Association between inhaled corticosteroids and upper respiratory tract infection in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials

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Abstract

Background: We aimed to assess the association between inhaled corticosteroids (ICSs) and the risk of upper respiratory tract infection (URTI) in patients with chronic obstructive pulmonary disease (COPD).

Methods: PubMed, Embase, Cochrane Library and Clinical Trials.gov were searched from inception to October 2019. Randomized controlled trials (RCTs) of any ICSs vs control for COPD with reporting of URTI as an adverse event were included. The study was registered with PROSPERO prospectively (#CRD42020153134).

Results: Seventeen RCTs (20,478 patients) were included. ICSs significantly increased the risk of URTI in COPD patients (RR, 1.13; 95% CI 1.03–1.24; $P = 0.01$; heterogeneity: $I^2 = 7\%$). Futher subgroup analyses suggested that short-term use of ICSs increased the risk of URTI (RR, 1.29; 95% CI 1.06–1.56; $P = 0.01$; heterogeneity: $I^2 = 14\%$) but not for long-term use (RR, 1.08; 95% CI 0.97–1.2; $P = 0.14$; heterogeneity: $I^2 = 0\%$). Short-term use of high-dose fluticasone increased the risk of URTI (RR, 1.33; 95% CI 1.03–1.71; $P = 0.03$; heterogeneity: $I^2 = 0\%$) but not for long-term use (RR, 1.12; 95% CI 0.97–1.29; $P = 0.13$; heterogeneity: $I^2 = 50\%$). Medium-dose (RR, 0.97; 95% CI 0.71–1.32; $P = 0.84$; heterogeneity: $I^2 = 0\%$) and low-dose (RR, 1.39; 95% CI 0.92–2.1; $P = 0.12$; heterogeneity: $I^2 = 30\%$) fluticasone did not increase the risk of URTI regardless of duration. Neither mometasone (RR, 1.05; 95% CI 0.87–1.26; $P = 0.61$; heterogeneity: $I^2 = 0\%$) nor budesonide (RR, 1.08; 95% CI 0.77–1.5; $P = 0.67$; heterogeneity: $I^2 = 46\%$) increased the risk of URTI, regardless of dosage or duration.

Conclusions: Long-term use of ICSs does not increase the risk of URTI in patients with COPD. Short-term use of high-dose fluticasone increases the risk of URTI in patients with COPD, but not mometasone or budesonide.

Keywords: Inhaled corticosteroids (ICS), Chronic obstructive pulmonary disease (COPD), Upper respiratory tract infection (URTI), Risk, Meta-analysis

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Chen *et al. BMC Pulmonary Medicine* (2020) 20:282

Page 2 of 13

Introduction

Chronic obstructive pulmonary disease (COPD) is currently the third leading cause of death and disability worldwide [1–3]. Exacerbation is the major reason for hospital admission of patients with COPD and related to a significantly worse survival outcome [4–6]. Inhaled corticosteroids (ICSs) or combined with long-acting bronchodilators have been recommended to treat COPD patients with repeated exacerbations [1].

Although ICSs are generally considered to be relatively safe and well tolerated in patients, some adverse effects associated with ICSs have also been observed, such as the development of oropharyngeal candidiasis [6], adrenal suppression [7], diabetes [8], and pneumonia [9]. However, the association between ICSs and risk of upper respiratory tract infection (URTI) remains unclear, though URTI is the most common respiratory infection and also an important cause of exacerbation of COPD [10]. The large prospective study Toward a Revolution in COPD Health (TORCH) trial reported ICSs might increase the morbidity of URTI in COPD patients [11]. Moreover, other randomized controlled trials (RCTs) reported different or even contrary outcomes, and most of these studies were inadequate to detect significant difference between ICSs treatment groups and control groups [12–17].

Whether ICSs increase the risk of URTI in COPD patients may depend on duration, dosage and type of ICSs. Lack of safety evidence may result in insufficient use or over use of ICSs. Therefore, we conducted this meta-analysis of RCTs to assess the association between ICSs use and the risk of URTI in patients with COPD. We also aimed to clarify the contributions of medication details for the association, including duration, dosage level and type of ICSs.

Methods

Study protocol

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [18]. And the study was registered with PROSPERO prospectively (#CRD42020153134).

Search strategy

Two reviewers independently searched PubMed, Embase, Cochrane Library and Clinical Trials.gov for eligible articles from inception to May 10, 2019, and updated on October, 16, 2019. Both free words and MeSH terms referring to inhaled corticosteroid and the risk of URTI were used as search terms, including "Pulmonary Disease, Chronic Obstructive" OR "chronic obstructive pulmonary disease" OR "COPD" OR "airflow obstruction, chronic" OR "chronic airflow obstruction" OR "chronic obstructive airway disease" OR "chronic obstructive lung disease" OR "Bronchitis" OR "emphysema" AND "ICS" OR "inhaled corticosteroids" OR "fluticasone" OR "flunisolide" OR "budesonide" OR "beclomethasone" OR "triamcinolone" OR "mometasone" OR "ciclesonide". We also conducted a manual search using the reference lists of key articles.

Eligibility criteria

Eligible studies were identified through the PICOS criteria (participants, interventions, comparators, outcomes and study design) [18]. Inclusion criteria included: (1) patients with COPD; (2) The interventions included any type of inhaled corticosteroids, including ICSs alone or combined with long-acting bronchodilators; (3) non-ICSs treatment as control, including placebo or other inhaled drugs of corticosteroid free; (4) only trials reporting data on URTI as the outcome were included; (5) Only RCTs were included. Exclusion criteria included: (1) non-RCTs, such as observational studies, case series and reviews; (2) non-English articles; (3) Patients with asthma or unknown diagnosis; (4) ICSs was used in both the treatment group and the control group.

Data collection process

Two investigators independently extracted relevant data from the included RCTs into standardized collection forms for the outcomes and evidence. Disagreements between the two investigators were resolved by discussion, and a third investigator was consulted if necessary. The corresponding authors were contacted when relevant data were not available.

Risk of bias assessment and quality of evidence

Two investigators independently performed the risk assessment using the Cochrane Collaboration risk of bias tool [19]. Any disagreements between the two investigators were resolved by discussion, and a third investigator was consulted if necessary. The included RCTs were assessed according to the following features (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment;(5) selective reporting; (6) incomplete outcome data; (7) other bias. Each item was assessed as low, unclear, or high risk of bias.

Statistical analysis

We performed meta-analyses for quantitative data synthesis using Revman Software (v.5.3, Cochrane Collaboration, London, UK). The weights of each study were estimated by Mantel-Haenszel method. We calculated the risk ratio (RR) and 95% confidence interval (CI) for the risk of URTI. A two-tailed p value < 0.05 was set for statistical significance. Heterogeneity was assessed using

Chen *et al. BMC Pulmonary Medicine* (2020) 20:282

Page 3 of 13

the I^2 test, with $I^2 > 50\%$ indicating a substantial heterogeneity [20]. A random-effect model would be used when a substantial level of heterogeneity was found, otherwise a fixed-effect model would be used.

Subgroup analysis

Subgroup analyses were conducted according to the following variables: (1) duration (long [≥ 6 months] and short [< 6 months]); (2) dosage of ICSs [21] (high dose [defined as > 500 μg/day of fluticasone propionate or equivalent], medium dose [defined as > 250–500 μg/day of fluticasone propionate or equivalent] and low dose [defined as 100–250 μg/day of fluticasone propionate or equivalent]); (3) type of ICSs, including fluticasone, mometasone, budesonide, and beclomethasone.

Results

Study selection and study characteristics

Figure 1 shows the study selection process. A total of 3011 references were identified after an initial search, and 17 RCTs [11–17, 22–31] including 20,478 patients were finally included in the meta-analysis. Of the 17 RCTs, 16 were multicenter, double-blind, randomized trials. These studies were published from 2002 to 2019, with population sizes ranging from 149 to 6184 participants. Duration of the trials ranged from 1 month to 36 months, with 10 trials [11, 12, 15, 16, 24–27, 29, 30] longer than or equal to 6 months, and 7 trials [13, 14, 17, 22, 23, 28, 31] shorter than 6 months. Eleven trials [11, 13, 15–17, 23, 25, 26, 28–30] investigated a high-dose ICSs treatment, 8 trials [12, 16, 22, 24, 27, 29–31] investigated a medium-dose ICSs treatment, and 5 trials [12, 14, 17, 27, 28] investigated a low-dose ICSs treatment. Fluticasone was evaluated in 10 trials [11, 13–15, 17, 22–24, 26, 28], mometasone in 4 trials [16, 25, 29, 30], budesonide in 3 trials [12, 27, 31], and beclomethasone in 1 trial [27]. Table 1 shows the main characteristics of the included studies.

Risk of bias and quality of evidence

All trials were assessed using the Cochrane Collaboration risk of bias assessment tool. RCTs with four or more features were considered to be of high quality. Seventeen RCTs were regarded as high quality according to the risk of bias assessment tool and were included in the meta-analysis. All studies had low risk of selective reporting bias. One study had high risk of blinding of participants and personnel bias, 1 study had high risk of blinding of outcome assessment bias, and 1 study had high risk of incomplete outcome data. One study had unclear risk of random sequence generation bias, 2 studies had unclear risk of allocation concealment bias, 1 study had unclear risk of incomplete outcome data bias and 7 studies had other bias (Fig. 2).

Risk of URTI associated with ICSs

All 17 RCTs with 20,478 patients reported URTI as an adverse event. The risk of URTI was 8.6% (991 of 11,587 patients) in the ICSs treatment groups, 7.7% (686 of 8891 patients) in the control groups, and 8.2% in all patients (1677 of 20,478 patients). Compared with non-ICSs treatment, ICSs was associated with a significantly increased the risk of URTI in patients with COPD (RR, 1.13; 95% CI 1.03–1.24; $P = 0.01$; heterogeneity: $I^2 = 7\%$) (Fig. 3).

Risk of URTI associated with ICSs for different durations

Long-term use of ICSs [11, 12, 15, 16, 24–27, 29, 30] (10 RCTs, 15,634 patients) did not increase the risk of URTI (RR, 1.08; 95% CI 0.97–1.2; $P = 0.14$; heterogeneity: $I^2 = 0\%$), whereas short- term use of ICSs [13, 14, 17, 22, 23, 28, 31] (7 RCTs, 4844 patients) was associated with a significantly increased the risk of URTI (RR, 1.29; 95% CI 1.06–1.56; $P = 0.01$; heterogeneity: $I^2 = 14\%$) (Fig. 4).

Risk of URTI associated with different doses of ICSs

High-dose ICSs [11, 13, 15–17, 23, 25, 26, 28–30] treatment (11 RCTs, 12,930 patients) was associated with a significantly increased the risk of URTI (RR, 1.14; 95% CI 1.02–1.27; $P = 0.02$; heterogeneity: $I^2 = 0\%$), but neither medium-dose ICSs (8 RCTs, 4849 patients) [12, 16, 22, 24, 27, 29–31] (RR, 1.02; 95% CI 0.82–1.27; $P = 0.86$; heterogeneity: $I^2 = 0\%$) nor low-dose ICSs (5 RCTs, 2699 patients) [12, 14, 17, 27, 28] (RR, 1.25; 95% CI 0.9–1.74; $P = 0.18$; heterogeneity: $I^2 = 1\%$) increased the risk of URTI (Fig. 5).

Risk of URTI associated with high-dose ICSs for different durations

Long-term use of high-dose ICSs [11, 15, 16, 25, 26, 29, 30] (7 RCTs, 12,916 patients) did not increase the risk of URTI (RR, 1.09; 95% CI 0.98–1.22; $P = 0.13$; heterogeneity: $I^2 = 0\%$), whereas short- term use of high-dose ICSs [13, 17, 23, 28] (4 RCTs, 2509 patients) was associated with a significantly increased the risk of URTI (RR, 1.31; 95% CI 1.02–1.67; $P = 0.03$; heterogeneity: $I^2 = 7\%$) (Fig. 6).

Risk of URTI associated with fluticasone

Fluticasone [11, 13–15, 17, 22–24, 26, 28] (10 RCTs, 12,547 patients) was associated with a significantly increased the risk of URTI for all dose groups (RR, 1.16; 95% CI 1.04–1.3; $P = 0.01$; heterogeneity: $I^2 = 27\%$). Subgroup analyses suggested that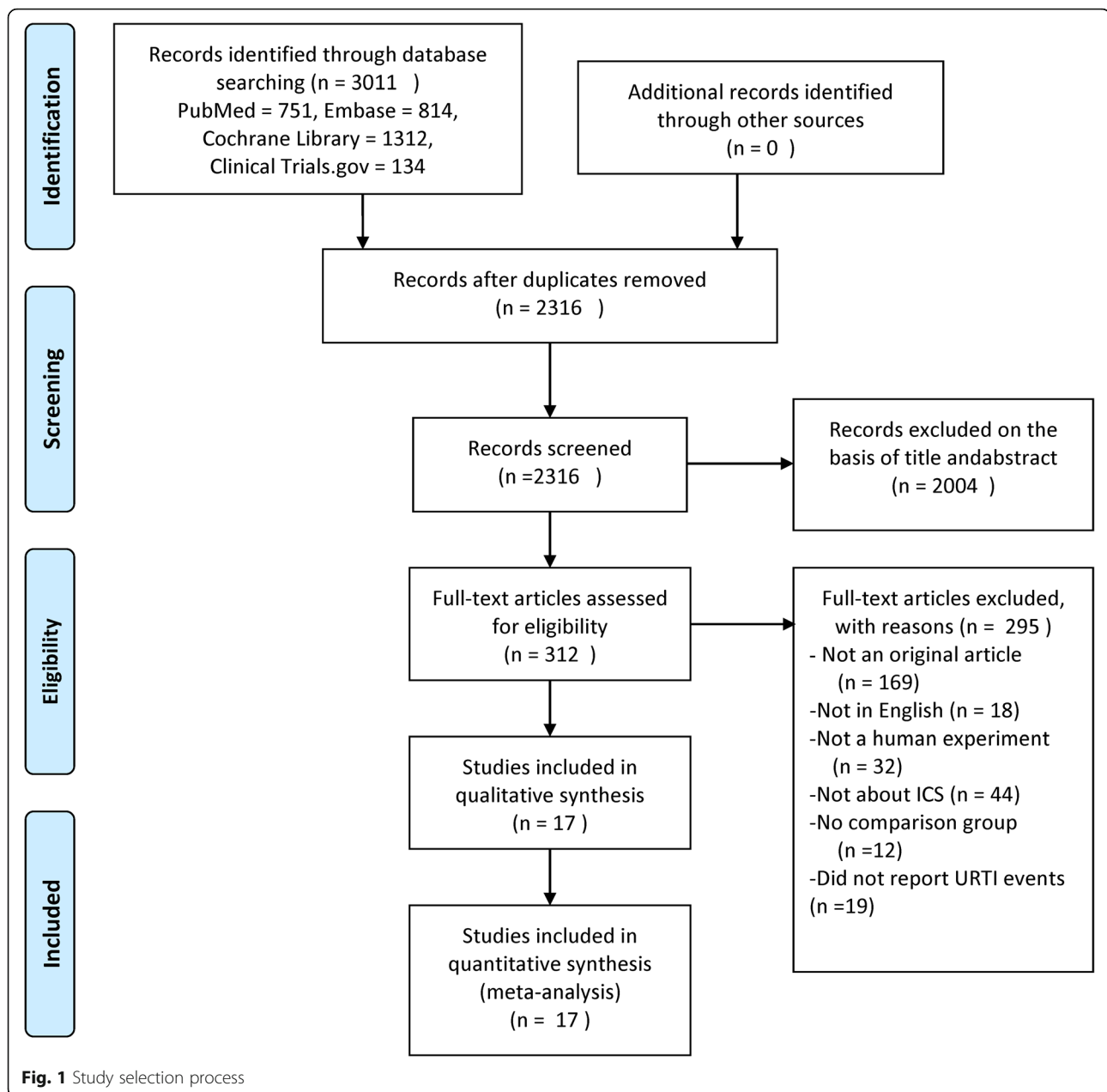 high-dose fluticasone [11, 13, 15, 17, 23, 26, 28] (7 RCTs, 9537patients) was associated with a significantly increased the risk of URTI (RR, 1.17; 95% CI 1.03–1.32; $P = 0.02$; heterogeneity: $I^2 = 27\%$), but neither medium-dose fluticasone (2 RCTs, 1505patients) [22, 24] (RR, 0.97; 95% CI 0.71–1.32; $P = 0.84$; heterogeneity: $I^2 = 0\%$) nor low- dose fluticasone (3

Fig. 1 Study selection process

RCTs, 1964 patients) [14, 17, 28] (RR, 1.39; 95% CI 0.92–2.1; $P = 0.12$; heterogeneity: $I^2 = 30\%$) increased the risk of URTI. Moreover, long-term use of high-dose fluticasone (3 RCTs, 7503 patients) [11, 15, 26] did not increase the risk of URTI (RR, 1.12; 95% CI 0.97–1.29; $P = 0.13$; heterogeneity: $I^2 = 50\%$), whereas short-term use of high-dose fluticasone (4 RCTs, 2034 patients) was associated with a significantly increased the risk of URTI (RR, 1.33; 95% CI 1.03–1.71; $P = 0.03$; heterogeneity: $I^2 = 0\%$) (Fig. 7).

Risk of URTI associated with mometasone
Mometasone [16, 25, 29, 30] (4 RCTs, 5413 patients) did not increase the risk of URTI for all dose groups (RR,

1.05; 95% CI 0.87–1.26; $P = 0.61$; heterogeneity: $I^2 = 0\%$). Subgroup analyses suggested that neither high-dose mometasone (4 RCTs, 4521 patients) [16, 25, 29, 30] (RR, 1.06; 95% CI 0.87–1.28; $P = 0.57$; heterogeneity: $I^2 = 0\%$) nor medium-dose mometasone (3 RCTs, 2692 patients) [16, 29, 30] (RR, 0.98; 95% CI 0.67–1.43; $P = 0.93$; heterogeneity: $I^2 = 0\%$) increased the risk of URTI (Fig. 8).

Risk of URTI associated with budesonide
Budesonide [12, 27, 31] (3 RCTs, 2518 patients) did not increase the risk of URTI (RR, 1.08; 95% CI 0.77–1.5; $P = 0.67$; heterogeneity: $I^2 = 46\%$) (Fig. 9).

Chen *et al. BMC Pulmonary Medicine*   (2020) 20:282

Page 5 of 13

Table 1 Characteristics of the 17 RCTs included in the meta-analysis of ICSs and risk of URTI

Study	Duration (months)	Mean Age (years)	FEV1 (%predicted)	Male (%)	Interventions	NO. of URTI/Total
Mahler et al. [13]	5.5	63.5	40.8	66.0	T:FP 500 µg bid or FSC (S 50 µg /FP 500 µg) bid	T:84/342
					C: Placebo or S 50 µg bid	C: 56/349
Hanania et al. [22]	5.5	63.8	41.8	63.2	T:FP 250 µg bid or FSC (S 50 µg /FP 250 µg) bid	T:40/361
					C: Placebo or S 50 µg bid	C: 42/362
Calverley et al. [11]	36	65.0	44.0	75.5	T:FP 500 µg bid or FSC (S 50 µg /FP 500 µg) bid	T:309/3098
					C: Placebo or S 50 µg bid	C: 277/3086
Zheng et al. [23]	5.5	66.2	47.0	89.2	T:FSC (S 50 µg /FP 500 µg) bid	T:32/297
					C: Placebo	C: 14/148
Ferguson et al. [24]	12	65.0	32.8	55.0	T:FP 250 µg bid	T:31/394
					C: S 50 µg bid	C: 31/388
Calverley et al. [25]	12	65.1	NR	68.3	T: MF 800 µg qd or MF 400 µg bid	T:164/616
					C: Placebo	C: 71/295
Anzueto et al. [26]	12	65.4	34	54.0	T:FSC (S 50 µg /FP 500 µg) bid	T:41/394
					C: Placebo	C: 30/403
Calverley et al. [27]	11	63.6	42.2	80.7	T:BDP/FM 200/12 µg bid or BUD/FM 400/12 µg bid	T:3/479
					C: FM 12 µg bid	C: 5/239
Tashkin et al. [30]	6	59.8	NR	77.5	T: MF/FM 200/10 µg bid or MF/FM 400/10 µg bid or MF 400 µg bid	T:19/634
					C: Placebo or FM 10 µg bid	C:13/421
Tashkin et al. [16]	12	59.7	39.1	76.0	T: MF/FM 200/10 µg bid or MF/FM 400/10 µg bid or MF 400 µg bid	T:58/1351
					C: Placebo or FM 10 µg bid	C: 39/900
Doherty et al. [29]	6	59.6	38.6	75.2	T: MF/FM 200/10 µg bid or MF/FM 400/10 µg bid or MF 400 µg bid	T:39/717
					C: Placebo or FM 10 µg bid	C: 26/479
Sharafkhaneh et al. [12]	12	63.0	37.7	62.0	T:BUD/FM 320/9 µg bid or BUD/FM 160/9 µg bid	T:90/815
					C: FM 9 µg bid	C: 39/403
Boscia et al. [28]	1	57.9	49.8	46.3	T:FF/VI 50/25 µg qd or FF/VI 100/25 µg qd or FF/VI 200/25 µg qd	T:2/98
					C: Placebo	C: 1/51
Vogelmeier et al. [15]	6	63.3	60.3	70.9	T: FSC (S 50 µg /FP 500 µg) bid	T:2/264
					C: QVA149 110/50 µg qd	C: 7/258
Kerwin et al. [14]	5.5	62.5	48.3	66.6	T:FF/VI 50/25 µg qd or FF/VI 100/25 µg qd or FF 100 µg qd	T:50/618
					C: Placebo or VI 25 µg qd	C: 19/412
Martinez et al. [17]	5.5	61.5	47.9	72.3	T:FF/VI 100/25 µg qd or FF/VI 200/25 µg qd or FF 100 µg qd or FF 200 µg qd	T:23/816
					C: Placebo or VI 25 µg qd	C: 14/408
Huang et al. [31]	2.8	64.1	NR	86.4	T: BUD/FM 320/9 µg bid, I 40 µg qid and T 100 mg bid	T:4/293
					C:I 40 µg qid and Th 100 mg bid	C: 2/289

Abbreviations: *ICSs* Inhaled corticosteroids, *URTI* Upper respiratory tract infection, *FEV₁* Forced expiratory volume in 1 s, *T* Treatment group, *C* Control group, *NR* Not reported, *FP* Fluticasone propionate, *S* Salmeterol, *FSC* Fluticasone propionate/salmeterol, *P* Placebo, *MF* Mometasone furoate, *BUD* Budesonide, *FM* Formoterol, *BDP* Beclomethasone, *QVA149* Indacaterol/glycopyrronium, *FF* Fluticasone furoate, *VI* Vilanterol, *I* Ipratropium, *Th* Theophylline, *QD* Once a day, *BID* Twice a day, *QID* Four times a day
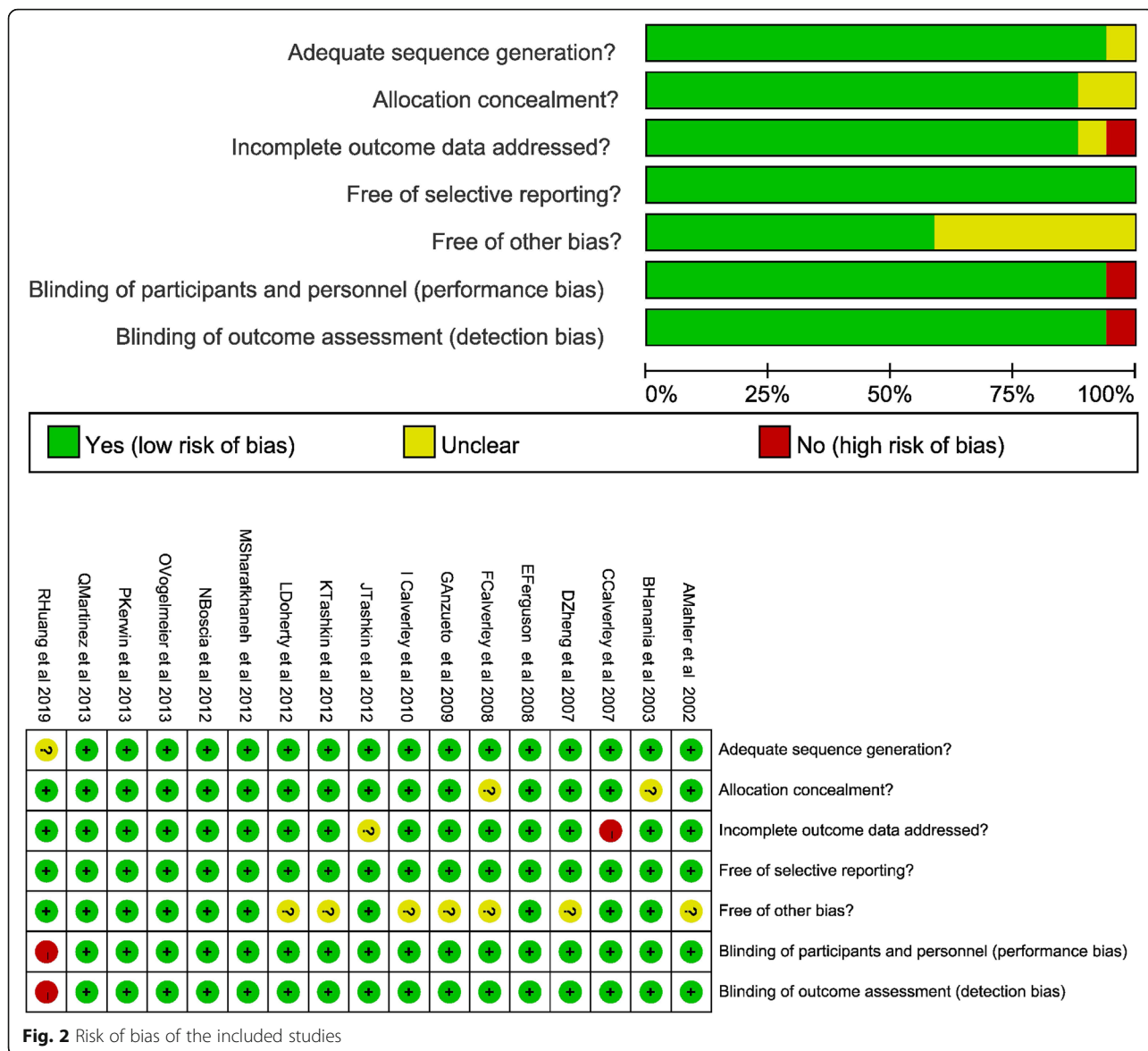
Fig. 2 Risk of bias of the included studies

Discussion

This meta-analysis of 17 multicenter RCTs (including 20,478 patients) suggested that short-term use of ICSs increased the risk of URTI but not for long-term use. Futher subgroup analyses revealed that only short-term use of high-dose fluticasone increased the risk of URTI but not for long-term use of high-dose fluticasone. Medium-dose and low-dose fluticasone did not increase the risk of URTI regardless of duration. Neither mometasone nor budesonide increased the risk of URTI, regardless of dosage or duration.

Exacerbation is common in patients with COPD affecting about 20% of patients with 40–45% of predicted FEV_1 (1.3 events per year). Repeated exacerbations lead to worse survival outcome of patients [5]. Daily use of ICSs has been proved to decrease the frequency of exacerbations and improve quality of life in patients with FEV_1 less than 50% predicted [1, 4]. However, daily use of ICSs may cause drug-related adverse events, such as increased risks of fracture and infections [32, 33], but may not increase the risk of cardiovascular events [34]. URTI is the most common respiratory infections and also an important cause of exacerbation of COPD. Moreover, URTI can significantly reduce the quality of life in patients [10]. However, the association between ICSs and the risk of URTI remains unclear.

Our results suggested that use of ICSs was associated with a significantly increased the risk of URTI in COPD patients. However, further subgroup analyses suggested that only short-term use of ICSs significantly increased the risk of URTI but not for long-term use of ICSs in COPD patients. The result was unexpected. We

Fig. 3 Risk of URTI associated with ICSs. URTI, upper respiratory tract infection; ICSs, inhaled corticosteroids

Fig. 4 Risk of URTI associated with ICSs for different duration. URTI, upper respiratory tract infection; ICSs, inhaled corticosteroids

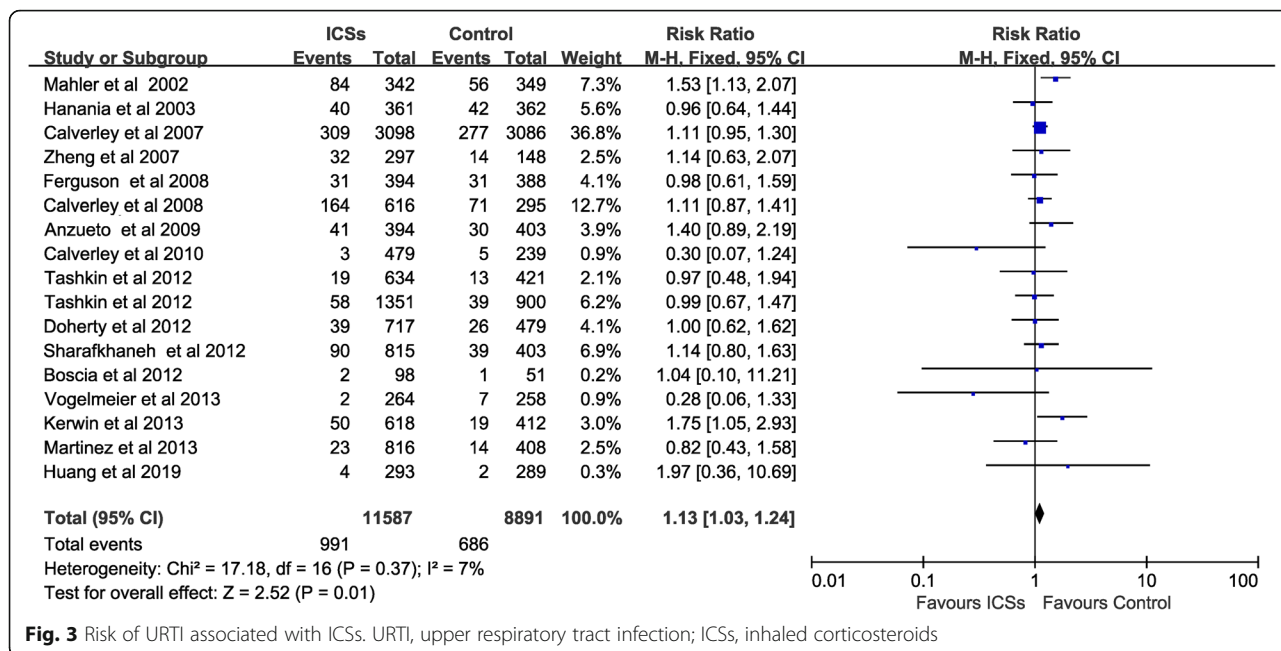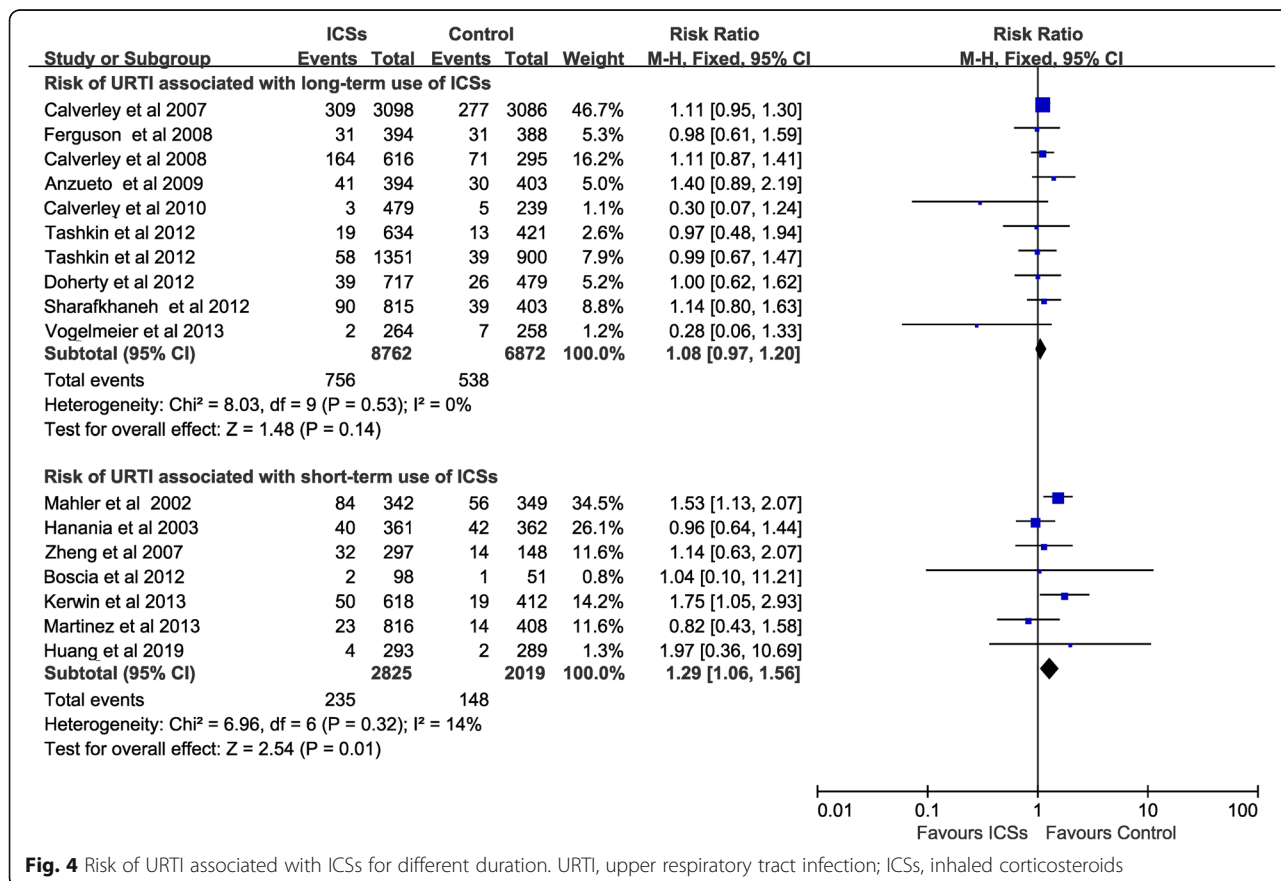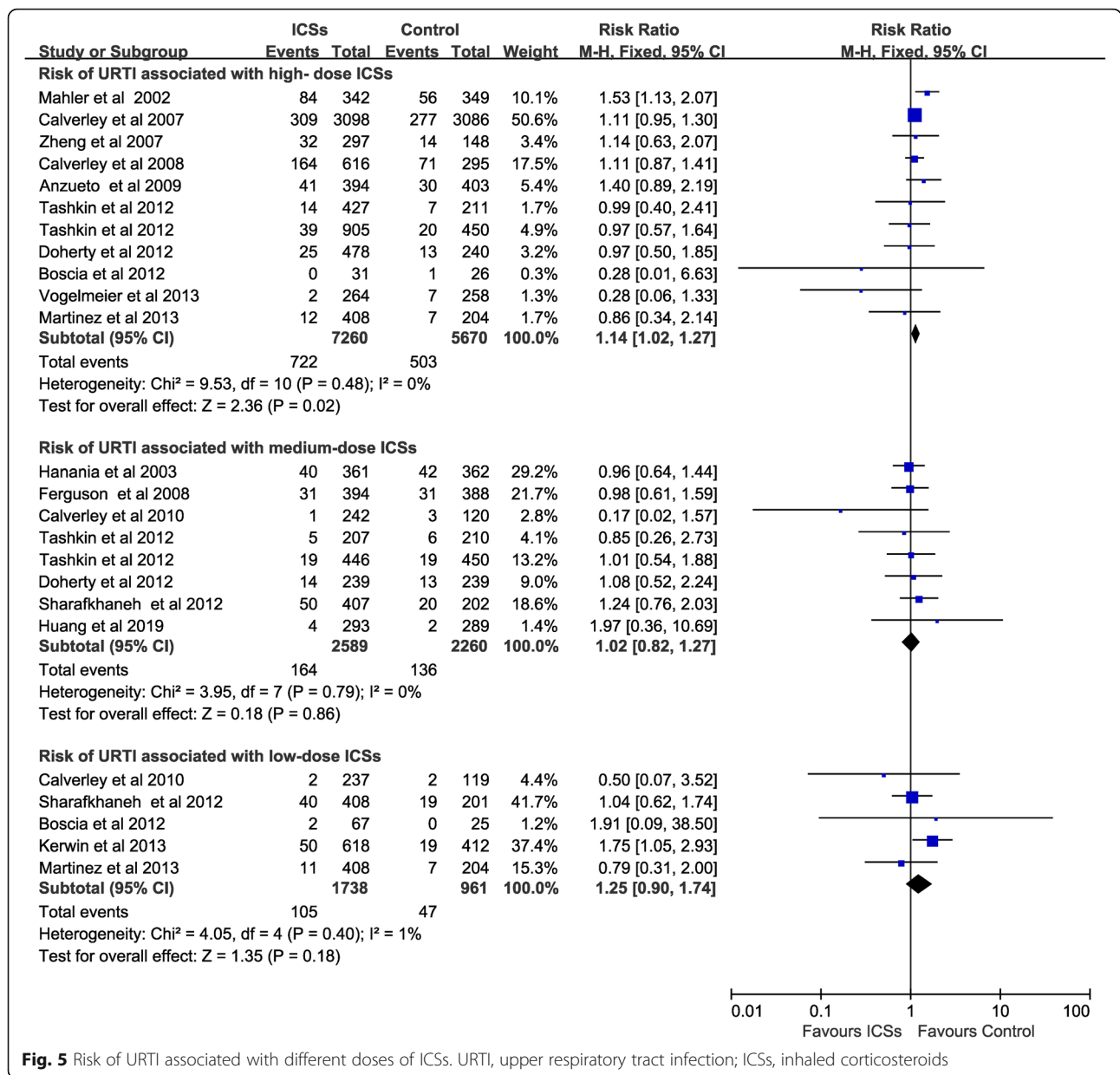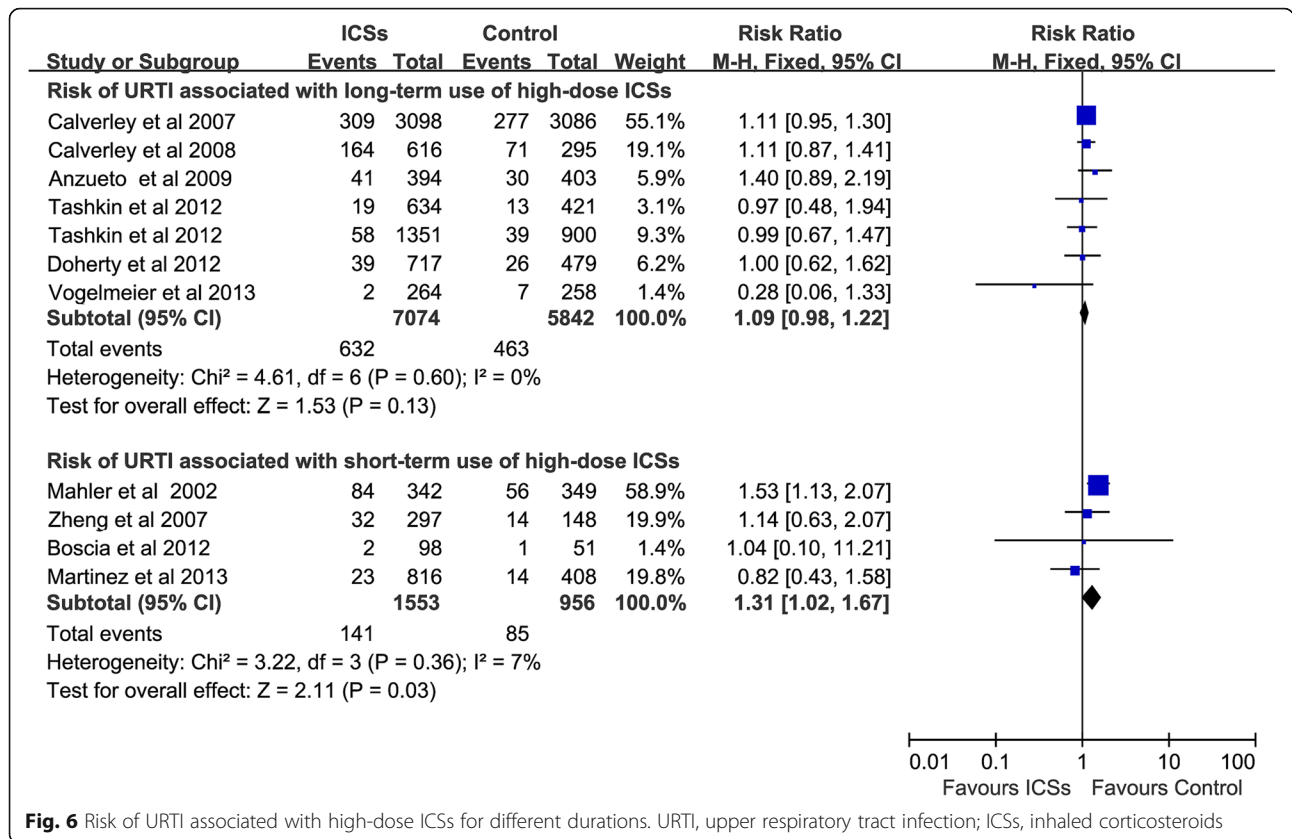| Study or Subgroup	ICSs Events	ICSs Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Risk of URTI associated with high- dose ICSs							
Mahler et al 2002	84	342	56	349	10.1%	1.53 [1.13, 2.07]	
Calverley et al 2007	309	3098	277	3086	50.6%	1.11 [0.95, 1.30]	
Zheng et al 2007	32	297	14	148	3.4%	1.14 [0.63, 2.07]	
Calverley et al 2008	164	616	71	295	17.5%	1.11 [0.87, 1.41]	
Anzueto et al 2009	41	394	30	403	5.4%	1.40 [0.89, 2.19]	
Tashkin et al 2012	14	427	7	211	1.7%	0.99 [0.40, 2.41]	
Tashkin et al 2012	39	905	20	450	4.9%	0.97 [0.57, 1.64]	
Doherty et al 2012	25	478	13	240	3.2%	0.97 [0.50, 1.85]	
Boscia et al 2012	0	31	1	26	0.3%	0.28 [0.01, 6.63]	
Vogelmeier et al 2013	2	264	7	258	1.3%	0.28 [0.06, 1.33]	
Martinez et al 2013	12	408	7	204	1.7%	0.86 [0.34, 2.14]	
Subtotal (95% CI)		7260		5670	100.0%	1.14 [1.02, 1.27]	
Total events	722		503				
Heterogeneity: Chi² = 9.53, df = 10 (P = 0.48); I² = 0%							
Test for overall effect: Z = 2.36 (P = 0.02)							
Risk of URTI associated with medium-dose ICSs							
Hanania et al 2003	40	361	42	362	29.2%	0.96 [0.64, 1.44]	
Ferguson et al 2008	31	394	31	388	21.7%	0.98 [0.61, 1.59]	
Calverley et al 2010	1	242	3	120	2.8%	0.17 [0.02, 1.57]	
Tashkin et al 2012	5	207	6	210	4.1%	0.85 [0.26, 2.73]	
Tashkin et al 2012	19	446	19	450	13.2%	1.01 [0.54, 1.88]	
Doherty et al 2012	14	239	13	239	9.0%	1.08 [0.52, 2.24]	
Sharafkhaneh et al 2012	50	407	20	202	18.6%	1.24 [0.76, 2.03]	
Huang et al 2019	4	293	2	289	1.4%	1.97 [0.36, 10.69]	
Subtotal (95% CI)		2589		2260	100.0%	1.02 [0.82, 1.27]	
Total events	164		136				
Heterogeneity: Chi² = 3.95, df = 7 (P = 0.79); I² = 0%							
Test for overall effect: Z = 0.18 (P = 0.86)							
Risk of URTI associated with low-dose ICSs							
Calverley et al 2010	2	237	2	119	4.4%	0.50 [0.07, 3.52]	
Sharafkhaneh et al 2012	40	408	19	201	41.7%	1.04 [0.62, 1.74]	
Boscia et al 2012	2	67	0	25	1.2%	1.91 [0.09, 38.50]	
Kerwin et al 2013	50	618	19	412	37.4%	1.75 [1.05, 2.93]	
Martinez et al 2013	11	408	7	204	15.3%	0.79 [0.31, 2.00]	
Subtotal (95% CI)		1738		961	100.0%	1.25 [0.90, 1.74]	
Total events	105		47				
Heterogeneity: Chi² = 4.05, df = 4 (P = 0.40); I² = 1%							
Test for overall effect: Z = 1.35 (P = 0.18)							

Fig. 5 Risk of URTI associated with different doses of ICSs. URTI, upper respiratory tract infection; ICSs, inhaled corticosteroids

speculated that short-term use of ICSs could not effectively control the airway inflammation, whereas the immunosuppression effects of corticosteroids due to local high concentration might cause susceptibility to URTI in patients with COPD. On the contrary, long-term use of ICSs may improve health status of COPD patients by decreasing the frequency of exacerbations and improving clinical symptoms. In addition, the immune compensation mechanism of patients may play a role in resisting the immunosuppression of corticosteroid in the long term. A previous RCT conducted by Eichenhorn et al. may support our findings [35]. In their study, Eichenhorn et al. evaluated the effects of inhaled triamcinolone on adrenal function in 221 patients who were recruited

from patients already enrolled in the Lung Health Study II, and found that use of triamcinolone (1200 μg daily) for 3 years did not have suppression effects on adrenal function [35, 36].

Subgroup analyses were performed according to different dosage of ICSs. The results suggested that high-dose ICSs significantly increased the risk of URTI but not for medium- and low-dose ICSs. These findings may be explained by the possible dose-response effect of ICSs [7, 37]. In the further analysis, we found that only short-term use of high-dose ICSs was associated with a significantly increased the risk of URTI but not for long-term use of high-dose ICSs. The results further supported that long-term use of ICSs did not increase ICS-related risk of URTI.

Study or Subgroup	ICSs Events	ICSs Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Risk of URTI associated with long-term use of high-dose ICSs						
Calverley et al 2007	309	3098	277	3086	55.1%	1.11 [0.95, 1.30]
Calverley et al 2008	164	616	71	295	19.1%	1.11 [0.87, 1.41]
Anzueto et al 2009	41	394	30	403	5.9%	1.40 [0.89, 2.19]
Tashkin et al 2012	19	634	13	421	3.1%	0.97 [0.48, 1.94]
Tashkin et al 2012	58	1351	39	900	9.3%	0.99 [0.67, 1.47]
Doherty et al 2012	39	717	26	479	6.2%	1.00 [0.62, 1.62]
Vogelmeier et al 2013	2	264	7	258	1.4%	0.28 [0.06, 1.33]
Subtotal (95% CI)		7074		5842	100.0%	1.09 [0.98, 1.22]
Total events	632		463			
Heterogeneity: Chi² = 4.61, df = 6 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.53 (P = 0.13)						
Risk of URTI associated with short-term use of high-dose ICSs						
Mahler et al 2002	84	342	56	349	58.9%	1.53 [1.13, 2.07]
Zheng et al 2007	32	297	14	148	19.9%	1.14 [0.63, 2.07]
Boscia et al 2012	2	98	1	51	1.4%	1.04 [0.10, 11.21]
Martinez et al 2013	23	816	14	408	19.8%	0.82 [0.43, 1.58]
Subtotal (95% CI)		1553		956	100.0%	1.31 [1.02, 1.67]
Total events	141		85			
Heterogeneity: Chi² = 3.22, df = 3 (P = 0.36); I² = 7%						
Test for overall effect: Z = 2.11 (P = 0.03)						

Risk Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100
Favours ICSs   Favours Control

Fig. 6 Risk of URTI associated with high-dose ICSs for different durations. URTI, upper respiratory tract infection; ICSs, inhaled corticosteroids

We also conducted subgroup analyses according to type of ICSs. The results suggested that high-dose fluticasone was associated with a significantly increased risk of URTI but not for mometasone, budesonide, and medium- and low-dose fluticasone. Previous studies have reported that fluticasone may effectively suppress innate immunoresponse of alveolar macrophages, and the immunosuppressive effects of fluticasone might be tenfold greater than those of budesonide in human airways [38, 39]. Moreover, the included RCTs mainly explored medium- or low-dose budesonid rather than high-dose. Similarly, we also found that short-term use of high-dose fluticasone was associated with a significantly increased the risk of URTI but not for long-term use of high-dose fluticasone. The results were consistent with the above results of the merged different types of ICSs.

Our results were not consistent with a previous meta-analysis conducted by Yang et al. in 2016 [40], which first reported that long-term use of ICSs may increase the risk of URTI in patients with COPD. However, that meta-analysis had limitations mainly because it did not include several large multicenter RCTs (including 3507 patients) published recently [14, 15, 17, 28, 31]. The smaller sample size of the previous meta-analysis may weaken the reliability and generalizability of the conclusion. Moreover, the previous meta-analysis failed to provide implication for clinical practice due to lack of subgroup analyses according to medication details including duration, dosage level and type of ICSs.

The strengths of our study were that we used a comprehensive search strategy and explicit inclusion criteria including 17 multicenter RCTs (20,478 patients), which met the requirements of sequential analysis. In addition, we conducted multiple subgroup analyses according to medication details including duration, dosage, and type of ICSs, that minimized the heterogeneity of pooled analyses and provided implications for clinical practice.

This study also had some limitations which mainly stemmed from the quality of reported data. First, since some adverse events (such as URTI) were not the predefined outcomes and there were no homogeneous definitions among the clinical trials, these adverse events may be misclassified. This inherent methodological defect of clinical trials is one of the factors limiting the results of meta-analyses on drug safety. However, as most of the included trials in this meta-analysis were double blind, such misclassification would not have a substantial impact on the results of the meta-analysis, because the direction of bias may be toward the null. Second, the possibility of asthma-COPD overlap (ACO) in the study population may be one of the confounding factor of results. However, as a result of randomization, this confounding factor could not substantially affect the results
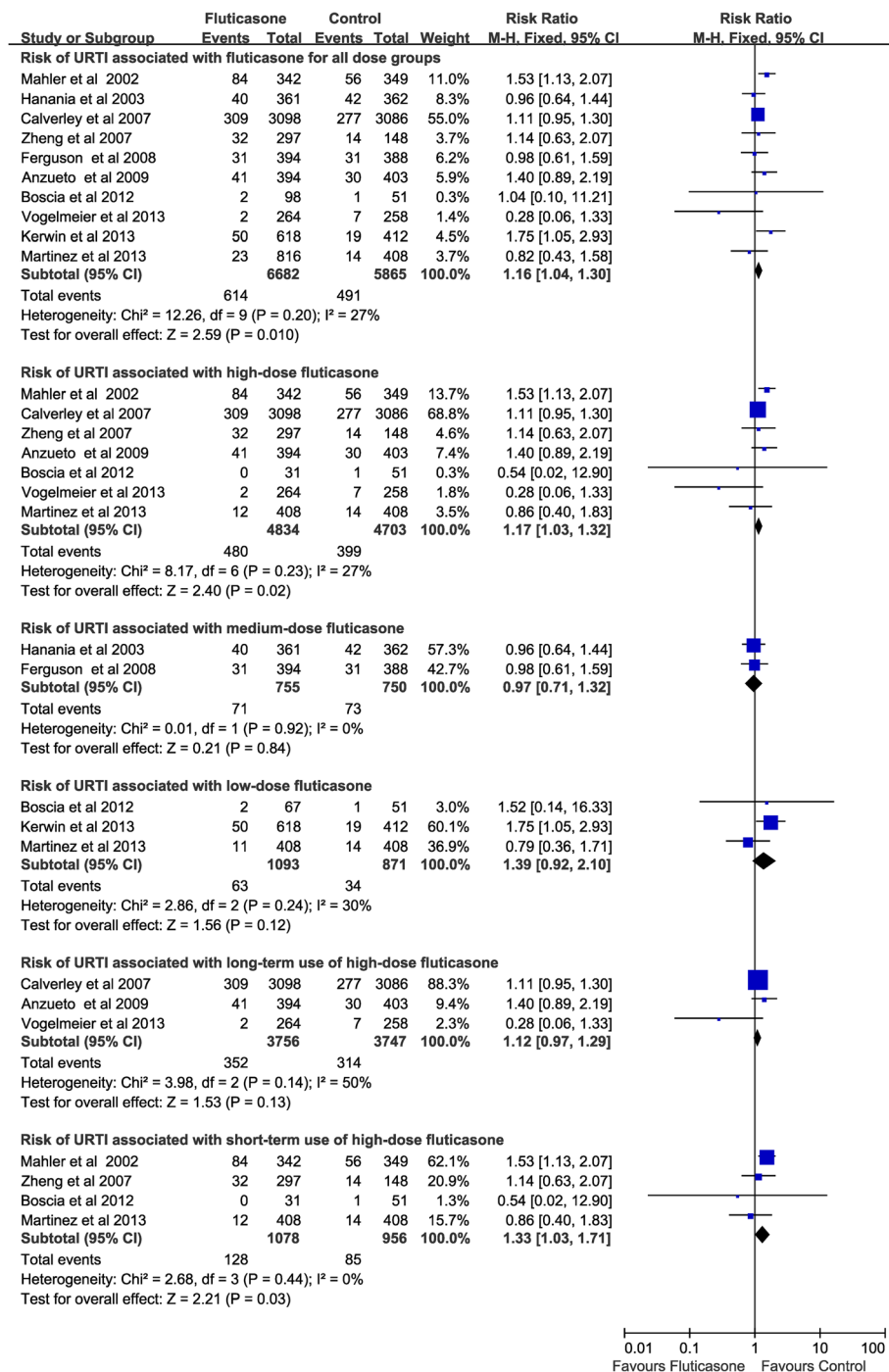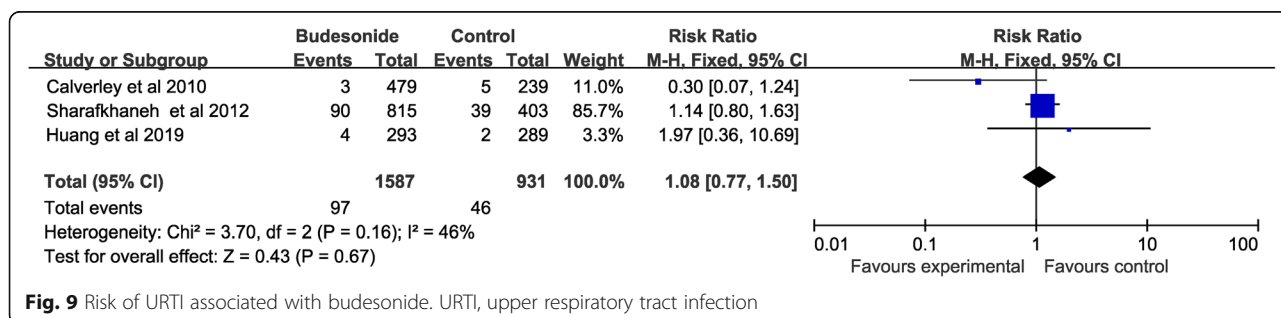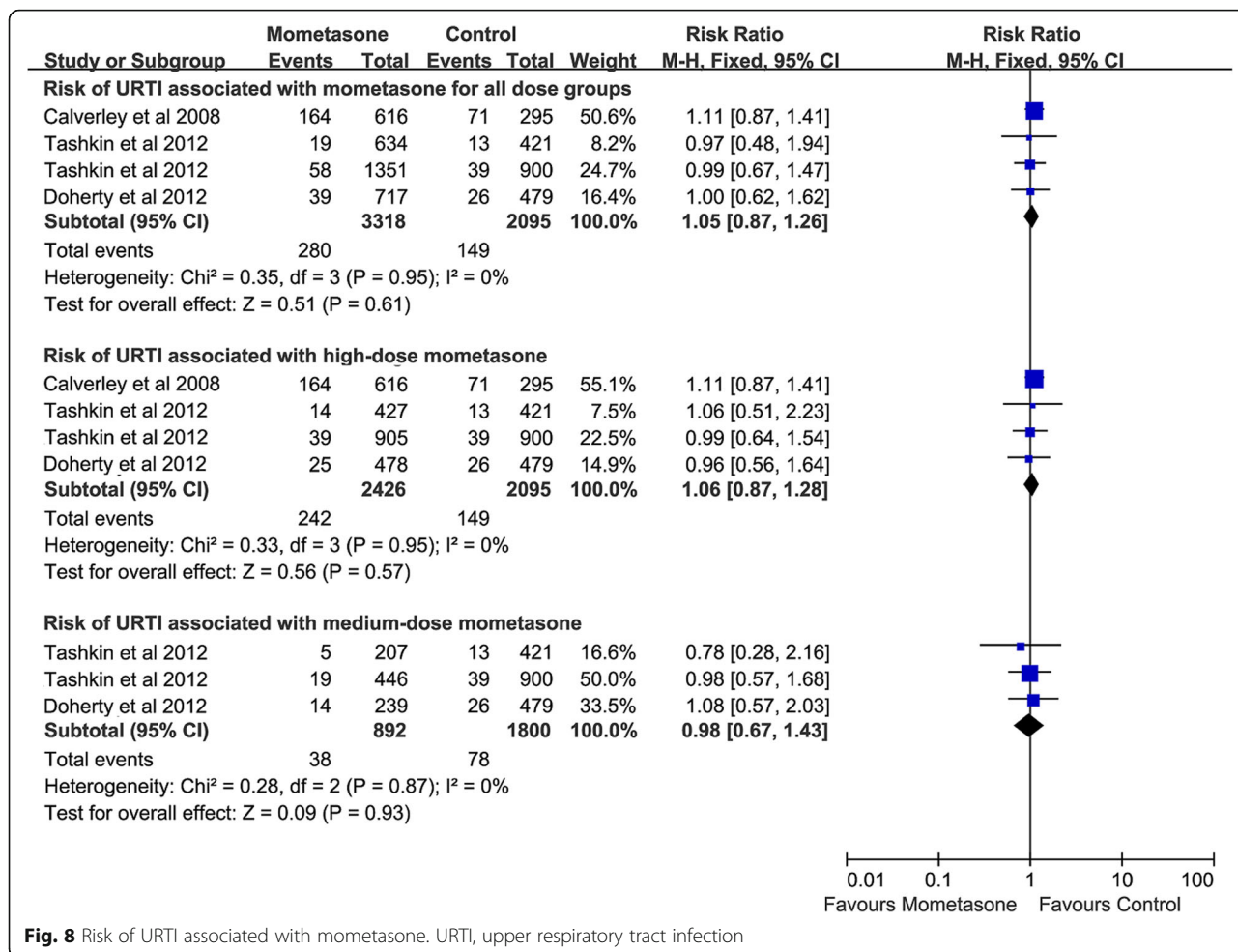
Fig. 7 Risk of URTI associated with fluticasone. URTI, upper respiratory tract infection

of the meta-analysis as ACO may be approximately evenly distributed between the ICSs treatment group and the control group. Third, further subgroup analyses could not be performed due to lack of some patient related information, such as eosinophil count, exacerbations in the past year, comorbidities, smoking status and preexisting ICSs use and this may be a confounding factor of results.

Conclusions

Long-term use of ICSs does not increase the risk of URTI in patients with COPD. Short-term use of high-

Chen *et al. BMC Pulmonary Medicine* (2020) 20:282

Page 11 of 13

Study or Subgroup	Mometasone Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Risk of URTI associated with mometasone for all dose groups							
Calverley et al 2008	164	616	71	295	50.6%	1.11 [0.87, 1.41]	
Tashkin et al 2012	19	634	13	421	8.2%	0.97 [0.48, 1.94]	
Tashkin et al 2012	58	1351	39	900	24.7%	0.99 [0.67, 1.47]	
Doherty et al 2012	39	717	26	479	16.4%	1.00 [0.62, 1.62]	
Subtotal (95% CI)		**3318**		**2095**	**100.0%**	**1.05 [0.87, 1.26]**	
Total events	280		149				
Heterogeneity: Chi² = 0.35, df = 3 (P = 0.95); I² = 0%							
Test for overall effect: Z = 0.51 (P = 0.61)							
Risk of URTI associated with high-dose mometasone							
Calverley et al 2008	164	616	71	295	55.1%	1.11 [0.87, 1.41]	
Tashkin et al 2012	14	427	13	421	7.5%	1.06 [0.51, 2.23]	
Tashkin et al 2012	39	905	39	900	22.5%	0.99 [0.64, 1.54]	
Doherty et al 2012	25	478	26	479	14.9%	0.96 [0.56, 1.64]	
Subtotal (95% CI)		**2426**		**2095**	**100.0%**	**1.06 [0.87, 1.28]**	
Total events	242		149				
Heterogeneity: Chi² = 0.33, df = 3 (P = 0.95); I² = 0%							
Test for overall effect: Z = 0.56 (P = 0.57)							
Risk of URTI associated with medium-dose mometasone							
Tashkin et al 2012	5	207	13	421	16.6%	0.78 [0.28, 2.16]	
Tashkin et al 2012	19	446	39	900	50.0%	0.98 [0.57, 1.68]	
Doherty et al 2012	14	239	26	479	33.5%	1.08 [0.57, 2.03]	
Subtotal (95% CI)		**892**		**1800**	**100.0%**	**0.98 [0.67, 1.43]**	
Total events	38		78				
Heterogeneity: Chi² = 0.28, df = 2 (P = 0.87); I² = 0%							
Test for overall effect: Z = 0.09 (P = 0.93)							

0.01   0.1   1   10   100
Favours Mometasone   Favours Control

Fig. 8 Risk of URTI associated with mometasone. URTI, upper respiratory tract infection

Study or Subgroup	Budesonide Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Calverley et al 2010	3	479	5	239	11.0%	0.30 [0.07, 1.24]	
Sharafkhaneh et al 2012	90	815	39	403	85.7%	1.14 [0.80, 1.63]	
Huang et al 2019	4	293	2	289	3.3%	1.97 [0.36, 10.69]	
Total (95% CI)		**1587**		**931**	**100.0%**	**1.08 [0.77, 1.50]**	
Total events	97		46				
Heterogeneity: Chi² = 3.70, df = 2 (P = 0.16); I² = 46%							
Test for overall effect: Z = 0.43 (P = 0.67)							

0.01   0.1   1   10   100
Favours experimental   Favours control

Fig. 9 Risk of URTI associated with budesonide. URTI, upper respiratory tract infection

Chen *et al. BMC Pulmonary Medicine*   (2020) 20:282

Page 12 of 13

dose fluticasone increases the risk of URTI in patients with COPD, but not mometasone or budesonide.

Supplementary information

Additional file 1. Search strategy.

Abbreviations

ICSs: Inhaled corticosteroids; URTI: Upper respiratory tract infection; COPD: Chronic obstructive pulmonary disease; RCTs: Randomized controlled trials; FEV_1: Forced expiratory volume in 1 s; TORCH: The large prospective study Toward a Revolution in COPD Health; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Authors' contributions

Study design: HC. Drafting of the manuscript: HC. Literature search: HC, YF and KW. Risk of bias assessment: HC, YF and KW. Statistical analysis: HC, YD, KW and JY. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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