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ORIGINAL PAPER

Inhaled corticosteroids and risk of upper respiratory tract infection in patients with asthma: a meta-analysis

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Abstract

Background Recent studies have suggested a possible association between respiratory infection and the use of inhaled corticosteroids (ICS). We aimed to ascertain the risk of upper respiratory tract infection (URTI) with long-term inhaled corticosteroid use among patients with asthma.

Methods Through a comprehensive literature search of PubMed, Cochrane Library, EMBASE, and Google Scholar from inception to May 2018, we included randomized controlled trials of any ICS vs. a control treatment for asthma, with reporting of URTI as an adverse event. We conducted meta-analyses by the Peto approaches to generate summary estimates comparing ICS with non-ICS treatment on the risk of URTI.

Results Seventeen trials (15,336 subjects) were included. Compared with non-ICS treatment, ICSs were associated with a significantly increased risk of URTI (Peto OR, 1.24; 95% CI 1.08–1.42; $I^2 = 5\%$, $p = 0.002$). Subgroup analyses were performed for different dose, both high- and low-dose ICSs were associated with a significantly increased risk of URTI (high dose: Peto OR, 1.46; 95% CI 1.05–2.03; $I^2 = 0\%$; $p = 0.03$) (low dose: Peto OR, 1.20; 95% CI 1.04–1.39; $I^2 = 25\%$; p = 0.01). Moreover, fluticasone was observed with an increased risk of URTI (Peto OR, 1.18; 95% CI 1.02–1.38; $p = 0.03$; heterogeneity: $I^2 = 21\%$) but not budesonide, low-dose fluticasone treatment was associated with a significantly higher risk of URTI but not high dose.

Conclusions This study raises safety concerns about the risk of URTI associated with ICS use in patients with asthma, but it should be further investigated.

Keywords Inhaled corticosteroids (ICS) · Asthma · Upper respiratory tract infection (URTI) · Risk · Meta-analysis

Introduction

Inhaled corticosteroids (ICS) as an efficacious controller therapy are widely used for the treatment of asthma [1]. They can modulate airway inflammation with airway hypersensitivity induced by infections and allergens [2], reduce asthma symptoms, and improve lung function [3]. They are also recommended in combination with long-acting bronchodilators to treat patients whose asthma is not controlled by an ICS alone [4]. ICS are generally considered safe and well tolerated in both children and adults.

Although ICS have shown great advantages with minimal serious adverse effects in treatment, some clinical outcomes including cataracts, adrenal suppression, glaucoma, and hyperglycemia are still identified consequences complicating their use. ICS are also potent but nonspecific anti-inflammatory agents. In cases of extensive ICS use, it is also important to be considered that latent harmful effects on host immunity may facilitate an increased risk of respiratory infection. A recent study has raised concerns about increased risk of respiratory infection related to long-term use of ICS in patients with chronic obstructive pulmonary disease (COPD) [5]. Zhang and colleagues also revealed an increased risk of oropharyngeal colonization by Streptococcus pneumoniae in children with asthma regularly taking ICS [6]. In addition, the large Toward a Revolution in COPD Health (TORCH) trial also reviewed

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the morbidity rate of URTI in COPD patients, and suggested that ICS use increased the likelihood of upper respiratory tract infection (URTI) [7]. Those outcomes allowed for concerns to then arise about ICS use and the risk of respiratory infections in COPD and asthma patients [8]. As far as we know, no study has assessed the possible link between use of ICS and the risk of other respiratory infections besides pneumonia in asthmatic patients. Therefore, it seemed worthy to carry out a meta-analysis of randomized controlled trials to assess the risk of URTI that could be associated with ICS use in patients with asthma.

Accordingly, the main objectives of this study were to systematically examine the risk of URTI associated with regular ICS use in patients with asthma based on current evidences. We also aimed to ascertain the risk of URTI and various steroids and doses in these trials as a secondary objective.

Methods

Search strategy

Two reviewers independently and in duplicate searched PubMed, Cochrane Library, EMBASE, and Google Scholar using multiple search terms. The search strategy was as follows: ("ICS" OR "ICS/LABA") AND ("asthma" OR "wheezing" OR "CVA" OR "Cough Type Asthma"). ICS included fluticasone (FP), flunisolide, triamcinolone, ciclesonide, mometasone, beclomethasone, and budesonide (BUD). ICS/LABA combination drugs included FP/SAL (Advair), fluticasone furoate/vilanterol (Breo Ellipta), and BUD/FOR (Symbicort). Asthma data were also independently extracted by two reviewers. The search was conducted in January 2018 and updated in May 2018. There were no restrictions placed on race, language, ethnicity, date or geographic area.

Eligibility criteria

To be included in this meta-analysis, studies had to meet all of the following criteria: (1) randomized trials; (2) patients with asthma; (3) exposure to ICS [including ICS alone or in combination with long-acting 2-agonists (LABA)]; (4) non-ICS treatment as control; and (5) at least 1 of upper respiratory tract infection reported as adverse event. Exclusion criteria included: (I) abstracts and reviews; (II) non-English articles; (III) a case–control or cohort design; and (III) a randomized controlled trials of ICS in patients with COPD.

Quality assessment

Two investigators independently extracted relevant data from eligible trials. The Cochrane Toolkit was used for the assessment of bias of each trial. The following assessment were included in this meta-analysis: (1) allocation sequence generation; (2) blinding of participants and personnel; (3) blinding of outcome assessment; (4) allocation concealment; (5) selective reporting; and (6) other biases [9]. Any disagreements were resolved by discussion by two investigators until a consensus was reached.

Statistical analysis

We performed meta-analyses for quantitative data synthesis. Considering that the Peto OR does not need a continuity correction and provides the best CI coverage when events are rare, the risk of URTI was estimated with the Peto OR and 95% CI. We conducted subgroup analyses on the basis of the type and dose of drugs. A random effects model would be used when a substantial level of heterogeneity was found. All meta-analyses were performed by using Revman Software (v.5.3, Cochrane Collaboration, London, UK). Statistical heterogeneity was assessed using the I^2 statistic with $I^2 > 50\%$ indicating a substantial level of heterogeneity. A p value < 0.05 was considered to indicate a statistically significant difference.

Results

Studies included in the meta-analysis

A total of 2560 articles were identified after an initial search. 2543 of these studies were excluded for various reasons, including duplicate data, non-English language, URTI outcome unclear, and non-randomized controlled trial. Finally, 17 studies enrolled 15,336 subjects (Fig. 1) [10–26]. Most studies were multi-center, double-blind, randomized trials conducted across numerous countries. Trial characteristics are given in Table 1. The flowchart is shown in Fig. 1.

Risk of bias of included trials

All trials were assessed using a risk bias assessment tool. Studies with four or more features were regarded as high quality. Six RCTs were judged to be at low risk of bias (adequate sequence generation, double blinding, allocation concealment, selective outcome reporting, and other biases). One study had unclear risk of bias for performance, and one study had incomplete outcome data.

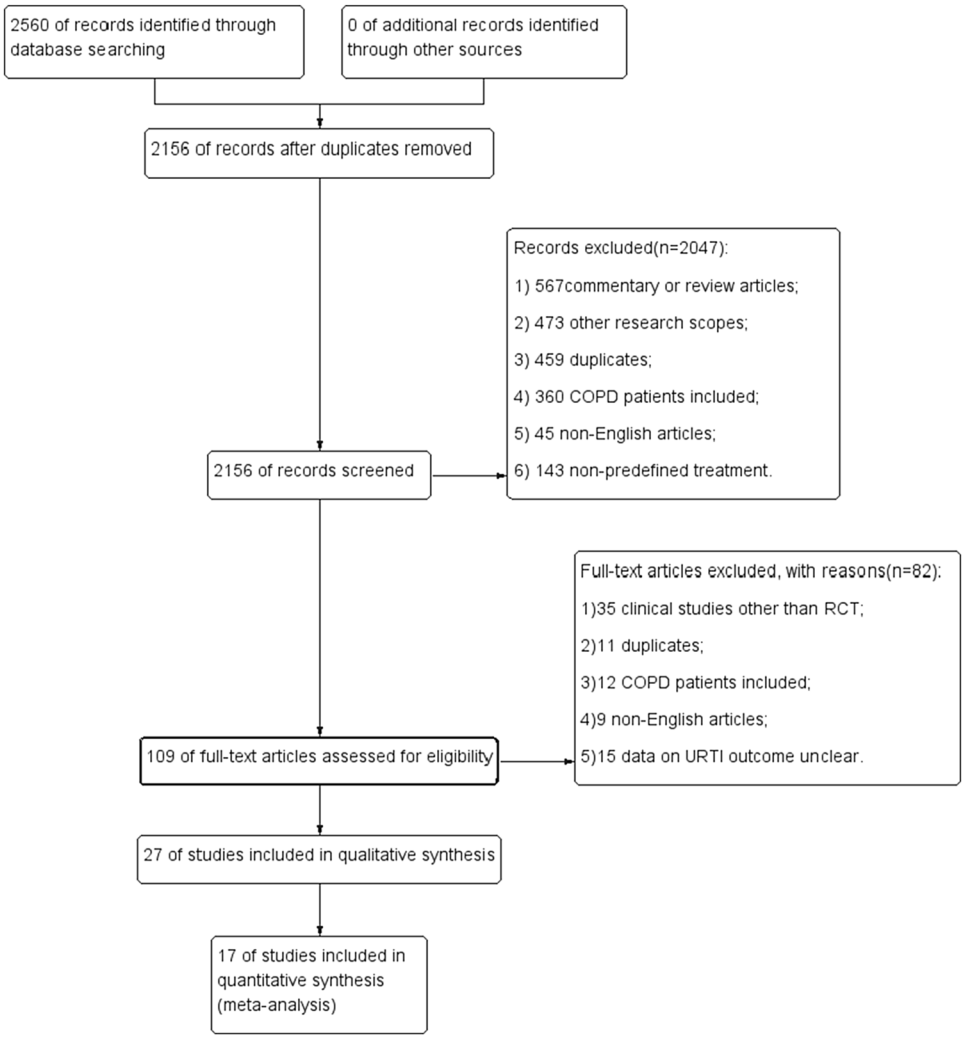

Fig. 1 Flow diagram of the literature search process. *RCT* randomized controlled trial, *URTI* upper respiratory tract infection

Moreover, four studies had an unclear risk of bias due to the other bias, mainly owing to the potential for funding bias[as some trials were performed by the authors who may be employed by the drug manufacturer or funded by a pharmaceutical company] (Fig. 2).

Use of ICS and risk of URTI

A summary of the findings of the meta-analysis about an association between use of ICS and the risk of URTI is provided in Fig. 3. For 17 included trials, the crude risk of URTI was 16.42% (1557 of 9481 patients) in the ICS treatment group and 6.59% (386 of 5855 patients) in the non-ICS treatment group. According to the Peto approach, ICS treatment was associated with a significantly increased risk of URTI vs. non-ICS treatment (Peto OR, 1.24; 95% CI 1.08–1.42; $p = 0.002$).There was evidence of low statistical heterogeneity among the included trials ($I^2 = 5\%$) (Fig. 3).

Risk of URTI associated with the different doses of ICS

Considering that occurrence of adverse events was closely related to the dose of ICS, subgroup analyses were performed next for different doses. Fourteen RCTs assessed low-dose ICS (fluticasone $\leq$ 250 μg/day; mometasone $\leq$ 400 μg/day; budesonide $\leq$ 320 μg/day; ciclesonide $\leq$ 160 μg/day), five RCTs assessed high-dose ICS (budesonide $\geq$ 800 μg/day; mometasone $\geq$ 800 μg/day; fluticasone $\geq$ 500 μg/day; ciclesonide $\geq$ 320 μg/day) (GINA 2012). According to the Peto method, use of high-dose ICS was associated with a significantly increased risk of URTI when compared with non-ICS treatment (Peto OR 1.46; 95% CI 1.05–2.03; heterogeneity: $I^2 = 0\%$; $p = 0.03$) (Fig. 4), and low-dose ICSs also showed a significantly increased risk of URTI (Peto OR 1.20; 95% CI 1.04–1.39; heterogeneity: $I^2 = 25\%$; $p = 0.01$) (Fig. 5).

Table 1 Characteristics of RCTs of inhaled corticosteroid use included in the analysis of respiratory infections

Author	No. of subjects: cases/E; controls/E	Interventions	Patients (years)	Duration, months
Sheffer et al. [10]	3630/23;3591/14	BUD vs. P	5–60	24
Corren et al. [11]	244/2;236/1	BUD vs. F; BUD vs. S	≧12	3
Karpel et al. [12]	85/11;38/2	MF/F vs. F; MF vs. P	≧12	3
Woodcock and Bateman et al. [13]	545/74;101/13	FP vs. P	≧12	3
Busse and Bleecker et al. [14]	519/62;103/8	FP vs. P	≧12	2
Busse and Bateman et al. [15]	232/54;115/23	FP vs. P	≧12	6
Chuchalin et al. [24]	1943/911;315/145	FP vs. P; SFC vs. P	12–79	12
Woodcock and Bleecker et al. [13]	367/18;187/5	FP/S vs. P	≧12	1
Lin et al. [16]	153/18;154/27	FP/VI vs. P	≧12	3
O'Byrne et al. [19]	121/14;121/15	FP vs. P	≧12	3
Lötvall et al. [26]	228/26;115/12	FP/F vs. F; FF vs. P	≧12	6
Oliver et al. [18]	54/4;54/1	FF/VI and FF vs. P and VI	18–65	0.75
Nathan et al. [17]	185/75;180/55	FP/F vs. F; FF vs. P	≧12	0.75
Lumry et al. [20]	311/105;104/22	FP vs. P	≧12	0.75
D'Urzo et al. [21]	317/110;83/19	MF vs. P	≧12	0.75
Chapman et al. [22]	219/47;110/23	C vs. P	18–70	0.5
Noonan et al. [23]	348/3;248/1	BUD vs. P	≧12	0.75

Adverse events. Only trials reporting on at least one URTI event were included in the meta-analysis

S salmeterol, *FP* fluticasone propionate, *FF* fluticasone furoate, *P* placebo, *VI* vilanterol, *E* upper respiratory tract infection events, *F* formoterol, *MF* mometasone furoate, *BUD* budesonide, *FM* formoterol, *FSC* fluticasone propionate/salmeterol, *BDP* beclomethasone, and average, *P* placebo, *C* ciclesonide

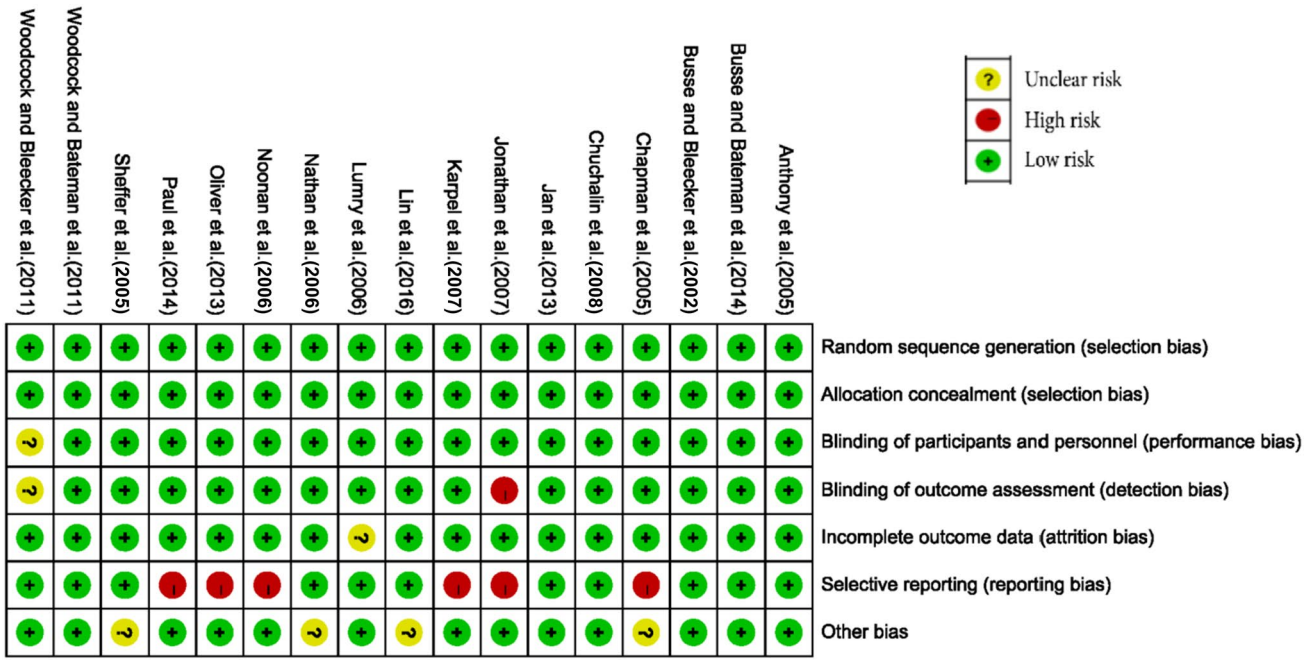

Fig. 2 Risk of bias. Risk of bias for the studies was assessed according to the information that comes from studies at low, high, or unclear risk of bias for each item in the risk of bias tool

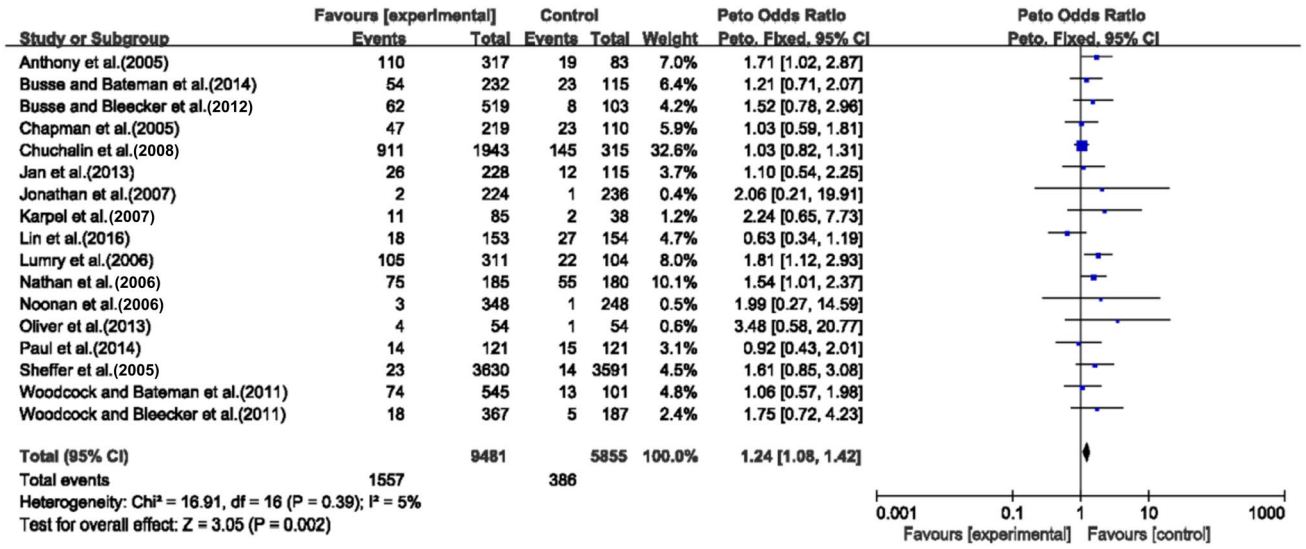

Fig. 3 Risk of URTI associated with ICS treatment compared with non-ICS treatment using the Peto approach

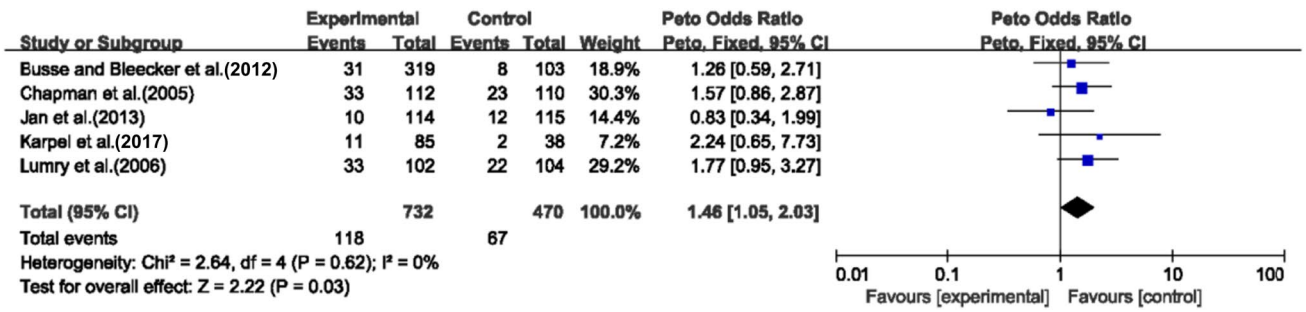

Fig. 4 Risk of URTI associated with high-dose ICS treatment compared with non-ICS treatment using the Peto approach

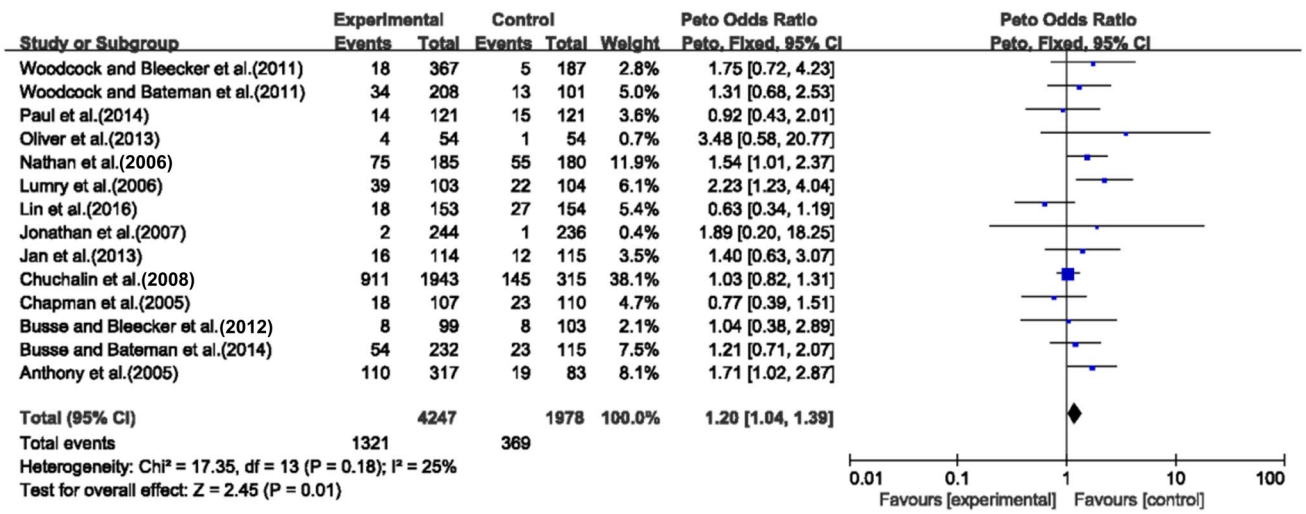

Fig. 5 Risk of URTI associated with low-dose ICS treatment compared with non-ICS treatment using the Peto approach

Risk of URTI associated with fluticasone and budesonide treatment

Of the eligible trials, 11, 2, 1, and 3 RCTs assessed fluticasone, mometasone, ciclesonide, and budesonide, respectively. According to the Peto method, fluticasone was observed with an increased risk of URTI vs. control group (Peto OR 1.18; 95% CI 1.02–1.38; $p = 0.03$; heterogeneity: $I^2 = 21\%$) (Fig. 6). Subgroup analyses were performed next for different fluticasone doses. Eleven and three RCTs assessed low- and high-dose fluticasone treatment, respectively. According to the Peto method, low-dose fluticasone was associated with a significantly increased risk of URTI vs. control group (Peto OR 1.19; 95% CI 1.01–1.39; $p =$

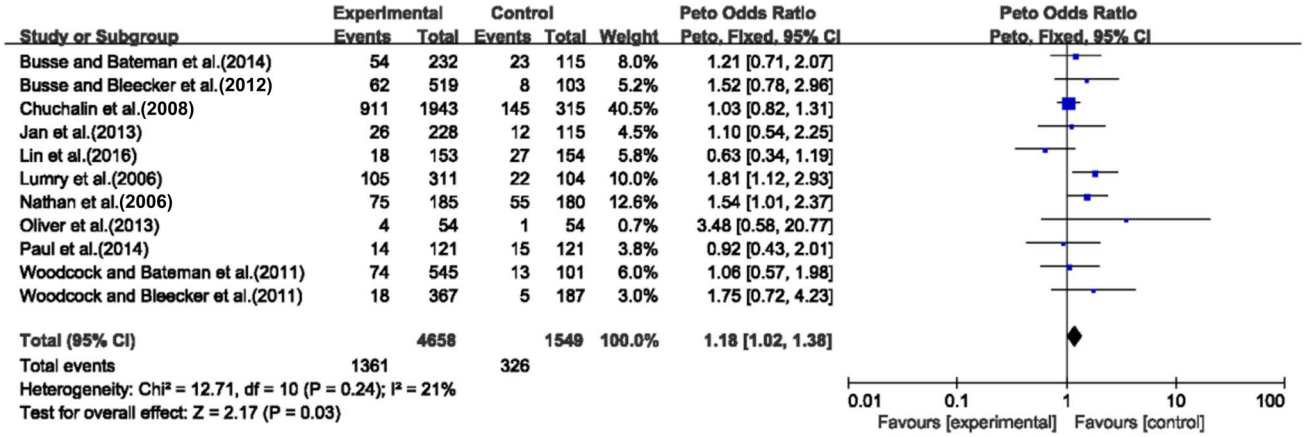

Fig. 6 Risk of URTI associated with fluticasone treatment compared with non-fluticasone treatment using the Peto approach

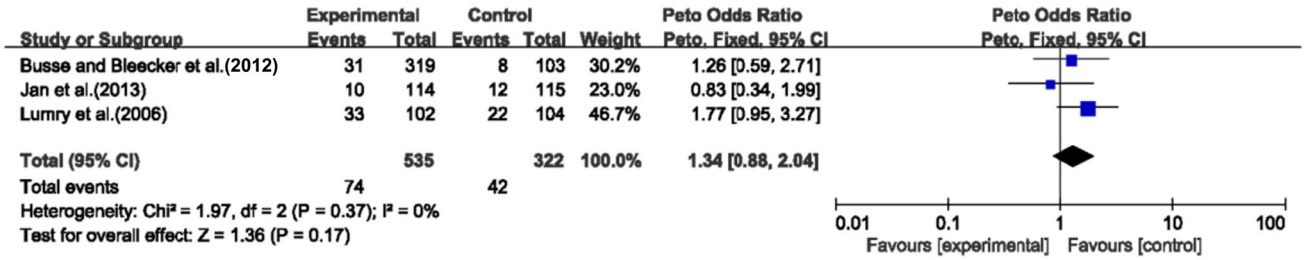

Fig. 7 Risk of URTI associated with high-dose fluticasone treatment compared with non-ICS treatment using the Peto approach

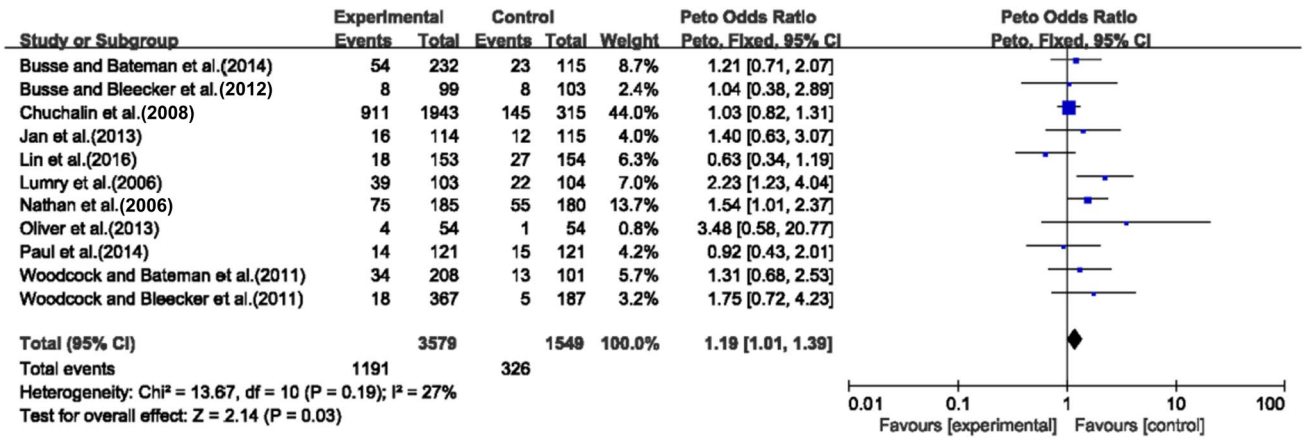

Fig. 8 Risk of URTI associated with low-dose fluticasone treatment compared with non-ICS treatment using the Peto approach

0.03; heterogeneity: $I^2 = 27\%$) (Fig. 8); this was not so with high-dose fluticasone (Peto OR 1.34; 95% CI 0.88–2.04; $p = 0.17$; heterogeneity: $I^2 = 0\%$) (Fig. 7). Three RCTs assessed budesonide. According to the Peto method, budesonide showed a marginally but nonsignificantly increased risk of URTI vs. non-ICS treatment (Peto OR 1.66; 95% CI 0.92–3.01; $p = 0.09$). There was no evidence of statistical heterogeneity among the included trials ($I^2 = 0\%$) (Fig. 9).

Discussion

This meta-analysis of randomized trials suggests that patients with asthma receiving inhaled corticosteroid (ICS) are likely to increase the risk of upper respiratory tract infection (URTI). To our knowledge, this is the first systematic review and meta-analysis of all available RCTs to assess the association between ICS use and risk of URTI in patients with asthma. Findings here could be used as references when weighing the benefits and risks of ICS in management of asthma.

Asthma is a common, chronic, and heterogeneous disease, and features reversible airflow limitation caused by airway hyperresponsiveness which usually associated with an increased inflammatory response [27, 28]. The regular daily inhaled corticosteroid is highly effective at reducing symptoms due to its good anti-inflammatory effects [29]. Nevertheless, regular use of ICS may be accompanied by various systemic side effects, including reductions in host resistance. Such changes undoubtedly likely lead to the other observations linking ICS use, i.e., increased occurrences of tuberculosis, pneumonia, oropharyngeal candidiasis, and other respiratory infections [8, 30, 31]. This study performed here was undertaken to verify the hypothesis that ICS increased the risk of URTI in patients with asthma.

There has been a clinical controversy regarding the risk of URTI in patients on ICS with COPD and asthma. Several meta-analyses hinted that ICS did not increase the risk of pneumonia in children with asthma [32, 33]. The TORCH study reported increased incidence of URTI among COPD patients receiving ICS [34]. In this paper, the risk of URTI among asthma patients receiving ICS appeared to be substantially increased. In addition, the increased risk of URTI was statistically significant among patients receiving high-dose ICS (vs. asthma patients not receiving ICS). Low-dose ICS treatment also resulted in a significant increase in risk. There was a low overall risk of bias and heterogeneity. These results may provide a warning for patients undergoing long-term ICS. The precise mechanism underlying the increased risk of URTI with ICS use in asthma patients is uncertain. ICS achieve locally high concentrations in the respiratory tract and may increase the risk of URTI owing to their immunosuppressive effects [35, 36].

Considering that the present pooled analysis may not avoid heterogeneity due to the included various glucocorticoids, subgroup analysis was performed next. Fluticasone is widely used in the treatment of asthma. In this review, 11 RCTs assessed fluticasone-related side effects. The meta-analysis of 11 trials reveals a significant association between use of fluticasone and risk of URTI in patients with asthma. Further subgroup analysis revealed that low-dose fluticasone was associated with a significantly increased risk of URTI, and high-dose just showed a marginally but nonsignificantly increased risk of URTI. The risk of URTI is not positively correlated with the dose of inhaled fluticasone. The above outcomes were basically consistent with the previous pooled analysis, and further confirmed the importance of raising safety concerns about the risk of URTI with inhaled treatments (like fluticasone) among asthma patients.

Budesonide was used for three RCTs. The data also suggested that budesonide treatment increased risk of URTI but not statistically significant. The most likely explanation was that fewer RCTs were included. The number of budesonide trials was limited, which prevented us from conducting further subgroup analyses, and might result in failure in objectively reflecting the overall reality. Despite nonsignificant findings in the budesonide treatment, it also should be acknowledged that ICS could increase the risk of URTI.

Our meta-analysis has several limitations, which mainly stem from the quality of reported data. First, these studies did not consistently use an objective definition of URTI, which may lead to reporting bias in terms of morbidity.

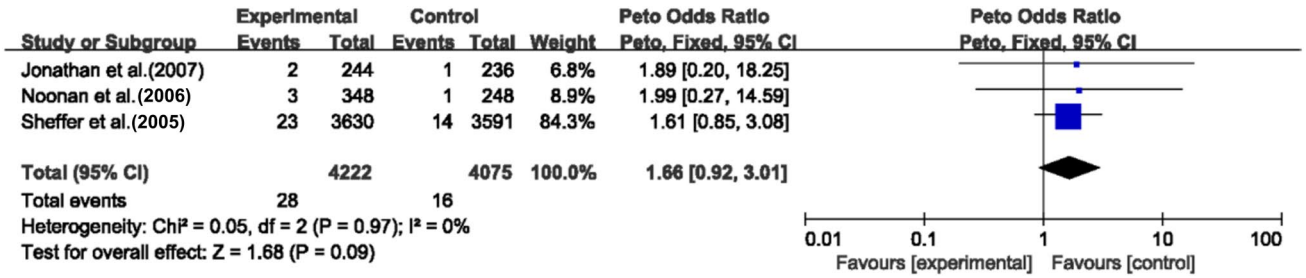

Fig. 9 Risk of URTI associated with budesonide treatment compared with non-budesonide treatment using the Peto approach

Second, this sample size was not large enough to provide decisional clinical evidences. This meta-analysis was limited to 17 RCTs with 15,336 subjects. In the subgroup analysis, only three RCTs assessed budesonide. The analysis of mometasone and ciclesonide cannot be conducted due to the limited number of RCT. Third, some related studies with insufficient information were excluded, which may lead to selection bias.

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