity associated with a risk of pneumonia. Use of NSAIDs, anti-depressants and narcotics	Age, BMI, smoking and centre	Age, sex, insurance type, hospital type, Charlson Comorbidity Index, hospitalisation, and ICS use	LAMA use, SABA use, SAMA use, OCS use, presence of TB sequelae, immunosuppressant use, other comorbidities (malignancy, diabetes, chronic renal failure/ dialysis, silicosis, malabsorption, HIV/AIDS and transplantation), Charlson Comorbidity Index and healthcare usage	Income, rurality, aggregated diagnostic groups, comorbidities (bronchiectasis, chronic kidney disease, gastro-oesophageal reflux disease, HIV, interstitial lung disease, rheumatoid arthritis), prior TB, medication use, and surrogates of severity of OLD and exacerbations of OLD (medications for OLD (any inhaled β-agonist, inhaled anticholinergic, oral corticosteroid or methylxanthine), hospitalisation for OLD, spirometry, home oxygen use)
Crude results	Risk of pneumonia/ LRTI: OR=1.46 for beclomethasone, OR=1.82 for budesonide, OR=0.95 for ciclesonide/ mometasone, OR=2.71 for fluticasone propionate	Rate ratio (risk of pneumonia in ICS users with that in non-users): RR current users=2.59	N/A	OR, 2.00; 95% CI 1.97 to 2.02	OR=1.22 (0.96–1.55)	OR of NTM-PD with current ICS use=1.76 (1.23–2.51)
Adjusted results	Risk of pneumonia/ LRTI: OR=1.09 for beclomethasone, OR=1.20 for budesonide, OR=0.71 for ciclesonide/ mometasone, OR=1.64 for fluticasone propionate	Rate ratio (risk of pneumonia in ICS users with that in non-users): RR current users=1.83	IRR of pneumonia: fluticasone 6 years=7.92 (2.32–27.0) No significant effect found with <6 years or with budesonide	OR=1.38; 95% CI 1.36 to 1.41	Adjusted OR=1.46 (1.11–1.96)	Adjusted OR of NTM-PD with current ICS use=1.56 (0.93–2.62)

BMI, body mass index; GP, general practitioner; HIRA, health insurance review and assessment; ICD-10, international classification of diseases 10th revision; ICS, inhaled corticosteroid; IRR, incidence rate ratio; LAMA, long-acting muscarinic antagonist; LRTI, lower respiratory tract infection; NIH, national institute of health; NSAID, non-steroidal anti-inflammatory drug; NTM-PD, non-tuberculous mycobacterial pulmonary disease; OCS, oral corticosteroids; OLD, obstructive lung disease; RAMQ, Régie de l'assurance maladie du Québec; RR, relative risk; SABA, short-acting beta agonist; SAMA, short-acting muscarinic antagonist; TB, tuberculosis.

Table 3 Description of observational studies with an ocular disorder as an outcome

Primary author	Smeeth[29]
Year	2003
Study design	Case-control study
Length of study/follow-up	At least 180 days
Population	UK primary care electronic medical records (Clinical Practice Research Datalink)
Sample size	15 479 people with cataract and 15 479 controls
Age range	40 years +
Asthma diagnosis definition	N/A
ICS type (drug/name)	Beclomethasone, budesonide, fluticasone
Control/comparison	General population matched controls with no ICS ever
Primary outcome	Cataracts
Secondary outcomes of study	N/A
Statistical analysis	Conditional logistic regression
Adjusted covariates	Only OCS and consultation rate for the asthma effect estimate
Crude results	1.52 (95% CI 1.41 to 1.65)
Adjusted results	1.05 (95% CI 0.95 to 1.16)

ICS, inhaled corticosteroid; OCS, oral corticosteroids.

The most common reason for excluding articles was that people with asthma were not identified, either because the reason for ICS use was not reported or because the effects on people with asthma were not reported separately from the effects on people with COPD.

The main outcomes of studies eligible to be included were loss of BMD and risk of a respiratory infection. However, due to small sample size, insufficiently recorded ICS and/or OCS exposure, and studies using alternative ways of measuring BMD, there is currently a deficiency of evidence to determine if ICS reduces BMD in people with asthma. Furthermore, only one study specifically addressed the risk of bone fractures. The four studies addressing risk of pneumonia were much larger and mostly found an increased risk, but the studies had significant bias—including misclassification, due to the lack of hospital diagnosed pneumonia—and lack of generalisability, including a study population of only young adults. Two studies assessed pulmonary mycobacterial infection risk, and both reported an elevated risk with ICS, but the studies' low outcome prevalence is likely to have caused a lack of statistical power to make firm conclusions. Only one study that measured an ocular disorder as the outcome was eligible to be included. The study, which had moderate bias in the confounding and intervention classification categories, found an increased risk associated with ICS use.

Although most of the studies in this systematic review had biases and limitations in generalisability, there is a suggestion that ICS use in people with asthma can lead to systemic adverse effects. This is perhaps not surprising as all ICS have been found to exhibit dose-related systemic adverse effects when measuring adrenal suppression,[14] and high dose ICS has been shown to have an equivalent systemic absorption as low dose OCS.[11] In addition, several adverse systemic effects have been found to be associated with ICS use in people with COPD, although caution should be used in extrapolating findings in people with COPD to those with asthma. First, people with COPD tend to be older, have more comorbidities, have higher exposure to cigarette smoke and have differing underlying pulmonary immunopathology and systemic inflammation, which may affect the risk of developing adverse effects. For example, osteoporosis has been found to be increased in people with COPD, even without ICS use.[30] Second, many people with asthma use much higher doses of ICS and have used ICS for much of their lifetime—unlike COPD, where lower doses of ICS are licensed as treatment and patients typically start ICS treatment at

Table 4 Risk of bias assessment of trials

Study	Outcome	Random sequence	Allocation concealment	Reporting bias	Other bias	Performance bias	Detection bias	Attrition bias
Tattersfield *et al*[19]	Bone density	Low	Unclear	Low	Unclear	High	Low	Unclear
Kemp *et al*[17]	Bone density	Low	Low	Low	Unclear	Low	Low	Low

Table 5 Risk of bias assessment of observational studies

		Preintervention		At intervention	Postintervention			
Study	**Outcome**	**Confounding**	**Participant selection**	**Intervention classification**	**Deviation from intended intervention**	**Missing data**	**Measurement of outcomes**	**Reporting results**
Sasagawa *et al*[22]	Bone density	Critical	Serious	Serious	Low	No information	No information	Low
Sosa *et al*[20]	Bone density	Serious	Serious	Low	Low	No information	Moderate	Low
Langhammer *et al*[21]	Bone density	Low	Moderate	Low	Low	No information	No information	Low
Israel *et al*[18]	Bone density	Low	Moderate	Moderate	Low	Low	Low	Low
McKeever *et al*[23]	Pneumonia	Low	Moderate	Moderate	Low	Serious	Moderate	Low
Qian *et al*[24]	Pneumonia	Moderate	Serious	Moderate	Low	Low	Low	Low
Ekbom *et al*[25]	Pneumonia	Moderate	Moderate	Low	Low	No information	Low	Low
Kim *et al*[26]	Pneumonia	Moderate	Low	Serious	Low	No information	Serious	Low
Lee *et al*[27]	TB	Low	Low	Serious	Low	No information	Low	Low
Brode *et al*[28]	NTM	Low	Low	Low	Low	No information	No information	Low
Smeeth *et al*[29]	Cataracts	Moderate	Low	Moderate	Low	Low	Low	Low

NTM, non-tuberculous mycobacterial; TB, tuberculosis.

between 60 years and 70 years of age.[31] There is little debate that ICS use in people with COPD is associated with elevated risk of pneumonia.[32] Studies of patients with COPD have also found an increased risk of TB in at-risk populations,[33] a modest but statistically significant augmented risk of fractures[34] and in studies not distinguishing between patients with asthma and COPD, the risk of cataracts is around 25% for each 1000 mcg per day (beclometasone equivalent).[35] Very few studies have assessed the risk of new-onset diabetes or worsening glycaemia, allied to ICS use, in any population.[36]

Limitations

The main limitation of this review is the small number of studies eligible to be included, which precludes the calculation of an overall effect estimate for any of the outcomes. Furthermore, in the BMD articles, different studies used different density measurement tools, in different bones. The lack of adequate control for confounding from OCS exposure represents another inherent limitation. It was not possible to draw conclusions on the association between systemic adverse effects and the dose, duration or type of ICS from the included studies. In studies with a short follow-up it was not possible to consider longer-term adverse effects that may occur, such as bone mineral loss. In this systematic review we have chosen not to include all trials reporting adverse effects as these rely on spontaneous adverse event reports in short-term clinical trials, with no formal measurement of the outcome; furthermore, there is always a high risk of selection bias as only around 10% of people with asthma are eligible to participate in clinical trials.

CONCLUSIONS

Asthma is a highly prevalent disorder that in many people requires regular ICS to ensure symptom control and prevent asthma attacks, most of whom are prescribed medium dose or high dose ICS.[2] Yet, we found in this review that surprisingly few studies have assessed the potential risk, in an asthma population, of the known adverse systemic effects that accompany OCS use. While these limited studies do suggest ICS use increases the risk of respiratory infections, cataracts and loss of BMD in people with asthma, there were several biases and limitations associated with the studies. A key message from this review is the urgent need for further well-controlled and detailed longitudinal cohort studies to quantify the nature and magnitude of the risk of systemic adverse effects. These studies should try to establish which ICS drugs, which patients and what doses are associated with the highest risk for each outcome. This information is crucial for making informed, shared decisions with patients about how to manage their asthma. Although the risk of side effects is often not considered by primary care physicians, it is considered by patients to be a priority in treatment choices;[12 37] bridging this evidence gap will help improve joint management decisions.

Acknowledgements The authors thank Vivienne Tickle and Sharon Simons for their critical review of the manuscript.

Contributors CIB, RP and SAN conducted the literature search, reviewed titles and full-text articles, extracted data, analysed data, wrote the manuscript. CG critically revised the manuscript. All authors read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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