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

Roshni Patel, Sumrah A Naqvi, Chris Griffiths, Chloe I Bloom

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.

INTRODUCTION

Asthma is a highly prevalent global disease; for example, around 8% of adults in the UK and the USA have active asthma. Since the 1970s, inhaled corticosteroids (ICS) have been the mainstay of treatment—significantly reducing morbidity and mortality, thus they are recommended as first-line preventive treatment in national and international guidelines. For most people, maximal clinical benefit can be achieved with low-dose ICS. 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). 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. 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. 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, 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 systemic 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 least 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 forced expiratory 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 period, previous OCS (oral corticosteroids) use was not accounted for in two of the four observational studies.

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.

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; 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,25 and the fourth study only included people aged 12–35 years old.

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 30 000 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 (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 26 or not including oral corticosteroids—potentially the largest confounder,20 22 24–26 Seven studies had at least a moderate risk of selection bias,19 25–29 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,19 22–24 26 27 28 29 many did not take any account of how long participants were on ICS for. 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. Three studies had at least moderate risk of bias in measurement of outcomes20 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.

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

<table>
<thead>
<tr>
<th>Primary author</th>
<th>Sasagawa</th>
<th>Sosa</th>
<th>Langhammer</th>
<th>Israel</th>
<th>Tattersfield</th>
<th>Kemp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Case-control</td>
<td>Cross-sectional</td>
<td>Cross-sectional</td>
<td>Cohort</td>
<td>RCT</td>
<td>Double blind RCT</td>
</tr>
<tr>
<td>Length of study/follow-up</td>
<td>Follow-up was 6 months</td>
<td>ICS &gt;1 year before study entry</td>
<td>Variable</td>
<td>3 years</td>
<td>2 years</td>
<td>104 weeks</td>
</tr>
<tr>
<td>Population</td>
<td>Japan</td>
<td>Canary Islands, Spain</td>
<td>Norway</td>
<td>Premenopausal women</td>
<td>19 centres across France, New Zealand, Spain and the UK</td>
<td>Not reported</td>
</tr>
<tr>
<td>Sample size</td>
<td>198 ICS users; 93 controls</td>
<td>105 cases; 133 controls</td>
<td>8624</td>
<td>109</td>
<td>239</td>
<td>160</td>
</tr>
<tr>
<td>Age range</td>
<td>16 years +</td>
<td>18 years +</td>
<td>20 years +</td>
<td>18–45 years</td>
<td>20–60 years</td>
<td>18–50 years for men, 18–40 years for women</td>
</tr>
<tr>
<td>Asthma diagnosis definition</td>
<td>Physician diagnosed, no details</td>
<td>Physician diagnosed, no details</td>
<td>Self-reported</td>
<td>Physician diagnosed, no details</td>
<td>Relatively mild asthma and prebronchodilator FEV₁ of 65% predicted or above</td>
<td>Mean FEV₁, 82%–85% of predicted</td>
</tr>
<tr>
<td>ICS type (drug/name)</td>
<td>Fluticasone propionate, budesonide, beclomethasone</td>
<td>Not specified</td>
<td>Beclometasone dipropionate, budesonide, fluticasone propionate</td>
<td>Triamcinolone acetonide</td>
<td>Budesonide, beclomethasone</td>
<td>Fluticasone propionate</td>
</tr>
<tr>
<td>Control/comparison group</td>
<td>Volunteers or other diseases—not using ICS</td>
<td>Friends and neighbours of the patients, not on ICS or have asthma</td>
<td>Never used corticosteroids and not used β₂-agonists in the last month; asthma or randomly selected general population</td>
<td>Premenopausal asthmatic women taking no ICS</td>
<td>Non-ICS for example, LABA, sodium cromoglycate, nedocromil sodium, ipratropium bromide or theophylline</td>
<td>Placebo</td>
</tr>
<tr>
<td>Bone tested</td>
<td>Calcaneus</td>
<td>Calcaneus and lumbar and femur</td>
<td>Wrist</td>
<td>Lumbar and femur and trochanter</td>
<td>Femur and lumbar</td>
<td>Lumbar and femur</td>
</tr>
<tr>
<td>Density measure</td>
<td>Ultrasound</td>
<td>Ultrasound and DEXA</td>
<td>Single energy X-ray absorptiometry</td>
<td>DEXA</td>
<td>DEXA</td>
<td>DEXA</td>
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<tr>
<td>Secondary outcome of study</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Statistical analysis</td>
<td>$\chi^2$</td>
<td>Logistic regression</td>
<td>Linear regression</td>
<td>Proc Mixed programme of the SAS software package</td>
<td>ANOVA</td>
<td>ANCOVA</td>
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Continued
<table>
<thead>
<tr>
<th>Primary author</th>
<th>Sasagawa 22</th>
<th>Sosa 20</th>
<th>Langhammer 21</th>
<th>Israel 18</th>
<th>Tattersfield 19</th>
<th>Kemp 17</th>
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</thead>
<tbody>
<tr>
<td>Adjusted covariates</td>
<td>N/A</td>
<td>Age</td>
<td>Age, square age, height, BMI, number of pack years cigarettes, physical activity, work physical load, family history of osteoporosis, years since menopause, HRT</td>
<td>Age, use of oral contraceptives, use of oral glucocorticoids, use of topical nasal glucocorticoid preparations</td>
<td>Baseline BMD, age (group), sex and country. Change was related to dose of ICS, mean lung function and change in markers of bone metabolism</td>
<td>Baseline value, investigator, sex and age effect</td>
</tr>
<tr>
<td>Crude results</td>
<td>First %OSI controls=100.7; cases=102.8 (p=0.12) second %OSI controls=100.5; cases=102.1 (p=0.12)</td>
<td>N/A</td>
<td>In all women, yearly change (g/cm²/puff)—total hip: −0.00044±0.00017; trochanter: −0.00044±0.00016; femoral neck: −0.00005±0.00028; spine: −0.00008±0.00019</td>
<td>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%</td>
<td>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%</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Continued

Adjusted mean difference in distal BMD (x10^-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/cm^2/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

In women who received 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

Table 1 Continued

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<thead>
<tr>
<th>Primary author</th>
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<th>Langhammer^21</th>
<th>Israel^18</th>
<th>Tattersfield^19</th>
<th>Kemp^17</th>
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<tr>
<td>Adjusted results</td>
<td>N/A</td>
<td>Age-adjusted OR=2.79 (95% CI 1.19 to 6.54)</td>
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<tr>
<td></td>
<td></td>
<td>Adjusted mean difference in distal BMD (x10^-3): control versus ICS only</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>▶ Women: −11.5 (p&lt;0.01), 95% CI −17.1 to −6.0</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>▶ Men: −12.4 (p&lt;0.01), 95% CI −18.2 to −6.5</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>In all women, yearly change (g/cm^2/puff) — total hip:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| | | - −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; FEV1, forced expiratory volume in 1 s; FP, fluticasone propionate; 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>
<thead>
<tr>
<th>Primary author</th>
<th>McKeever</th>
<th>Qian</th>
<th>Ekbom</th>
<th>Kim</th>
<th>Lee</th>
<th>Brode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>2013</td>
<td>2017</td>
<td>2019</td>
<td>2019</td>
<td>2013</td>
<td>2017</td>
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<tr>
<td>Study design</td>
<td>Case-control</td>
<td>Cohort</td>
<td>Cohort</td>
<td>Cross-section</td>
<td>Case-control</td>
<td>Case-control</td>
</tr>
<tr>
<td>Length of study/follow-up</td>
<td>90 days</td>
<td>Average of 4.8 years</td>
<td>Length of study: 2005–2010</td>
<td>Up to 3 years</td>
<td>1 January 2001 to 31 December 2013</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>UK primary care patients in THIN (The Health Improvement Network) database</td>
<td>Pharmacy claims databases from 40% Quebec population and health databases of RAMQ (&gt;7 million people)</td>
<td>Longitudinal Respiratory Health in Northern Europe (RHINE) Study</td>
<td>Total of 16804 sites (43 tertiary general hospitals, 280 secondary general hospitals and 14745 primary clinics)</td>
<td>HIRA database (Seoul, South Korea)</td>
<td>Registered residents of Ontario, Canada</td>
</tr>
<tr>
<td>Sample size</td>
<td>6857 patients with asthma and pneumonia/LRTI, 36312 control subjects</td>
<td>152 412 subjects</td>
<td>7284 in total, 587 with asthma</td>
<td>831613</td>
<td>427 cases have asthma and 2352 controls</td>
<td>219 asthma cases and 872 controls</td>
</tr>
<tr>
<td>Age range</td>
<td>18–80 years</td>
<td>12–35 years</td>
<td>28–54 years</td>
<td>15 years +</td>
<td>20 years+</td>
<td>&gt;66 years</td>
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<tr>
<td>Asthma diagnosis definition</td>
<td>GP records via NIH database</td>
<td>&gt;1 prescription for a respiratory medication</td>
<td>Self-reported diagnosis or asthma-related symptoms</td>
<td>Treated with asthma medications or received inpatient care for asthma using insurance asthma codes</td>
<td>ICD-10 codes</td>
<td>Validated algorithms</td>
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<tr>
<td>ICS type (drug/name)</td>
<td>Beclomethasone, budesonide, fluticasone propionate, ciclesonide/mometasone</td>
<td>Budesonide, fluticasone ‘and others’</td>
<td>Fluticasone propionate, budesonide</td>
<td>No mention</td>
<td>Beclomethasone, budesonide, fluticasone, triamcinocline, ciclesonide, flunisolide</td>
<td>Beclomethasone, budesonide, ciclesonide, fluticasone propionate or mometasone</td>
</tr>
<tr>
<td>Control/comparison group</td>
<td>Asthma with no ICS in 90 days before index</td>
<td>No ICS ever in population using respiratory medication at least once</td>
<td>ICS not used, both people with and without asthma</td>
<td>Not using ICS during undefined study period</td>
<td>Asthma, no ICS</td>
<td>Asthma, no ICS</td>
</tr>
<tr>
<td>Primary outcome of study—LRTI or pneumonia</td>
<td>Pneumonia/LRTI recorded in GP database</td>
<td>Hospitalised pneumonia using hospital records</td>
<td>Hospitalised pneumonia from hospital records</td>
<td>Pneumonia using insurance pneumonia codes—not told where pneumonia was treated (primary or secondary care)</td>
<td>TB</td>
<td>NTM-PD</td>
</tr>
<tr>
<td>Secondary outcomes of study</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>TB</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>Conditional logistic regression</td>
<td>Quasi-cohort methodology</td>
<td>Poisson regression</td>
<td>Logistic regression</td>
<td>Conditional logistic regression</td>
<td>Conditional logistic regression</td>
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### Table 2: Continued

<table>
<thead>
<tr>
<th>Primary author</th>
<th>McKeever(^{23})</th>
<th>Qian(^{24})</th>
<th>Ekbom(^{25})</th>
<th>Kim(^{26})</th>
<th>Lee(^{27})</th>
<th>Brode(^{28})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted covariates</td>
<td>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</td>
<td>Age (matched by design), gender, severity of disease and other comorbidity associated with a risk of pneumonia. Use of NSAIDs, antidepressants and narcotics</td>
<td>Age, BMI, smoking and centre</td>
<td>Age, sex, insurance type, hospital type, Charlson Comorbidity Index, hospitalisation, and ICS use</td>
<td>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</td>
<td>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 (\beta)-agonist, inhaled anticholinergic, oral corticosteroid or methylxanthine), hospitalisation for OLD, spirometry, home oxygen use)</td>
</tr>
</tbody>
</table>

#### 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=0.90 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.
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>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Case-control study</td>
</tr>
<tr>
<td>Length of study/follow-up</td>
<td>At least 180 days</td>
</tr>
<tr>
<td>Population</td>
<td>UK primary care electronic medical records (Clinical Practice Research Datalink)</td>
</tr>
<tr>
<td>Sample size</td>
<td>15 479 people with cataract and 15 479 controls</td>
</tr>
<tr>
<td>Age range</td>
<td>40 years +</td>
</tr>
<tr>
<td>Asthma diagnosis definition</td>
<td>N/A</td>
</tr>
<tr>
<td>ICS type (drug/name)</td>
<td>Beclomethasone, budesonide, fluticasone</td>
</tr>
<tr>
<td>Control/comparison</td>
<td>General population matched controls with no ICS ever</td>
</tr>
<tr>
<td>Secondary outcomes of study</td>
<td>Cataracts</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>Conditional logistic regression</td>
</tr>
<tr>
<td>Adjusted covariates</td>
<td>Only OCS and consultation rate for the asthma effect estimate</td>
</tr>
<tr>
<td>Crude results</td>
<td>1.52 (95% CI 1.41 to 1.65)</td>
</tr>
<tr>
<td>Adjusted results</td>
<td>1.05 (95% CI 0.95 to 1.16)</td>
</tr>
</tbody>
</table>

ICS, inhaled corticosteroid; OCS, oral corticosteroids.

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Random sequence</th>
<th>Allocation concealment</th>
<th>Reporting bias</th>
<th>Other bias</th>
<th>Performance bias</th>
<th>Detection bias</th>
<th>Attrition bias</th>
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</thead>
<tbody>
<tr>
<td>Tattersfield et al19</td>
<td>Bone density</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>Kemp et al17</td>
<td>Bone density</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
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 a modest but statistically significant augmented risk of fractures34 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 density measurement tools were used, and the lack of adequate control for confounding from OCS exposure represents another inherent limitation. 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 there is little ability to distinguish between patients with asthma and COPD, with COPD having an increased risk of TB in patients with COPD.32 Studies of patients with COPD have also found a modest but statistically significant augmented risk of fractures34 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

## 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. 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 risks of systemic adverse effects. These studies should try to establish the nature and magnitude of the risks of systemic adverse effects. These studies should try to establish the nature and magnitude of the risks of systemic adverse effects. These studies should try to establish the nature and magnitude of the risks of systemic adverse effects. These studies should try to establish the nature and magnitude of the risks of systemic adverse effects. These studies should try to establish the nature and magnitude of the risks of systemic adverse effects. These studies should try to establish the nature and magnitude of the risks of systemic adverse effects. These studies should try to establish the nature and magnitude of the risks of systemic adverse effects. These studies should try to establish the nature and magnitude of the risks of systemic adverse effects.
physicians, it is considered by patients to be a priority in treatment choices;13,17 bridging this evidence gap will help improve joint management decisions.

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