Original article

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Inhaled corticosteroids and incident pneumonia in patients with asthma: Systematic review and meta-analysis

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Objectives. To systematically review all available studies on inhaled corticosteroid use and incident pneumonia in asthma patients. **Methods.** We performed a literature search from January 1, 1993, through August 15, 2015, using PubMed, Medline, CENTRAL, EMBASE, Scopus, ISI, Regulatory Documents, Web of Science and manufacturers' web clinical trial registries with multiple search terms. We included studies that compared the risk of incident pneumonia among patients utilizing and not utilizing inhaled corticosteroids. We then summarized risk estimates into two random-effect meta-analyses; one including randomized controlled trials and another one including observational studies. **Results.** Fourteen studies were estimable; ten randomized controlled trials included 19,098 participants and four observational studies included 44,016 participants. There was no heterogeneity in randomized trials and summed risk ratio demonstrated the use of inhaled corticosteroids was protective of pneumonia; risk ratio 0.74, 95% CI 0.57to 0.95, p=0.02. On the contrary, observational studies showed summed odds ratio of 1.97; 95% CI 1.87to 2.07, p<0.0001, I^2=0%, suggesting increased risk of pneumonia with use of inhaled corticosteroids in asthma patients. **Conclusions**. Inhaled corticosteroids are associated with decreased risk of incident pneumonia in patients with asthma based on meta-analysis of available randomized trials. Although observational studies in similar patients suggested higher risk of pneumonia, the inherent methodological limitations confer lower grade of confidence in these studies.

Introduction

Inhaled corticosteroids (ICS) are the most efficacious controller therapy for persistent asthma in all ages. ICS have been shown to modulate the airway inflammation underlying airway hypersensitivity to viral infections, allergens and irritants (1, 2), reduce asthma symptoms (3), and improve lung function and quality of life (3), by reducing the frequency and severity of exacerbations (4), and the risk of hospitalization (5). They may also decrease asthma mortality (6), and possibly attenuate loss of lung function in adults. The combination of an ICS and long-acting beta agonists is commonly prescribed for patients with asthma and is the preferred treatment for patients whose asthma is not controlled by an ICS alone (7, 8).

Although ICS demonstrate a favorable risk profile with minimal serious adverse effects, cataracts (9, 10), and hyperglycemia (11-13), are identified consequences complicating their use. Since the Toward a

Revolution in Chronic Obstructive Pulmonary Disease (COPD) Health (TORCH) trial (14), evidence has suggested that ICS use may be associated with an increased risk of pneumonia in patients with COPD (15-17). In contrast to COPD, several investigations failed to demonstrate an association between ICS use and the development of pneumonia in patients with asthma (18-22). Recently, McKeever et al. suggested an increased risk of pneumonia and lower respiratory tract infections (LRTI) in asthma patients utilizing ICS (23). However, this study lacked systematic and radiographic ascertainment of pneumonia, thus limiting the validity of the conclusions.

Although asthma is an independent risk factor for pneumonia (24-28), it is not clear whether ICS are further independently associated with an increased risk of pneumonia in people with asthma. Due to the conflicting results of prior investigations and their methodological limitations, we systematically reviewed the relevant medical literature and performed a meta-analysis to investigate the association of inhaled corticosteroids on the incidence of pneumonia in patients with asthma.

Methods

The review protocol was written by a senior investigator (E.F.) as a part of the Master's Program at Mayo Clinic Center for Clinical and Translational Science, CTSC 5740: Systematic Reviews and Meta-Analysis (http://www.mayo.edu/ctsa/education/current-courses-in-clinical-and-translational-science-at-mayo-graduate-school/mayo-graduate-school-course-descriptions) and was not publicly registered.

Eligibility criteria

The specific inclusion criteria for this systematic review were: (1) randomized controlled trials with minimum follow up of 4 weeks or an observational study with follow up for duration of hospitalization in participants with asthma, (2) use of any ICS medication alone or in combination with other medication as intervention versus a control group not using ICS, (3) diagnosis of incident pneumonia or lower respiratory tract infection (LRTI), or non-tuberculous mycobacterial pneumonia (NTM). Thus, reviewed studies included in our meta-analysis were RCTs and observational studies comparing the unadjusted risk of incident pneumonia (community acquired, LRTI, NTM) between patients on ICS and not on ICS. The minimal duration of exposure to ICS was not limited. Studies of patients with COPD were not eligible.

Search strategy and study selection

The search strategy was designed and conducted by a head reference librarian at Mayo Clinic, Rochester, MN. Two reviewers (V.B., M.A.M.) independently and in duplicate searched PubMed, Medline, CENTRAL, EMBASE, Scopus, Web of Science and manufacturers' web clinical trial registries (GlaxoSmithKline, AstraZeneca) using multiple search terms with no language restrictions, from January 1, 1993, through August 15, 2015. They screened all titles and abstracts identified by the preliminary library search to accrue potentially eligible studies. Then, the same reviewers independently assessed all selected full-text manuscripts for the eligibility. Disagreements regarding eligibility between 2 reviewers were resolved through consensus and after an input from a third reviewer (E.F.).

Study characteristics and quality assessment

In order to adhere to principles of sound methodological quality, we selected data col-

lection forms for RCTs based on Cochrane Collaboration risk assessment tool. For each study, we ascertained the methods for randomization sequence, allocation concealment, and identified imbalances in baseline patient characteristics, which groups were blinded, study attrition rate, and if the analyses were conducted with intention to treat (ITT). We used terms "low risk" and "high risk" of bias at the study level instead of scoring. For observational studies we adopted Newcastle-Ottawa scales for cohort and case-control studies, as applicable. Quality assessments were done independently and discrepancies were achieved by consensus. At the outcome level, we assessed risk of bias by using GRADE profiler, version 3.6 (GRADE working group).

Outcome measures

Among all studies on ICS use in asthma, those which measured and reported pneumonia (including LRTI and NTM) were analyzed in detail. Pneumonia was reported as a safety or adverse effect in all RCTs; all except one of the observational studies (23) included a more systematic assessment for pneumonia, including radiographic confirmation.

Data extraction

Two reviewers (V.B. M.A.M.) independently reviewed and abstracted data on pneumonia incidence and ICS use for each eligible RCT and observational study of patients with asthma. If there were multiple reports stemming from a single specific study database, data from the study version that provided the most robust information on pneumonia were extracted with other contributing studies included in the bibliography. When specific data was missing, corresponding authors were contacted through email, maximum of two attempts for each author. Of four authors, two replied to the first email and one of these two was able to provide required information, while two others did not respond after two attempts. Reviewers sorted data separately in all stages of study selection, data extraction, and quality assessment. All discrepancies found between 2 reviewers were resolved with consensus and after inputs from other two authors.

Quantitative data synthesis and sensitivity analysis

We analyzed data in Review Manager Software, version 5.2 (Nordic Cochrane Center, Copenhagen, Denmark), to evaluate combined risk ratio (RR) for RCTs and odds ratio (OR) for observational studies (due to inclusion of three case-control studies) with respective 95% confidence intervals (CI) using a random-effects model. All reported *p*-values are 2-sided, with significance set at less than 0.05. The statistical heterogeneity was assessed using the I^2 statistic where values of 50% or more were considered as a substantial level of heterogeneity. Where substantial statistical heterogeneity was present, we explored additionally study characteristics and to determine a potential source of heterogeneity. The subgroup analysis was defined by RCTs versus observational studies. Sensitivity analyses were planned to explore the influences on effect size by: statistical models (fixed vs random effects), individual trials and cohort versus case-control studies.

Results

Initial library search identified 463 potentially relevant citations after removing duplicates in the EndNote (version X4). We excluded 430 articles after the title and abstract reviews. Eleven additional studies were identified through the reviews of web-based pharmaceutical clinical trial registries; of these, 4 were published and 7

were unpublished. There were no disagreements between 2 reviewers at this stage. We then investigated why 7 latter studies were not included in our initial library search results and discovered that their published versions did not contain the specific term "pneumonia", which our search was based on. We subsequently performed full review of 44 studies; of those, 18 studies fulfilled the inclusion criteria for qualitative analysis and 14 of those were estimable and therefore included in 2 quantitative analyses. The flowchart is shown in Figure 1, study characteristics are shown in Tables 1 and 2 and reasons for excluded studies are shown in Table 3.

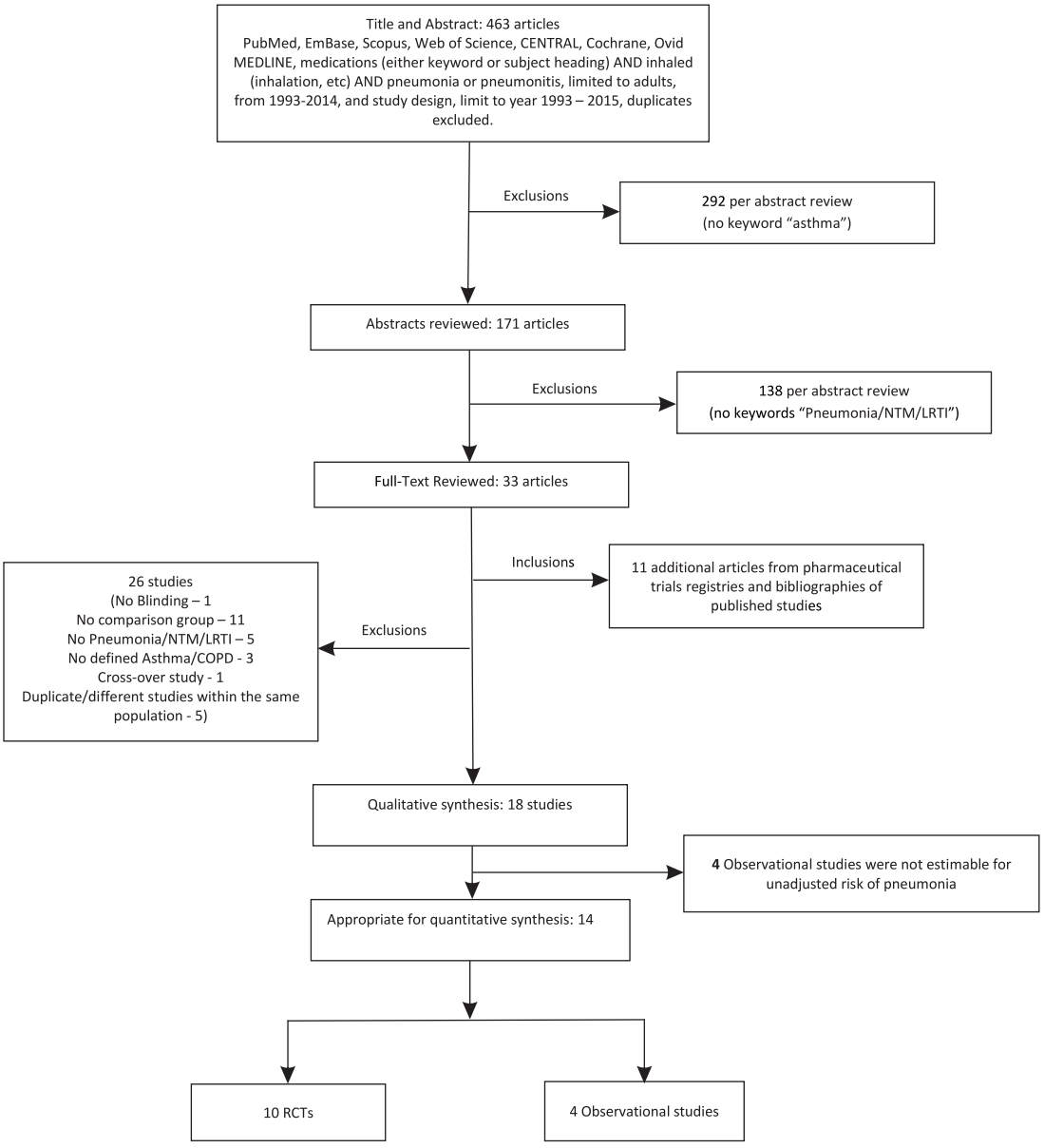

Figure 1 Study flow-chart.

Table 1a Study characteristics for RCTs*

Source	Patients	Setting	Duration†	Interventions	Enrolled/ Analyzed
ADA103575 (29)	Mild to moderate persistent asthma with age 15 years or older	Outpatient	4	Fluticasone/salmeterol 100/50 µg + Fluticasone propionate 200 µg nasal spray+ Placebo capsule	182/140
				Fluticasone/salmeterol 100/50 µg + Placebo spray + Placebo capsule	180/137
				Fluticasone/salmeterol 100/50 µg +Placebo nasal spray + Montelukast 10mg	182/129
				Placebo discus +placebo nasal spray +Montelukast 10 mg	181/138
Corren 2007 (32)	Mild to Moderate persistent asthma with age 12 years or older	Outpatient	12	Budesonide +Formoterol 160/9 µg pMDI	123/105
				Budesonide 160 µg pMDI	121/103
				Formoterol 9 µg DPI	114/79
				Placebo	122/60
FFA115285/ Busse 2014 (37)	Mild to Moderate persistent asthma with age 12 years or older	Outpatient	27	Fluticasone propionate 100 µg	115/95
				Fluticasone furoate 50 µg	117/91
				Placebo	115/77
Maspero 2013 (36)	Mild to moderate persistent asthma in adult patients (women aged 18-40 years, men aged 18-50 years)	Outpatient	52	Mometasone furoate 400 µg DPI	137/103
				Mometasone furoate 200 µg DPI	140/105
				Fluticasone propionate 250µg pMDI	147/109
				Montelukast 10 mg orally	142/111
Noonan 2006 (31)	Moderate-Severe persistent asthma with age 12 years or older	Outpatient	12	Budesonide/Formoterol 320/9 µg pMDI	124/97
				Budesonide 320µg pMDI + Formoterol 9µg DPI	115/86
				Budesonide 320µg pMDI +Placebo DPI	109/78
				Formoterol 9µg DPI + Placebo pMDI	123/60
				Placebo pMDI + Placebo DPI	125/50
Sheffer 2005 (30)	Mild persistent asthma with age 5-66 years	Outpatient	156 (3 years)	Budesonide	3630/2640
				Placebo	3591/2571
Woodcock 2011 (34)	Mild to moderate persistent with age 12 years or older	Outpatient	8	Fluticasone furoate 200 µg OD AM	105/85
				Fluticasone furoate 200 µg OD PM	103/82
				Fluticasone furoate 400 µg OD AM	111/96
				Fluticasone furoate 400 µg OD PM	113/96
				Fluticasone furoate 200 µg BID	113/96
				Placebo	101/65
Busse 2012 (35)	Mild to moderate persistent asthma that was not controlled using medium-dose ICS with age 12 years or older	Outpatient	12	Fluticasone furoate 200 µg OD Diskus/Accuhaler PM	99/81
				Fluticasone furoate 400 µg OD Diskus/Accuhaler PM	101/93
				Fluticasone furoate 600 µg OD Diskus/Accuhaler PM	107/94
				Fluticasone furoate 800 µg OD Diskus/Accuhaler PM	102/85
				Fluticasone propionate 500µg BID Diskus/ Accuhaler + Placebo OD Novel DPI	110/97
				Placebo Novel DPI	103/65
Karpel 2007 (33)	OCS dependent severe persistent asthma for at least 12 mos. with age 12 years or older	Outpatient	13 (3 months of double-blind, placebo controlled treatment phase)	Mometasone furoate MDI 400 µg BID	42/42
				Mometasone furoate MDI 800 µg BID	43/43
				Placebo (22 patient in placebo, 9 in MF-MDI 400 µg, 5 patients in MF-MDI 800 µg discontinued before 3 months due to treatment failure, 1 death in MF-MDI 400 µg before 3 month but analysis done for 123 patients as enrolled)	38/38

*Data on 26 unpublished RCTs from O'Byrne et al. (21) is not included in the table. †Duration in weeks; OCS=Ooral corticosteroids; pMDI=Delivered via metered-dose inhaler; DPI=Delivered via dry powder inhaler; AM=Morning dosing; PM=Evening dosing; OD=Once daily; BID=Twice daily.

Table 1b Quality assessment tables for RCTs*

Study ID	Risk of Bias	Grade†	Support for judgement	Funding
ADA103575 (29)	Random sequence generation (selection bias)	Low risk	Randomization criteria were assigned but not described further	GlaxoSmithKline
	Allocation concealment (selection bias)	Low risk	Allocated blindly	
	Blinding of participants and personnel (performance bias)	Low risk	Double-blind	
	Blinding of outcome assessment (detection bias) regarding pneumonia-related outcome	Low risk	Safety measures included adverse events and asthma exacerbations	
	Incomplete outcome data (attrition bias) regarding pneumonia-related outcome	High risk	Uneven withdrawal rates, no description of imputation to account for dropout	
	Selective reporting (reporting bias)	Low risk	Key expected outcome was reported	
	Systemic ascertainment of pneumonia-related outcome	High risk	Not reported	
Corren 2007 (32)	Random sequence generation (selection bias)	Low risk	By computerized randomization	AstraZeneca
	Allocation concealment (selection bias)	Low risk	Allocated done by computer-generated allocation schedule	
	Blinding of participants and personnel (performance bias)	Low risk	Double-blind (presumed participants and personnel/investigators)	
	Blinding of outcome assessment (detection bias) regarding pneumonia-related outcome	Low risk	All ranges/outcomes were pre specified before study unblinding as part of the statistical analysis plan	
	Incomplete outcome data (attrition bias) regarding pneumonia-related outcome	High risk	Uneven withdrawal rates, no description of imputation to account for dropout	
	Selective reporting (reporting bias)	Low risk	Key expected outcome was reported	
	Systemic ascertainment of pneumonia-related outcome	High risk	Not reported	
FFA115285/ Busse 2014 (37)	Random sequence generation (selection bias)	Low risk	Randomized in accordance with a central randomization schedule	GlaxoSmithKline
	Allocation concealment (selection bias)	Unclear risk	Not reported	
	Blinding of participants and personnel (performance bias)	Low risk	Double-blind	
	Blinding of outcome assessment (detection bias) regarding pneumonia-related outcome	Low risk	Safety endpoints were incidence of adverse events (AEs) and of protocol-defined severe asthma exacerbations during the treatment period	
	Incomplete outcome data (attrition bias) regarding pneumonia-related outcome	High risk	The withdrawal rates were very high compared to the number of events for the different outcomes	
	Selective reporting (reporting bias)	Low risk	Key expected outcome was reported	
	Systemic ascertainment of pneumonia-related outcome	Low risk	Suspected pneumonia was confirmed by X-ray	
Maspero 2013 (36)	Random sequence generation (selection bias)	Low risk	Randomization was centrally administered by using an interactive voice response system	Merck & Co Inc.
	Allocation concealment (selection bias)	Unclear risk	Not reported	
	Blinding of participants and personnel (performance bias)	Low risk	Double-blind	
	Blinding of outcome assessment (detection bias) regarding pneumonia-related outcome	Low risk	Rescue medication use and symptom scores were documented, and the patients were examined at all visits	

Continuation of Table 1b Quality assessment tables for RCTs

Study ID	Risk of Bias	Grade†	Support for judgement	Funding
Maspero 2013 (36)	Incomplete outcome data (attrition bias) regarding pneumonia-related outcome	High risk	The withdrawal rates were very high compared to the number of events for the different outcomes	Merck & Co Inc.
	Selective reporting (reporting bias)	Low risk	Key expected outcome was reported	
	Systemic ascertainment of pneumonia-related outcome	High risk	Not reported	
Noonan 2006 (31)	Random sequence generation (selection bias)	Low risk	Randomization was performed using a computer generated allocation schedule and stratified by asthma severity, based on the daily dose of ICS before entering the study	AstraZeneca
	Allocation concealment (selection bias)	Low risk	Computer generated allocation	
	Blinding of participants and personnel (performance bias)	Low risk	Double-blind	
	Blinding of outcome assessment (detection bias) regarding pneumonia-related outcome	Low risk	Safety was evaluated based on adverse events, laboratory evaluations, vital signs, ECGs, 24-hour Holter monitoring and physical examinations	
	Incomplete outcome data (attrition bias) regarding pneumonia-related outcome	High risk	The withdrawal rates were very high compared to the number of events for the different outcomes	
	Selective reporting (reporting bias)	Low risk	Key expected outcome was reported	
	Systemic ascertainment of pneumonia-related outcome	High risk	Not reported	
Sheffer 2005 (30)	Random sequence generation (selection bias)	Low risk	Randomization was stratified into two strata according to age; age less than 11 years or age at least 11 years Within each stratum, patients were randomized in blocks of ten, five in each treatment group	AstraZeneca
	Allocation concealment (selection bias)	Low risk	Randomly allocated	
	Blinding of participants and personnel (performance bias)	Low risk	Double-blind	
	Blinding of outcome assessment (detection bias) regarding pneumonia-related outcome	Unclear risk	Safety outcomes of the START clinical study included all AEs and asthma-related events from spontaneous reporting and patient's responses to standard questioning during the 3-year study period (6 and 12 weeks after randomization and then every 3 months up to 3 years)	
	Incomplete outcome data (attrition bias) regarding pneumonia-related outcome	High risk	The withdrawal rates were very high compared to the number of events for the different outcomes	
	Selective reporting (reporting bias)	Low risk	Key expected outcome was reported	
	Systemic ascertainment of pneumonia-related outcome	High risk	Not reported	
Woodcock 2011 (34)	Random sequence generation (selection bias)	Low risk	The central randomization schedule was generated by the sponsor using a validated computerized system	GlaxoSmithKline
	Allocation concealment (selection bias)	Low risk	Allocated randomly by using Registration and Medication Ordering System (RAMOS), an automated, interactive telephone based system	
	Blinding of participants and personnel (performance bias)	Low risk	Double-blind	

Continuation of Table 1b Quality assessment tables for RCTs

Study ID	Risk of Bias	Grade†	Support for judgement	Funding
Woodcock 2011 (34)	Blinding of outcome assessment (detection bias) regarding pneumonia-related outcome	Low risk	The following safety endpoints were evaluated: incidence of adverse events (AEs) and serious AEs (SAEs), vital signs, hematology, clinical chemistry, and urinalysis parameters, oropharyngeal examinations, and withdrawals due to worsening asthma. AEs/SAEs were coded using the Medical Dictionary for Regulatory Activities	GlaxoSmithKline
	Incomplete outcome data (attrition bias) regarding pneumonia-related outcome	High risk	The withdrawal rates were very high compared to the number of events for the different outcomes	
	Selective reporting (reporting bias)	Unclear risk	Authors used upper respiratory tract infection and respiratory tract infection separately in AE. We presumed RTI was LRTI	
	Systemic ascertainment of pneumonia-related outcome	High risk	Not reported	
Busse 2012 (35)	Random sequence generation (selection bias)	Low risk	The central randomization schedule was generated by the sponsor using a validated computerized system	GlaxoSmithKline
	Allocation concealment (selection bias)	Low risk	Allocated randomly by using Registration and Medication Ordering System (RAMOS), an automated, interactive telephone based system	
	Blinding of participants and personnel (performance bias)	Low risk	Double-blind	
	Blinding of outcome assessment (detection bias) regarding pneumonia-related outcome	Low risk	Adverse events (defined using the Medical Dictionary for Regulatory Activities V.11) were documented during the 8-week treatment period	
	Incomplete outcome data (attrition bias) regarding pneumonia-related outcome	High risk	The withdrawal rates were very high compared to the number of events for the different outcomes	
	Selective reporting (reporting bias)	Low risk	Key expected outcome was reported	
	Systemic ascertainment of pneumonia-related outcome	High risk	Not reported	
Karpel 2007 (33)	Random sequence generation (selection bias)	Low risk	Randomization criteria were assigned but not described further	No source of funding/support mentioned in article
	Allocation concealment (selection bias)	Unclear risk	Not reported	
	Blinding of participants and personnel (performance bias)	Low risk	Double-blind	
	Blinding of outcome assessment (detection bias) regarding pneumonia-related outcome	Low risk	All patients were monitored for adverse events and changes in physical findings, vital signs, hematological and blood chemistry profiles, and electrocardiographic profiles	
	Incomplete outcome data (attrition bias) regarding pneumonia-related outcome	High risk	The withdrawal rates were very high compared to the number of events for the different outcomes	
	Selective reporting (reporting bias)	Low risk	Key expected outcome was reported	
	Systemic ascertainment of pneumonia-related outcome	High risk	Not reported	

*Data on 26 unpublished RCTs from O'Byrne et al. (21) is not included in the table; †Graded by authors; LRTI=Lower respiratory tract infection; NTM= Nontuberculous pulmonary mycobacteriosis / non-tuberculous mycobacterial pneumonia.

Table 2a Study characteristics for observational studies

Source	Type of study	Patients	Setting	Duration	Interventions	Subjects (n)	Risk of bias	
Almirall 2010 (20)	Case control study	Diagnosis of community-acquired pneumonia patient with three chronic respiratory diseases that require inhaled therapy were included: chronic bronchitis, COPD and asthma with age 14 years or older	Outpatient	1 year (1999-2000)	Asthma ICS	30	Selection	Low
					Asthma Non-ICS	344	Indication	High
Andrejak 2013 (41)	Population based case-control study	Adult patient (age 15 years or older) with microbiologically confirmed NTM pulmonary disease with any chronic respiratory diseases	Outpatient	12 years (1997-2008)	Asthma ICS	30	Selection	Low
					Asthma Non-ICS	3	Indication	High
Festic 2014 (22)	Cohort study	Adult patients hospitalized with at least 1 major risk factor for acute respiratory distress syndrome	Inpatient	Hospitalization Mar. 2009-Aug. 2009	Asthma ICS	149	Selection	Low
					Asthma Non-ICS	291	Indication	High
Mckeever 2013 (23)	Nested Case control study	Adult asthma patients (age 18 to 80) with pneumonia or lower respiratory tract infection	Outpatient	3 years (2004-2007)	Asthma ICS	15594	Selection	High
					Asthma Non-ICS	27575	Indication	High
To M 2004 (19)	Retrospective cohort study	Asthma patients who required hospitalization for community-acquired pneumonia with age 16 year or older	Inpatient	Hospitalization 13 years (1989-2001)	Asthma ICS	37	Selection	Low
					Asthma Non-ICS	25	Indication	High
Ferrer 2014 (42)	Prospective observational cohort study	Patients aged ≥16 years hospitalized with a diagnosis of CAP	Inpatient	Hospitalization Jan. 2003-Oct. 2005	Asthma ICS	12	Selection	Low
					Asthma Non-ICS	28	Indication	High
Sellares 2013 (40)	Prospective observational cohort study	Patients admitted to the emergency room with a diagnosis of CAP with age 16 year or older	Inpatient	Hospitalization Jan. 1997-Jul. 2008	Asthma ICS	81	Selection	Low
					Asthma Non-ICS	72	Indication	High
Terraneo 2014 (43)	Prospective observational cohort study	Adult patients hospitalized with CAP	Inpatient	Hospitalization in Jan. 2000-Dec. 2011	Asthma ICS	72	Selection	Low
					Asthma Non-ICS	67	Indication	High

COPD=Chronic obstructive pulmonary disease; ICS=Inhaled corticosteroids; CAP=Community-acquired pneumonia.

Table 2b Quality assessment tables for observational studies

Case Control studies

Study	Selection	Comparability	Exposure
Almirall 2010	3/5	1/2	4/4
Andrejak 2013	3/5	1/2	3/4
Mckeever 2013	3/5	1/2	3/4

Note: Points assessed in lieu of actual over possible stars per Quality Assessment Scale used (Supplementary material).

Cohort studies

Study	Selection	Comparability	Outcome
Ferrer 2014	3/5	2/2	3/3
Festic 2014	5/5	2/2	3/3
Sellares 2013	3/5	2/2	3/3
Terraneo 2014	3/5	2/2	3/3
To m 2004	3/5	2/2	3/3

Note: Points assessed in lieu of actual over possible stars per Quality Assessment Scale used (Supplementary material).

Table 3 Excluded studies

Study ID	Reason for exclusion
D589IL00001/NCT01232348	No blinding, no control group
Beasley 2015	No control group
D5890L00008/NCT00242411	No control group
D5890L00009/NCT00290264	No control group
Hojo 2012	No control group
Lin 2015	No control group
Lukaszyk 2011	No control group
Lukaszyk 2011-2	No control group
SAM 106538/NCT00363480	No control group
Peters SP 2010	No control group
Teichert 2014	No control group
Woodcock 2014	No control group
Corren 2013	No pneumonia reported
HZA106827/ NCT01165138/ Bleecker 2014	No pneumonia reported
Nathan 2012	No pneumonia reported
Pearlman 2013	No pneumonia reported
Price 2013	No pneumonia reported
Cheng 2013	Cross-over design
Almirall 2008	Duplicate publication, same study population as in Almirall 2010
Almirall 2013	Duplicate publication, same study population as in Almirall 2010
D5254C00111/NCT00641914/O'Byrne 2009	Duplicate publication, same study population as in Sheffer 2005
NCT01232335	Duplicate publication, same study population as in D589IL00001/NCT01232348
Pauwels 2003	Duplicate publication, same study population as in Sheffer 2005
Almirall 1999	No distinction between Asthma versus COPD cases
Eurich 2013	No distinction between Asthma versus COPD cases
Farr 2000	No distinction between Asthma versus COPD cases

Randomized controlled trials

There were 9 RCTs (29-37) and one additional study (21) that reported results of 26 unpublished pharmaceutical trials on different formulations of budesonide compared to placebo. Together, these studies included 19,098 patients, of whom 12,008 received ICS and 7,090 did not. The duration of trials ranged from 4 weeks to 3 years, with median duration of 12 weeks. All published RCTs were deemed high quality studies based on the sequence generation, allocation concealment and double-blinding (Table 1b). At the outcome-level, RCTs were judged to be at high risk of bias because ascertainment of pneumonia was not performed systematically (Table 4). However, this bias would be non-differential as in blinded RCTs it would then similarly affect both intervention and control groups.

Table 4 Outcome-level quality assessment and summary of findings (GRADE)

Pneumonia with ICS versus non-ICS											
Quality assessment							Summary of findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Non-ICS	ICS		Non-ICS	Risk with ICS (95% CI)
RCT											
19,098 (10 studies)	High[1]	No serious inconsistency	No serious indirectness	No serious imprecision[2]	Undetected	⨁⨁⨁⊖ Moderate[1,2] due to risk of bias	128/ 7,090 (1.8%)	116/ 12,008 (1%)	RR 0.74 (0.57 to 0.95)	Study population	
										18 per 1000	5 fewer per 1000 (from 1 fewer to 8 fewer)
										Moderate	
										3 per 1000	1 fewer per 1000 (from 0 fewer to 1 fewer)
Observational											
44,016 (4 studies)	Very high[3,4,5]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⨁⊖⊖⊖ Very low[3,4,5] due to risk of bias	3,733/ 28,213 (13.3%)	3,517/ 15,803 (22.3%)	OR 1.97 (1.87 to 2.07)	Study population	
										133 per 1000	99 more per 1000 (from 90 more to 108 more)
										Moderate	
										333 per 1000	163 more per 1000 (from 150 more to 175 more)

[1]Limited pneumonia ascertainment; [2]Although several trials had wide confidence intervals, these represented less than 5% of the weight; [3]Case control and historical cohort designs; [4]Unaccounted step up in ICS therapy due to persistent respiratory symptoms preceding the diagnosis of pneumonia; [5]One study carried 98% of overall weight.

The estimated overall unadjusted risk of pneumonia with the use of ICS in RCTs, was in protective range; RR 0.74, 95% CI 0.57 to 0.95, p=0.02, without any heterogeneity (Figure 2). As the details on 26 unpublished RCTs reported in the single study by O'Byrne et al. (21) were not available, we performed a sensitivity analysis. When we excluded results of O'Byrne study (21), the confidence interval extended to 1 (95% CI

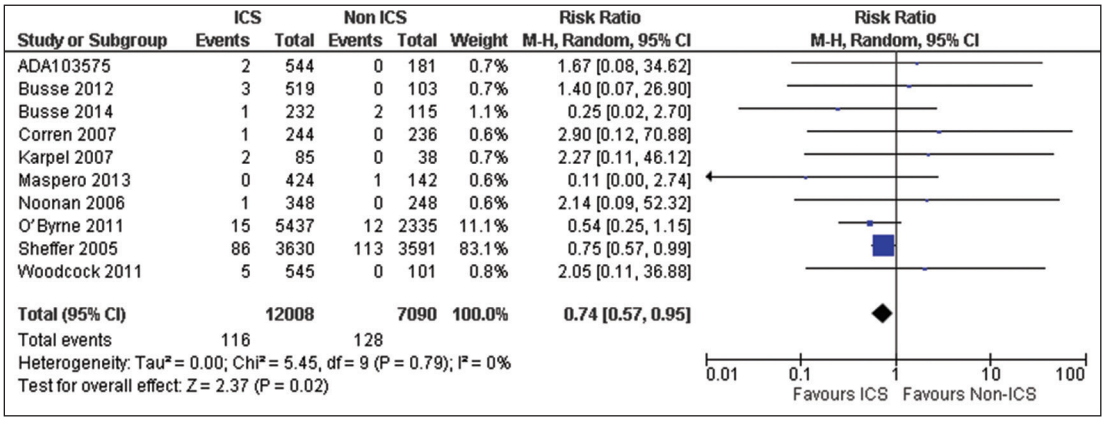

Figure 2 Meta-analysis of RCTs for incident pneumonia.

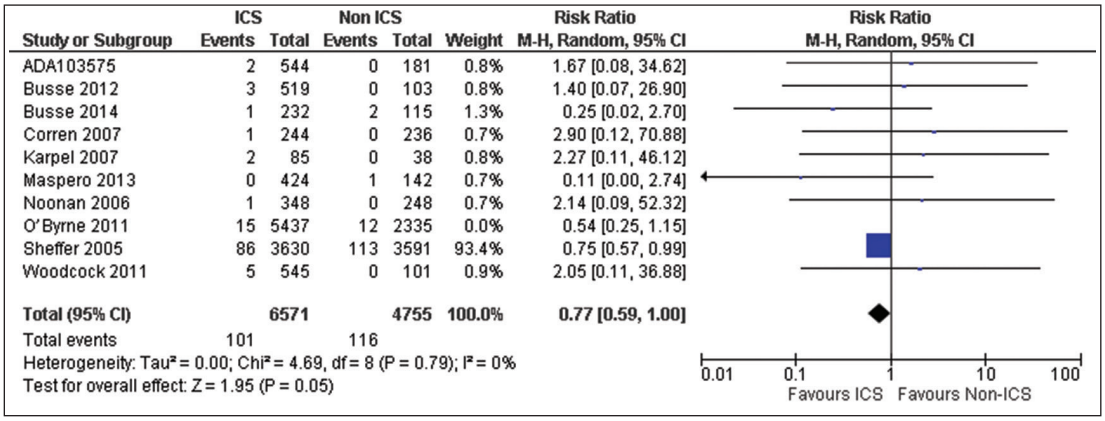

Figure 3 Sensitivity analyses of RCT data - A) Without O'Byrne 2011 study data.

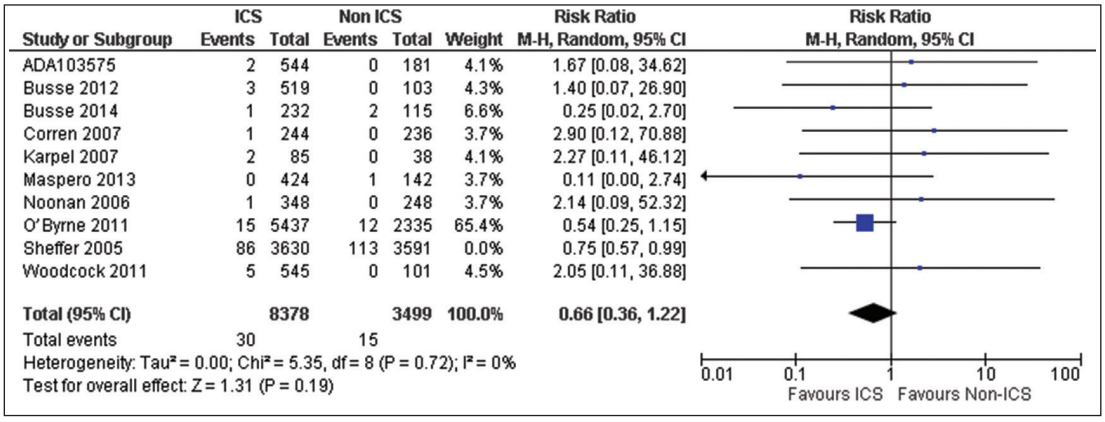

Figure 3 Sensitivity analyses of RCT data - B) Without Sheffer 2005 study data.

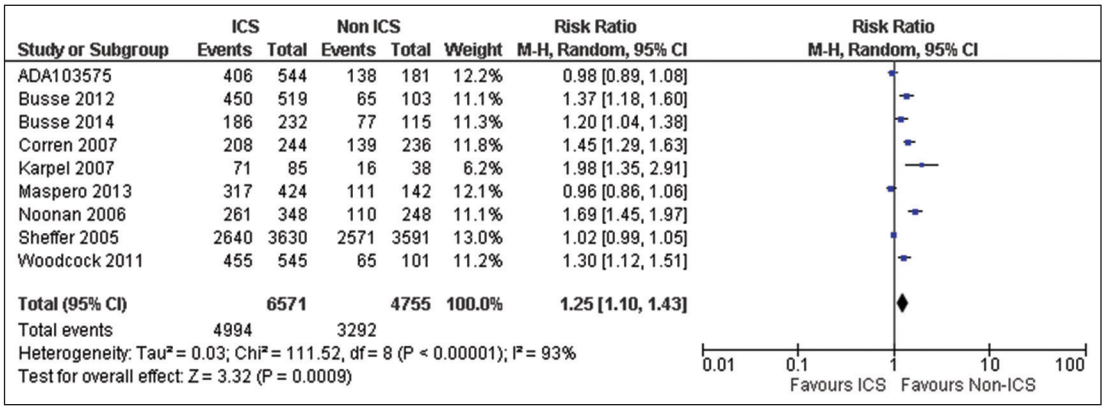

Figure 4 Study completion rates comparing ICS and non-ICS groups.

0.59-to 1, p=0.05) (Figure 3A). As a result, the weight of study by Sheffer et al. (30) in the meta-analysis consequently increased from 83.1% to 93.4%. This study was one of the three published START trial reports (30, 38, 39). Once the study by Sheffer et al. was removed because of the overly dominant weight, in a subsequent sensitivity analysis the pre-hospital use of ICS in asthma patients did not show significant protective effect for pneumonia any longer (RR 0.66, 95% CI 0.36 to 1.22, p=0.19) possibly due to loss of power, as 80% of pneumonia cases were consequently excluded from the analysis (Figure 3B).

We also assessed the study completion rates between the ICS and non-ICS groups in the RCTs. Eight RCTs were estimable and the trial completion rate was higher in the non-ICS than in the ICS group; RR 1.25; 95% CI 1.10to 1.43, p=<0.001; I^2=93% (Figure 4). Only 2 RCTs reported occurrence of deaths; there were total of 13 deaths, 5 in ICS and 8 in non-ICS group, respectively (30, 33).

Observational studies

We initially included 8 observational studies (19, 20, 22, 23, 40-43). Five cohort studies (19, 22, 40, 42, 43) excluded patients on systemic corticosteroids and three case-control studies (20, 23, 41) adjusted for systemic corticosteroid use. Two studies assessed risk of outpatient pneumonia (20, 23), five assessed pneumonias requiring admission to the hospital (19, 22, 40, 42, 43), and one study (41) assessed risk of non-tuberculous mycobacteriosis by using NTM index rate. Although ascertainment of pneumonia in observational studies was more systematic by using not only clinical diagnosis but radiographic assessment as well, all observational studies were judged to be at very high risk of bias (Tables 2 and 4). Four observational studies were not estimable for unadjusted risk of pneumonia as they included only patients with pneumonia so the unadjusted differential risk of ICS could not be estimated. The remaining 4 estimable studies included 44,016 patients, of whom 15,803 were on ICS and 28,213 were not on ICS. The risk of incident pneumonia was found to be increased; OR 1.97; 95% CI 1.87to 2.07, p<0.0001, with no observed heterogeneity (Figure 5). Three studies were case-control studies and one was secondary analysis of a large cohort (Table 2). Of note, recently published study by McKeever et al. (23) carried almost complete weight (98%) in this meta-analysis. Once this study was excluded in a sensitivity analysis (Figure 6), the estimated effect decreased appreciably to OR 1.57; 95% CI 1.09 to 2.25). Exclusion of a single study that assessed risk of NTM (41) did not change the results significantly.

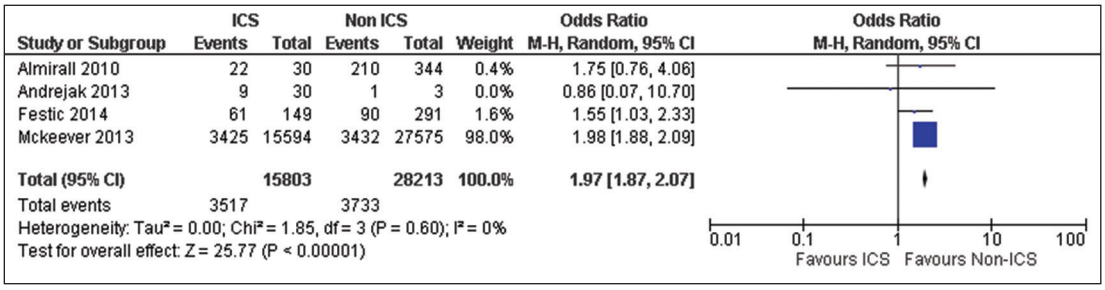

Figure 5 Meta-analysis of observational studies for incident pneumonia.

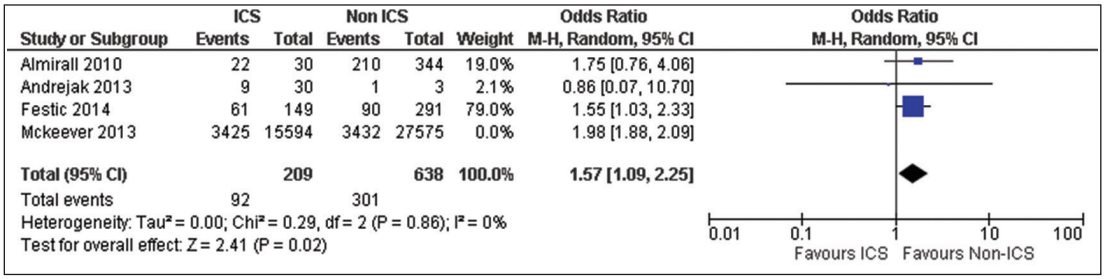

Figure 6 Sensitivity analysis for observational studies.

Mortality was reported only in two observational studies (20, 43); 2 in ICS and 6 in non-ICS group. The observed low mortality rates in both RCTs and observational studies precluded performance of pooled analysis.

Discussion

Based on available RCTs, this meta-analysis suggests that ICS are associated with decreased risk of incident pneumonia in asthma patients for the duration of respective clinical trials. Although observational studies suggested increased risk of incident pneumonia in similar patients using ICS, the inherent methodological limitations and higher risk of bias conferred lower grade of confidence in the findings of the observational studies. To our knowledge, this is the first systematic review and meta-analysis of all available RCTs and observational studies assessing the association between ICS use and risk of incident pneumonia in asthma patients.

There has been a clinical controversy regarding the risk of pneumonia in patients on ICS with COPD and asthma. Since the TORCH study reported increased incidence of pneumonia among COPD patients in 2007 (14), several well-designed trials and meta-analyses demonstrated the similar risk (44-49). However, the risk for developing community acquired pneumonia among asthma patients on ICS did not appear to be substantially increased (18-22).

Our meta-analysis of RCTs suggests that ICS are associated with decreased risk of incident pneumonia in asthmatic patients. There was no heterogeneity and there was overall less risk of bias compared to observational studies. It is uncertain why the use of ICS may be associated with an increased risk of incident pneumonia in patients with COPD but not asthma. It has been hypothesized that ICS more efficiently reduce airway inflammation, segmental atelectasis, mucoid impaction, and thus, subsequent pneumonia in patients with asthma compared with those with COPD (50). Additionally, patients with COPD are commonly of older age and have a greater burden of comorbid diseases than asthmatics, which are recognized risk fac-

tors for pneumonia. Thus, higher observed pneumonia rates in COPD patients compared to patients with asthma may be partly explained by difference in age and comorbidities. Importantly, two RCTs (29, 34) in asthma patients were shorter than 12 weeks, while the shortest clinical trials in COPD patients were 24-week long. It is conceivable that any proposed medication adverse effect could become more apparent in the studies of longer duration. Moreover, we observed higher study completion rate among non-ICS patients compared to ICS patients in eight estimable RCTs in asthma patients, however with very high heterogeneity.

We believe that it is safer to conclude that the incident risk of pneumonia with the ICS use in RCTs of asthma patients was not increased, rather than it was decreased. Although the primary meta-analysis of RCTs suggested that ICS might carry protective effect, once we excluded the trial by Sheffer et al. (30) in a sensitivity analysis, the protective effect was not statistically significant any longer. A possible explanation for the "overinflated" protective effect observed in this particular study could have been incorrect allocation of respiratory events known to be improved by ICS as pneumonia adverse events. These events could have been: segmental atelectasis due to mucous impaction that is more often seen in children with poorly controlled asthma; increased cough and mucous production; or mild asthma exacerbations. This interpretation is supported by the fact that the most frequent reporting of pneumonia adverse events was in children aged 5 to 11 years, in whom atelectasis is more frequently seen as a consequence of asthma exacerbation than in adult patients (21). Since ICS effectively improve flow limitation in asthma patients, the patients on ICS could have had less incorrectly allocated respiratory events as pneumonia. Moreover, study by Sheffer et al. included only preparations of budesonide, which has been shown previously to have more rapid clearance from the airways and to be less potent than fluticasone (51, 52). However, this is only speculative and would require future well designed prospective studies with a strict definition for pneumonia to fully resolve.

On the contrary, the pooling of observational studies suggested higher risk of pneumonia in patients with asthma. A single study by McKeever et al. carried almost complete weight in this meta-analysis (23). This recently published case-control study showed that asthma patients admitted with pneumonia were more likely to have prescription for ICS than the control subjects in the preceding 90 days; they were also more likely to use reliever inhalers and oral steroids in the previous year. The investigators used clinical diagnosis of pneumonia and did not necessarily base it on the findings on chest radiographs. Therefore, we propose that a substantial number of patients who were retrospectively included in this study (and other similar observational studies) may have had unrecognized pneumonia leading to persistent respiratory symptoms prompting increased asthma therapy containing ICS. The authors recognize this limitation of their study (23) and concluded that the prescribers should consider possibility of incipient infection rather than underlying asthma being responsible for the worsening respiratory symptoms before prescribing or increasing ICS dose. The similar was also previously demonstrated in a study on COPD patients by Calverley et al. (47). The data interpretation from this study's daily record cards suggested identical numbers of de novo pneumonias in both ICS and non-ICS arms, but more unresolved exacerbations preceding pneumonia events in the ICS-treated COPD patients. Finally, it is possible that some patients with concomitant COPD were included in the observational studies of asthma patients, which was likely not the case in RCTs.

Although the overall pneumonia ascertainment was more systematic in most of the observational studies compared to RCTs, the resulting overall grade of confidence was lower for observational studies compared to the randomized trials due to very high risk of bias (mainly indication and selection bias) (Table 4). Of note, using GRADE profiler for outcome-level quality assessment may be associated with the rater-dependent subjectivity. After cautiously analyzing and weighing all available pertinent factors, we proposed "moderate" and "very low" quality grades for analyzed RCTs and observational studies, respectively. The limitation of RCTs lacking systematic ascertainment of pneumonia would be an example of non-differential bias; therefore we labeled this as "high" rather than "very high" risk of bias. However, even if RCTs were downgraded to "low" quality given concerns with pneumonia ascertainment, the overall resulting grades of confidence would still favor RCTs rather than observational studies on the topic, which were not necessarily population-based observational studies.

Our meta-analysis has several limitations, some of which are attributable to methodological shortcomings in the studies included. We were somewhat surprised with the relatively small number of studies retrieved by our search. The reason for this could be that either study investigators did not systematically measure incident pneumonia events (including radiographic assessment), or less likely they did not report those in their publications. Therefore, our review is prone to the reporting bias as we depended solely on the reporting of outcomes. There is also publication bias risk as all RCT were pharmaceutical industry-funded. However, we reviewed the clinical trials registry and included both published and unpublished studies. The resulting funnel plot of RCTs did not suggest publication bias (Supplemental material). Although the risk of pneumonia was unadjusted, the large number of patients included in the meta-analysis partially alleviated this concern. We did not have individual-patient data, so we could not detect any differences in pneumonia based on demographics, asthma severity or presence of comorbidities. The time of follow-up in included studies differed widely, which may have also impacted results. We considered all patients on ICS as ICS users regardless of ICS being used alone or in combination with another medication. Also, non-ICS users were considered all patients not on ICS regardless of use of additional medications, such as long-acting beta agonists or placebo. This is justified by our stated main intention of assessment for the overall association of ICS and pneumonia. Only future prospective trials of ICS designed to systematically assess and monitor pneumonia as a pre-specified outcome using an objective pneumonia definition could alleviate the above-mentioned limitations.

Conclusion

Results from our meta-analysis on available RCTs suggest that ICS use in patients with asthma was associated with decreased risk of pneumonia. On the contrary, a meta-analysis of observational studies suggested a higher risk of pneumonia in similar patients; however, the grade of confidence in this subgroup's results is lower due to inherent methodological limitations. The design of future prospective trials of ICS should include systematic assessment and monitoring of pneumonia as a pre-specified outcome.

What is already known on this subject

Inhaled corticosteroids are the mainstay of asthma treatment for all ages. Their use has been previously associated with increased risk of pneumonia among COPD patients. It is uncertain if there is an association between long-term use of inhaled corticosteroids and the incident pneumonia among asthmatic patients.

What this study adds

This is the first systematic review on use of inhaled corticosteroids and incident pneumonia in asthmatic patients. It includes randomized clinical trials as well as observational studies, which were pooled in the two separate meta-analyses. While randomized clinical trials showed decreased risk of incident pneumonia, this risk was increased in observational studies, which were at higher risk of bias and conferred lower grade of confidence.

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Authors' contributions: Conception and design: EF, VB, MAM and MMJ; Acquisition analysis and interpretation of data: EF, VB, MAM and MMJ; Drafting the article: EF, VB, MAM and MMJ; Revising it critically for important intellectual content: EF, VB, MAM and MMJ.

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Supplementary material

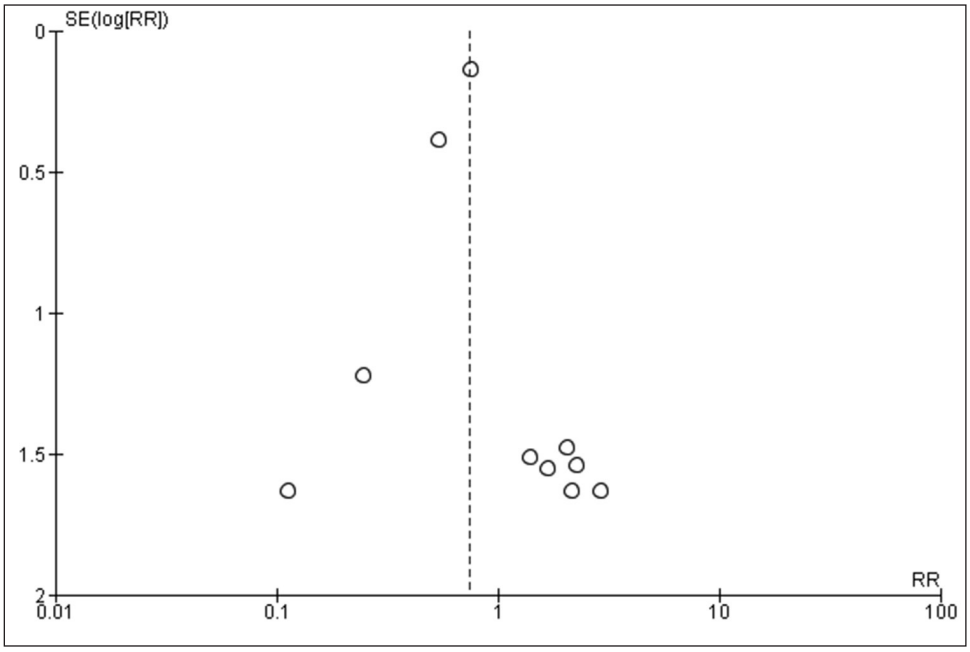

Figure S1 Funnel plot of RCTs suggesting no significant publication bias.

Search strategy (complete copied electronic search sequence)

((corticosteroid* OR beclomethasone OR triamcinolone* OR flunisolide OR budesonide OR fluticasone OR mometasone OR ciclesonide) AND (inhal* OR bronchodilat*) AND pneumoni* AND (los OR hospitali* OR ventilat* OR "length of stay")) NOT MEDLINE[sb] PubMed 15 August 2015 = 17

Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to Present			
	Searches	Results	Search Type
1	(beclomethasone or triamcinolone* or flunisolide or budesonide or fluticasone or mometasone or ciclesonide).mp.	21486	Advanced
2	exp glucocorticoids/ or 1	174737	Advanced
3	exp pneumonia/ or pneumoni*.mp.	177636	Advanced
4	2 and 3	3240	Advanced
5	(inhal* or ics).mp. or administration, inhalation/	139726	Advanced
6	4 and 5	308	Advanced
7	limit 6 to ("young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")	134	Advanced
8	6 and adult*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	77	Advanced
9	7 or 8	145	Advanced
10	limit 9 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or observational study or randomized controlled trial)	56	Advanced
11	9 and ("case adj control*" or observational* or cohort* or retrospective* or prospective*).mp.	30	Advanced
12	10 or 11	72	Advanced
13	limit 12 to yr="1993 - 2015"	65	

Manually excluded studies on COPD patients; Central=48, same strategy 1993-2015; Embase 1988 to 2015.

#	Searches	Results	Search Type
1	(beclomethasone or triamcinolone* or flunisolide or budesonide or fluticasone or mometasone or ciclesonide).mp.	46276	Advanced
2	exp pneumonia/ or pneumoni*.mp.	262692	Advanced
3	exp asthma/ or asthma*.mp. or copd.mp. or "chronic obstructive".mp. or pulmonary disease, chronic obstructive/	264244	Advanced
4	exp glucocorticoid/ih	9549	Advanced
5	(1 and inhal*.mp.) or 4 [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	16826	Advanced
6	2 and 3 and 5	830	Advanced
7	limit 6 to (adult <18 to 64 years> or aged <65+ years>)	235	Advanced
8	exp case control study/ or exp case study/ or exp clinical trial/ or exp "clinical trial (topic)"/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/	3160131	Advanced
9	7 and 8	138	Advanced
10	7 and (cohort* or observation*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	25	Advanced
11	9 or 10	143	Advanced
12	remove duplicates from 11	140	Advanced
13	limit 12 to yr="1993-2015"	140	

Manually excluded studies on COPD patients

Web of Science

TS=(beclomethasone OR triamcinolone* OR flunisolide OR budesonide OR fluticasone OR mometasone OR ciclesonide OR (inhal* OR ics) SAME (corticosteroid* OR steroid OR glucocorticoid*)) AND TS=(trial* OR random* OR cohort* OR prospective* OR retrospective* OR observation* OR "case control*" OR study OR studies) AND TS=(asthma* OR copd OR "chronic obstructive" OR pneumoni*) NOT TI=(child* OR baby OR babies OR infant* OR newborn OR neonat* OR child* OR pediatr* OR paediatr* OR adolescen* OR teen*) 292

1993-2015

Scopus

TITLE-ABS-KEY ((beclomethasone OR triamcinolone* OR flunisolide OR budesonide OR fluticasone OR mometasone OR ciclesonide OR (inhal* W/5 (corticosteroid* OR ics OR steroid* OR glucocorticoid*)))) AND TITLE-ABS-KEY ((trial* OR random* OR cohort* OR prospective* OR retrospective* OR observation*) AND (asthma* OR copd OR "chronic obstructive") AND pneumoni*) AND NOT TITLE-ABS-KEY ((child* OR baby OR babies OR infant* OR newborn OR neonat* OR child* OR pediatr* OR paediatr* OR adolescen* OR teen*)) AND PUBYEAR > 1992 483

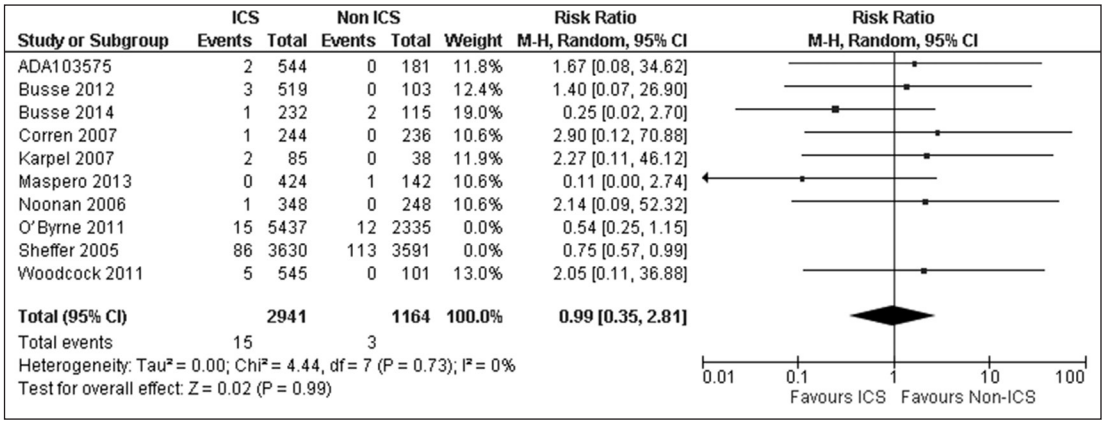

Figure S2 Sensitivity analysis for RCTs: Without Sheffer 2005 and O'Byrne 2011 studies data.

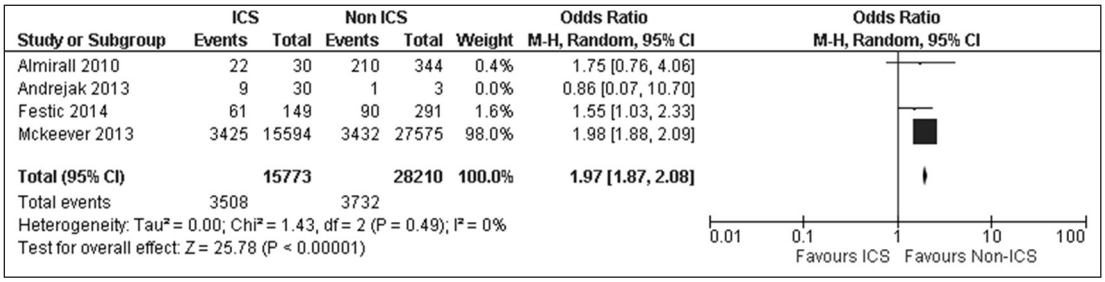

Figure S3 Sensitivity analyses for observational studies: Without Andrejak 2013 (NTM) study data.

Quality assessment scale for cohort studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
   A. Truly representative of patients with asthma on ICS in the community ⁎
   B. Somewhat representative of patients with asthma on ICS in the community⁎
   C. Selected group of participants
   D. No description of the derivation of the cohort
2) Selection of the non-exposed cohort
   A. Drawn from the same community as the exposed cohort ⁎
   B. Drawn from a different source
   C. No description of the derivation of the non-exposed cohort
3) Ascertainment of exposure (ICS)
   A. Prescription, medical records ⁎
   B. Self-report
   C. No description
4) Demonstration that outcome of interest (pneumonia) was not present at start of study
   A. Yes ⁎
   B. No

Comparability

5) Comparability of cohorts on the basis of the design or analysis: (a maximum of 2 stars can be allotted)
   A. Adjusted analysis (age = ⁎, other adjustments also = ⁎, i.e. Demographics, comorbidities, medications etc.)
   B. Unadjusted

Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

Outcome

6) Assessment of outcome (pneumonia)
   A. Radiographic plus clinical diagnosis⁻ ⁎
   B. Clinical diagnosis only ⁎
   C. No description

   Assessment of outcome (pneumonia-related mortality, deaths in those with pneumonia)
   A. Reported ⁎
   B. Not clear

   Assessment of outcome (overall mortality, all deaths)
   A. Reported ⁎
   B. Not clear
7) Was follow-up long enough for outcomes to occur
   A. Yes (≥ 30 days or hospitalization for pneumonia) ⁎
   B. No
8) Adequacy of follow up of cohorts:
   A. Adequate follow up: >90% of subjects accounted for ⁎
   B. Acceptable follow up: >50% of subjects accounted for and unlikely to introduce bias or described ⁎

C. Follow up rate at the end of the study was < 50% and no description of those lost
D. No description

Quality assessment scale for case-control studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection
1) Is the case definition adequate (pneumonia)?
   A. Clinical diagnosis ⁎
   B. No reference
2) Representativeness of the cases
   A. All eligible cases over a defined period of time/catchment area ⁎
   B. Appropriate sample of cases (random sample)
   C. Not stated
3) Selection of controls
   A. Same population as above (same community) ⁎
   B. Hospital controls
   C. No description
4) Definition of Controls
   A. No current (recent) ICS use ⁎
   B. Not stated

Comparability
5) Comparability of cases and controls on the basis of the design or analysis
   A. Study controls for age = ⁎
   B. Study controls for other factors = ⁎, i.e. severity, comorbidities, etc.)

Exposure
6) Ascertainment of exposure (ICS)
   A. Secure record (prescription, medical chart etc.)¯ ⁎
   B. No description or not as above
7) Same method of ascertainment for cases and controls
   A. Yes ⁎
   B. No
8) Non-Response rate
   A. Same no consent rate (refusal) for both/all groups ⁎
   B. Different no consent (refusal) rate non respondents described

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