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Inhaled corticosteroids and risk of pneumonia in patients with chronic obstructive pulmonary disease: A meta-analysis of randomized controlled trials

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ABSTRACT

Objective: Inhaled corticosteroids (ICS) are generally used to treat patients with chronic obstructive pulmonary disease (COPD) who suffer from repeated exacerbations. Recently, it was reported that ICS treatment increased the risk of pneumonia in COPD patients. But it is controversial. The objective of this paper is to clarify the associations between ICS treatment and the risk of pneumonia in COPD patients.

Methods: PubMed, Cochrane Library, Clinical Trials.gov, and Embase were searched from February 2019 to June 2019. Randomized clinical trials (RCTs) were incorporated that compared ICS with non-ICS treatment on the risk of pneumonia in COPD patients. Meta-analyses were conducted by the Peto and Mantel-Haenszel approaches with corresponding 95% CIs.

Results: Twenty-five trials (N = 49,982 subjects) were included. Pooled results demonstrated a significantly increased risk of pneumonia with ICS use in COPD patients (RR, 1.59, 95% CI, 1.33–1.90; I^2 = 51%). ICS treatment also increased the risk of severe pneumonia (RR, 2.17, 95% CI, 1.47–3.22; I^2 = 29%). The results of subgroup analysis based on doses of ICS were consistent with the above. However, subgroup analyses based on types of ICS revealed that fluticasone therapy was associated with an increased risk of pneumonia but not budesonide. In addition, medium- and low-doses of budesonide treatment also did not increase the risk of pneumonia.

Conclusions: Use of ICS increases the risk of pneumonia in patients with COPD. The above is prominent for fluticasone-containing ICSs but not for budesonide-containing ICSs.

1. Introduction

COPD is characterised by persistent airflow limitation, progressive incapacity, and significant societal burdens [1]. Periods of acute exacerbation of COPD often result in an increased risk of death and a decreased quality of life [2]. In order to prevent COPD repeated exacerbations and reduce their associated hospital admissions, some pharmacologic therapies, such as long-acting muscarinic antagonist (LAMA), ICS, and long-acting β-agonist (LABA), had been developed. Especially, ICSs are generally used to treat patients who suffer from repeated exacerbations. They are usually recommended in combination with LABA and/or LAMA to reduce the duration, frequency, and severity of exacerbations, and improve quality of life [3,4].

However, ICS-related safety issues remain a serious concern. ICSs are potent but non-specific anti-inflammatory agents. Because of widespread use of ICS, it is important to consider the potential harmful effects on host immunity, which may accelerate the occurrence of respiratory infection [5]. Some studies have revealed that ICS may result in several adverse effects, such as upper respiratory tract infection, pneumonia, and oropharyngeal candidiasis [6,7]. In particular, an increased risk of pneumonia associated with ICS use has been widely reported in some observational studies [8,9]. Several meta-analyses are also consistent with the above viewpoint [10,11]. But a recent retrospective study reported that ICS treatment might not increase the risk of pneumonia in Japanese patients with COPD [12]. A cohort study also revealed that fluticasone-containing ICSs were significantly associated with the risk of pneumonia but not for budesonide-containing ICS [7]. Furthermore, a recent systematic review also concluded that there was

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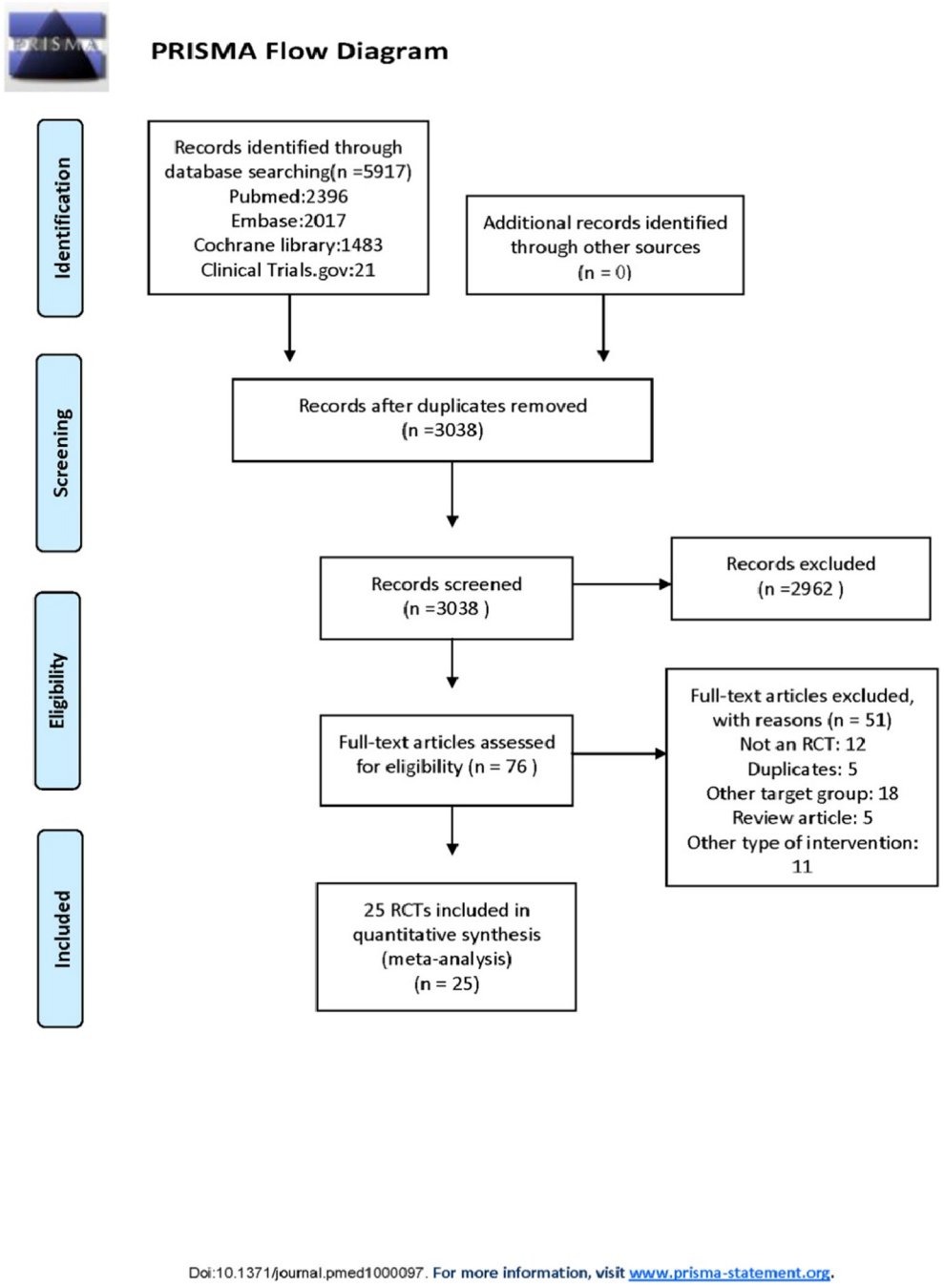

Fig. 1. Flow of study selection.

no correlation between ICS treatment and the risk of pneumonia [13]. Therefore, previous studies provided conflicting results. The relationship between use of ICS and the risk of pneumonia in COPD patients is still controversial.

Several meta-analyses have been published, assessing the association of use of ICS and the risk of pneumonia in patients with COPD. Among these, three studies reported that ICS significantly increased the risk of pneumonia [10,11,14]. But these studies only provided a general summary, and didn't perform further subgroup analysis according to different doses and types of ICS. In addition, their results were also limited owing to imprecision, significant heterogeneity, and small size. One meta-analysis concluded that budesonide-containing ICSs might not increase the risk of pneumonia in COPD patients but no information about other ICSs [13]. Therefore, there are doubts about the clinical significance of differences reported in the different studies. This finding of above differences offered an impetus to reappraise all available randomized clinical trials (RCTs).

2. Methods

2.1. Protocol and guidance

As this is a meta-analysis, ethics committee approval is not applicable. The study protocol was conducted following PRISMA guidelines [15].

2.2. Search strategy

We searched PubMed, Cochrane Library, Clinical Trials.gov, and Embase from February 2019 to June 2019, with no geographic area and

Table 1
Characteristics of RCTs of ICS use included in the meta-analysis.

Authors	No.of S (P/cases)		Years		Doses	Duration, months	Interventions
	ICS	controls	ICS	controls			
Gary et al. (2008)	29/394	15/388	64.9 ± 9	65.0 ± 9.1	250/50 bid	13	FSC versus S
Sharafkhaneh et al. (2012)	45/815	11/403	≥40	≥40	320/9 or 160/9 bid	12	BUD/F versus F
Aaron et al. (2007).	1/145	1/304	67.8 ± 8.9	67.9 ± 8.6	250/25 bid	13	FSC versus S
Mark et al. (2013)	177/2437	28/818	63.6 ± 9.3	63.6 ± 9.2	200or100or50/25qd	13	FF/VI versus VI
Calverley et al. (2011)	50/658	24/665	≥60	≥60	500/50 bid	24	SFC versus Tio
Antonio et al. (2009)	26/394	10/403	65.4 ± 9.1	65.3 ± 8.8	250/50 bid	13	FSC versus S
Calverley et al. (2003)	13/511	9/511	≥40	≥40	320/9;400 bid	12	BUD/F or BUD vs. F or P
Calverley et al. (2010)	5/232;7/238	1/233	63.5 ± 9.0	63.7 ± 8.8	200/24;400/24 bid	12	BDP/F vs.F; BUD/F vs. F
Dennis et al. (2012)	16/717	6/479	60.3 ± 8.7	59.2 ± 9.1	400or200/10;400 bid	13	MF/F vs. F; MF vs. P
Kardos et al. (2007)	23/507	7/487	63.8 ± 8.3	64 ± 8.2	500/50 bid	11	SFC vs S
Martinez et al. (2013)	10/816	2/408	61.7 ± 8.6	61.7 ± 8.3	200/25;100/25 qd	6	FF/VI vs. FF; FP vs.P
Rennard et al. (2009)	30/988	40/976	63.4 ± 9	62.9 ± 9.1	320/9;160/9 bid	12	BUD/FM vs. FM or P
Tashkin et al. (2012)	19/1351	9/900	60.2 ± 8.8	59.3 ± 8.8	400/10;400 bid	13	MF/F vs. F;MF vs.P
Tashkin et al. (2008)	8/1120	2/584	63.3 ± 9.0	63.4 ± 9.5	320or160/9 bid	6	BUD/F vs. FM;BUD vs.P
Vestbo et al. (1999)	16/145	24/145	59 ± 8.3	59.1 ± 9.7	400 bid	36	BUD vs.P
Pauwels et al. (1999)	33/634	16/643	52.5 ± 7.5	52.4 ± 7.7	400 bid	36	BUD vs.P
Szafranski et al. (2003)	20/406	15/406	64	64	160/9;200/4.5 bid	12	BUD/F vs.F or P
Vogelmeier et al. (2013)	4/264	0/259	63.2 ± 8.2	63.4 ± 7.7	500/50 bid	6.5	SFC vs. F
Kerwin et al. (2013)	12/618	8/412	62.6 ± 9.1	62.8 ± 9.1	100/25; 50/25 bid	6	FF/VI vs. VI or P
Ferguson et al. (2017)	3/605	6/613	63.1 ± 8.7	63.9 ± 8.7	320/9 bid	6	BUD/F vs. F
Fukuchi et al. (2013)	8/636	7/657	64.5	65.6	160/4.5 bid	3	BUD/F vs. F
Huang et al. (2019)	1/293	0/289	63.8 ± 8.8	64.4 ± 8.8	160/4.5 bid	3	BUD/F plus I + T vs. I + T
Wedzicha et al. (2008)	50/658	24/665	64	65	500/50 bid	24	SFC vs. Tio
Calverley et al. (2007)	217/3098	124/3086	65.0 ± 8.4	65.1 ± 8.2	500/50 bid	36	FP vs.P; SFC vs. F
Vestbo et al. (2016)	465/8297	377/8271	65.0 ± 8.0	65.1 ± 8.0	100/25 bid	22	FF/VI vs. VI or P

FSC, fluticasone propionate/salmeterol; ICS, inhaled corticosteroids; P, pneumonia. BUD, budesonide; F, formoterol; S, salmeterol; VI, vilanterol; FF, fluticasone furoate; Tio, tiotropium bromide; SFC, SAL plus FP combination; BDP, beclomethasone dipropionate; S, subjects; MF, mometasone furoate.

language restrictions. The search strategy was as follows: ("budesonide" or "Pulmicort" or "mometasone" or "flunisolide" or "beclomethasone" or "Foradil" or "FP/SAL (Advair)" or "Inhaled corticosteroids" or "ICS") and ("COPD" or "chronic airflow obstruction" or "chronic obstructive pulmonary disease" or "emphysema") and randomized protocol design. Disagreements between two reviewers were resolved by discussion until a consensus was reached.

2.3. Eligibility criteria

The inclusion criteria were described below: (1) patients with COPD of any severity; (2) double-blind and randomized trials; (3) exposure to inhaled corticosteroid (including ICS alone or ICS plus LAMA and/or LABA); (4) ICS as an intervention drug, and non-ICS treatment as a control (including LABA, LAMA, or placebo); and (5) studies providing data on pneumonia (including zero events). Exclusion criteria: (I) included patients with asthma and/or bronchiectasis; (II) studies were published in reviews, abstracts, or protocols; (III) a cohort design or case-control; and (IV) the number of pneumonia in both groups was not provided.

2.4. Data collection process and assessment of risk of bias

Two reviewers (Mingjin Y. and Yuejun D.) extracted data independently and in duplicate from eligible trials. The Cochrane risk of bias tool was used for assessing the risk of bias of included RCTs [16]. Disagreements between two reviewers were resolved by discussion and consensus.

2.5. Statistical analysis

A meta-analysis was implemented to evaluate whether exposure to inhaled corticosteroids was associated with risk of pneumonia. We used Review Manager 5.3 software (v.5.3, Cochrane Collaboration, London, UK) to calculate pooled Peto odds ratio (OR) with 95% confidence intervals (CIs). We also computed the pooled Mantel-Haenszel relative risk (RR) for RCTs with zero events in ICS treatment or control. Statistical heterogeneity was assessed using the I^2 test, with a value ≥50% being considered substantial. When substantial statistical heterogeneity was present, a random effect model was used. A p-value less than 0.05 was defined as statistically significant. The GRADEpro Guideline Development Tool was used for rating of quality of included evidence. The findings were presented in 'Summary of findings' tables.

3. Results

3.1. Study selection

Our search identified 25 published studies that met the eligibility criteria [17–41]. The flowchart is shown in Fig. 1. The 25 included RCTs enrolled 49,982 subjects, of whom 26,977 received ICS treatment and 23,005 received non-ICS treatment.

3.2. Study characteristics

The included trials were published from 1999 to 2019. Population sizes ranged from 290 to 16,568 subjects. Among the studies, 16 studies were multicenter trials. Nine studies investigated the use of high-dose ICS (mometasone furoate > 440 ug/day; fluticasone propionate > 500 ug/day; budesonide > 800 ug/day; fluticasone furoate > 200 ug/day; beclomethasone dipropionate > 400 ug/day), twelve investigated the use of medium-dose ICS (mometasone furoate > 220–440 ug/day; budesonide > 400–800 ug/day; fluticasone propionate > 250–500 ug/day; beclomethasone dipropionate > 200–400 ug/day), and nine investigated the use of low-dose ICS (mometasone furoate 110–220 ug/day; fluticasone propionate 100–250 ug/day; budesonide 200–400 ug/day; beclomethasone dipropionate 100–200 ug/day) [42]. Of the 25 RCTs, 12 RCTs used fluticasone, 11 RCTs used budesonide, 2 RCTs used mometasone furoate, and 1 RCT used beclomethasone dipropionate. Trials characteristics are presented in Table 1.

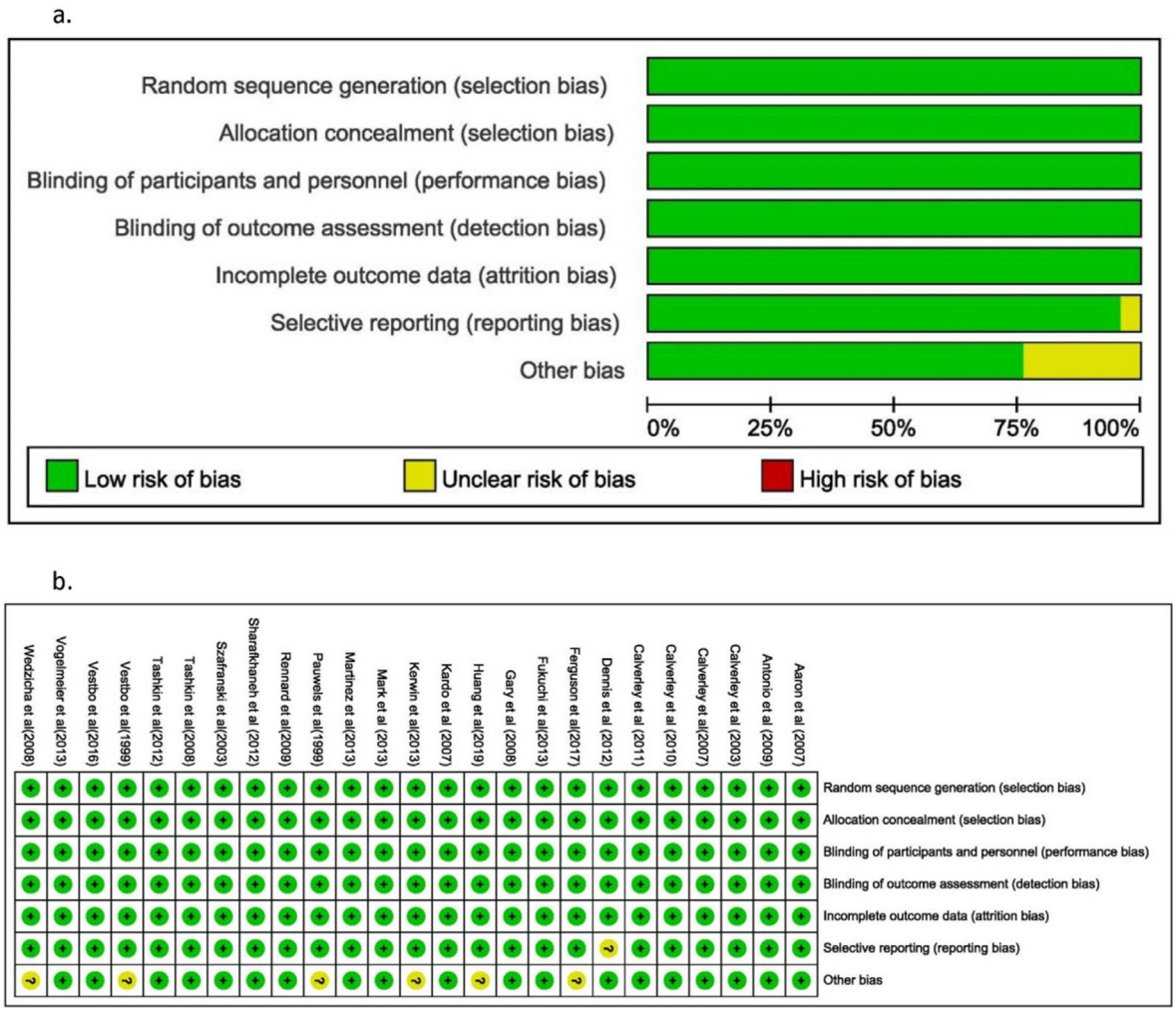

Fig. 2. (a and b) Risk of bias of the included studies.

3.3. Risk of bias and quality of evidence

All RCTs were evaluated using a risk bias assessment tool. The results of assessments are reported in Fig. 2a and b. Seventeen trials had a low risk of bias. One trial had an unclear risk for selective reporting. Seven RCTs had an unclear risk due to the other bias, principally owing to the potential for funding bias. The findings of the GRADE assessment of each study are reported in Table 2.

3.4. Use of ICS and risk of pneumonia

Twenty-five studies provided information on pneumonia. Meta results demonstrated a significantly increased risk of pneumonia with ICS therapy in COPD patients (RR, 1.59, 95% CI, 1.33–1.90; $I^2 = 51\%$) (Fig. 3). Considering that statistical heterogeneity among the included studies might reduce the reliability of above results, subgroup analyses were performed next for different doses. Nine studies assessed the use of high-dose ICS, twelve studies assessed medium-dose ICS, and nine studies assessed low-dose ICS. Meta results revealed that high- (Peto OR, 1.98, 95% CI, 1.70–2.31; $I^2 = 0\%$), medium- (OR, 1.48, 95% CI, 1.02–2.16; $I^2 = 52\%$), and low-doses (Peto OR, 1.44, 95% CI, 1.12–1.85; $I^2 = 13\%$) of ICSs were all associated with an increased risk of pneumonia vs control group (Figs. 4, 5, 6). These comparisons were rated as high quality evidence by GRADE (Table 2).

3.5. Risk of pneumonia associated with fluticasone treatment

Of the eligible trials, twelve assessed the use of fluticasone. The pooled results revealed that fluticasone therapy was associated with an increased risk of pneumonia vs control group (RR, 1.84, 95% CI, 1.47–2.30; $I^2 = 58\%$) (Fig. 7.). These comparisons were rated as high quality evidence by GRADE (Table 2). Then subgroup analysis was performed according to different doses. Seven, three, and three studies investigated the use of high-, medium-, and low-doses fluticasone treatment, respectively. Results of the Peto approach demonstrated that high- (Peto OR, 2.01 95% CI, 1.71–2.36; $I^2 = 0\%$), medium- (Peto OR, 2.21 95% CI, 1.42–3.44; $I^2 = 0\%$), and low-doses (Peto OR, 1.73 95% CI, 1.24–2.40; $I^2 = 0\%$) of fluticasone treatment were all associated with an increased risk of pneumonia vs non-ICS treatment (Figs. 8, 9, 10). These comparisons were rated as moderate or high quality evidence by GRADE (Table 2).

3.6. Risk of pneumonia associated with budesonide treatment

Of the eligible trials, eleven assessed the use of budesonide. Results of the Peto approach revealed that budesonide treatment was not associated with an increased risk of pneumonia vs control group (Peto OR, 1.24, 95% CI, 0.98–1.56; $I^2 = 48\%$) (Fig. 11). The above comparisons were rated as moderate quality evidence by GRADE (Table 2). Then subgroup analysis was performed according to different doses. Nine and five studies investigated the use of medium- and low-dose budesonide treatment, respectively. Considering the substantial level of

Table 2
GRADE summary of findings. ICS use and risk of pneumonia in patients with COPD.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with ICS treatment (95% CI)
Use of ICS and risk of pneumonia	49982 (25 studies) 3–36 months	⊕⊕⊕⊕ **HIGH**[1,2] due to risk of bias, inconsistency, large effect, plausible confounding would change the effect	**RR 1.59** (1.33–1.9)	**Study population** **33 per 1000** **Moderate** **19 per 1000**	**20 more per 1000** (from 11 more to 30 more) **11 more per 1000** (from 6 more to 17 more)
Risk of pneumonia associated with high-dose ICS treatment	16000 (9 studies)	⊕⊕⊕⊕ **HIGH** due to risk of bias, large effect	**OR 1.98** (1.7–2.31)	**Study population** **29 per 1000** **Moderate** **14 per 1000**	**27 more per 1000** (from 19 more to 35 more) **13 more per 1000** (from 10 more to 18 more)
Risk of pneumonia associated with medium-dose ICS treatment	11587 (12 studies)	⊕⊕⊕⊕ **HIGH** due to risk of bias, large effect	**OR 1.48** (1.02–2.16)	**Study population** **24 per 1000** **Moderate** **21 per 1000**	**11 more per 1000** (from 0 more to 26 more) **10 more per 1000** (from 0 more to 23 more)
Risk of pneumonia associated with low-dose ICS treatment	10029 (9 studies) 3–12 months	⊕⊕⊕⊖ **MODERATE** due to risk of bias	**OR 1.44** (1.12–1.85)	**Study population** **21 per 1000** **Moderate** **13 per 1000**	**9 more per 1000** (from 2 more to 17 more) **6 more per 1000** (from 2 more to 11 more)
Risk of pneumonia associated with fluticasone treatment	34452 (12 studies) 3–36 months	⊕⊕⊕⊕ **HIGH**	**RR 1.84** (1.47–2.3)	**Study population** **38 per 1000** **Moderate** **30 per 1000**	**32 more per 1000** (from 18 more to 50 more) **25 more per 1000** (from 14 more to 39 more)
Risk of pneumonia associated with high-dose fluticasone treatment	12799 (7 studies)	⊕⊕⊕⊕ **HIGH** due to risk of bias, large effect	**OR 2.01** (1.71–2.36)	**Study population** **33 per 1000** **Moderate** **34 per 1000**	**31 more per 1000** (from 22 more to 41 more) **32 more per 1000** (from 23 more to 43 more)
Risk of pneumonia associated with medium-dose fluticasone treatment	2028 (3 studies)	⊕⊕⊕⊖ **MODERATE** due to risk of bias	**OR 2.21** (1.42–3.44)	**Study population** **24 per 1000** **Moderate** **25 per 1000**	**27 more per 1000** (from 10 more to 53 more) **29 more per 1000** (from 10 more to 56 more)
Risk of pneumonia associated with low-dose fluticasone treatment	4290 (3 studies)	⊕⊕⊖⊖ **LOW** due to risk of bias, inconsistency	**OR 1.73** (1.24–2.4)	**Study population** **23 per 1000** **Moderate** **19 per 1000**	**16 more per 1000** (from 5 more to 31 more) **13 more per 1000** (from 4 more to 25 more)

(*continued on next page*)

Table 2 (*continued*)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with ICS treatment (95% CI)
Risk of pneumonia associated with budesonide treatment	11851 (11 studies) 3–36 months	⊕⊕⊕⊖ **MODERATE** due to risk of bias, inconsistency, large effect	**RR 1.23** (0.98–1.54)	**Study population** **24 per 1000**	**6 more per 1000** (from 0 fewer to 13 more)
				Moderate **18 per 1000**	**4 more per 1000** (from 0 fewer to 10 more)
Risk of pneumonia associated with medium-dose budesonide treatment	8793 (9 studies)	⊕⊕⊕⊕ **HIGH** due to risk of bias, large effect	**OR 1.31** (0.85–2.02)	**Study population** **27 per 1000**	**8 more per 1000** (from 4 fewer to 27 more)
				Moderate **25 per 1000**	**7 more per 1000** (from 4 fewer to 24 more)
Risk of pneumonia associated with low-dose budesonide treatment	5021 (5 studies)		**OR 1.1** (0.74–1.64)	**Study population** **21 per 1000**	**2 more per 1000** (from 5 fewer to 13 more)
				Moderate **11 per 1000**	**1 more per 1000** (from 3 fewer to 7 more)
Use of ICS and risk of severe pneumonia	8022 (5 studies) 6–24 months	⊕⊕⊕⊖ **MODERATE** due to risk of bias	**RR 2.17** (1.47–3.22)	**Study population** **12 per 1000**	**14 more per 1000** (from 5 more to 26 more)
				Moderate **8 per 1000**	**9 more per 1000** (from 4 more to 18 more)

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio.
Bibliography: Patient or population: Patients with COPD; Intervention: ICS; Settings: Community.
[1] Some included studies provided conflicting results. The relationship between inhaled corticosteroids and the risk of pneumonia in COPD patients is still controversial.
[2] The 25 included RCTs enrolled 49,982 subjects, of whom 26,977 received ICS treatment and 23,005 received non-ICS treatment.

heterogeneity, the random effect model was used for meta-analysis of medium-dose budesonide trials. Results of Mantel-Haenszel approach revealed that medium-dose budesonide treatment was also not associated with the risk of pneumonia vs control group (OR, 1.31 95% CI, 0.85–2.02; I^2 = 56%) (Fig. 12). The pooled results of low-dose budesonide treatment was also consistent with the above (Peto OR, 1.10 95% CI, 0.74–1.64; I^2 = 13%) (Fig. 13). These comparisons were rated as moderate or low quality evidence by GRADE (Table 2).

3.7. Use of ICS and risk of severe pneumonia

About the evaluation of the risk of pneumonia in COPD patients, severity of pneumonia is an important issue. We therefore assessed the association between use of ICS and the risk of severe pneumonia next. Only five studies provided information on severe pneumonia. The pooled results revealed that ICS treatment increased the risk of severe pneumonia in COPD patients (RR, 2.17, 95% CI, 1.47–3.22; I^2 = 29%) (Fig. 14). These comparisons were rated as moderate quality evidence by GRADE (Table 2).

4. Discussion

In this meta-analysis of 25 trials (including 49,982 subjects), ICS treatment was associated with a significantly increased risk of pneumonia in patients with COPD. Similarly, ICS also increased the risk of severe pneumonia. Considering that the above pooled results might not avoid heterogeneity due to the included different types and doses of ICS, subgroup analysis was performed next. The results of subgroup analysis based on doses of ICS further verify the above views. However, subgroup analyses based on types of ICS revealed that fluticasone treatment was associated with an increased risk of pneumonia but not budesonide. In addition, it was revealed that high-, medium-, and low-doses of budesonide did not increase the risk of pneumonia.

The above results revealed that fluticasone-containing ICSs were associated with an increased risk of pneumonia, while no risk was found for budesonide-containing ICSs. It is unclear why different types of ICS show differential effects on the risk of pneumonia in patients with COPD. It is reported that fluticasone could suppress effectively innate immunoresponse to bacterial triggers in alveolar macrophages [43]. The immunosuppressive effects of fluticasone could be up to tenfold greater than that of budesonide in the human airways/lungs [44]. Differences in immunosuppression may be an important reason

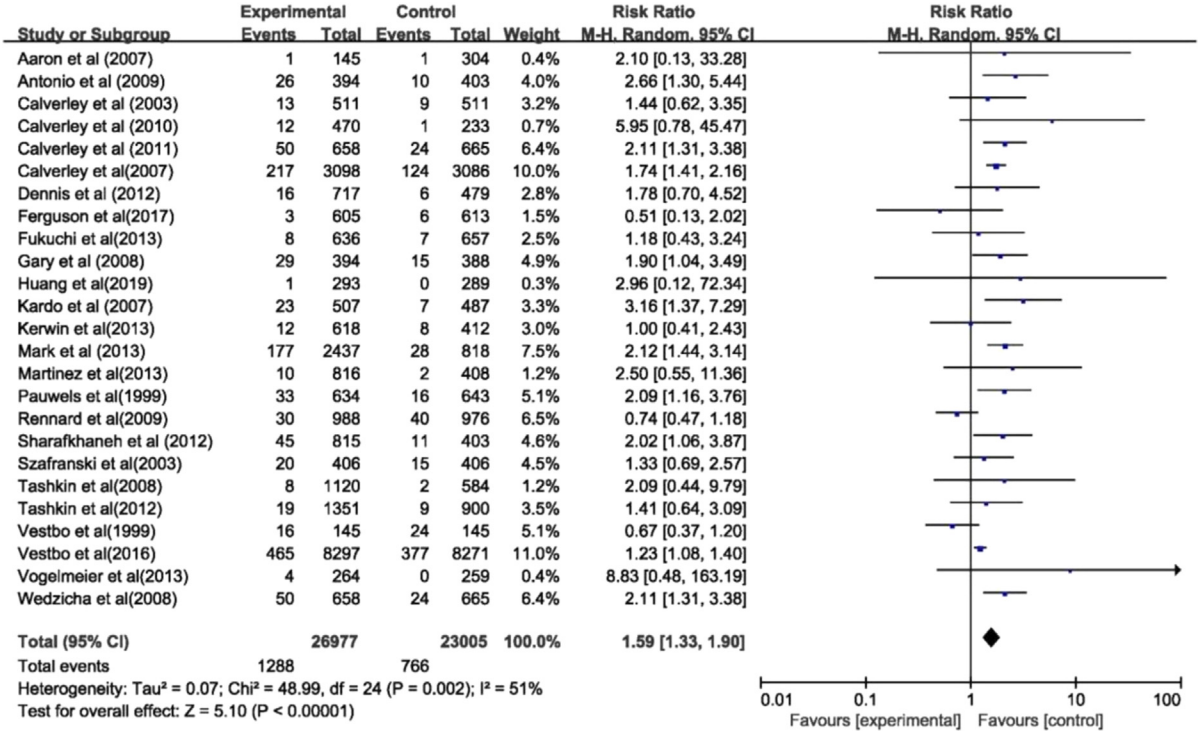

Fig. 3. Risk of pneumonia associated with ICS therapy (ICS alone and ICS plus LABA). Risk estimates shown are relative risks (RR).

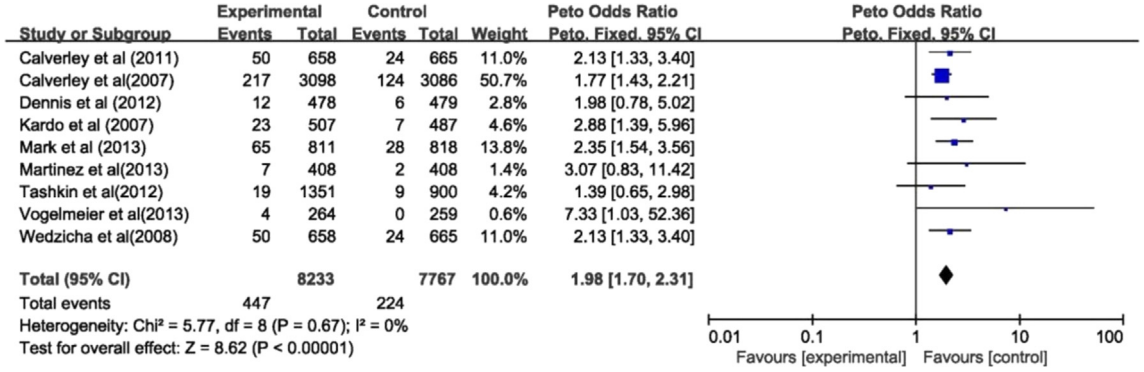

Fig. 4. Risk of pneumonia associated with high-dose ICS (ICS alone and LABA-ICS). Risk estimates shown are Peto odds ratio (OR).

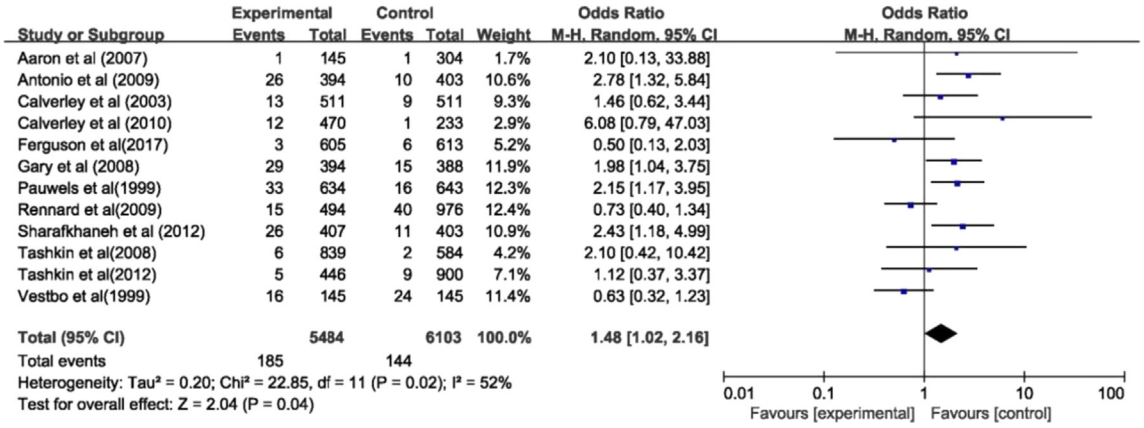

Fig. 5. Risk of pneumonia associated with medium-dose ICS (ICS alone and LABA-ICS). Risk estimates shown are odds ratio (OR).

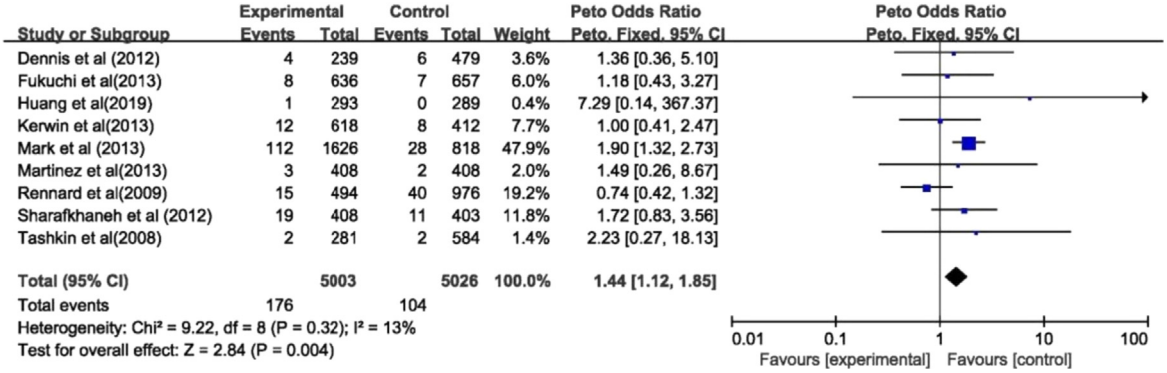

Fig. 6. Risk of pneumonia associated with low-dose ICS (ICS alone and LABA-ICS). Risk estimates shown are Peto odds ratio (OR).

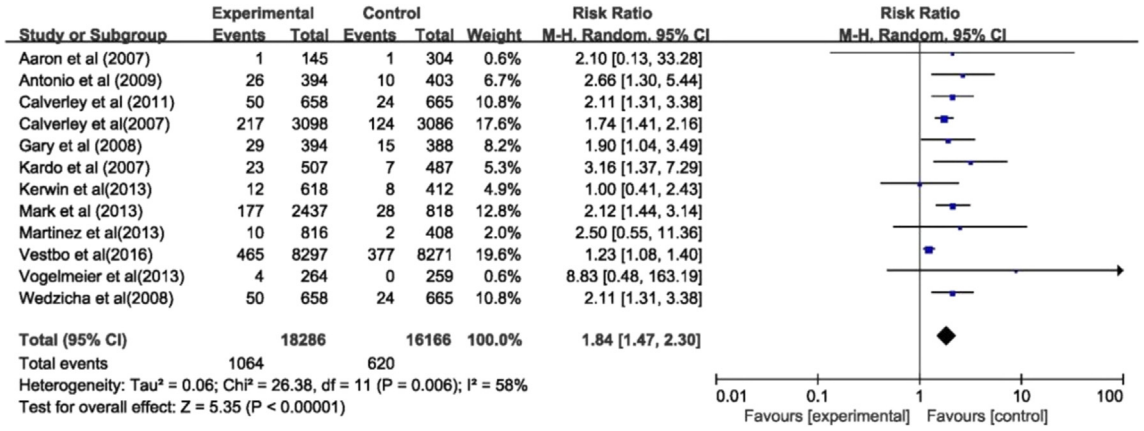

Fig. 7. Risk of pneumonia associated with fluticasone therapy. Risk estimates shown are relative risks (RR).

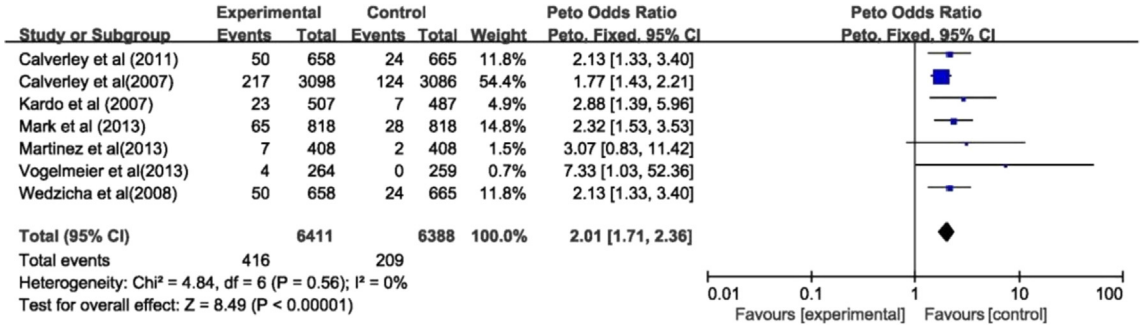

Fig. 8. Risk of pneumonia associated with high-dose fluticasone therapy. Risk estimates shown are Peto odds ratio (OR).

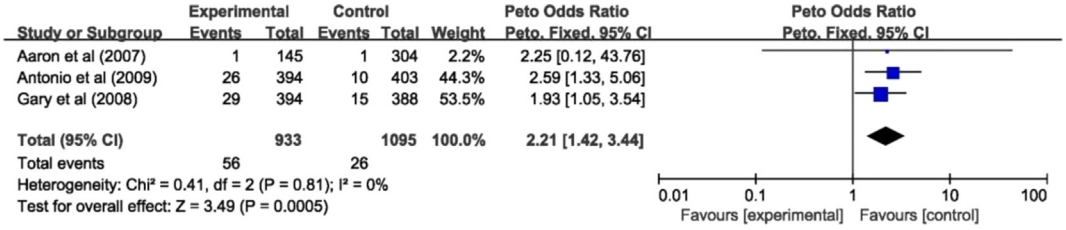

Fig. 9. Risk of pneumonia associated with medium-dose fluticasone therapy. Risk estimates shown are Peto odds ratio (OR).

why different types of ICS exhibit different effects on the risk of pneumonia. In the future, further studies may fully appreciate the mechanistic roles of ICS in this immunoresponse process.

Currently, various doses of ICS (including high-, medium-, and low-doses ICS) are widely used to control COPD inflammation in clinical practice [18,45,46]. But the optimal dosage of ICS treatment for COPD patients remains unknown [45]. This study highlights that only part types of ICS may increase the risk of pneumonia. In addition, the existing evidences suggested that there was no positive correlation between the risk of pneumonia and the ICS dose within the current conventional doses. Although the issue is not novel, it is crucial to the development of treatment plans. These findings could be used for reference in the management of COPD.

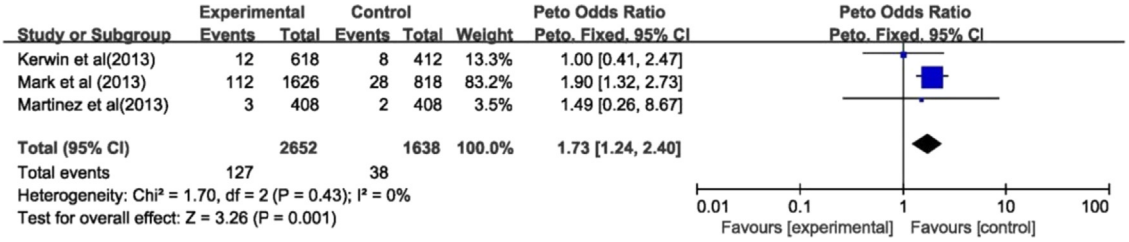

Fig. 10. Risk of pneumonia associated with low-dose fluticasone therapy. Risk estimates shown are Peto odds ratio (OR).

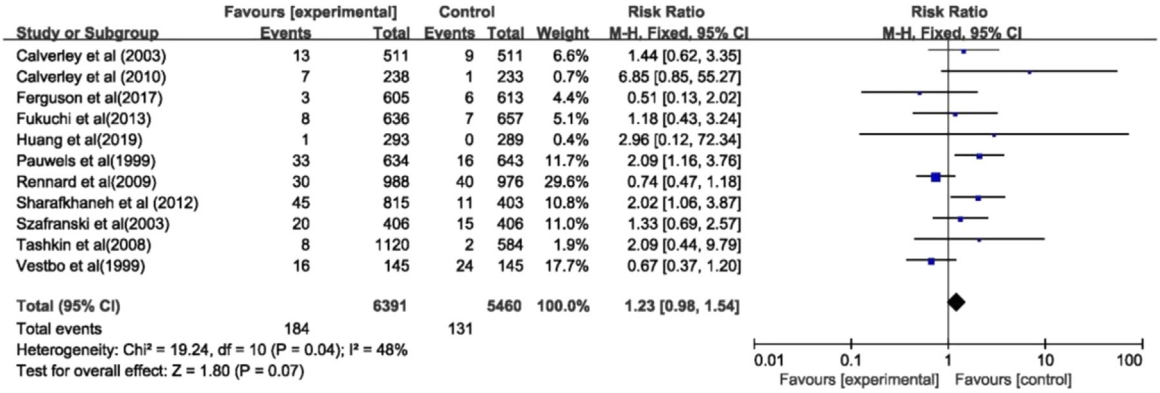

Fig. 11. Risk of pneumonia associated with budesonide therapy. Risk estimates shown are Peto odds ratio (OR).

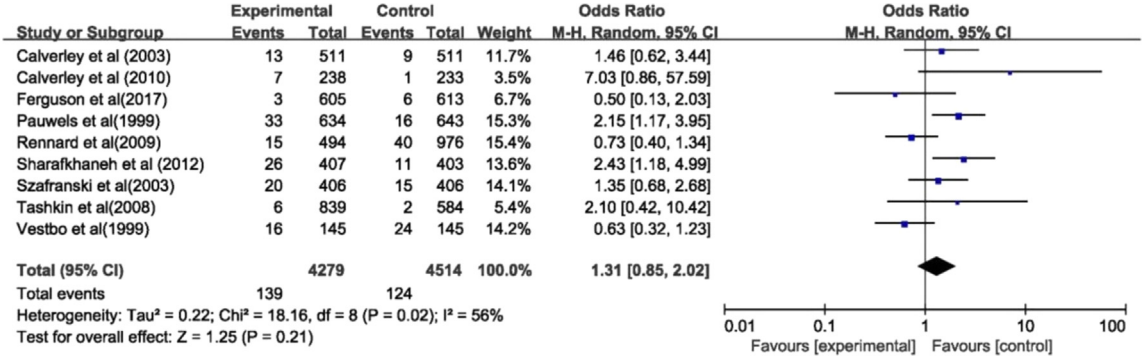

Fig. 12. Risk of pneumonia associated with medium-dose budesonide therapy. Risk estimates shown are odds ratio (OR).

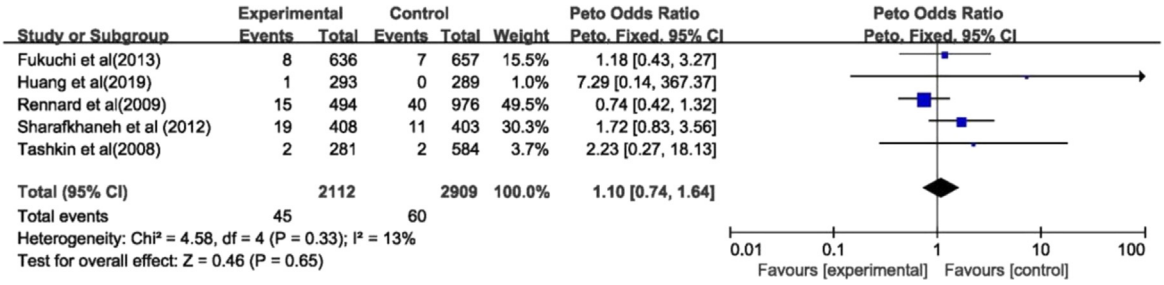

Fig. 13. Risk of pneumonia associated with low-dose budesonide therapy. Risk estimates shown are Peto odds ratio (OR).

4.1. Compared with other studies

Several meta-analyses have assessed the association between the use of ICS and the risk of pneumonia in COPD patients. In 2008, Drummond and colleagues identified 11 eligible trials and revealed that ICS therapy could increase the risk of pneumonia in COPD patients [13]. In 2009, Singh and colleagues published a meta-analysis including a total of 18 RCTs enrolling 16,996 subjects [12]. Findings in their study also confirmed that ICS use for at least 6 months is significantly associated with an increased risk of serious pneumonia. Unfortunately, the above meta-analyses did not perform further subgroup analysis based on doses and types of ICS. Their results were limited owing to imprecision, significant heterogeneity, and small size. In 2016, an additional systematic review was published [14]. This study also compared budesonide with placebo in subgroup analysis and found that budesonide did not increase risk of pneumonia. But that study included fewer budesonide-related RCTs and also did not perform further subgroup analysis based on doses of ICS. In addition, Tang et al published a meta-analysis including a total of 8 RCTs recently [11]. Their results showed that budesonide/formoterol did not cause more adverse events (e.g. pneumonia) than placebo or

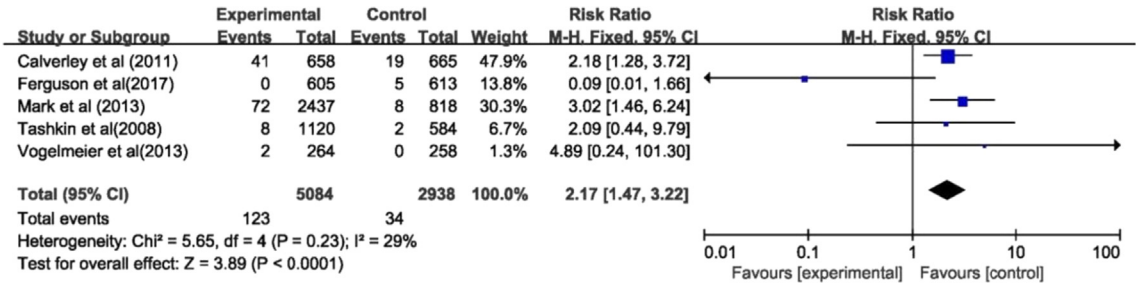

Fig. 14. Risk of severe pneumonia associated with ICS treatment. Risk estimates shown are relative risks (RR).

formoterol in patients with COPD. But their study mostly evaluated combination therapy (budesonide plus formoterol), provided no information about other ICSs, and did not perform further analysis based on doses of ICS. Furthermore, their results were also limited owing to sample size.

4.2. Strengths and limitations

The strengths of this meta-analysis were that it includes a comprehensive search strategy and explicit inclusion criteria. In addition, it included 25 RCTs enrolling more than 49,982 subjects, which meet the basic requirements of sequential analysis, and multiple subgroups. All included studies were rigorously graded according to the quality of evidence by the GRADE approach.

This meta-analysis had several limitations. First, significant clinical heterogeneity weakened the results of our study. This meta-analysis included RCTs developed almost 2 decades ago. The therapeutic techniques of COPD, including type of ICS, inhaler device, dose of corticosteroids, management plan, and duration of therapy, have evolved. In addition, baseline characteristics of patients may be also important factors affecting the occurrence, progression, and prognosis of pneumonia. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has reported that patients at higher risk of pneumonia include those with who are aged ≧55 years, currently smoke, have a body mass index $< 25\,kg/m^2$, a history of prior pneumonia or exacerbations, a severe airflow limitation and/or poor MRC dyspnea grade [47]. The above factors might be important contributors to heterogeneity in this study. Second, the results of this meta-analysis were also limited owing to sample size. Only two trials assessed mometasone. The subgroup analysis of mometasone could not be performed due to the limited number of trials. Third, selection bias could not be avoided due to the exclusion of some related studies with insufficient information.

5. Ethics approval and informed consent

Not applicable.

Author contributions

Conceived and designed the study: Mingjin Yang. Performed the experiments: Mingjin Yang. Analyzed the data: Mingjin Yang, Zhibo Xu. Contributed reagents/materials/analysis tools: Hong Chen, Yuejun Du, Depeng Jiang. Wrote the first draft of the manuscript: Mingjin Yang, Zhibo Xu. Agree with the manuscript's results and conclusions:Mingjin Yang, Yuejun Du, Hong Chen, Depeng Jiang, Zhibo Xu.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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