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[Intervention Review]

Combined corticosteroid and long-acting beta$_2$-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease

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ABSTRACT

Background

Both long-acting beta$_2$-agonists and inhaled corticosteroids have been recommended in guidelines for the treatment of chronic obstructive pulmonary disease (COPD). Their co-administration in a combined inhaler is intended to facilitate adherence to medication regimens and to improve efficacy. Three preparations are currently available: fluticasone propionate/salmeterol (FPS). budesonide/formoterol (BDF) and mometasone furoate/formoterol (MF/F).

Objectives

To assess the efficacy and safety of combined long-acting beta$_2$-agonist and inhaled corticosteroid (LABA/ICS) preparations, as measured by clinical endpoints and pulmonary function testing, compared with inhaled corticosteroids (ICS) alone, in the treatment of adults with chronic obstructive pulmonary disease (COPD).

Search methods

We searched the Cochrane Airways Group Specialised Register of trials, which is compiled from systematic searches of multiple literature databases. The search was conducted in June 2013. In addition, we checked the reference lists of included studies and contacted the relevant manufacturers.

Selection criteria

Studies were included if they were randomised and double-blind. Compared studies combined LABA/ICS with the ICS component.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. The primary outcomes were exacerbations, mortality and pneumonia. Health-related quality of life (as measured by validated scales), lung function and side effects were secondary outcomes. Dichotomous data were analysed as fixed-effect odds ratios with 95% confidence intervals (CIs), and continuous data as mean differences or rate ratios and 95% CIs.

Main results

A total of 15 studies of good methodological quality met the inclusion criteria by randomly assigning 7814 participants with predominantly poorly reversible, severe COPD. Data were most plentiful for the FPS combination. Exacerbation rates were significantly reduced with combination therapies (rate ratio 0.87, 95% CI 0.80 to 0.94, 6 studies, N = 5601) compared with ICS alone. The mean exacerbation rate in the control (ICS) arms of the six included studies was 1.21 exacerbations per participant per year (range 0.88 to 1.60), and we would expect this to be reduced to a rate of 1.05 (95% CI 0.97 to 1.14) among those given combination therapy. Mortality was also lower with the combination (odds ratio (OR) 0.78, 95% CI 0.64 to 0.94, 12 studies, N = 7518) than with ICS alone, but this was heavily weighted by a three-year study of FPS. When this study was removed, no significant mortality difference was noted. The reduction in exacerbations did not translate into significantly reduced rates of hospitalisation due to COPD exacerbation (OR 0.93, 95% CI 0.80 to 1.07, 10 studies, N = 7060). Lung function data favoured combination treatment in the FPS, BDF and MF/F trials, but the improvement was small. Small improvements in health-related quality of life were measured on the St George's Respiratory Questionnaire (SGRQ) with FPS or BDF compared with ICS, but this was well below the minimum clinically important difference. Adverse event profiles were similar between the two treatments arms, and rates of pneumonia when it was diagnosed by chest x-ray (CXR) were lower than those reported in earlier trials.

Authors' conclusions

Combination ICS and LABA offer some clinical benefits in COPD compared with ICS alone, especially for reduction in exacerbations. This review does not support the use of ICS alone when LABAs are available. Adverse events were not significantly different between treatments. Further long-term assessments using practical outcomes of current and new 24-hour LABAs will help determine their efficacy and safety. For robust comparisons as to their relative effects, long-term head-to-head comparisons are needed.

PLAIN LANGUAGE SUMMARY

Combination therapy of inhaled steroids and long-acting beta$_2$-agonists compared to inhaled steroids alone for people with COPD

Combinations of two classes of medication (long-acting beta$_2$-agonists (LABAs) and inhaled corticosteroids (ICS)) in one inhaler have been developed to treat people with COPD, as this may make it easier to take the medication. Three brands of combined inhaler are currently available: budesonide/formoterol (BDF — 'Symbicort'), fluticasone propionate/salmeterol (FPS — 'Advair' or 'Seretide') and mometasone furoate/formoterol (MF/F — 'Dulera'). Both the ICS part and the LABA component of each inhaler are aimed at reducing flare-ups of COPD, which can be debilitating and costly. In addition, the LABA component may improve day-to-day symptoms such as breathlessness and exercise tolerance.

Our review found 15 studies that compared a combination of ICS/LABA with ICS alone. We found that on the whole, combination inhalers reduced the frequency of flare-ups (not including hospitalisations) compared with ICS alone. The studies showed that on average, the number of exacerbations per participant was reduced, as was the probability of death, during treatment. Quality of life and lung function showed improvement with combination treatment compared with ICS, but no difference between them was noted in terms of adverse effects, or the likelihood of having no flare-ups at all. Future research should assess the efficacy of BDF and MF/F because most evidence gathered to date, including for mortality, has been drawn from FPS studies.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. All combined inhalers—participants with one or more exacerbations

Combined steroid/LABA inhalers versus LABA alone for people with COPD

Patient or population: patients with COPD
Settings: community
Intervention: All combined inhalers—primary outcomes

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	All combined inhalers—primary outcomes				
Exacerbation rates per participant per year	**1.21**[1]	**1.05** (0.97 to 1.14)	**Rate ratio 0.87** (0.80 to 0.94)	5601 (6 studies)	⊕⊕⊕⊖ **moderate**[2]	
Mortality	**71 per 1000**	**56 per 1000** (47 to 67)	**OR 0.78** (0.64 to 0.94)	7518 (12 studies)	⊕⊕⊕⊕ **high**[3]	
Pneumonia	**85 per 1000**	**91 per 1000** (78 to 107)	**OR 1.08** (0.91 to 1.28)	7320 (12 studies)	⊕⊕⊖⊖ **low**[2,4]	
Hospitalisations due to COPD exacerbations	**127 per 1000**	**119 per 1000** (104 to 134)	**OR 0.93** (0.8 to 1.07)	7060 (10 studies)	⊕⊕⊖⊖ **low**[2,4]	
Adverse events—serious Fluticasone/salmeterol (FPS) versus fluticasone (FP)	**54 per 1000**	**57 per 1000** (45 to 71)	**OR 1.05** (0.82 to 1.34)	5055 (7 studies)	⊕⊕⊖⊖ **low**[2,4]	
Adverse events—serious events Budesonide/formoterol (BDF) versus budesonide (BD)	**207 per 1000**	**195 per 1000** (158 to 240)	**OR 0.93** (0.72 to 1.21)	1469 (3 studies)	⊕⊖⊖⊖ **very low**[2,4,5]	
Adverse events—serious Mometasone/formoterol (MF/F) versus Mometasone (MF)	**78 per 1000**	**80 per 1000** (50 to 123)	**OR 1.03** (0.63 to 1.67)	905 (2 studies)	⊕⊕⊖⊖ **low**[2,4]	

*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; **OR:** Odds ratio.

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.

[1]Mean exacerbation rate in the ICS arms of the included studies (range 0.88 to 1.60 per participant per year).
[2](-1 limitations) due to high risk of attrition bias.
[3]We did not deduct a point for attrition bias because most of the data on mortality were derived from TORCH.
[4](-1 imprecision) confidence interval cannot rule out differences in either direction.
[5]A point is deducted to reflect the considerable heterogeneity in this analysis (I^2 = 66%).

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in most industrialised countries but is projected to be the third leading cause of death worldwide by 2020 (GOLD 2011). An estimated three million people are affected by COPD in the UK alone (NCGC 2010). In the most recent global guidelines, COPD is defined as "a common preventable and treatable disease, characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients" (GOLD 2011).

The disease is caused predominantly by smoking. Smoke and other irritants trigger airway inflammation (i.e. bronchial infiltration of neutrophils, macrophages, lymphocytes and mast cells and increasing evidence of autoimmunity) (Cosio 2009). As a result, patients generally show progressive loss of lung function, accompanied by worsening respiratory symptoms, more frequent exacerbations and deterioration in health status (GOLD 2011]. In addition to these effects on patients, exacerbations are costly to the healthcare system.

All cases of COPD are characterised by airway obstruction, which is defined as a reduced post-bronchodilator lung function ratio (forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) < 0.7), but in reality, COPD is a heterogeneous syndrome (GOLD 2011). It has been suggested that some phenotypes of COPD involved more chronic systemic inflammation, which has an impact on co-morbidities, such as cardiovascular disease (Garcia-Aymerich 2011). Some patients deteriorate more quickly than others, and variability in the degree of airways reversibility exhibited to bronchodilators has been noted. Previously, COPD severity was defined solely by FEV_1 % predicted compared with normal. The most recent definition grades severity of COPD using a combination of symptoms, lung function and number of exacerbations per year (GOLD 2011).

All patients with COPD should be considered for smoking cessation interventions, pulmonary rehabilitation, annual influenza vaccination and five-yearly pneumococcal vaccination (GOLD 2011). Smoking cessation is the only intervention that slows the decline in lung function (Kohansal 2009). In the absence of a significant disease-modifying effect, use of medication in COPD is largely guided by patient symptoms and exacerbation frequency. An increasing array of medicines are used in COPD, both alone and in combination. Some of these medicines are relatively expensive, so it is important to assess their relative benefits, so as to guide rational usage. It should be noted that in the decades to come, a disproportionate burden of the costs of COPD will be borne by developing countries, where smoking rates, and thus COPD prevalence, remain high.

Inhaled corticosteroids (ICS), long-acting $beta_2$-agonists (LABAs) and long-acting anti-muscarinic agents (LAMAs) have been shown to be effective for some clinical outcomes in COPD, such as symptoms, exercise tolerance, quality of life and exacerbations.

Use of ICS may be associated with short-term increases in FEV_1 and significant reduction in exacerbations (Yang 2012). On the other hand, use of ICS has been associated with an increase in the number of cases of pneumonia (TORCH; GOLD 2011) and of other adverse outcomes such as hoarseness and oral candidiasis. GOLD 2011 recommended that ICS should be used in patients with an FEV_1 < 50% predicted (GOLD stages 3 and 4 or quadrant C and D) and a history of ≥ 2 exacerbations (GOLD 2011). National Institute for Health and Clinical Excellence (NICE) guidelines have recommended adding a LABA (or LAMA) to an ICS in a combination inhaler, if FEV_1 is < 50% predicted. NICE has also recommended use of a combined LABA/ICS inhaler in people with stable COPD with an FEV_1 ≥ 50% who remain breathless or have exacerbations despite maintenance therapy with a LABA (NICE 2010; GOLD 2011).

Description of the intervention

The two medicines of interest in this review are LABAs and ICS, with a particular focus on the comparison between use of a combination inhaler of LABA and ICS versus ICS alone. These medicines are taken by inhaler twice a day.

How the intervention might work

Both ICS and LABA components have been shown to prevent some COPD exacerbations and to improve health-related quality of life. LABAs also improve symptoms and exercise tolerance (Appleton 2006). Inhaled corticosteroids reduce the frequency and severity of exacerbations (Yang 2012) but have not yet been shown to slow disease progression or improve mortality rates (TORCH). It is postulated that ICS work by reducing airways inflammation, but the dose response is not the same as that seen in asthma (GOLD 2011). Other possibilities include the effects on chronic systemic inflammation and on autoimmunity. Finally, some evidence of a synergistic action has been reported when ICS and LABAs are jointly administered. LABAs and ICS may interact in a beneficial way, with corticosteroids preventing loss of function of $beta_2$-agonists with long-term use, whereas $beta_2$-agonists may potentiate the local anti-inflammatory actions of corticosteroids (Barnes 2002).

Why it is important to do this review

The aim of this series of reviews is to document available evidence for the relative effectiveness of two commonly used treatments in COPD (ICS and LABAs) when given in combination. The convenience and complementary effects of anti-inflammatory and bronchodilator when combined in a single inhaler is appealing but needs to be borne out in trials. The possibility of harmful effects needs to be explored, especially in the light of concerns over pneumonia associated with ICS.

OBJECTIVES

To assess the efficacy and safety of combined long-acting $beta_2$-agonist and inhaled corticosteroid (LABA/ICS) preparations, as measured by clinical endpoints and pulmonary function testing, compared with inhaled corticosteroids (ICS) alone, in the treatment of adults with chronic obstructive pulmonary disease (COPD).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, double-blind, parallel-group clinical trials of at least four weeks' duration comparing combination ICS and LABA with its component ICS alone.

Types of participants

Adult patients (age > 40 years) with known, stable COPD fulfilling American Thoracic Society (ATS), European Respiratory Society (ERS) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria. Patients were to be clinically stable and without evidence of an exacerbation for one month before study entry. Patients with significant diseases other than COPD —a diagnosis of asthma, cystic fibrosis, bronchiectasis or other lung diseases—were excluded; however, patients with partial reversibility on pulmonary function testing were included.

Types of interventions

- Fluticasone propionate/salmeterol (FPS) versus fluticasone propionate (FP)
- Budesonide/formoterol (BDF) versus budesonide (BD)
- Mometasone furoate/formoterol (MF/F) versus mometasone furoate (MF)

Study duration was a minimum of four weeks. Concomitant therapy was permitted; however, trials in which participants were randomly assigned to tiotropium+combined ICS/LABA therapy versus tiotropium+ICS were excluded from the review, as this comparison is already considered in Karner 2011.

Studies in which the ICS dose in the ICS/LABA arm was less than 80% of the ICS dose in the ICS-only arm were excluded.

Types of outcome measures

Primary outcomes

- All exacerbations
- Hospitalisations due to COPD exacerbation
- Mortality
- Pneumonia

Secondary outcomes

- Change in FEV_1 and change in FVC: trough, peak and average; and other measures of pulmonary function
- Exercise performance—six-minute walk and other measures
- Quality of life (as measured on a validated scale, e.g. St George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Disease Questionnaire (CRDQ))
- Self-rated symptom score/symptoms of breathlessness
- Inhaled rescue medication used during the treatment period and concomitant medication usage, including antibiotics and steroids
- Number of days (or nights) participant experienced symptoms
- Area under the curve as the $beta_2$-agonist response after the first and last morning doses of LABA/ICS
- Per cent response to salbutamol from baseline FEV_1, with tachyphylaxis noted
- Pharmacoeconomic advantages
- Adverse events—palpitations, tremor, hoarseness/dysphonia, oral candidiasis, cataracts, skin bruising, bone fracture, bone density, plasma cortisol level
- Rate of withdrawal due to lack of efficacy or COPD deterioration .
- Rate of withdrawal due to adverse events

Search methods for identification of studies

Electronic searches

We searched the Cochrane Airways Group Specialised Register of trials, which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and by handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). All records in the Specialised Register coded as 'COPD' were searched using the following terms:

(((beta* and agonist*) and long*) or ((beta* and adrenergic*) and long*) and (*steroid or steroid* OR corticosteroid*)) or (fluticasone and salmeterol) or Seretide or Advair or (formoterol and budesonide) or Symbicort

The search was conducted in June 2013, and no restriction on the language of the publication was applied.

Searching other resources

We reviewed reference lists of all primary studies and review articles for additional references. We contacted authors of identified randomised trials about other published and unpublished studies. In addition, we contacted Allen & Hanburys Ltd, for GlaxoSmithKline (GSK), the manufacturer of fluticasone/salmeterol (Advair/Seretide/Viani), and AstraZeneca, which manufactures budesonide/formoterol (Symbicort), and consulted their online registers of trials.

Data collection and analysis

Selection of studies

Step I. Two review authors independently identified abstracts of trials that appeared potentially relevant.

Step II. Using the full text of each study, two review authors independently selected trials for inclusion in the review. Simple agreement was required, and third party adjudication was used to resolve differences.

Step III. After a preliminary review of all studies to confirm the basic requirements, two review authors assessed the methodological quality of included trials with particular emphasis on concealment of allocation, which was ranked using the Cochrane risk of bias tool (Higgins 2011).

Data extraction and management

Two review authors independently extracted data from included trials and entered results into the Cochrane Collaboration software

program (RevMan 5.2). In some cases, we estimated information regarding outcomes from graphs. Data extraction included the following items.

- **Population**: age, gender, smoking status, study setting (country, practice setting), inclusion and exclusion criteria.
- **Intervention**: dose, delivery device, duration.
- **Control**: concurrent treatments (ipratropium, beta$_2$-agonist, inhaled and systemic corticosteroids).
- **Outcomes**: Pulmonary function measures (baseline and follow-up FEV_1 and FVC), timing of pulmonary function measures, 6-minute walk, urgent visits, admissions, self-rated symptom score/symptoms, quality-of-life instruments, adverse events (palpitations, dry mouth, blurred vision, urinary obstruction and constipation), assessors, adjudicator of clinical endpoints. Mortality outcome data were collected from studies of longer than one year's duration, when they were available.
- **Design**: method of randomisation, presence and type of run-in period, study design (parallel, cross-over).

Assessment of risk of bias in included studies

The risk of bias in included studies was assessed using the Cochrane Collaboration's risk of bias tool (Higgins 2011). Two review authors (SJM, AK) assessed the risk of bias for all included studies with regard to random sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Each item was assessed as high, low or unclear risk of bias when relevant information was reported in the randomised controlled trial.

Measures of treatment effect

For continuous variables, a fixed-effect mean difference (MD) was used for outcomes measured on the same metric. Standardised mean difference (SMD) and 95% confidence interval (CI) were calculated for outcomes for which data were combined from studies using different metrics. All similar studies were to be pooled using fixed-effect MD/SMD and 95% CIs. When mean treatment differences were reported, data were entered as generic inverse variance (GIV), provided a standard error for the difference could be extracted or imputed. When this method was used, the effect size was reported from the original papers, for example, as rate ratio. This method (GIV) was not available when the protocol was written for the review, so it was not prespecified.

For dichotomous variables, a fixed-effect odds ratio (OR) with 95% CI was calculated for individual studies. All similar studies were pooled using fixed-effect OR and 95% CIs.

The reported confidence interval or P value was used to calculate standard deviations, or standard errors, for results when these were not reported and could not be obtained from the authors of the papers.

Unit of analysis issues

The unit of analysis was the participant, so dichotomous outcomes were analysed for participants who suffered one or more events (such as admission to hospital).

Dealing with missing data

If outcome data or information on trial design was missing, we attempted to contact authors for clarification.

Assessment of heterogeneity

For pooled effects, heterogeneity was tested using the I^2 measurement of the degree of variation between studies, not attributable by the play of chance. If heterogeneity was found (I^2 statistic > 20%), a random-effects model was used to determine the impact of heterogeneity on the overall pooled effect. In addition, the robustness of the results was tested when possible, using a sensitivity analysis based on the quality of the trials.

I^2 (Higgins 2011) was also considered and interpreted in relation to the following guidance.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: may represent considerable heterogeneity.

The Chi^2 test was similarly considered (P value < 0.10), but we regarded I^2 as our primary measure of heterogeneity.

Assessment of reporting biases

We planned to evaluate publication bias using visual inspection of funnel plots if the number of trials aggregated in the analyses was adequate (> 10). However, we recognised that an asymmetrical funnel plot can reflect heterogeneity, outcome reporting bias and small study effects and therefore is not necessarily a reflection of publication bias.

Data synthesis

We combined trials using RevMan 5.2. Continuous variables were combined using an MD or an SMD and were reported together with a 95% CI. We combined dichotomous variables using an OR with 95% CI. The pooled OR and its 95% CI were used to calculate numbers needed to treat for an additional harmful/beneficial outcome (NNTH/NNTB) using Visual Rx. The control event rates used to calculate illustrative NNTHs and NNTBs were taken from the event rates in the individual trials and have been reported along with the corresponding duration of the trial (because NNTH and NNTB are time dependent; Cates 2012).

Subgroup analysis and investigation of heterogeneity

Although we separated steroids and long-acting beta$_2$-agonists by type, we pooled studies with differing dosages of the same drug. We planned *a priori* subgroups as follows.

- Disease severity (related to baseline FEV_1 and placebo group exacerbation rate) according to GOLD staging = 2A, 2B (moderate COPD, characterised by deteriorating lung function (A = FEV_1 < 80% predicted; B = FEV_1 < 50% predicted) and progression of symptoms) and 3 (severe COPD, characterised by severe airflow limitation (FEV_1 < 30% predicted) and the presence of respiratory failure or clinical signs of right heart failure (GOLD 2011)).
- Prior inhaled corticosteroid plus long-acting beta$_2$-agonist use (dichotomised as yes/no).

- Concurrent therapy with routine beta$_2$-agonist use (short- or long-acting) and corticosteroid (systemic or inhaled) or theophylline use (dichotomised as yes/no).
- Reversibility of airflow obstruction with beta$_2$-agonist therapy (dichotomised as partial/none). Definition: > 12% and > 200 mL from baseline FEV_1 or > 12% as a per cent of the predicted normal value following metered-dose inhaler (MDI) salbutamol 200 to 400.
- Dose, duration and delivery method of therapy.

Sensitivity analysis

In addition, sensitivity analyses were performed using the following domains.

- Methodological quality: using a quality-weighted analysis to allow for the use of all trials.
- Random-effects versus fixed-effect modelling.

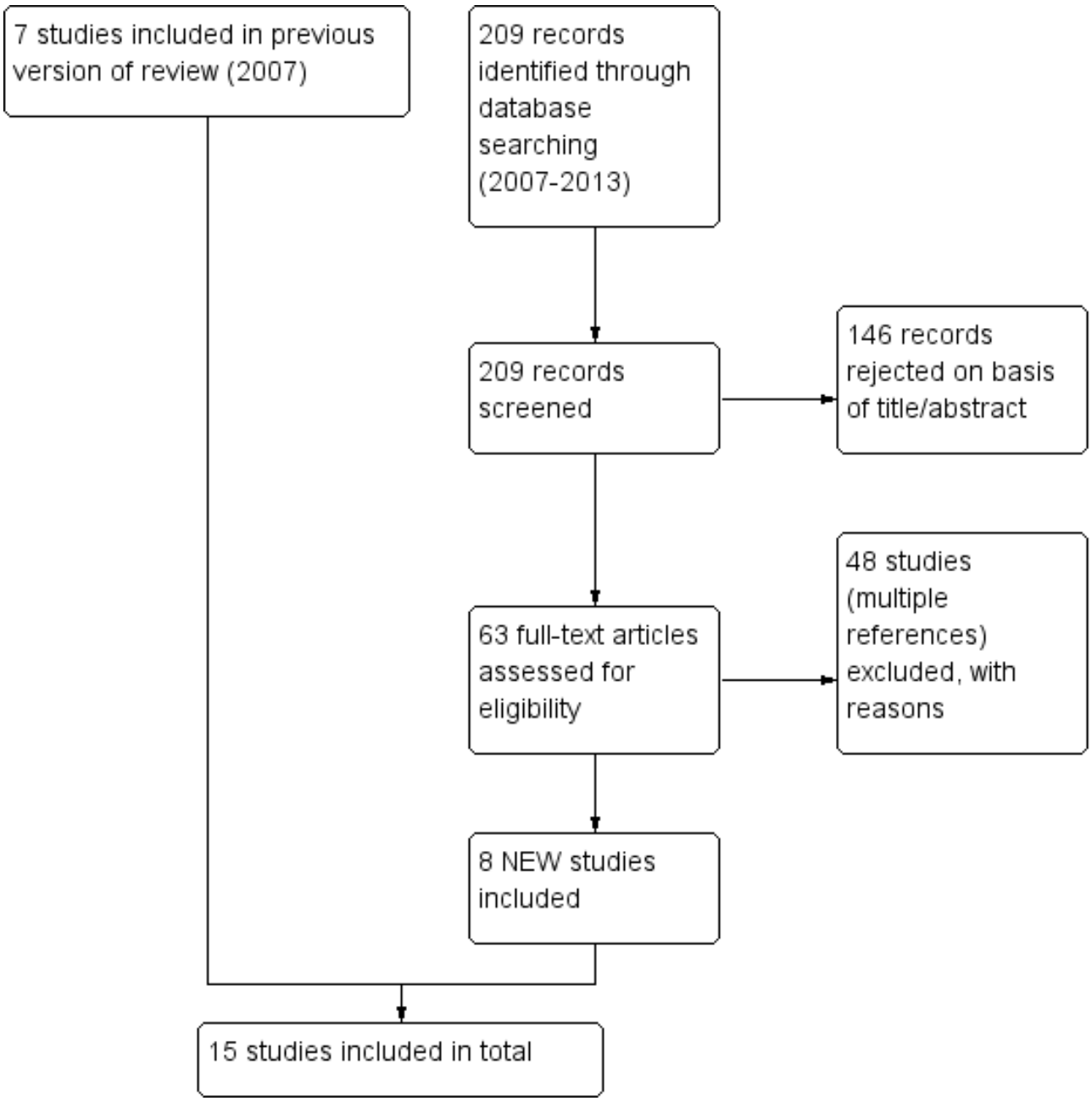
RESULTS

Description of studies

Results of the search

For details of the search history, see Table 1. For the study flow diagram, see Figure 1.

Figure 1. Study flow diagram.



Included studies

Fifteen studies, with a total of 7814 participants, met the review entry criteria. For a full description of baseline characteristics, methods used and inclusion and exclusion entry criteria of individual studies, see Characteristics of included studies.

Design

All trials had a randomised, double-blind, parallel-group design. Details of randomisation and blinding are included in Characteristics of included studies.

Participants

Participants suffered from COPD, with variable definitions of COPD and reversibility. COPD was defined by national or international criteria, including ATS (Hanania 2003; Mahler 2002), ERS (TORCH; TRISTAN) and GOLD (Calverley 2003; Lapperre 2009; Sin 2008; Szafranski 2003). In seven studies, the definition was based on lung function tests (Bourbeau 2007; Doherty 2012; NCT00358358; SFCT01, Tashkin 2008; Tashkin 2012; Zhong 2012). Participant populations in the studies suffered from moderate and severe COPD. Hanania 2003 and Mahler 2002 enrolled participants with both reversible and non-reversible COPD.

Interventions

Three comparisons were made. The first was fluticasone propionate/salmeterol (FPS) versus fluticasone (9 studies, 5132 participants: Bourbeau 2007; Hanania 2003; Lapperre 2009; Mahler 2002; NCT00358358; SFCT01; Sin 2008; TORCH; TRISTAN), the second budesonide/formoterol versus budesonide (4 studies, 1777 participants: Calverley 2003; Szafranski 2003; Tashkin 2008; Zhong 2012) and the third mometasone furoate and formoterol combined (MF/F) versus mometasone furoate (MF). Only two studies were identified, with a total of 905 participants (Doherty 2012; Tashkin 2012).

In one of the fluticasone propionate/salmeterol studies, the combination of ICS/LABA was FPS at a dose of 250 mcg/50 mcg twice daily versus fluticasone propionate (FP) 250 mcg twice daily (Hanania 2003). In the remainder of the FPS studies (Bourbeau 2007; Lapperre 2009; Mahler 2002; NCT00358358; SFCT01; Sin 2008; TORCH; TRISTAN), the dose was 500 mcg/50 mcg twice daily versus FP 500 mcg twice daily.

In two of the budesonide/formoterol studies (Calverley 2003 and Szafranski 2003), the combination ICS/LABA was budesonide/formoterol (BDF) (320 mcg/9 mcg twice daily). This was compared with budesonide (BD; 400 mcg twice daily). The dosage of the combined preparation and of the separate medications remained stable throughout the studies. In Calverley 2003, all participants had a two-week run-in treatment with oral corticosteroids, inhaled formoterol and prn short-acting beta$_2$-agonists. In Tashkin 2008, the comparison was made between BDF (160/4.5 mcg/dose) 2 inhalations twice daily versus BD (160 mcg/dose) 2 inhalations twice daily, and in Zhong 2012, the comparison was between BDF (160/4.5 mcg/dose) 2 inhalations twice daily versus BD (200 mcg/dose) 2 inhalations twice daily.

In the two mometasone furoate and formoterol combined (MF/F) versus mometasone furoate (MF) studies (Doherty 2012; Tashkin 2012), the comparison was between MF/F 400/10 mcg twice daily versus MF 400 mcg twice daily. For details of co-medication and run-in periods on all 15 studies, please see Characteristics of included studies.

Duration

- 156 weeks: TORCH.
- 128 weeks: Lapperre 2009
- 52 weeks: Calverley 2003; SFCT01; Szafranski 2003; TRISTAN.
- 26 weeks: Doherty 2012; Tashkin 2008; Tashkin 2012.
- 24 weeks: Hanania 2003; Mahler 2002; Zhong 2012.
- 16 weeks: Bourbeau 2007.
- 12 weeks: NCT00358358.
- 4 weeks: Sin 2008.

Outcomes

Exacerbations were stratified by medication given (oral steroid and/or antibiotic treatment in Calverley 2003; SFCT01; Szafranski 2003; TORCH; TRISTAN) or hospitalisation (TORCH; TRISTAN). In Tashkin 2008, exacerbations were defined as worsening of COPD symptoms that required treatment with oral corticosteroids and/or hospitalisation. Sin 2008 and Zhong 2012 also included the use of antibiotics, an emergency room visit or both in their definition. Doherty 2012 and Tashkin 2012 stratify exacerbations into mild, moderate or severe. Exacerbation data were not reported in Lapperre 2009, NCT00358358 or Bourbeau 2007. Hanania 2003 and Mahler 2002 withdrew participants whose condition was exacerbated.

Lung function, if reported, was measured as FEV_1 or peak expiratory flow (PEF) in all studies. Quality of life assessments by the SGRQ or the CRDQ were available for Calverley 2003; Doherty 2012; Hanania 2003; Lapperre 2009; Mahler 2002; SFCT01; Szafranski 2003; Tashkin 2008; Tashkin 2012; TORCH; TRISTAN; Sin 2008; and Zhong 2012. Quality of life assessment was not reported for NCT00358358 or Bourbeau 2007. All-cause mortality was reported by TORCH. Mortality data were also reported for Doherty 2012; NCT00358358; Tashkin 2008; Tashkin 2012; and Zhong 2012,, although death was not one of their pre-defined outcomes.

Excluded studies

A total of 48 studies were excluded—36 (75%) because the comparison was not made between combined LABA/ICS versus ICS; 5 (10%) because participants were also randomly assigned to receive tiotropium as a co-intervention; 2 (4%) because asthma patients were combined in the study; 2 (4%) because ICS dose in the ICS/LABA condition was less than 80% of the ICS dose in the ICS-only condition; 1 (2%) because investigators provided an aggregated report of two studies; 1 (2%) because it examined the acute effect of combined LABA/ICS and 1 (2%) because the focus was on sleep quality in COPD. A list of excluded studies is provided in Characteristics of excluded studies.

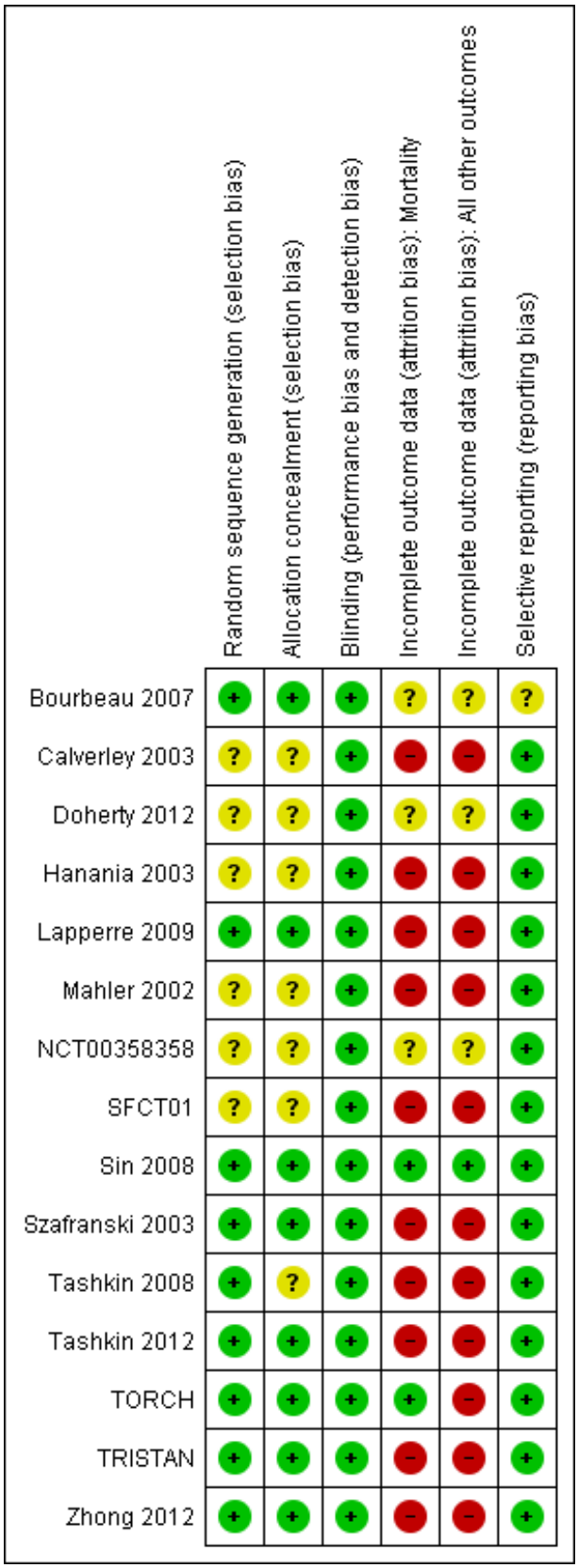
Risk of bias in included studies

Intention-to treat (ITT) analyses were reported in all studies for their primary outcomes. TORCH reported incomplete data for FEV_1 and SGRQ scores. Concealment of allocation was reported in Calverley 2003; Szafranski 2003; TORCH; and TRISTAN. Blinding of treatment was reported for all studies. Identical delivery devices for treatment

groups were reported in Calverley 2003; Szafranski 2003; TORCH; and TRISTAN.

An overview of the judgements we have made regarding the risk of bias for each study is given in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In nine of the fifteen studies, the risk of selection bias was judged as low, and in the remaining six, the risk was viewed as unclear. Among the FPS versus fluticasone trials (9 studies, 5132 participants), five (Bourbeau 2007; Lapperre 2009; Sin 2008; TORCH; TRISTAN) were judged to be at low risk of selection bias, and in the remaining four (Hanania 2003; Mahler 2002 SFCT01; NCT00358358), the risk was considered to be unclear. Three of the four BDF versus BD studies (1777 participants; Szafranski 2003; Tashkin 2008; Zhong 2012) were regarded as having low risk of selection bias in terms of sequence generation, although the issue of allocation concealment in Tashkin 2008 was unclear; in Calverley 2003, the risk of selection bias in terms of sequence generation and allocation concealment was regarded as unclear.

Of the two MF/F versus MF trials (905 participants), Tashkin 2012 was judged to be at low risk of selection bias, and for Doherty 2012, the risk was considered to be unclear. A summary of the selection bias is provided in Figure 2.

Blinding

The risk of performance and detection bias was judged to be low in all fifteen trials.

Incomplete outcome data

Dropout rates were uniformly high (> 20%) in the long-term (longer than 6 months) studies, and most studies were judged to be at high risk of attrition bias, whereas the shorter-term studies (Bourbeau 2007; Doherty 2012; NCT00358358; Sin 2008) had lower dropout rates and were judged to be at low (dropout rate < 10%) or unclear (dropout rate 10% to 20%) risk of attrition bias. The TORCH study, however, ascertained the mortality results for those participants who withdrew from the study and so was judged to have low risk of attrition bias for mortality (Figure 2).

Selective reporting

In only one trial was the risk of reporting bias considered unclear: Bourbeau 2007. In all other cases, the risk of reporting bias was judged to be low.

Effects of interventions

See: **Summary of findings for the main comparison** All combined inhalers — participants with one or more exacerbations

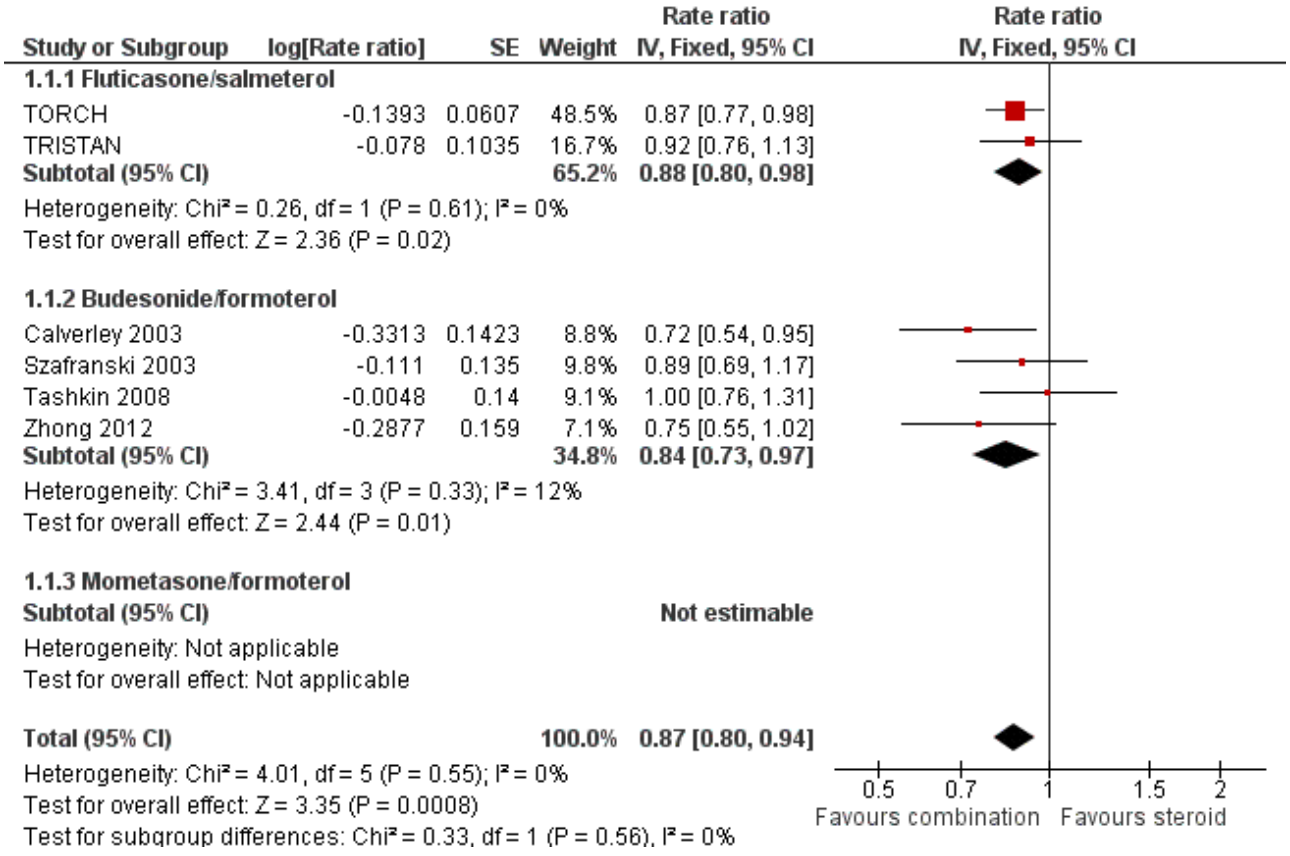
Primary outcomes

Exacerbation rates

Pooled results for FPS, BDF and MF/F versus ICS alone

A significant reduction was noted in the rate of exacerbations requiring oral corticosteroids with combination therapy when compared with ICS (6 studies: N = 5601; rate ratio (RR) 0.87; 95% CI 0.80 to 0.94; Analysis 1.1; Figure 3). A summary of definitions of exacerbations in the included studies is provided in Table 2. The mean exacerbation rate in the ICS-only arms of the included studies was 1.21 exacerbations per patient per year (range 0.88 to 1.60), and we would expect an equivalent rate of 1.05 (95% CI 0.97 to 1.14) with combination therapy (see Summary of findings for the main comparison).

Figure 3. Forest plot of comparison: 1 All Combined Inhalers—Primary Outcomes, outcome: 1.1 Exacerbation rates (exacerbations requiring oral corticosteroids).



FPS versus FP

Two studies compared FPS versus FP (TORCH; TRISTAN). A significant reduction was noted in the rate of exacerbations with combination therapy when compared with FP (2 studies; N = 3789; RR 0.88; 95% CI 0.80 to 0.98; Analysis 1.1).

BDF versus BD

Four studies compared BDF versus BD (Calverley 2003, Szafranski 2003; Tashkin 2008; Zhong 2012). A significant effect on pooled exacerbation rates was seen with BDF versus BD (4 studies; N = 1777; RR 0.84; 95% CI 0.73 to 0.97; Analysis 1.1).

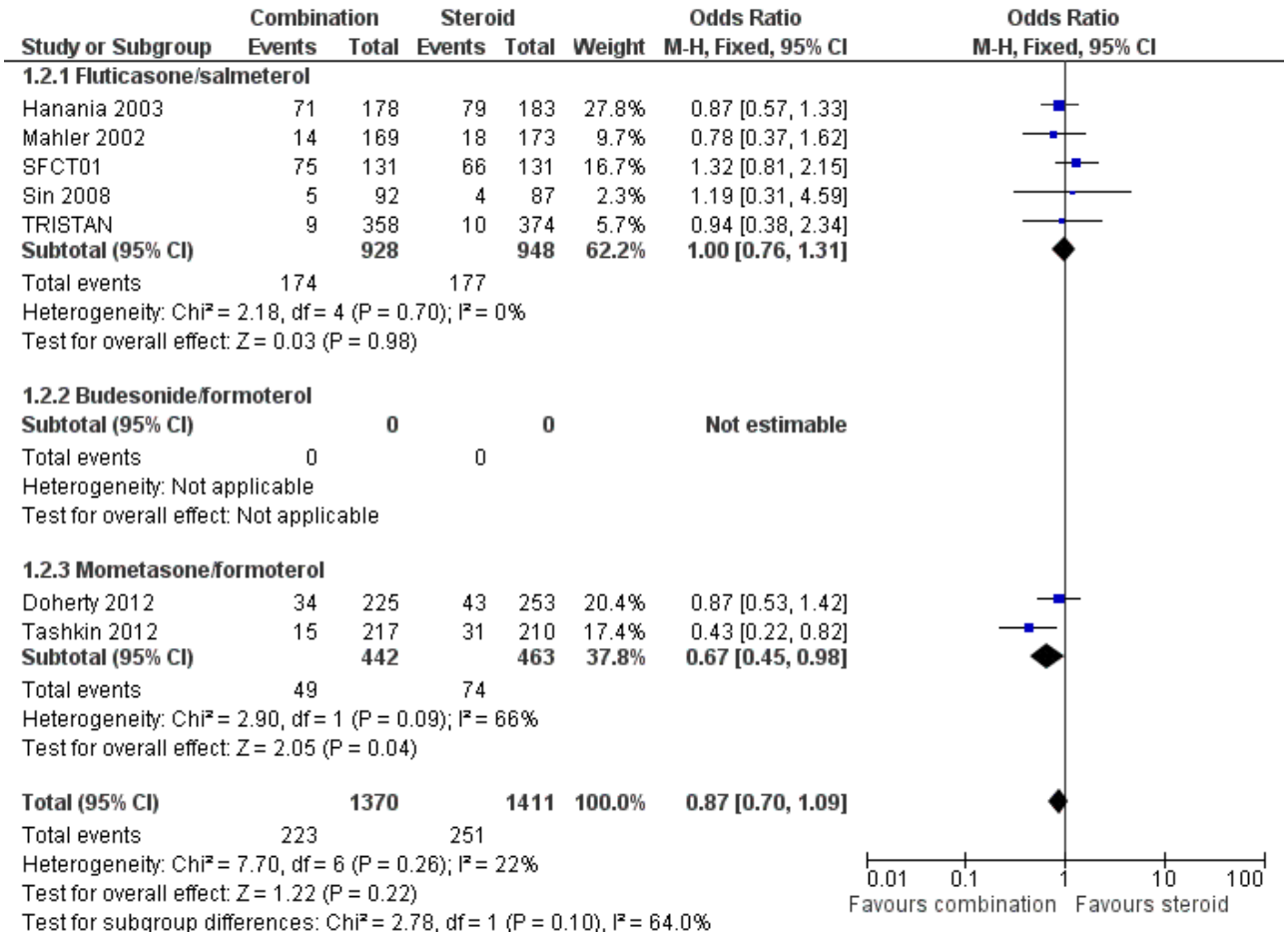
MF/F versus MF

The two studies comparing MF/F versus MF did not report rate data for exacerbations.

Number of participants with one or more exacerbation

No significant difference was seen with combination therapy when compared with ICS (7 studies: N = 2781, OR 0.87, 95% CI 0.70 to 1.09; Analysis 1.2; Figure 4).

Figure 4. Forest plot of comparison: 1 All Combined Inhalers—Primary Outcomes, outcome: 1.2 Number of participants with one or more exacerbation.



FPS versus FP

No significant difference was observed between FPS and FP in the reports of participants with one or more exacerbations (3 studies (SFCT01; Sin 2008; TRISTAN); N = 1173, OR 1.22, 95% CI 0.81 to 1.84); this outcome was not reported in TORCH. However, some evidence suggests that FPS leads to a lower rate of exacerbations requiring oral steroids (2 studies (TORCH; TRISTAN); N = 3824; RR 0.89, 95% CI 0.81 to 0.98; Analysis 2.5).

BDF versus BD

No studies that compared BDF versus BD reported this outcome.

MF/F versus MF

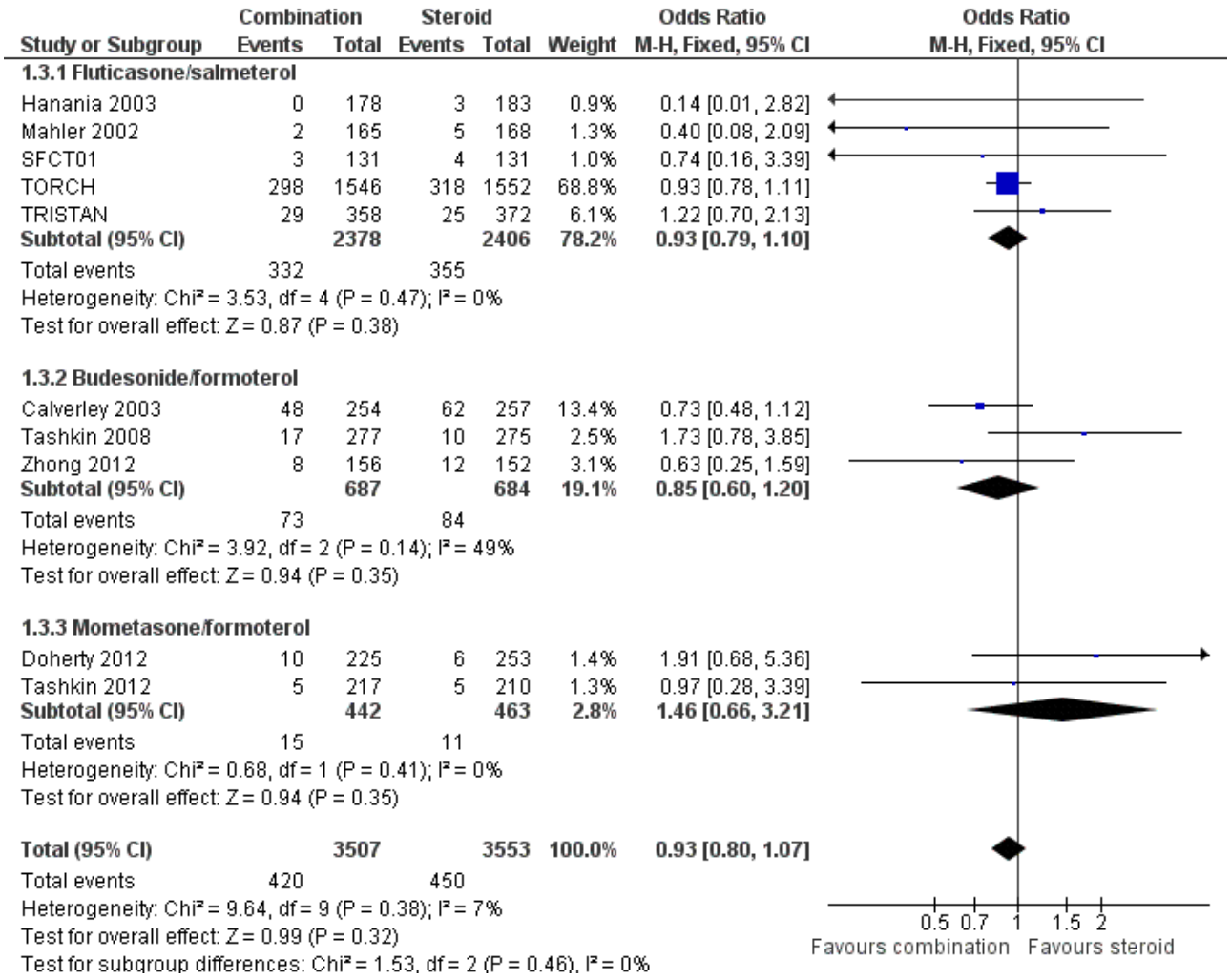
A significant difference was noted between MF/F and MF with respect to the numbers of participants with moderate and severe exacerbations (2 studies (Doherty 2012; Tashkin 2012); N = 905, OR 0.67, 95% CI 0.45 to 0.98; Analysis 4.1).

Hospitalisations due to COPD exacerbations

Pooled results for FPS, BDF and MF/F versus ICS alone

No significant difference was described between combined LABA/ICS and ICS-alone treatments in hospitalisations due to COPD exacerbations (10 studies: Calverley 2003; Doherty 2012; Hanania 2003; Mahler 2002; SFCT01; Tashkin 2008; Tashkin 2012; TORCH; TRISTAN; Zhong 2012; N = 7060, OR 0.93, 95% CI 0.80 to 1.07; Analysis 1.3; Figure 5).

Figure 5. Forest plot of comparison: 1 All Combined Inhalers—Primary Outcomes, outcome: 1.3 Hospitalisations due to COPD exacerbations.



FPS versus FP

Data related to this outcome were obtained from five studies for the comparison of FPS versus FP (Hanania 2003; Mahler 2002; SFCT01; TORCH; TRISTAN; N = 4799, OR 0.93, 95% CI 0.79 to 1.10), and no significant difference was noted between combined LABA/ICS and ICS alone.

BDF versus BD

Three studies (Calverley 2003; Tashkin 2008; Zhong 2012) provided relevant data (N = 1371, OR 0.85, 95% CI 0.60 to 1.20), and no significant difference was described between BDF and BD in hospitalisations due to COPD exacerbations.

MF/F versus MF

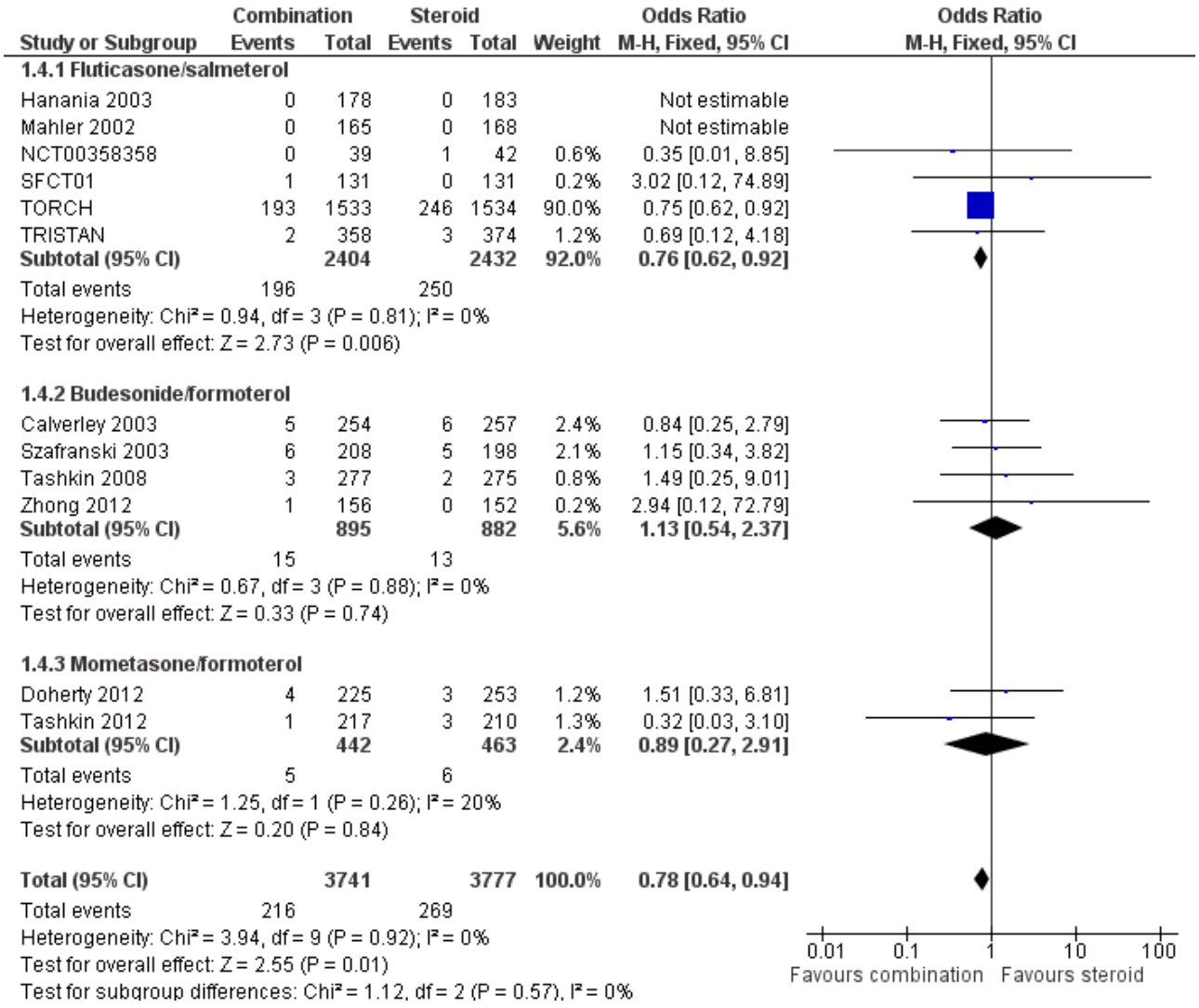
Similarly, the two studies comparing MF/F versus MF (Doherty 2012; Tashkin 2012) reported no significant benefit derived from the LABA with respect to hospitalisations due to COPD exacerbations (N = 905, OR 1.46, 95% CI 0.66 to 3.21).

Mortality

Pooled results for FPS, BDF and MF/F versus ICS alone

When data were combined for both treatments and their respective comparators, the odds of death were significantly lower after combination treatment than after mono-component steroid (12 studies; N = 7518, OR 0.78, 95% CI 0.64 to 0.94; Analysis 1.4; Figure 6). Because differing lengths of follow-up across studies and differing event rates in the control arm hinder the calculation of pooled NNTB values, we have tabulated this for each study individually (see Table 3). The three-year NNTB (using the baseline risk of 16% in the ICS arm of TORCH) to prevent one extra death is 32 (95% CI 19 to 123). In contrast, in lower-risk participants (using the baseline risk of 0.8% in the ICS arm of TRISTAN), the one-year NNTB is much higher at 547 to prevent one extra death (95% CI 340 to 2100).

Figure 6. Forest plot of comparison: 1 All Combined Inhalers—Primary Outcomes, outcome: 1.4 Mortality.



FPS versus FP

Trials varied in length from 12 to 156 weeks. Compared with FP, a significant reduction was noted in the odds of death at the end of treatment (6 studies; Hanania 2003; Mahler 2002; NCT00358358; SFCT01; TORCH; TRISTAN; N = 4836, OR 0.76, 95% CI 0.62 to 0.92).

BDF versus BD

The length of studies ranged from 24 to 52 weeks. Investigators did not identify a significant difference between BDF and BD with regard to mortality (4 studies; Calverley 2003; Szafranski 2003; Tashkin 2008; Zhong 2012; N = 1777, OR 1.13, 95% CI 0.54 to 2.37).

MF/F versus MF

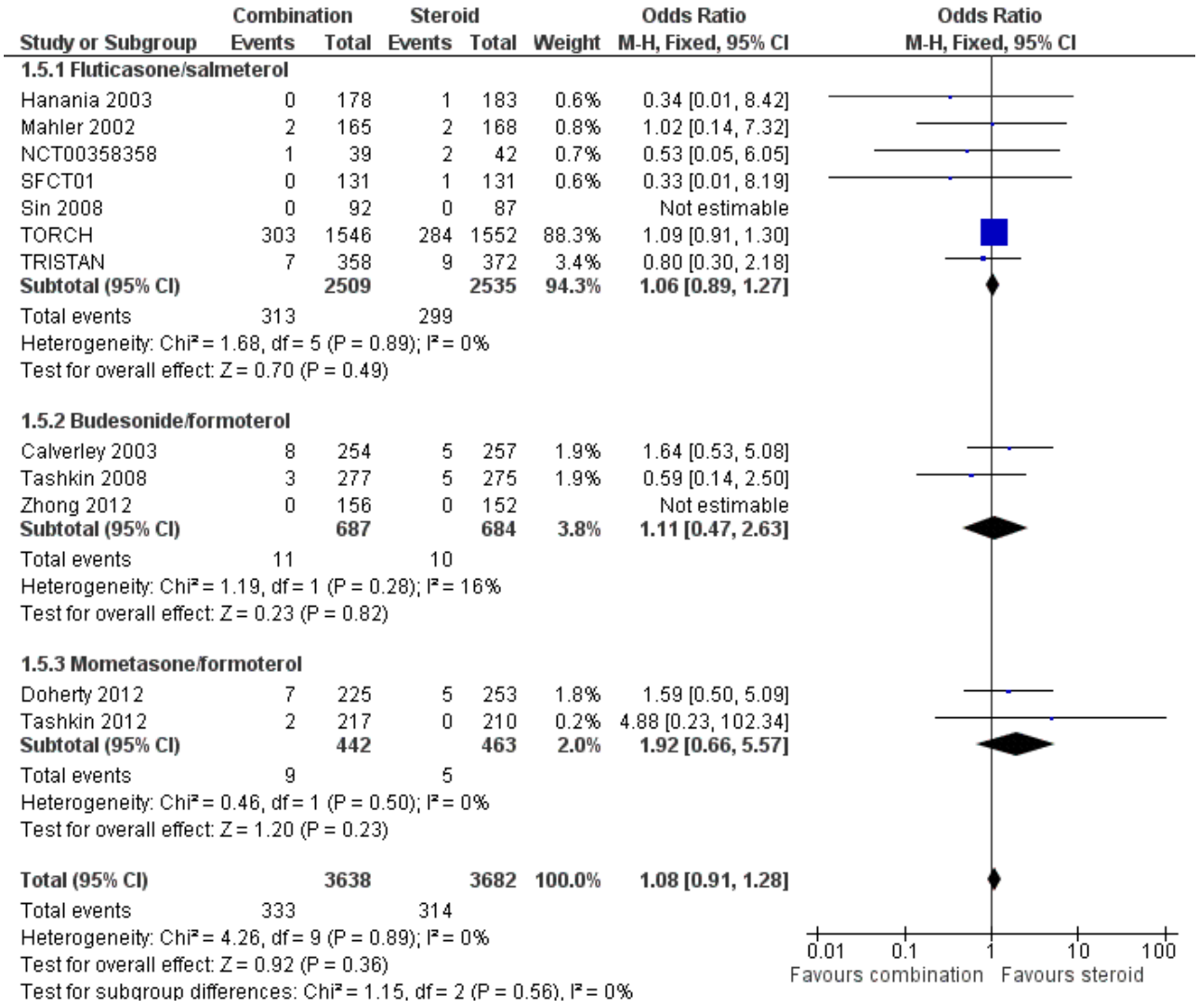
Two trials were identified: one 26 weeks in duration (Tashkin 2012) and the other 52 weeks (Doherty 2012). No significant difference was reported between MF/F and MF on this outcome (N = 905, OR 0.89, 95% CI 0.27 to 2.91).

Pneumonia

Pooled results for FPS, BDF and MF/F versus ICS alone

When data were combined for both treatments and their respective comparators, the odds of pneumonia were not significantly different after combination treatment than after mono-component steroid (12 studies; N = 7315, OR 1.08, 95% CI 0.91 to 1.28; Analysis 1.5; Figure 7).

Figure 7. Forest plot of comparison: 1 All Combined Inhalers—Primary Outcomes, outcome: 1.5 Pneumonia.



FPS versus FP

No significant difference between FPS and FP was observed in the number of participants with pneumonia at the end of treatment (7 studies; Hanania 2003; Mahler 2002; NCT00358358; SFCT01; Sin 2008; TORCH; TRISTAN; N = 5015, OR 1.06, 95% CI 0.89 to 1.27).

BDF versus BD

The three studies that reported pneumonia (Calverley 2003; Tashkin 2008; Zhong 2012) did not identify a significant difference between BDF and BD (N = 1371, OR 1.11, 95% CI 0.47 to 2.63).

MF/F versus MF

Both studies (Tashkin 2012 and Doherty 2012) included pneumonia in their range of outcomes. No significant difference between MF/F and MF was noted in the number of participants with pneumonia at the end of treatment (N = 905, OR 1.92, 95% CI 0.66 to 5.57).

Secondary outcomes

Change in lung function (FEV_1)

FPS versus FP

A significant difference in pre-dose FEV_1 change from baseline favoured FPS (2 studies; Hanania 2003; Mahler 2002; N = 699, MD 0.05 L, 95% CI 0.02 to 0.09; Analysis 2.11).

Similarly, a significant difference in post-dose FEV_1 change from baseline favoured FPS (6 studies; Hanania 2003; Lapperre 2009; Mahler 2002; SFCT01; TORCH; TRISTAN; N = 4833, MD 0.05 L, 95% CI 0.04 to 0.06; Analysis 2.12).

Data incorporated in this analysis from SFCT01 and TRISTAN were end of treatment data rather than change from baseline data.

BDF versus BD

The pre-dose FEV_1 change from baseline to the average over the randomised treatment period (1 study; N = 552, MD 0.08 L, 95% CI 0.05 to 0.11; Analysis 3.9) was significant. Only one study (Tashkin

2008) contributed to this outcome, and it included a partially reversible population (a mixed population).

The 1-hour post-dose FEV_1 change from baseline to the average over the randomised treatment period (1 study; N = 552, MD 0.17 L, 95% CI 0.14 to 0.20; Analysis 3.10) was also significant. Again, only one study (Tashkin 2008) contributed to this outcome, and it included a partially reversible population (a mixed population).

MF/F versus MF

We analysed change from baseline in FEV_1 $AUC_{0\text{-}12\ h}$ at week 13 (2 studies; Doherty 2012; Tashkin 2012; N = 905, MD 116.59 mL, 95% CI 68.59 to 164.59; Analysis 4.5) and at week 26 (same two studies; MD 109.34 mL, 95% CI 57.87 to 160.81; Analysis 4.4). In both cases, a significant benefit favoured MF/F. An effect in favour of MF/F was also observed in mean change from baseline in morning pre-dose FEV_1 at 13 weeks (MD 0.08 L, 95% CI 0.04 to 0.11; Analysis 4.6).

Quality of life

FPS versus FP

A significant improvement favoured FPS over FP: -1.30 units on the SGRQ (3 studies; SFCT01; TORCH; TRISTAN; N = 3001, SGRQ units -1.30, 95% CI -2.04 to -0.57; Analysis 2.8). Because of the high rate of attrition in TORCH, the data were presented for only a subset of those who were randomly assigned (2007/3091). Removing this study from the analysis resulted in a similar effect estimate (SGRQ units -1.56, 95% CI -2.66 to -0.46).

Data from two studies reporting quality of life as mean change in CRDQ suggested high levels of statistical variation (I^2 = 77%). Neither fixed-effect nor random-effects modelling revealed significant differences (2.12 units, 95% CI -0.50 to 4.75; and 2.34 units, 95% CI -3.15 to 7.82, respectively).

BDF versus BD

A significant effect favoured BDF versus BD on the SGRQ (change from baseline). Four studies contributed data (Calverley 2003; Szafranski 2003; Tashkin 2008; Zhong 2012; N = 1777, MD -2.80, 95% CI -3.99 to -1.61; Analysis 3.4). The effect was observed in a partially reversible population (mixed population) (1 study; Tashkin 2008; N = 552, MD -2.57, 95% CI -4.68 to -0.46) and in a poorly reversible population (3 studies; Calverley 2003; Szafranski 2003; Zhong 2012; N = 1225, MD -2.91, 95% CI -4.35 to -1.47).

MF/F versus MF

No significant effect difference was reported for MF/F versus MF on the SGRQ (change from baseline), with data contributed by both Doherty 2012 and Tashkin 2012 (2 studies; N = 905, MD -0.29, 95% CI -2.16 to 1.57; Analysis 4.3).

Symptom score

FPS versus FP

Pooled data from Mahler 2002 and Hanania 2003 indicated no significant difference between FPS and FP in TDI scores (2 studies; N = 690, MD 0.31, 95% CI -0.45 to 1.08; Analysis 2.9).

BDF versus BD

A significant benefit for BDF versus BD was observed in symptom change scores (3 studies; Calverley 2003; Szafranski 2003; Zhong 2012; N = 1225, MD -0.45, 95% CI -0.67 to -0.22; Analysis 3.5).

MF/F versus MF

Symptoms were considered in Doherty 2012 and Tashkin 2012 in terms of COPD symptom-free nights. In both studies, no significant difference was noted between MF/F and MF with respect to this outcome, although insufficient data were recorded to allow a meta-analysis.

Rescue medication

FPS versus FP

Pooled data from Mahler 2002 and Hanania 2003 indicated a significant reduction in mean puffs per day of short-acting $beta_2$-agonist usage in favour of FPS over FP (2 studies; N = 686, MD -0.80, 95% CI -1.31 to -0.29; Analysis 2.15).

TRISTAN reported a significant difference in median % of days without use of relief medication in favour of FPS over FP (P < 0.001).

BDF versus BD

BDF treatment reduced the requirement for reliever medication when compared with BD (4 studies; Calverley 2003; Szafranski 2003; Tashkin 2008; Zhong 2012; N = 1777, MD -0.72, 95% CI -0.92 to -0.52; Analysis 3.13).

MF/F versus MF

No data were reported for this outcome.

Safety and tolerability

FPS versus FP

No significant difference was noted between FPS and FP in the odds of any adverse event (Analysis 2.19 through to Analysis 2.21).

BDF versus BD

A significant difference between BDF and BD was observed in the adverse events included in this review for nasopharyngitis (1 study; Tashkin 2008; N = 552, OR 2.42, 95% CI 1.09 to 5.39; Analysis 3.22), with fewer cases in the BD group. Because this finding is provided by only one study, and because the level of significance (P = 0.03) is marginal, any evaluation of this outcome should be cautious until additional data become available. No significant difference between BDF and BD was reported for any other adverse event considered in the review for this comparison (Analysis 3.22).

MF/F versus MF

No significant difference was observed between MF/F and MF in the odds of any adverse event (Analysis 4.10 through to Analysis 4.12).

Withdrawals

FPS versus FP

Study withdrawal occurred significantly less frequently on FPS than on FP (9 studies; Bourbeau 2007; Hanania 2003; Lapperre 2009; Mahler 2002; NCT00358358; SFCT01; Sin 2008; TORCH; TRISTAN; N = 5132, OR 0.86, 95% CI 0.76 to 0.97; Analysis 2.16). When expressed as withdrawal due to lack of efficacy, no significant difference between

treatments was described (5 studies; Mahler 2002; SFCT01; Sin 2008; TORCH; TRISTAN; N = 4592, OR 0.77, 95% CI 0.53 to 1.13; Analysis 2.17). However, fewer withdrawals resulted from adverse events among FPS-treated participants than among those treated with FP (7 studies; Bourbeau 2007; Mahler 2002; NCT00358358; SFCT01; Sin 2008; TORCH; TRISTAN; N = 4712, OR 0.75, 95% CI 0.64 to 0.87; Analysis 2.18).

BDF versus BD

Data were pooled from Calverley 2003, Szafranski 2003 and Zhong 2012 for withdrawals due to worsening COPD symptoms and adverse events, and a very marginal significant difference in withdrawals due to worsening of COPD symptoms was noted when BDF was compared with BD (3 studies; N = 1225, OR 0.68, 95% CI 0.46 to 0.99; Analysis 3.18). Because the statistical significance of this effect is so very marginal, any evaluation of this finding should await the availability of additional data.

No significant difference was noted between BDF and BD in the likelihood of withdrawal due to adverse events other than COPD deterioration (4 studies; Calverley 2003, Szafranski 2003; Tashkin 2008; Zhong 2012; N = 1777, OR 0.95, 95% CI 0.66 to 1.37; Analysis 3.19).

MF/F versus MF

No significant difference regarding withdrawals was observed in the comparison between MF/F and MF (2 studies; Doherty 2012; Tashkin 2012; N = 905, OR 0.78, 95% CI 0.56 to 1.09; Analysis 4.7), and no significant difference was noted regarding withdrawals due to adverse events (2 studies; Doherty 2012; Tashkin 2012; N = 905, OR 1.38, 95% CI 0.71 to 2.68; Analysis 4.8) or withdrawals due to treatment failure (2 studies; Doherty 2012; Tashkin 2012; N = 905, OR 0.68, 95% CI 0.19 to 2.44; Analysis 4.9).

DISCUSSION

Summary of main results

We reviewed data from 15 randomised controlled trials (7814 participants; Table 4) assessing the effectiveness and safety of combined inhaled corticosteroid and long-acting beta$_2$-agonist in the treatment of chronic obstructive pulmonary disease (COPD) versus ICS alone for the clinically important primary outcomes of exacerbations, mortality, hospitalisation and pneumonia. Overall, available evidence suggests that combination therapy with ICS and LABA shows an advantage over ICS alone in reducing exacerbations and mortality throughout the study period, with no significant effect on hospitalisation or pneumonia. The greatest quantity of evidence comes from populations of poorly reversible participants who have more severe COPD. It should be noted that most of the evidence for a reduction in mortality (weighting of 90%) comes from the TORCH study, which compared FPS and FP in participants with an FEV_1 < 60% predicted. Furthermore, the mortality benefit is confined to the FPS combination only and is not seen in the others. If we remove the TORCH study, mortality rates are not significantly different between combination treatment and ICS alone. Furthermore, the TORCH study did not show any statistically significant mortality benefit at 2 years, only at 3 years, so we can only be sure that benefit would accrue over the longer period. Finally, about 14% of those in the TORCH study died, whereas mortality rates in the other studies reporting this outcome were in the order of 3%, and all were less than 12 months in duration. The TORCH study was the only study in this review that showed significantly fewer withdrawals in the combination group than in the ICS group, but it was also the only study that ascertained the vital status of all participants, including those who withdrew from the study.

If the mortality benefit seen in this review in association with the combined inhaler is confirmed in other three-year studies, the mechanism needs elucidation, and this is likely to be important. The TORCH investigators did find a significant difference between LABA/ICS and ICS alone, but not between LABA/ICS and placebo, although the P value for this comparison was 0.052. To date, the only approaches used in COPD to reduce mortality rates are smoking cessation and long-term oxygen therapy (LTOT) in hypoxic patients. On the basis of our findings, at best, 33 people with moderate to severe COPD need to be treated with a combination FPS inhaler for three years to prevent one excess death, compared with those treated with ICS alone. This reduction appears to involve COPD-related deaths. On the other hand, no evidence of a mortality benefit has been obtained for the other combination inhalers over their component ICS. From this review, we can conclude that combination treatment is related to fewer exacerbations, and probably to fewer severe exacerbations, than ICS alone, as is discussed later. Exacerbations are risky times for death; therefore this is a plausible explanation, but to be sure, we would need to use individual participant data to gather additional details on the causes and timing of death and modelling of the amount of variance in mortality that is explained by the reduced exacerbations. In contrast, the small change in lung function seems insufficient to account for a mortality benefit, but this needs to be tested in other, longer-term trials. It is interesting to contrast the finding of a possible mortality benefit of LABA/ICS combinations in COPD with the situation in asthma. In that disease, use of a LABA alone is associated with an increased death rate, but when combined with ICS, this is no longer the case (Rodrigo 2012).

Greater consistency was seen with the interventions for exacerbations, and the number of exacerbations was reduced by both FPS and BDF as was the proportion of participants with an exacerbation that was reduced by MF/F, compared with the component ICS alone. It is interesting to note that for the FPS studies, the reduction in the proportion of participants with an exacerbation was not significant, but those who experienced exacerbations had fewer of them, and fewer of these participants needed treatment with oral steroids. Yet, the differences in exacerbations with combination therapy did not translate to fewer hospitalisations for COPD, and this is difficult to explain. Hospitalisations are among the most costly aspects of COPD management, causing a negative impact on expectancy and quality of life. It is plausible that the hospital stays were shorter. Most studies clearly defined hospitalisation as a stay of at least 24 hours. Moreover, hospitalisations are relatively rare events that can be quantified only by larger and longer studies. To exemplify this point, on average about 7% of patients per year were hospitalised for COPD in the TORCH study, in part because of the lack of the inclusion criterion of a moderate to severe exacerbation 52 weeks before enrolment, as was required in more recent trials.

This review was unable to shed light on the debate as to whether or not ICS increase pneumonia in COPD, as it was administered in both intervention arms. This can be tested only when the comparator does not contain ICS. We found no significant difference, with

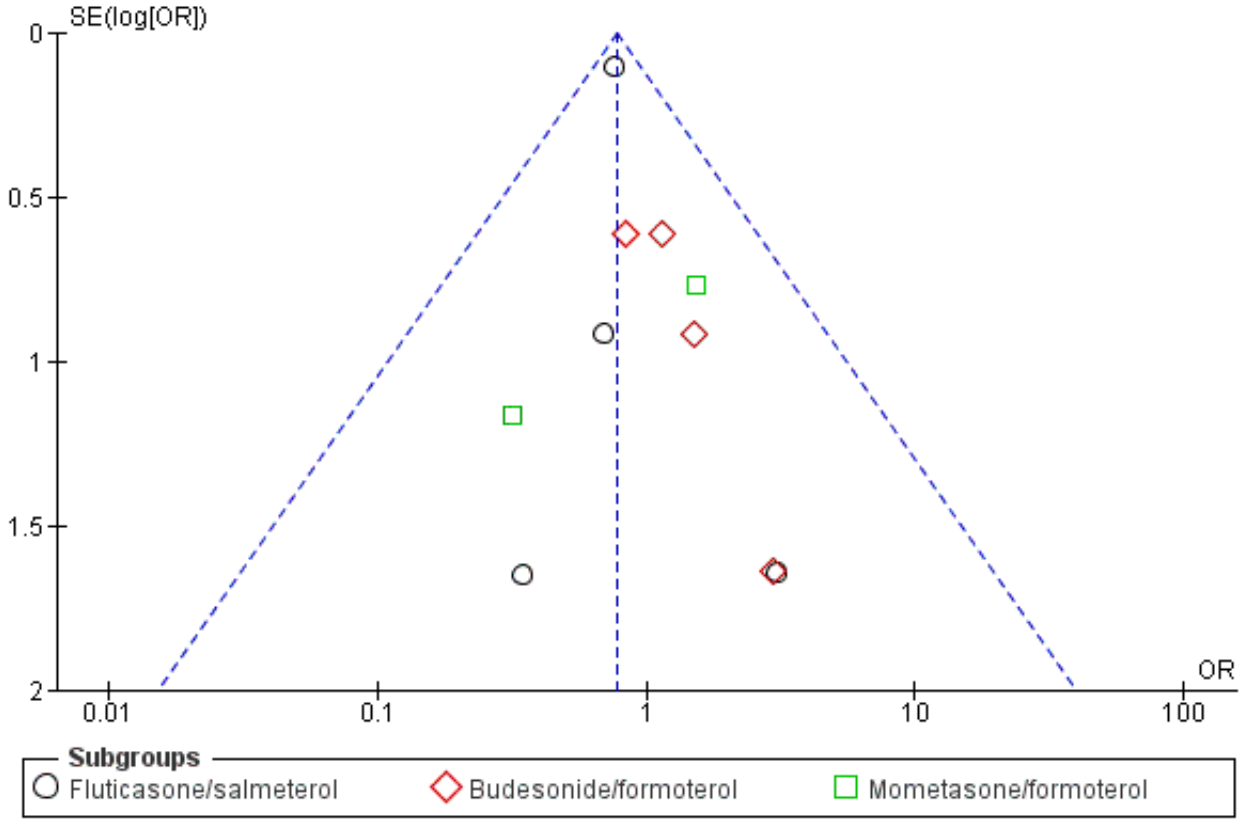
one interpretation being that LABAs do not reduce the risk of pneumonia with ICS. However, we also found that pneumonia was not a frequent adverse event when it was defined by chest x-ray. The shorter studies in Analysis 1.5 identified only 60 cases of pneumonia among 4222 participants (1.4%), in contrast to the three-year TORCH study, which reported 587 episodes of pneumonia from a sample of 3098 participants who received ICS treatment (19%). The results of Analysis 1.4 were the same, whether or not the TORCH study was included.

An internal consistency of the findings for primary outcomes and secondary outcomes was evident. All combination inhalers were associated with better lung function at the end of the study than was their ICS component, but this difference was relatively small. Two combinations (BDF and FPS) were associated with better quality of life, decreased use of rescue medication and withdrawals due to adverse events, but not with withdrawals due to lack of efficacy. The causes for withdrawals and for adverse events were coded slightly differently among the trials and thus were not combined, although this will be considered for future reviews. Improvement in quality of life was seen only when measured with the SGRQ, not with the CDRQ. The differences were small and were much less than a minimum clinically important difference (Jones 2002). This suggests that the clinical effects may be imperceptible to patients, or that any benefits may be offset by other harms. Fewer exacerbations may result in lower healthcare costs; although this review does not show a reduction in costly hospitalisations, bed days could still be reduced.

Overall completeness and applicability of evidence

In the review are fifteen studies, with a total of 7814 participants. All eligible studies addressed at least one of the primary outcomes. The participants and outcomes were typical of COPD patients. The most plentiful data are available for the FPS combination, which was the only one to show a mortality benefit. Fewer data are available for the MF/F combination, but no evidence suggests that it behaves differently from the other inhalers. A sufficient number of trials in the analysis provided the opportunity to include funnel plots for the primary analyses; they are presented in Figure 8.

Figure 8. Funnel plot of comparison: 1 All Combined Inhalers — Primary Outcomes, outcome: 1.4 Mortality.



We did not compare the efficacy and safety of combination therapy with the same treatment delivered in two separate inhalers, so we cannot comment on the relative effectiveness of a combination inhaler in comparison with the individual components delivered separately. Whilst we recognise that inhaled corticosteroids are rarely likely to be used as monotherapy in COPD, the trials in this review provide the best evidence for assessing the additional benefit of adding LABA to ICS.

Quality of the evidence

According to the results section, the risks of bias in allocation, blinding, attrition and selective reporting were judged to be low.

Potential biases in the review process

The Cochrane Airways Group provides an excellent level of support in the identification of potentially relevant trials. However, concern

with respect to study selection bias or publication bias in this process is inevitable. A matter of concern is that failure to identify unpublished trials may lead to an incomplete estimation of the effects of combined therapy versus ICS alone. However, an exhaustive search of the published literature, without language restrictions, for potentially relevant clinical trials was underpinned by a systematic search strategy to minimise the likelihood of bias. Of the 15 included studies, 13 were identified through the Cochrane Airways Group Register, an additional study (NCT00358358) was identified by the group from www.clinicaltrials.gov and SFCT01 was obtained via the GlaxoSmithKline Clinical Trials Register. Trial selection and data extraction followed a prespecified protocol, and the process was independently conducted by two investigators. Nevertheless, we acknowledge that additional unidentified trials may exist.

Agreements and disagreements with other studies or reviews

This Cochrane review confirms and builds upon an earlier one (Nannini 2007) In terms of exacerbations; reduction in moderate COPD exacerbation rates with combined therapy is now shown for three LABA/ICS combinations over ICS alone. A recent publication describing all inhaled medications in COPD concluded that LABA/ICS was associated with the lowest risk of death among all treatments (Dong 2013). Another systematic review (Drummond 2008) found in subgroup analyses that the highest risks of pneumonia were seen in those treated with the highest ICS dose (RR 1.46, 95% CI 1.10 to 1.92), a shorter duration of ICS use (RR 2.12, 95% CI 1.47 to 3.05) and combined ICS and bronchodilator therapy (RR 1.57, 95% CI 1.35 to 1.82), which does not disagree with our findings. We found a lower rate of pneumonia than was found by other studies when diagnosis was obtained by chest x-ray.

AUTHORS' CONCLUSIONS

Implications for practice

In participants with moderate and severe COPD, clinical benefit is evident when LABA and ICS are co-administered rather than ICS alone. Even though patients do not all perceive a better quality of life, they may live longer and have fewer exacerbations with combination therapy versus ICS alone. However, the evidence does not support the likelihood of being exacerbation-free or having fewer hospitalisations during the treatment period. The reduction in exacerbations varies, depending on the frequency of these events in individual patients. The mortality benefit will take at least two years to be evident and has been shown only for the FPS combination. Available evidence is most plentiful for the FPS combination and is heavily weighted by the three-year TORCH trial.

What is unclear is whether combination LABA/ICS therapy is better than LABA or ICS administered separately, or 4 times daily use of short-acting beta$_2$-agonists with ICS. All of the combination inhalers in this review were given twice a day. In addition to potential adherence benefits associated with the combination inhaler, its use guarantees that a patient receives both medicines simultaneously, which may not be the case if they are administered via separate inhalers. Further, evidence that LABAs and ICS have complementary and synergistic effects when delivered as combination therapy from a single inhaler is increasing (Hanania 2008). Although we conclude that unopposed ICS with no LABA co-administration is an inferior strategy in COPD, the minimum effective dose of inhaled steroids remains unclear. The three combination inhalers showed similar effects on review outcomes, including adverse effects, but should ideally be subjected to simple head-to-head comparisons over long periods of time. We have not been able to identify differences between the combination inhalers on the basis of currently available evidence.

Implications for research

The findings of the TORCH study need to be confirmed, as it is the only trial to show a decrease in mortality over the study period. We suggest that the circumstances surrounding any death should be fully documented and categorised as to likely clinical mechanism, and that all patients should have their vital status ascertained (whether they complete the study or drop out). If confirmed, a multipartite programme of clinical and basic science research should be enlisted to elucidate the mechanism of reduction in mortality, given that this is the only pharmaceutical yet shown to reduce mortality in COPD.

Future studies might address the impact of any reduction in exacerbations on health care utilisation (e.g. bed days, unscheduled general practitioner or emergency room visits). This could help inform a cost-benefit analysis.

Which combination and which dose and duration of ICS should be selected in COPD have not yet been explored adequately. We also do not know whether use of a combination is superior to separate administration of the two inhalers. Obviously the best way to test these relative benefits and adverse effects for each of the combinations is to perform a simple and direct long-term comparison among, for example, FPS, BDF and MF/F treatments. This might best be done in well-categorised, stable COPD patients receiving primary care.

New combinations of ICS with 24-hour LABAs such as indacaterol, vilanterol or olodaterol are emerging. Are these just "me too" medicines, or do they offer an advantage? Updating this review within a short space of time will be imperative.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bourbeau 2007

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial Trial duration: 16 weeks (including initial 4 week washout period from ICS and LABA)
Participants	Setting: 2 respiratory centres—the Montreal Chest Institute and Hopital Laval, Canada Participants randomly assigned: 39 in total. 19 to combined salmeterol xinafoate/fluticasone propionate (FPS), and 20 to fluticasone propionate (FP). Completed 19 (100%) FPS, 17 (85%) FP Severity: mild to very severe Diagnostic criteria: post-bronchodilator FEV_1 ≥ 25% of predicted value and FEV_1/forced vital capacity (FVC) ≤ 0.70 Baseline characteristics: mean age: 62 (SD: 9) FPS, 64 (SD: 8) FP. Severity: mild 4, moderate 6, severe/very severe 9 FPS; mild 3, moderate 10, severe/very severe 7 FP. Sex: male 19 (100%) FPS, male 15 (75%) FP. Baseline lung function: mean % predicted FEV_1 (SD) post-BD: 61 (24) FPS; 57 (19) FP. Smoking history: pack-years n (SD): 65 (33) FPS, 54 (24) FP Inclusion criteria: age ≥ 40 and ≤ 75 years; smoking history (≥ 10 pack-years); post-bronchodilator FEV_1 ≥ 25% of predicted value and FEV_1/forced vital capacity (FVC) ≤ 0.70 Exclusion criteria: no history of asthma, atopy (as assessed by an allergy skin prick test during screening) or any other active lung disease. Patients on home oxygen or with raised carbon dioxide tension (> 44 mm Hg), α1-antitrypsin deficiency, recent exacerbation (in the last 4 weeks), uncontrolled medical condition or hypersensitivity to inhaled corticosteroids and bronchodilators

Bourbeau 2007 *(Continued)*

Interventions	Run-in period: After a 4-week washout period from inhaled corticosteroids and long-acting b2 agonists, participants were randomly assigned to one of the treatment groups for 12 weeks Intervention: salmeterol xinafoate/fluticasone propionate (FPS; Advair/Seretide/Viani, control: GlaxoSmithKline) Diskus (50/500 mcg twice daily) versus fluticasone propionate (FP; Flovent/Flixotide, GlaxoSmithKline) Diskus (500 mcg twice daily) Co-medication: short-acting bronchodilators, short- and long acting anticholinergics or theophylline was allowed throughout the study. Oral corticosteroids and/or antibiotics could be given only in short courses for exacerbation treatment Inhaler device: Diskus
Outcomes	• Bronchial biopsies collected at visit 2 (before treatment initiation) and after 12 weeks of treatment at visit 4 • Pre- and post-bronchodilator spirometric measurements (FEV_1 and FVC) and administration of the CRQ were performed at visit 2 and after 4 and 12 w of treatment • The ATS-DLD 78 questionnaire was administered at visit 2, and measurements of lung volumes and carbon monoxide transfer factor (TLCO) were made • Bronchoalveolar lavage (BAL) fluid was collected after the bronchoscopy procedure and sputum induction was performed on three occasions (2–4 days before bronchoscopy at randomisation, after 4 weeks of treatment and at the end of treatment). Analysis of these samples (outcome 4) has not yet been completed and will be the subject of a future publication • Time points: data collected over 12-week period
Notes	This study was funded by an unrestricted research grant from GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a central computer-generated list of random numbers, which was stratified by centre and which used a block size of six set up by a data management/randomisation company (GEREQ, Montreal, Quebec). A procedure was established by GEREQ, which was in possession of the treatment code, to ensure that the treatment code would be broken only in accordance with the protocol and the criteria set up for unblinding the study (e.g. a serious adverse event possibly related to study treatment)
Allocation concealment (selection bias)	Low risk	As above
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias): Mortality	Unclear risk	0% withdrew on FPS and 15% on fluticasone
Incomplete outcome data (attrition bias): All other outcomes	Unclear risk	0% withdrew on FPS and 15% on fluticasone
Selective reporting (reporting bias)	Unclear risk	Not reported data for change in FEV_1 from baseline

Calverley 2003

Methods	Parallel-group study Randomisation: unclear Blinding: double-blind (identical inhaler devices) Trial duration: 52 weeks with two-week run-in of treatment optimisation Allocation concealment: unclear Withdrawals: stated Intention-to-treat analysis: stated Jadad score: 4
Participants	• Setting: 109 centres in 15 countries • Participants randomly assigned: 511 (BDF: 254; BUD: 257). Additional treatment groups not covered in this review: PLA: 256; F: 255 • Baseline characteristics: mean age: 64; mean FEV_1 L: 1; mean FEV_1 % predicted: 36; mean SGRQ: 48 • Inclusion criteria: GOLD defined COPD (stages 3 and 4); ≥ 40 years; COPD symptoms > 2 years; smoking history ≥ 10 pack-years; FEV_1/VC ≤ 70% pre-BD; FEV_1 ≤ 50% predicted; use of SABAs as reliever medication; ≥ 1 COPD exacerbation requiring OCS/antibiotics 2 to 12 months before 1st clinic visit • Exclusion criteria: history of asthma/rhinitis before 40 years of age; any relevant cardiovascular disorders; exacerbation of COPD requiring medical intervention within 4 weeks of run-in/during run-in phase; non-allowed medications: oxygen therapy; ICS (aside from study medication), disodium cromoglycate, leukotriene-antagonists, 5-LO inhibitors, BD (other than study medication and prn terbutaline 0.5 mg), antihistamines, medication containing ephedrine, β-blocking agents
Interventions	Run-in phase: All participants received 30 mg oral prednisolone BID and 2 × 4.5 mg formoterol BID (2 weeks). (1) BDF: 320/9 mcg bid. (2) BUD: 400 mcg bid. Additional treatment groups not covered in this review: (3) Placebo (lactose monohydrate). (4) F: 9 mcg bid. Inhaler device: Turbuhaler
Outcomes	Time to first exacerbation; change in post-medication FEV_1; number of exacerbations; time to and number of OCS-treated episodes; am and pm PEF, slow VC, HRQL, symptoms, use of reliever medication, AEs
Notes	Classified as 'poorly reversible population'. P values used to calculate pooled SEMs for the following outcomes: health-related quality of life; FEV_1; rescue medication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information reported
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias): Mortality	High risk	29% withdrew on BDF and 40% withdrew on budesonide
Incomplete outcome data (attrition bias): All other outcomes	High risk	29% withdrew on BDF and 40% withdrew on budesonide
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Doherty 2012

Methods	Randomised, placebo-controlled, double-blind, double-dummy, multicentre study Trial duration: 52 weeks (26-week treatment period and 26-week safety extension)
Participants	Setting: 164 centres in North, Central and South America, Europe, Africa, and Asia Participants randomly assigned: 225 to mometasone furoate and formoterol combined (MF/F), 253 to mometasone furoate (MF). Completed: 190 (84%) MF/F, 202 (80%) MF Severity: moderate to very severe Diagnostic criteria: males or females ≥ 40 years old with FEV_1/FVC ≤ 0.70, with a post-bronchodilator FEV_1 of 25% to 60% predicted Baseline characteristics: mean age (SD), y: 59.2 (9.1) MF/F, 60.5 (8.5) MF. Sex: male (%) 168 (75%) MF/F, 197 (78%) MF. Baseline lung function: mean FEV_1 reversibility %/mL (SD): 102 mL/8.69% (13.58) MF/F, 121 mL/9.67% (14.84) MF. Baseline lung function: mean % predicted FEV_1 (SD*) post BD*: 38.1 (10.8) MF/F, 40.2 (11.7) MF. Smoking history; pack-years n (SD): 54.8 (186.4) MF/F, 41.1 (23.5) MF Inclusion criteria: males or females ≥ 40 years old with FEV_1/FVC ≤ 0.70, with a post-bronchodilator FEV_1 of 25% to 60% predicted. Additional inclusion criteria were symptoms of COPD (e.g. chronic cough and sputum production not attributable to another disease) for at least 24 months before enrolment; current or ex-smokers with ≥ 10 pack-year history; no use of parenteral steroids, oral steroids or antibiotics within 4 weeks before screening; and clinically acceptable laboratory tests at screening. Female subjects of childbearing potential were required to use a medically acceptable, adequate form of birth control Exclusion criteria: current diagnosis of asthma, exhibited marked bronchodilator reversibility (increase in FEV_1 ≥ 400 mL) versus baseline pre-bronchodilator FEV_1, had a COPD exacerbation within 4 weeks before randomisation or required long-term administration of supplemental oxygen (> 15 hours/d). Additional exclusion criteria included a history of: lung cancer; alpha-1-antitrypsin deficiency; previous lung surgery; cataract extractions in both eyes; glaucoma or intraocular pressure ≥ 22 mm Hg in either eye; and the presence of clinically significant medical illness(es) that, in the opinion of the principal investigator, could interfere with the study
Interventions	Run in: 2-week washout/run-in period, in which previous long-acting COPD treatments (LABA, ICS, LABA/ICS FDC, or long-acting anticholinergic [e.g. tiotropium]) were discontinued and substituted with an open-label, short-acting β_2-agonist (SABA)/short-acting anticholinergic combination Intervention: 2 inhalations BID of MF/F 200/5 µg Control: 2 inhalations BID of MF 200 µg Inhaler device: MDI (spacers were not used in this study)
Outcomes	• Area under the curve from 0 to 12 hours post-dose (AUC 0–12 h) at the week 13 endpoint (last observation carried forward [LOCF]) to assess the added benefit of F on bronchodilation • AM predose (trough) FEV_1 at the week 13 endpoint to assess the added benefit of MF on trough FEV_1 • Assessment of changes from baseline in FEV_1 AUC 0–12 h at day 1, weeks 1, 13 and 26 and the 26-week endpoint (LOCF) • Assessment of changes from baseline in trough FEV_1 at each visit and at the 26-week endpoint The key secondary efficacy endpoints evaluated for the 26-week treatment period were: • respiratory health status scores, assessed with the St George's Respiratory Questionnaire (SGRQ); and • COPD symptom-free nights (combined score of 0 upon awakening for wheezing, cough and difficulty breathing); partly stable COPD and time to first mild, moderate or severe COPD exacerbation

Doherty 2012 *(Continued)*

	Time points: Efficacy and safety were evaluated over 6 months in the active treatment and placebo groups. 75% of participants in each active treatment group were randomly selected to participate in a 26-week safety extension, which began after the initial 26-week treatment period. Serial spirometry tests were performed at day 1, as well as at weeks 1, 13 and 26, which included measuring the pre-dose FEV_1 30 minutes and immediately before the AM dose, and then at 5, 15 and 30 minutes and at 1, 2, 3, 4, 6, 8,10, 11 and 12 hours post-dose
Notes	Funding: Merck Sharp & Dohme Corp

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned in a 1:1 ratio, but no specific information was included in trial report to clarify how participants were randomly assigned
Allocation concealment (selection bias)	Unclear risk	No specific information was included in trial report to clarify how participants were randomly assigned
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo-controlled, double-blind, double-dummy study. Double-blind treatment. All inhalers were MDIs Active and placebo MF/F and MF inhalers were identical in appearance, as were active and placebo F inhalers
Incomplete outcome data (attrition bias): Mortality	Unclear risk	15% withdrew on MF/F and 20% on mometasone furoate
Incomplete outcome data (attrition bias): All other outcomes	Unclear risk	16% withdrew on MF/F and 20% on mometasone furoate
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting

Hanania 2003

Methods	Parallel-group study Randomisation: method unclear Blinding: double-blind Allocation concealment: unclear Excluded: described Withdrawals: stated Trial duration: 24 weeks with 2-week run-in period. Intention to treat analysis: not stated Jadad score: 4
Participants	• Setting: USA, multi-centre (76 hospitals) • Participants randomly assigned: 366 (FPS: 183; FP: 183). Additional treatment groups not covered in this review; SAL: 177; PLA: 185 • Baseline characteristics: mean age: 64; mean FEV_1: 1.27 L (42% predicted) • Inclusion criteria: stable COPD, FEV_1 40% to 65% predicted, $FEV_1/FVC < 70\%$ predicted, symptoms of chronic bronchitis and moderate dyspnoea • Exclusion criteria: current diagnosis of asthma, use of oral steroids in past 6 weeks, abnormal ECG, LTOT, moderate to severe exacerbation in run-in. Other significant medical disorder

Hanania 2003 *(Continued)*

Interventions	Run-in: 2 weeks' treatment with placebo inhaler and prn SABA. (1) FPS 50/250 mcg bid. (2) FP 250 mcg bid. Additional treatment groups not covered in this review: (3) SAL 50 mcg bid. (4) placebo. Inhaler device: Diskus
Outcomes	Lung function: change in FEV_1 from baseline to end of study (M). PEF data not stratified by reversibility. Quality of life: CRDQ, CBSQ not stratified by reversibility. Dyspnoea and symptoms: transitional dyspnoea index, baseline dyspnoea index not stratified by reversibility. Exacerbations. Rescue salbutamol use
Notes	FEV_1 reversibility < 12% or 200 mL (of baseline FEV_1). Reversibility stratified data. Mean % increase non-reversible participants = 8.8

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias): Mortality	High risk	30% withdrew on FPS and 27% on fluticasone
Incomplete outcome data (attrition bias): All other outcomes	High risk	30% withdrew on FPS and 27% on fluticasone
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Lapperre 2009

Methods	Double-blind, parallel-group, placebo-controlled, randomised trial Trial duration: 30 months
Participants	Setting: 2 university medical centres in The Netherlands Participants randomly assigned: 28 to fluticasone and salmeterol (FPS) and 26 to fluticasone (FP). Completed (%) 21 (75%) FPS, 22 (85%) FP Severity: moderate to severe Diagnostic criteria: Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 2 and 3 Baseline characteristics: mean age (SD), y: 62 (8) FPS, 62 (8) FP. Sex: male (%) 22 (88%) FPS, 23 (88%) FP. Baseline lung function: post-bronchodilator FEV_1, mean % predicted FEV_1 (SD): 61 (9.4) FPS, 64 (9.1) FP. Change in FEV_1, % predicted (Reversibility in FEV_1 by 400 mcg salbutamol) 6.2 (6.3) FPS, 7.1 (4.0) FP. Smoking history: pack-years n (range) 47 (31-56) FPS, 44 (31-55) FP

Lapperre 2009 *(Continued)*

	Inclusion criteria: patients with COPD who were aged 45 to 75 years, were current or former smokers, had smoked for 10 or more pack-years and had lung function levels compatible with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 2 and 3 Exclusion criteria: asthma and receipt of ICS within 6 months before random assignment
Interventions	Intervention: fluticasone, 500 mcg twice daily, and salmeterol, 50 mcg twice daily, in a single inhaler for 30 months Control: fluticasone, 500 mcg twice daily, for 30 months Co-medication: short-acting bronchodilators Inhaler device: Diskus dry-powder inhalers
Outcomes	• Inflammatory cell counts in bronchial biopsies and induced sputum • Post-bronchodilator spirometry and hyperresponsiveness to methacholine PC20 • Dyspnoea score by the modified Medical Research Council (MRC) dyspnoea scale (range 1 to 5) • Health status by the St. George's Respiratory Questionnaire (SGRQ) (range 0 to 100; 100 = maximum disability) and the Clinical COPD Questionnaire (CCQ) (range 0 to 6; 6 = worst) Time points: symptoms, health status, self-reported smoking status, medication adherence and spirometry measured every 3 months, and checked adherence by counting the doses in the inhalers. Bronchoscopy, sputum induction and methacholine challenge at baseline and at 6 and 30 months
Notes	Funding: Netherlands Organization for Scientific Research, Netherlands Asthma Foundation, GlaxoSmithKline of The Netherlands, University Medical Center Groningen and Leiden University Medical Center

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	At entry, an independent randomisation centre provided participant and medication numbers by using a minimisation procedure that balanced treatment groups for centre, sex, smoking status, FEV_1/IVC (< 60% or ≥ 60%) and methacholine PC20 (the provocative concentration of methacholine that causes a 20% decrease in FEV_1) (< 2 mg/mL or ≥ 2 mg/mL)
Allocation concealment (selection bias)	Low risk	Study medications were individually numbered, and all active treatment medication and placebo were identical in appearance
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias): Mortality	High risk	25% withdrew on FPS and 15% on fluticasone
Incomplete outcome data (attrition bias): All other outcomes	High risk	25% withdrew on FPS and 15% on fluticasone
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting

Mahler 2002

Methods	Parallel-group study Randomisation: stratified by reversibility and investigative site Blinding: double-blind Allocation concealment: unclear Trial duration: 24 weeks Withdrawals: stated Intention-to-treat analysis: stated Jadad score: 3
Participants	• Setting: multi-centre study (65 centres) • Participants randomly assigned: 333 (FPS: 165; FP: 168). Additional treatment groups not covered in this review; SAL: 160; PLA: 181 • Baseline characteristics: mean age: 63; FEV_1: 1.2 to 3 L • Inclusion criteria: participants with COPD according to ATS guidelines. Baseline pre-bronchodilation FEV_1 < 65% predicted and > 0.70 L. Baseline pre-bronchodilation FEV_1/FVC < 70% predicted. Age > 40, 20 pack-year history smoking, day or night symptoms present on 4 out of last 7 days during run-in period • Exclusion criteria: history of asthma, corticosteroid use in last 6 weeks, abnormal ECG, oxygen therapy, moderate or severe exacerbation during run-in, significant concurrent disease
Interventions	Run-in: 2 weeks' treatment with placebo inhaler and prn SABA. (1) FPS 500/50 mcg bid. (2) FP 500 mcg bid. Additional treatment groups not covered in this review: (3) SAL 50 mcg bid. (4) Placebo. Inhaler device: Diskus
Outcomes	Lung function: change in FEV_1 from baseline to end of study (M). Quality of life: CRDQ, CBSQ not stratified by reversibility. Dyspnoea and symptoms: end of study dyspnoea (TDI). Exacerbations. Rescue salbutamol use
Notes	COPD participants reversible and non-reversible, < 15% (baseline) improvement in FEV_1 to salbutamol. Reversibility stratified data. Mean FEV_1 reversibility 11.0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias): Mortality	High risk	32% withdrew on FPS and 40% on fluticasone
Incomplete outcome data (attrition bias): All other outcomes	High risk	32% withdrew on FPS and 40% on fluticasone
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

NCT00358358

Methods	Randomised, double-blind, placebo-controlled, parallel-group study Trial duration: 12 weeks
Participants	Setting: 11 centres; four centres in the Russian Federation, four in the United States, two in Chile, and one in Estonia Participants randomly assigned: 39 to fluticasone propionate with salmeterol xinafoate (FPS) and 42 to fluticasone propionate (FP). N completed (%) 35 (90%) FPS, 35 (83%) FP. Severity: mild to moderate Diagnostic criteria: Participants had measured post-albuterol FEV_1/FVC ≤ 70% at Visit 1 (screening) and measured post-albuterol FEV_1 ≥ 30% and ≤ 70% of predicted normal Baseline characteristics: mean age (SD), y: 63.6 (7.75) FPS, 64.2 (11.23) FP. Sex: male (%) 32 (82%) FPS, 29 (69%) FP. Participants had measured post-albuterol FEV_1/FVC ≤ 70% at Visit 1 (screening) and measured post-albuterol FEV_1 ≥ 30% and ≤ 70% of predicted normal Inclusion criteria: Males or females of non-childbearing potential ≥ 40 years of age were eligible to participate if they had an established clinical history of COPD, evidence of bronchitis as a component of the COPD disease and a current or prior history of at least 10 pack-years of cigarette smoking. Participants had measured post-albuterol FEV_1/FVC ≤ 70% at Visit 1 (screening) and measured post-albuterol FEV_1 ≥ 30% and ≤ 70% of predicted normal Exclusion criteria: diagnosis of asthma, active respiratory disorder other than COPD, evidence of clinically significant uncontrolled non-pulmonary disease, carcinoma not in complete remission for last 5 years, lung volume reduction surgery in previous 12 months, nocturnal positive pressure for sleep apnoea. Other inclusion and exclusion criteria evaluated at the first study visit
Interventions	Intervention: fluticasone propionate 500 mcg with salmeterol xinafoate 50 mcg (FSC 500/50) Control: fluticasone propionate 500 mcg (FP 500) Details of co-medication not stated Inhaler: Advair DISKUS, Seretide Accuhaler
Outcomes	Pre-dose resistance difference between 5 Hz and 15 Hz (R5 to R15) as measured by IOS Pre-dose and 2-hour post-dose low-frequency reactance area (AX); 2-hour post-dose R5 to R15; post-albuterol computed tomography (CT) parameters of area of airway wall (Aaw) and area of airway lumen (Ai) Time points: pre-dose and 2 hours post-dose and change from baseline at 12 weeks
Notes	Funding: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not explicitly specified
Allocation concealment (selection bias)	Unclear risk	Not explicitly specified
Blinding (performance bias and detection bias)	Low risk	Double-blind study

NCT00358358 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias): Mortality	Unclear risk	10% withdrew on FPS and 17% on fluticasone
Incomplete outcome data (attrition bias): All other outcomes	Unclear risk	10% withdrew on FPS and 17% on fluticasone
Selective reporting (reporting bias)	Low risk	All outcomes pre-defined in the methods section are presented

SFCT01

Methods	Parallel-group design Randomisation: not clear Blinding: double-blind Allocation concealment: unclear Excluded: not described Withdrawals: described Trial duration: 52 weeks Withdrawals: stated Intention-to-treat analysis: stated Jadad score: 3
Participants	• Setting: 49 centres in Italy, 7 in Poland • Participantsrandomly assigned: 256 (FP/SAL: 131; FP: 131) ○ Additional treatment groups not covered in this review: PLA: 125 • Baseline characteristics: 65 years; FEV_1: not reported • Inclusion criteria: M/F ≥ 40 years of age; diagnosis of COPD; ≥ 10 pack-year; FEV_1 < 70% predicted and > 800 mL; reversibility < 10% predicted normal (and < 200 mL) • Exclusion criteria: not described
Interventions	Run-in: 2 weeks. All maintenance LABA and ICS treatment ceased. (1) FPS 500/50 mcg bid. (2) FP 500 mcg bid. Additional treatment groups not covered in this review: (3) Placebo. Inhaler device: MDI
Outcomes	Withdrawals; exacerbations; FEV_1; adverse events
Notes	Unpublished study downloaded from ctr.gsk.co.uk

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias)	Low risk	Identical inhaler devices

SFCT01 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias): Mortality	High risk	34.4% withdrew on FPS and 26% withdrew on fluticasone
Incomplete outcome data (attrition bias): All other outcomes	High risk	34.4% withdrew on FPS and 26% withdrew on fluticasone
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Sin 2008

Methods	Double-blind randomised, placebo-controlled trial Trial duration: 4-week treatment period
Participants	Setting: 11 centres in western Canada Participants randomly assigned: 92 to fluticasone propionate with salmeterol xinafoate (FPS) and 87 to fluticasone propionate (FP). N completed (%) 88 (96%) FPS, 85 (98%) FP Severity: moderate Diagnostic criteria: Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Spirometric criteria included FEV_1 of less than 80% of predicted with an FEV_1 to FVC ratio of less than 0.70 (post-bronchodilator values) Baseline characteristics: mean age (SD), y: 69.6 (9.3) FPS, 70.2 (9.0) FP. Sex: male 60.9% FPS, 64.4%. Baseline lung function: mean FEV_1 L (SD) 1.33 (0.62) FPS, 1.42 (0.53) FP Baseline lung function: mean % predicted FEV_1 (SD): 45.8 (16.4) FPS, 49.2 (15.3) FP. Smoking history: pack-years n (SD): 56.5 (39.0-73.7) FPS, 63.0 (50.0-75.8) FP Inclusion criteria: Spirometric criteria included FEV_1 of less than 80% of predicted with an FEV_1 to FVC ratio of less than 0.70 (post-bronchodilator values). Cigarette smoking history of more than 10 pack-years, clinical stability as defined by the absence of exacerbations for at least 4 weeks, age ≥ 40 years and absence of known chronic systemic infections or inflammatory conditions (e.g. rheumatoid arthritis, systemic lupus erythematosus, active sarcoidosis) Exclusion criteria: any known disseminated malignancy, known chronic systemic infection or inflammatory condition (e.g. rheumatoid arthritis, systemic lupus erythematosus, active sarcoidosis), previous solid organ transplantation, myocardial infarction or cerebrovascular accident within the past 3 months before study enrolment, females of child-bearing age (i.e. must be amenorrhoeic for at least 12 months), participation in a drug trial within the 4 weeks before study enrolment, any participant who is unlikely to survive longer than 6 months, recent upper respiratory tract infection within the 4 weeks before enrolment, unable to follow instructions, patients taking chronic oral theophyllines and unable or unwilling to come off theophyllines for the study period, oral corticosteroids or long-term immunosuppressive agents
Interventions	Run-in period: All participants underwent a run-in phase, during which they received fluticasone (500 mg twice daily) for 4 weeks. This was followed by a medication withdrawal phase, wherein inhaled corticosteroids, LABAs and theophylline products were withdrawn for 4 weeks Intervention: inhaled fluticasone/salmeterol combination (500/50 mcg twice daily) Control: inhaled fluticasone (500 mcg twice daily) Co-medication: all other medications, including short-acting β_2-adrenoceptor agonists, anticholinergics and tiotropium, were permitted during all phases of the study

Sin 2008 *(Continued)*

	Inhaler device: Diskus inhaler
Outcomes	Primary outcome. C-reactive protein (CRP) level. Secondary outcomes. • Changes in other inflammatory mediators such as IL-6 and surfactant protein D (SP-D). • Changes in SGRQ scores. • Changes in FEV_1. • Rates of exacerbations Time points: visit 1 (enrolment), visit 2 (run-in phase; 1 m fluticasone), visit 3 (withdrawal phase), visit 4 (RCT phase)
Notes	Funding: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally and was stratified according to current smoking status with allocation concealment in a 1 (placebo arm) to 2 (fluticasone arm) to 2 (fluticasone/salmeterol) distribution ratio
Allocation concealment (selection bias)	Low risk	As above
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias): Mortality	Low risk	4% withdrew on FPS and 2% on fluticasone
Incomplete outcome data (attrition bias): All other outcomes	Low risk	4% withdrew on FPS and 2% on fluticasone
Selective reporting (reporting bias)	Low risk	All outcomes pre-defined in the methods section are presented

Szafranski 2003

Methods	Parallel-group study Randomisation: randomised, double-blind, placebo-controlled parallel-group trial Duration: 52 weeks. Methods of randomisation: computer-generated scheme at AstraZeneca, Lund, Sweden. At each centre, eligible patients received an enrolment code, and then after run-in, participants were allocated the next consecutive participant number Allocation concealment: adequate Blinding: All the Turbuhaler inhalers were identical to ensure that the participant, the pharmacist and the investigator were blinded to the allocated treatment Withdrawals: stated Intention-to-treat analysis: stated

Szafranski 2003 *(Continued)*

	Jadad score: 5
Participants	• Setting: 89 centres in Central & South America, Europe and South Africa • Participants: 406 (BDF: 208; BUD: 198) • Additional treatment groups not covered in this review • ○ F: 201; PLA: 205 • Baseline characteristics: mean age: 64 years; mean FEV_1 % predicted: 36%; mean reversibility 6% predicted normal • Inclusion criteria: age ≥ 40 years; COPD for ≥ 2 years; smoking history ≥ 10 pack-years; FEV_1 ≤ 50% predicted; FEV_1/FVC ≤ 70%; symptom score ≥ 2 during at least 7 days of run-in; use of bronchodilators for reliever medication; ≥ 1 severe COPD exacerbation within 2 to 12 months before study entry • Exclusion criteria: history of asthma/rhinitis before age 40; use of beta-blockers; current respiratory tract disease other than COPD
Interventions	Run-in: 2 weeks. Treatment with prn SABA only. (1) BDF 320/9 mcg bid. (2) BUD 400 µg bid. Additional treatment groups not covered in this review: (3) Placebo. (4) F 9 µg bid. Inhaler device: Turbuhaler
Outcomes	Symptoms, adverse events, exacerbations, lung function
Notes	Classified as 'poorly reversible' subgroup. Jadad score: 5. Exacerbation defined as requirement of oral steroids and/or antibiotics and/or hospitalisation for respiratory symptoms. Mild exacerbation defined as requirement of ≥ 4 inhalations per day. P values used to calculate pooled SEMs for following outcomes: symptoms; rescue medication usage

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	As described above
Allocation concealment (selection bias)	Low risk	As described above
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias): Mortality	High risk	28% withdrew on BDF and 31% on budesonide
Incomplete outcome data (attrition bias): All other outcomes	High risk	28% withdrew on BDF and 31% on budesonide
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Tashkin 2008

Methods	Randomised, double-blind, double-dummy, placebo-controlled, parallel-group study

Tashkin 2008 *(Continued)*

	Trial duration: 6 months
Participants	Setting: 194 centres in the US, Czech Republic, the Netherlands, Poland and South Africa Participants randomly assigned: 277 to Symbicort (Sym) and 275 to budesonide (Bud). Completed: 238 (85.9%) Sym, 212 (77.1%) Bud Severity: moderate to very severe Diagnostic criteria: pre-bronchodilator $FEV_1 \leq 50\%$ of predicted normal. Prebronchodilator $FEV_1/FVC < 70\%$ Baseline characteristics: mean age (SD), y: 63.1 (9.0) Sym, 63.4 (8.8) bud. Sex: male,n (%) 188 (67.9%) Sym, 186 (67.6%) Bud. Baseline lung function: mean % predicted FEV_1 (SD) post-bronchodilator: 39.05 (11.78) Sym, 39.72 (12.01) bud. Smoking history: pack-years medians: 40 Sym, 41 bud Inclusion criteria: ≥ 40 years of age. Clinical diagnosis of COPD and symptoms for > 2 years, a history of at least 1 COPD exacerbation treated with a course of oral corticosteroids and/or antibiotics within 1 to 12 months before screening (visit 1), use of an inhaled SABA as rescue medication, pre-bronchodilator $FEV_1 \leq 50\%$ of predicted normal, pre-bronchodilator $FEV_1/FVC < 70\%$, Smoking history ≥ 10 pack-years, score ≥ 2 on the modified MRC dyspnoea scale, a breathlessness-cough-sputum scale (BSCC) score ≥ 2 per day for at least half of the 2-week run-in period Exclusion criteria: history of asthma or allergic rhinitis before 40 years of age, significant/unstable cardiovascular disorder, clinically significant respiratory tract disorder other than COPD Homozygous α_1-antitrypsin deficiency or any other clinically significant co-morbidities that could preclude participation in the study or interfere with the study results, as determined by the investigator. If additions or alterations to their usual COPD maintenance therapy needed or an increment in rescue therapy due to worsening symptoms within 30 days before screening or during the run-in period. Oral or ophthalmic non-cardioselective B-adrenoceptor antagonists, oral corticosteroids, pregnancy and breast feeding were excluded
Interventions	Run-in period: 2-week run-in period, during which participants continued ICS monotherapy if they had previously been receiving ICS alone or in combination with a LABA, and participants who had previously been receiving anticholinergic therapies were placed on stable doses of ipratropium bromide. A SABA agonist was allowed for rescue use. At visit 2 (after the run-in period), any ICS therapy was discontinued, and all participants were then given study rescue medication (salbutamol pMDI) for as-needed use Intervention: Symbicort 160/4.5 µg × 2 inhalations (320/9 µg) bid Control: budesonide 160 µg × 2 inhalations (320 µg) bid Co-medication: ephedrine-free (or other bronchodilator-free) antitussives and mucolytics, nasal corticosteroids, stable-dose non-nebulised ipratropium bromide (not to be used within 8 hours of each clinic visit), oral or ophthalmic cardioselective β-adrenoceptor antagonists, study-provided salbutamol as rescue medication (not to be used within 6 hours of each clinic visit). Medications allowed for exacerbations after randomisation: oral and parenteral corticosteroids, acute use of xanthines, increased use of inhaled β_2-adrenoceptor agonists and ipratropium bromide, nebulised β_2-adrenoceptor agonists and ipratropium bromide Inhaler device: formoterol DPI (Turbuhaler), budesonide via an HFA pMDI
Outcomes	Primary outcomes: pre-dose FEV_1 and 1 hour post-dose FEV_1 Secondary outcomes: • Secondary pulmonary function variables: 12-hour spirometry, pre-dose and 1-hour post-dose IC, morning and evening PEFR • Secondary efficacy variables: dyspnoea, HR-QOL using the SGRQ, COPD exacerbations • Secondary symptom variables: cough and sputum score, sleep score, rescue medication use

Tashkin 2008 *(Continued)*

	Time points: screening visit (visit 1), a 2-week run-in period, a randomisation visit (visit 2), four subsequent visits during the 26-week treatment period and a follow-up telephone call 30 days after the last study visit. Visits 3 to 6 were scheduled at 1, 2, 4 and 6 months after randomisation
Notes	Funding: AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned in balanced blocks according to a computer-generated randomisation scheme at each site to one of six treatments administered twice daily
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias): Mortality	High risk	14.1% withdrew on BDF and 22.9% on budesonide
Incomplete outcome data (attrition bias): All other outcomes	High risk	14.1% withdrew on BDF and 22.9% on budesonide
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting

Tashkin 2012

Methods	Randomised, placebo-controlled, parallel-group, multicenter, double-blind, double-dummy study Trial duration: 26 weeks
Participants	Setting: 131 centres located in South America, Asia, Africa, Europe and North America Participants randomly assigned: 217 to mometasone furoate and formoterol (MF/F) and 210 to mometasone furoate (MF). N completed (%): 176 (81%) MF/F, 164 (78%) MF Severity: moderate to very severe COPD Diagnostic criteria: pre-bronchodilator FEV_1/forced vital capacity (FVC) ratio ≤ 0.70 Baseline characteristics: mean age (SD), y: 59.7 (9.1) (MF/F), 59.8 (8.9) (MF). Sex: male (%) 171 (79%) (MF/F), 164 (78%) (MF). Baseline FEV_1 AUC(0–12 h); LS mean mL 1186 (MF/F), 1255 (MF). Smoking history: mean pack-years (SD) 39.73 (28.43) (MF/F), 40.03 (29.28) (MF) Inclusion criteria: adult males and females who were current or former smokers with a smoking history of ≥ 10 pack-years, ≥ 40 years of age, diagnosis of moderate to very severe COPD, based on a pre-bronchodilator FEV_1/forced vital capacity (FVC) ratio ≤ 0.70. Symptoms of COPD (chronic cough and sputum production not attributable to another disease process) for ≥ 24 months, post-bronchodilator FEV_1 ≤ 60% predicted normal and ≥ 25% predicted normal at screening, Females with childbearing potential were required to use a medically acceptable form of birth control Exclusion criteria: patients with an increase in absolute volume ≥ 400 mL at the screening visit or before the baseline visit within 30 minutes after administration of 4 inhalations of albuterol/salbutamol (total

Tashkin 2012 *(Continued)*

	dose of 360 to 400 mcg) or nebulised 2.5 mg albuterol-salbutamol. Patients requiring long-term administration of oxygen (.15 hours per day) or who experienced an exacerbation of COPD requiring medical intervention within four weeks before randomisation, β-blocking agents, or treatment with additional excluded medication (other than SABA-short-acting anticholinergic to be used as rescue medication) were not enrolled, Patients with a history of significant medical illness or a disorder that might interfere with the study or that required treatment that might interfere with the study, pregnancy or breast-feeding, a diagnosis of asthma, lung cancer, or alpha-1-antitrypsin deficiency or a history of lobectomy, pneumonectomy, lung volume reduction surgery, cataract extractions in both eyes or other significant ocular problems (glaucoma, trauma, opacification)
Interventions	Run-in period: open-label run-in period in which long-acting bronchodilators and corticosteroids were discontinued and were substituted with a short-acting β_2-agonist (SABA)-anticholinergic fixed-dose combination Intervention: MF/F 400/10 mcg bid Control: MF 400 mcg bid Co-medication: unclear Inhaler device: MDI
Outcomes	Mean change from baseline in FEV_1 area under the curve from 0 to 12 hours post-dose ($AUC_{0-12\,h}$) at the week 13 endpoint Mean change from baseline in morning pre-dose FEV_1 at the week 13 endpoint Change in health status as assessed according to total scores on the St George's Respiratory Questionnaire (SGRQ) Change in symptom-free nights Time-to-first mild, moderate or severe COPD exacerbation The proportion of participants with partly stable COPD Time points: All randomly assigned participants had study visits at screening, baseline(day 1) and weeks 1, 4, 13 and 26 in the treatment period. Participants in the safety extension had additional visits at weeks 39 and 52
Notes	Funding: Merck Sharp & Dohme Corp

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The sponsor's statistician produced a computer-generated randomisation schedule with treatment codes in blocks using SAS. Randomisation was stratified according to the participant's smoking status at the time of randomisation. Random treatment assignment was provided to the investigative site by means of an interactive voice response system at the time participants were randomly assigned
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind

Tashkin 2012 *(Continued)*

Incomplete outcome data (attrition bias): Mortality	High risk	19% withdrew on MF/F and 22% on MF
Incomplete outcome data (attrition bias): All other outcomes	High risk	19% withdrew on MF/F and 22% on MF
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting

TORCH

Methods	Parallel-group design Randomisation: permuted block randomisation with stratification for smoking status and country Blinding: double-blind (identical inhaler devices) Allocation concealment: adequate Excluded: described Withdrawals: described Trial duration: 156 weeks Withdrawals: stated Intention-to-treat analysis: stated Jadad score: 5
Participants	• Setting: 444 centres in North America, Central America and Asia Pacific • Participants randomly assigned: 3091 (FP/SAL: 1546; FP: 1551) • Additional treatment groups not covered in this review: ○ SAL: 1542; PLA: 1545 • Baseline characteristics: 65 years; male: 76% • Inclusion criteria: M/F 40 to 80 years of age; diagnosis of COPD (ERS); < 10% reversibility of predicted FEV_1; FEV_1/FVC ratio < 70%; FEV_1 < 60% predicted; ≥ 10 pack-year smoking history • Exclusion criteria: asthma or respiratory diseases other than COPD; LVRS/lung transplant; requirement for > 12 hours/d LTOT; long-term OCS therapy; serious uncontrolled disease likely to interfere with medication/cause of death in next three years
Interventions	Run-in: 2 weeks. All maintenance treatment with ICS and LABA ceased. (1) FP/SAL combination 500/50 mcg BID. (2) FP 500 mcg BID. Additional treatment groups not covered in this review: (3) Placebo. (4) SAL 50 mcg BID Inhaler device: DPI
Outcomes	All-cause mortality; change in SGRQ; exacerbations (requiring antibiotics, steroids, hospitalisation or combination of these); lung function; withdrawals; adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	As described above
Allocation concealment (selection bias)	Low risk	As described above
Blinding (performance bias and detection bias)	Low risk	Idenitical inhaler devices

TORCH *(Continued)*
All outcomes

Incomplete outcome data (attrition bias): Mortality	Low risk	Mortality was the primary outcome and vital status was checked in those who withdrew
Incomplete outcome data (attrition bias): All other outcomes	High risk	34.1% withdrew on FPS and 38.3% on fluticasone
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

TRISTAN

Methods	Parallel-group design Randomisation: computer generated. Numbers were generated off-site. Once a treatment number had been assigned to a participant, it could not be assigned to any other participant Blinding: double-blind. Participants received identically packaged and presented placebos Withdrawals: described Trial duration: 2-week run-in period, 52 weeks treatment, 2-week follow-up Intention-to-treat analysis: stated Jadad score: 5
Participants	• Setting: 196 centres in Europe, South Africa and Australia • Participants randomly assigned: 733 (FPS: 358; FP: 375) • Additional treatment groups not covered in this review: ○ SAL: 372; PLA: 361 • Baseline characteristics: mean age 63 years, mean FEV_1 1.26 L (44% predicted) • Inclusion criteria: baseline FEV_1 25% to 75% predicted; FEV_1/ FVC ratio ≤ 70%; poor reversibility < 10% increase of predicted FEV_1 30 minutes after inhaling 400 mcg salbutamol; at least 10 pack-year smoking history; history of exacerbations (at least 1 in the last year) requiring OCS and/or antibiotics. At least one episode of acute COPD per year in the previous 3 years • Exclusion criteria: respiratory disorders other than COPD. Oxygen treatment, systemic corticosteroids, high doses of inhaled corticosteroids (> 1000 mcg daily beclomethasone dipropionate, budesonide or flunisolide or > 500 mcg daily fluticasone) or antibiotics in the four weeks before the 2-week run-in period
Interventions	Run-in: 2 weeks. All maintenance treatment with ICS and LABA ceased. (1) FPS 50 mcg/500 mcg bid. (2) FP 500 mcg bid. Additional treatment groups not covered in this review: (3) SAL 50 mcg bid. (4) Placebo. Inhaler device: DPI
Outcomes	FEV_1; PEF; exercise tolerance; quality of life: SGRQ; dyspnoea and symptoms (symptom score for shortness of breath, cough and sputum production); exacerbations (defined as requirement for antibiotics, oral steroids or both); rescue salbutamol use
Notes	FEV_1 reversibility (% predicted normal), Mean reversibility (% predicted) 3.8

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	As described above

TRISTAN *(Continued)*

Allocation concealment (selection bias)	Low risk	As described above
Blinding (performance bias and detection bias) All outcomes	Low risk	Idenitical inhaler devices
Incomplete outcome data (attrition bias): Mortality	High risk	25% withdrew on FPS and 29% on fluticasone
Incomplete outcome data (attrition bias): All other outcomes	High risk	25% withdrew on FPS and 29% on fluticasone
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

Zhong 2012

Methods	Multicentre, randomised, parallel-group, double-blind, double-dummy study Trial duration: 24 weeks
Participants	Setting: 12 centres in China Participants randomly assigned: 156 to budesonide/formoterol (BUD/FORM), 152 to budesonide (BUD). N completed (%) 133 (85.3%) BUD/FORM, 117 (77.0%) BUD Severity: moderate to very severe Diagnostic criteria: FEV_1 ≤ 50% predicted; FEV_1/FVC < 70% Baseline characteristics: mean age (SD), y: 65.70 (8.75) BUD/FORM, 64.71 (9.61) BUD. Sex: male (%) 153 (98.1%) BUD/FORM, 140 (92.1) BUD. COPD severity: moderate: 7 (4.5%), severe: 98 (62.8%), very severe: 51 (32.7%) BUD/FORM, moderate: 5 (3.3%) severe: 94 (61.8%), very severe: 53 (34.9%) BUD. Baseline lung function (post-bronchodilator): mean % predicted FEV_1 (SD): 36.15 (10.97) BUD/FORM, 36.28 (10.40) BUD Inclusion criteria: male or female outpatients ≥ 40 years with diagnosis of COPD; pre-bronchodilator FEV_1 ≤ 50% predicted; FEV_1/FVC < 70%; at least 1 COPD exacerbation (defined as use of oral/IV corticosteroids and/or antibiotics and/or emergency room treatment/hospitalisation due to respiratory symptoms) during 2 to 12 months before the study; a smoking history of ≥ 10 pack-years Exclusion criteria: a history of asthma; seasonal allergic rhinitis with onset < 40 years; COPD exacerbation within 4 w of study entry or during the run-in period; post-bronchodilator FEV_1 ≥ 80% of predicted normal value during the reversibility test at baseline; any other serious diseases or disorders that were considered to influence the study results or to increase the risk of participation in the study
Interventions	Run-in period: 2-week oral prednisolone acetate 20 mg/d + prn terbutaline 0.25 mg/dose Intervention: budesonide/formoterol (160/4.5 mcg/dose) 2 inhalations BID Control: budesonide (200 mcg/dose) 2 inhalations BID Co-medication: terbutaline 0.25 mg/dose prn. No other bronchodilator was permitted Inhaler device: Turbuhaler

Zhong 2012 *(Continued)*

Outcomes	1-hour post-dose FEV_1 FVC (pre-dose and 1 hour post-dose) FEV_1 (pre-dose and 15 minutes post-dose) St George's Respiratory Questionnaire (SGRQ) score COPD symptom scores Morning and evening PEF COPD exacerbations Time points: weeks 0, 2, 4, 8, 12, 19, 24
Notes	Funding: Astra Zeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation schedule was generated using a computer program at AstraZeneca, Sweden. Participants were randomly assigned in equal proportions to either BUD/FORM and placebo, or BUD and placebo
Allocation concealment (selection bias)	Low risk	Treatment codes were not broken for the planned analyses of data until all decisions on the evaluable data from each individual participant had been made and documented
Blinding (performance bias and detection bias) All outcomes	Low risk	All participants used the two dry powder inhalers during the treatment period: one containing active drug and one containing placebo (double-dummy design)
Incomplete outcome data (attrition bias): Mortality	High risk	14.7% withdrew on BDF and 23% on budesonide
Incomplete outcome data (attrition bias): All other outcomes	High risk	14.7% withdrew on BDF and 23% on budesonide
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting

ICS = inhaled corticosteroids; OCS = oral corticosteroids; LABA = long-acting β_2-agonist; SABA = short-acting β_2-agonist; FPS = salmeterol xinafoate/fluticasone propionate; FP = fluticasone propionate; BUD = budesonide; BDF = budesonide/formoterol; MF/F = mometasone furoate and formoterol; MF = mometasone furoate; SAL = salmeterol; F = fluticasone; PLA = placebo; BiD = twice daily; AEs = adverse events; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; VC = vital capacity; PEF = peak expiratory flow; SGRQ = St. George's Respiratory Questionnaire; GOLD = Global Initiative for Chronic Obstructive Lung Disease; CRDQ = Chronic Respiratory Disease Questionnaire; TDI = Transitional Dyspnoea Index; BCSS = breathlessness, cough and sputum score; CCQ = Clinical COPD Questionnaire; CBSQ = Chronic Bronchitis Symptoms Questionnaire; MDI = metered-dose inhaler; DPI = dry powder inhaler; ATS-DLD = American Thoracic Society-Division of Lung Disease; TLCO = carbon monoxide transfer factor; BAL = bronchoalveolar lavage; HRQL = health-related quality of life; LTOT = long-term oxygen therapy.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aaron 2007	Combined ICS/LABA therapy not compared with ICS
Bathoorn 2008	Trial focuses on treatment of COPD exacerbations
Bleecker 2011	Assessment of effects of Gly16Arg genotype in response to budesonide/formoterol in two clinical trials
Calverley 2005	Combined ICS/LABA therapy not compared with ICS
Cukier 2007	Nebulised saline versus nebulised salbutamol and a cross-over trial
D5899C00001	Combined ICS/LABA therapy not compared with ICS
De Backer 2011	Assessment of the acute effect of budesonide/formoterol
Ferguson 2006	Trial did not compare combined ICS/LABA therapy versus ICS
GlaxoSmithKline 2004	Trial includes patients with asthma
GlaxoSmithKline 2004a	Trial includes patients with asthma
GlaxoSmithKline 2006	Focus is on sputum cell measures of inflammation
Golabi 2006	Cross-over trial comparing tiotropium versus salmeterol/fluticasone
Haque 2006	Focuses on macrophages and glucoreceptor proteins and a cross-over trial
INSPIRE	Trial compared tiotropium versus seretide
Jiang 2011	Combined ICS/LABA therapy not compared with ICS
Jung 2012	Combined ICS/LABA therapy not compared with ICS
Laties 2010	Combined ICS/LABA therapy not compared with ICS
Lindberg 2007	Cross-over study examining effect of only a single dose (two inhalations) of budesonide/formoterol, salmeterol/fluticasone, salbutamol or placebo
Mittmann 2010	Participants were randomly assigned to tiotropium+combined ICS/LABA therapy versus tiotropium+placebo
Mittmann 2011	Participants were randomly assigned to tiotropium+combined ICS/LABA therapy versus tiotropium+placebo
NCT00269126	Cross-over study examining effect of adding fluticasone to salmeterol
NCT00476099	Combined ICS/LABA therapy not compared with ICS
NCT00549146	ICS dose in the ICS/LABA condition was < 80% the ICS dose in the ICS-only condition. The steroid dose in the ICS/LABA combination therapy group is not equivalent to the steroid dose in the ICS-only group; the trial was designed to compare double the dose of ICS with an ICS/LABA combination
Rennard 2008	No steroid control arm
Rennard 2009	No steroid control arm

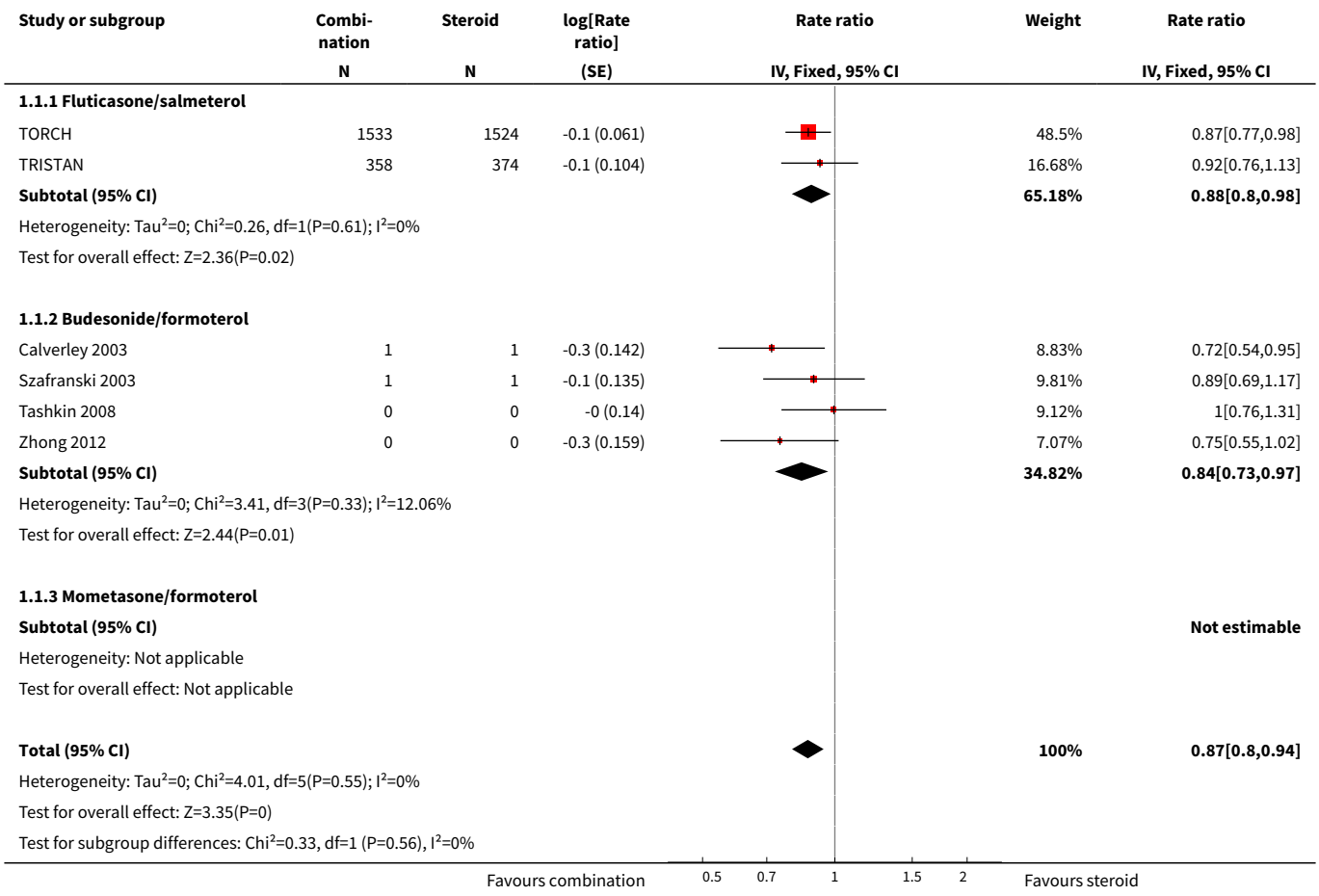
Study	Reason for exclusion
Rennard 2009a	No steroid control arm
Rennard 2010	No steroid control arm
Sagcan 2007	Focus of study is on sleep quality of COPD patients
Schermer 2007	ICS dose in the ICS/LABA condition was < 80% the ICS dose in the ICS-only condition. The steroid dose in the ICS/LABA combination therapy group is not equivalent to the steroid dose in the ICS-only group; the trial was designed to compare double the dose of ICS with an ICS/LABA combination
SCO100250	Combined ICS/LABA therapy not compared with ICS
SCO40043	Combined ICS/LABA therapy not compared with ICS
Sethi 2006	Bacterial colonisation in sputum and a cross-over trial
Shaker 2009	Trial compared budesonide versus placebo
Sharafkhaneh 2011	Combined ICS/LABA therapy not compared with ICS
Southard 2011	Combined ICS/LABA therapy not compared with ICS
Stallberg 2008	Trial focuses on treatment of COPD exacerbations
Sutherland 2006	Trial compares seretide versus salmeterol
Trofimenko 2006	Trial not blinded and no steroid control arm
Welte 2009	Trial focuses on budesonide/formoterol added to tiotropium
Welte 2009a	Trial focuses on budesonide/formoterol added to tiotropium
Welte 2009b	Trial focuses on budesonide/formoterol added to tiotropium
Welte 2009c	Trial focuses on budesonide/formoterol added to tiotropium
Welte 2009d	Trial focuses on budesonide/formoterol added to tiotropium
Wilson 2007	Comparison of patients' preferences among 4 dry powder inhalers
Worth 2009	Combined ICS/LABA therapy not compared with ICS
Worth 2009a	Combined ICS/LABA therapy not compared with ICS
Worth 2010	Combined ICS/LABA therapy not compared with ICS
Zheng 2006	Combined ICS/LABA therapy not compared with ICS

DATA AND ANALYSES

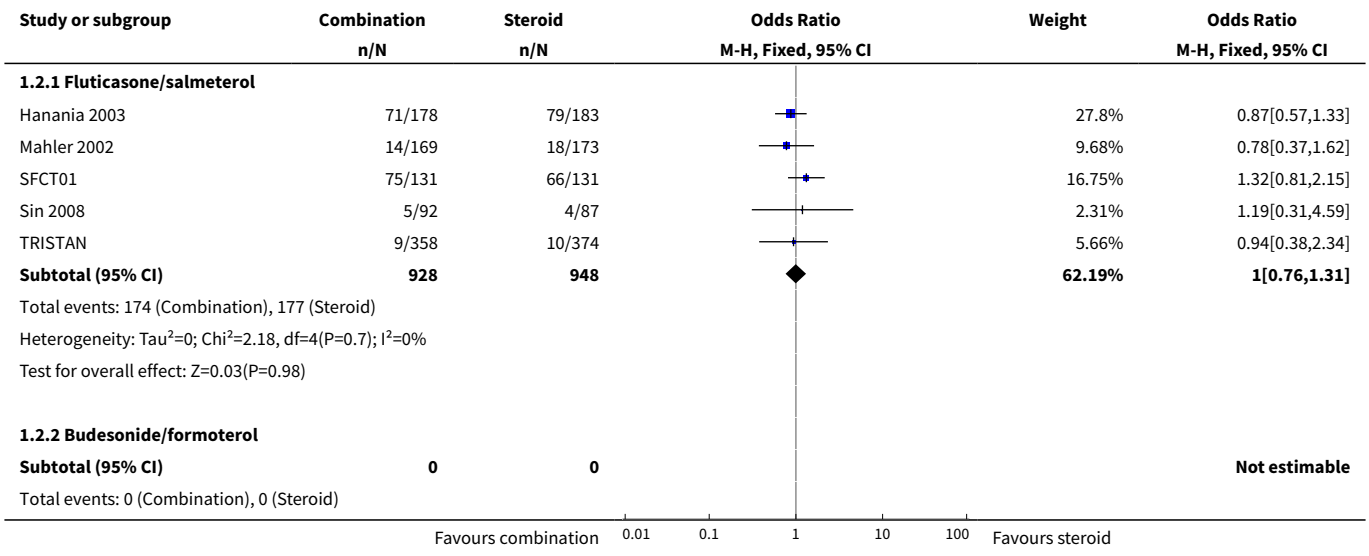
Comparison 1. All Combined Inhalers - Primary Outcomes

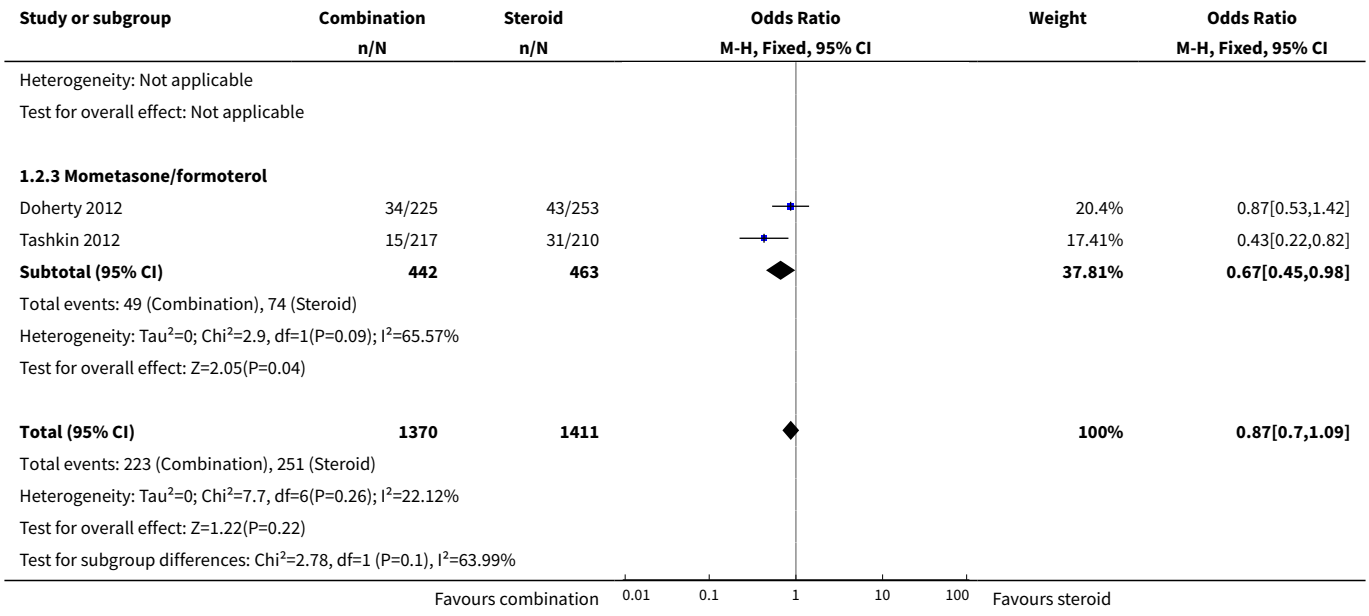
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbation rates (exacerbations requiring oral corticosteroids)	6		Rate ratio (Fixed, 95% CI)	0.87 [0.80, 0.94]
1.1 Fluticasone/salmeterol	2		Rate ratio (Fixed, 95% CI)	0.88 [0.80, 0.98]
1.2 Budesonide/formoterol	4		Rate ratio (Fixed, 95% CI)	0.84 [0.73, 0.97]
1.3 Mometasone/formoterol	0		Rate ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Number of participants with one or more exacerbation	7	2781	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.70, 1.09]
2.1 Fluticasone/salmeterol	5	1876	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.76, 1.31]
2.2 Budesonide/formoterol	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Mometasone/formoterol	2	905	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.45, 0.98]
3 Hospitalisations due to COPD exacerbations	10	7060	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.80, 1.07]
3.1 Fluticasone/salmeterol	5	4784	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.10]
3.2 Budesonide/formoterol	3	1371	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.60, 1.20]
3.3 Mometasone/formoterol	2	905	Odds Ratio (M-H, Fixed, 95% CI)	1.46 [0.66, 3.21]
4 Mortality	12	7518	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.64, 0.94]
4.1 Fluticasone/salmeterol	6	4836	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.62, 0.92]
4.2 Budesonide/formoterol	4	1777	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.54, 2.37]
4.3 Mometasone/formoterol	2	905	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.27, 2.91]
5 Pneumonia	12	7320	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.91, 1.28]
5.1 Fluticasone/salmeterol	7	5044	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.89, 1.27]
5.2 Budesonide/formoterol	3	1371	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.47, 2.63]
5.3 Mometasone/formoterol	2	905	Odds Ratio (M-H, Fixed, 95% CI)	1.92 [0.66, 5.57]

Analysis 1.1. Comparison 1 All Combined Inhalers - Primary Outcomes, Outcome 1 Exacerbation rates (exacerbations requiring oral corticosteroids).

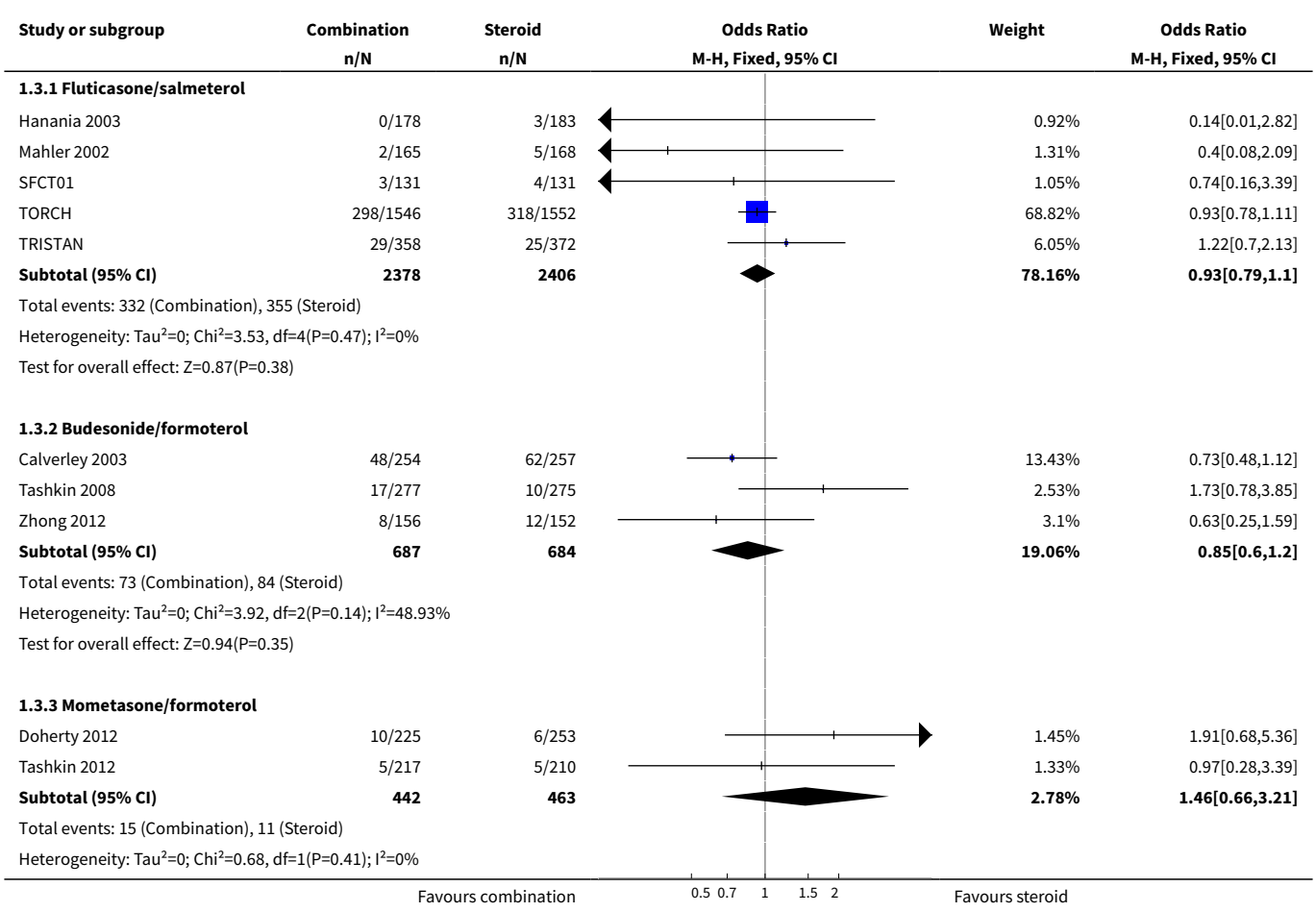


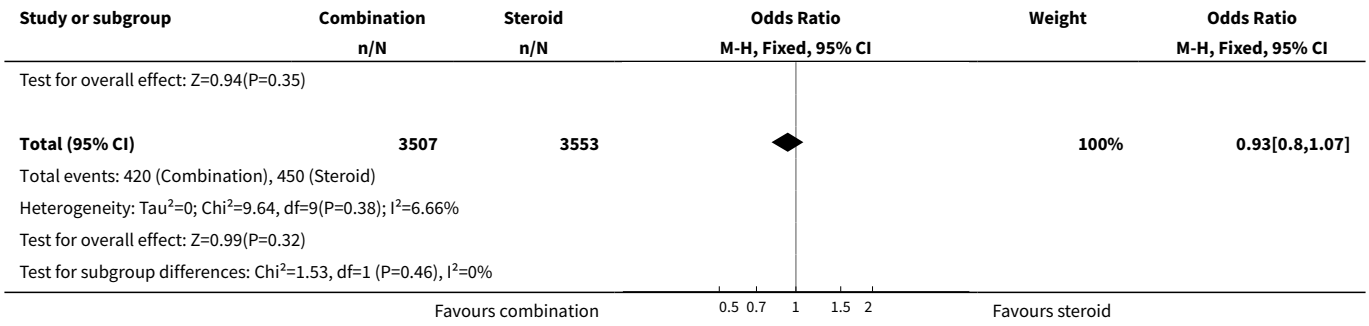
Analysis 1.2. Comparison 1 All Combined Inhalers - Primary Outcomes, Outcome 2 Number of participants with one or more exacerbation.



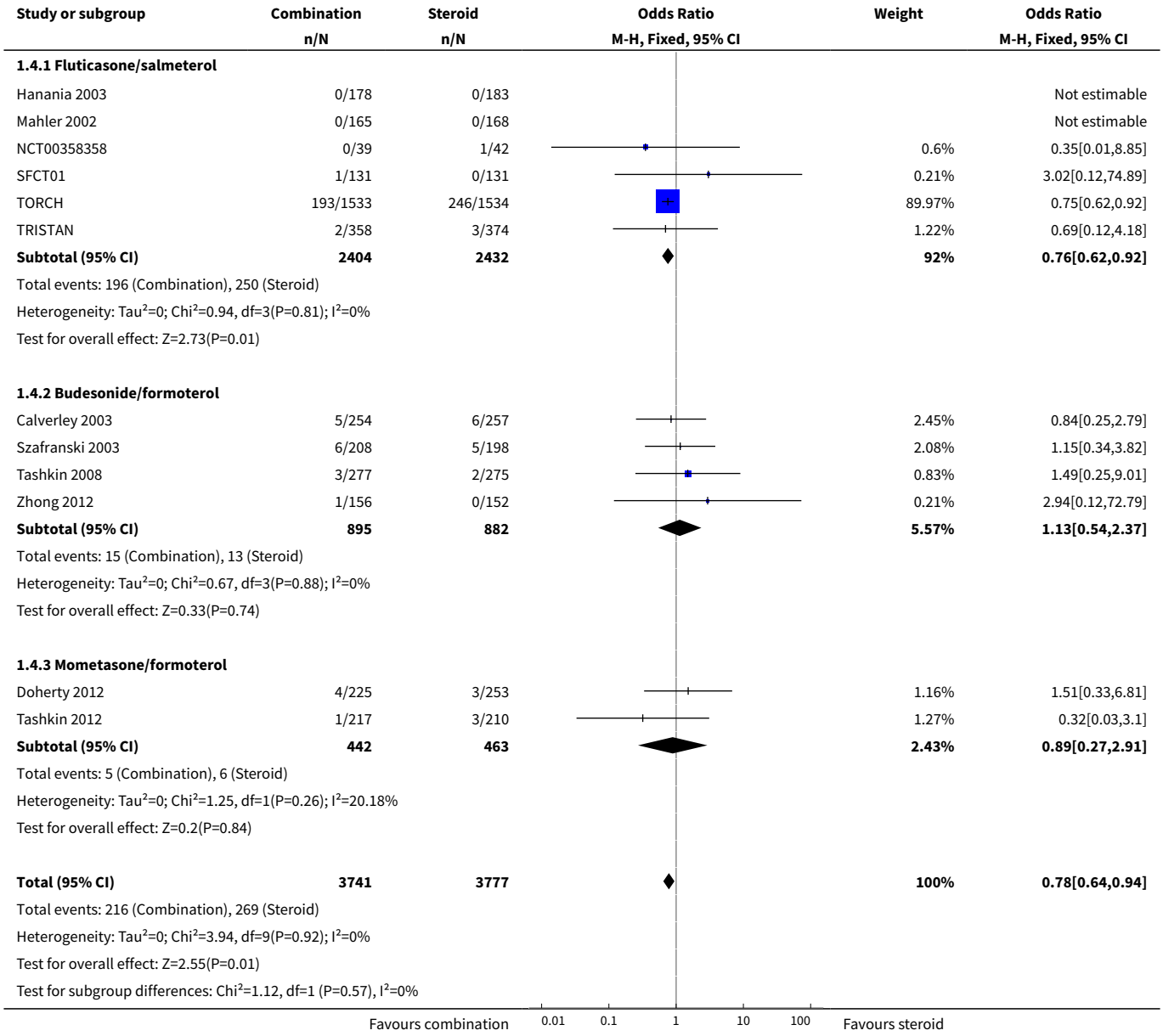


Analysis 1.3. Comparison 1 All Combined Inhalers - Primary Outcomes, Outcome 3 Hospitalisations due to COPD exacerbations.

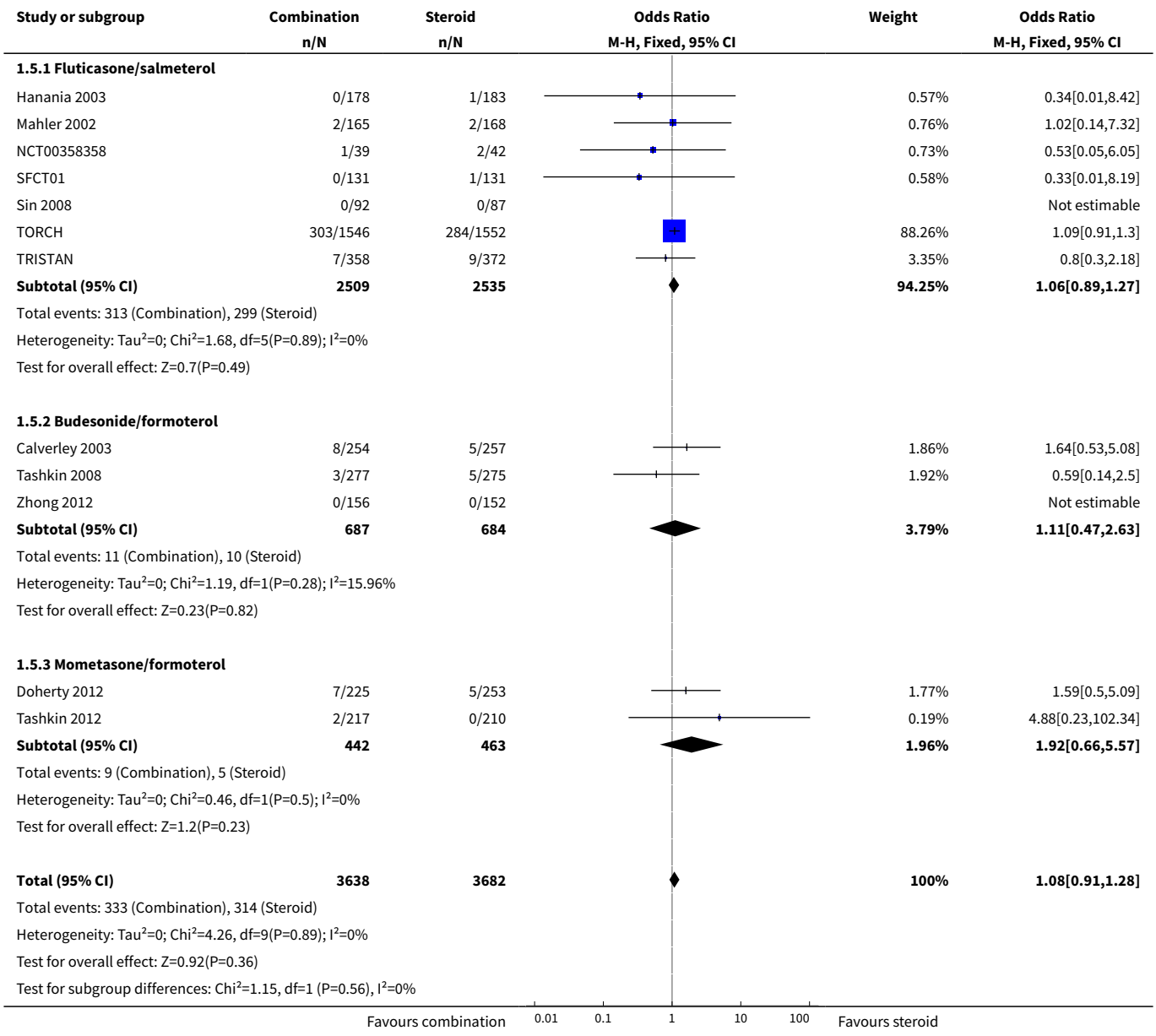




Analysis 1.4. Comparison 1 All Combined Inhalers - Primary Outcomes, Outcome 4 Mortality.



Analysis 1.5. Comparison 1 All Combined Inhalers - Primary Outcomes, Outcome 5 Pneumonia.



Comparison 2. Fluticasone/salmeterol (FPS) versus fluticasone (FP)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbation rates	2		Rate ratio (Fixed, 95% CI)	0.88 [0.80, 0.98]
1.1 Poorly reversible population	2		Rate ratio (Fixed, 95% CI)	0.88 [0.80, 0.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number of participants with one or more exacerbation	5	1876	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.76, 1.31]
2.1 Partially reversible population (mixed population)	2	703	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.59, 1.22]
2.2 Poorly reversible population	2	994	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.80, 1.88]
2.3 Unclear reversibility	1	179	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.31, 4.59]
3 End of treatment mean number of exacerbations per participant	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Poorly reversible population	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Number of participants with one or more exacerbations by type	1	262	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.69, 1.92]
4.1 Requirement for oral steroids	1	262	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.69, 1.92]
4.2 Requirement for antibiotic treatment	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Requirement for oral steroid or antibiotic treatment	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 Hospitalisation	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Exacerbations by type	2		Rate ratio (Random, 95% CI)	Subtotals only
5.1 Hospitalisation	1		Rate ratio (Random, 95% CI)	0.95 [0.82, 1.11]
5.2 Requirement for antibiotic treatment	0		Rate ratio (Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Requirement for oral steroid or antibiotic treatment	0		Rate ratio (Random, 95% CI)	0.0 [0.0, 0.0]
5.4 Requirement for oral steroids	2		Rate ratio (Random, 95% CI)	0.89 [0.81, 0.98]
6 Mortality	6	4836	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.62, 0.92]
6.1 Mortality: three-year data	1	3067	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.62, 0.92]
6.2 Mortality: one-year data	2	994	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.23, 4.57]

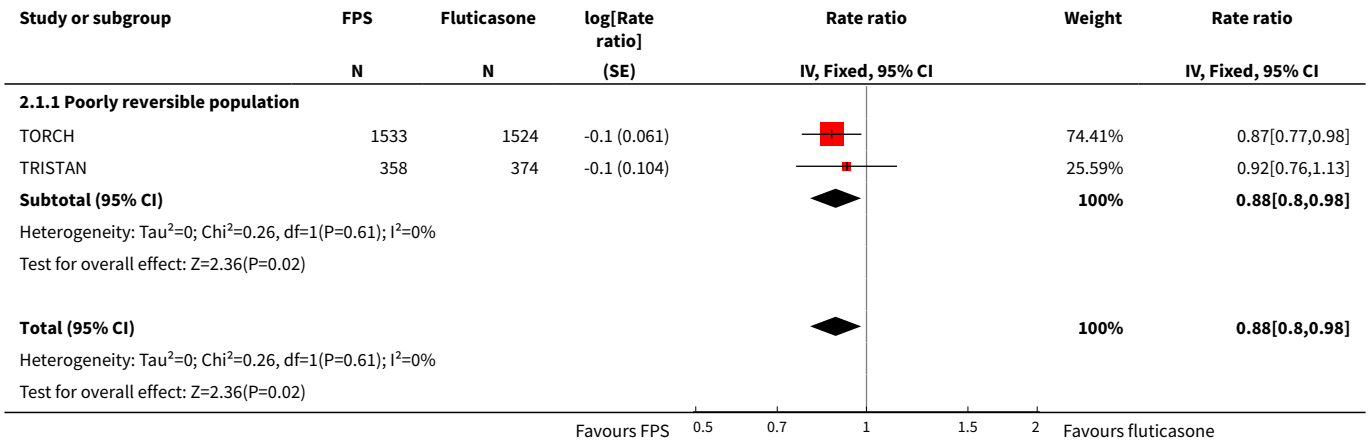
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Mortality: six-month data	2	694	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 Mortality: three-month data	1	81	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.85]
7 Mortality—cause specific	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 COPD-related death	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Cancer	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Cardiovascular	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Change from baseline in St George's Respiratory Questionnaire (total score)	3		SGRQ units (Fixed, 95% CI)	-1.30 [-2.04, -0.57]
8.1 Poorly reversible population	3		SGRQ units (Fixed, 95% CI)	-1.30 [-2.04, -0.57]
9 Change from baseline in Transitional Dyspnoea Index (TDI)	2	690	Mean Difference (IV, Random, 95% CI)	0.31 [-0.45, 1.08]
9.1 Partially reversible population (mixed population)	2	690	Mean Difference (IV, Random, 95% CI)	0.31 [-0.45, 1.08]
10 Change from baseline in Chronic Respiratory Disease Questionnaire scores	2	696	Mean Difference (IV, Random, 95% CI)	2.34 [-3.15, 7.82]
10.1 Partially reversible population (mixed population)	2	696	Mean Difference (IV, Random, 95% CI)	2.34 [-3.15, 7.82]
11 Change from baseline in predose FEV_1	2		Mean Difference (Fixed, 95% CI)	0.05 [0.02, 0.09]
11.1 Reversible population	2		Mean Difference (Fixed, 95% CI)	0.07 [0.01, 0.12]
11.2 Poorly reversible population	2		Mean Difference (Fixed, 95% CI)	0.04 [-0.01, 0.09]
12 Change from baseline in postdose FEV_1	6		Mean Difference (Fixed, 95% CI)	0.05 [0.04, 0.06]
12.1 Reversible population	2		Mean Difference (Fixed, 95% CI)	0.15 [0.09, 0.21]
12.2 Poorly reversible population	6		Mean Difference (Fixed, 95% CI)	0.05 [0.03, 0.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 End of treatment am PEF (L/min)	2		Mean Difference (Fixed, 95% CI)	Totals not selected
13.1 Poorly reversible population	2		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Absolute shuttle walk test	1		Metres (Fixed, 95% CI)	Totals not selected
14.1 Poorly reversible population	1		Metres (Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Change from baseline in rescue medication usage (puffs/d)	2	686	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-1.31, -0.29]
15.1 Partially reversible population (mixed population)	2	686	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-1.31, -0.29]
16 Withdrawals	9	5106	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.76, 0.97]
16.1 Partially reversible population (mixed population)	2	694	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.63, 1.20]
16.2 Poorly reversible population	3	4062	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.76, 0.98]
16.3 Unclear reversibility	4	350	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.35, 1.66]
17 Withdrawal due to lack of efficacy/exacerbation	5	4574	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.53, 1.13]
17.1 Partially reversible population (mixed population)	1	333	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.20, 5.12]
17.2 Poorly reversible population	3	4062	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.48, 1.08]
17.3 Unclear reversibility	1	179	Odds Ratio (M-H, Fixed, 95% CI)	1.93 [0.34, 10.82]
18 Withdrawals due to adverse events	7	4723	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.64, 0.87]
18.1 Partially reversible population (mixed population)	1	342	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.22, 1.02]
18.2 Poorly reversible population	3	4082	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.65, 0.90]
18.3 Unclear reversibility	3	299	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.22, 2.28]
19 Adverse events — any event	8	5094	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.80, 1.09]

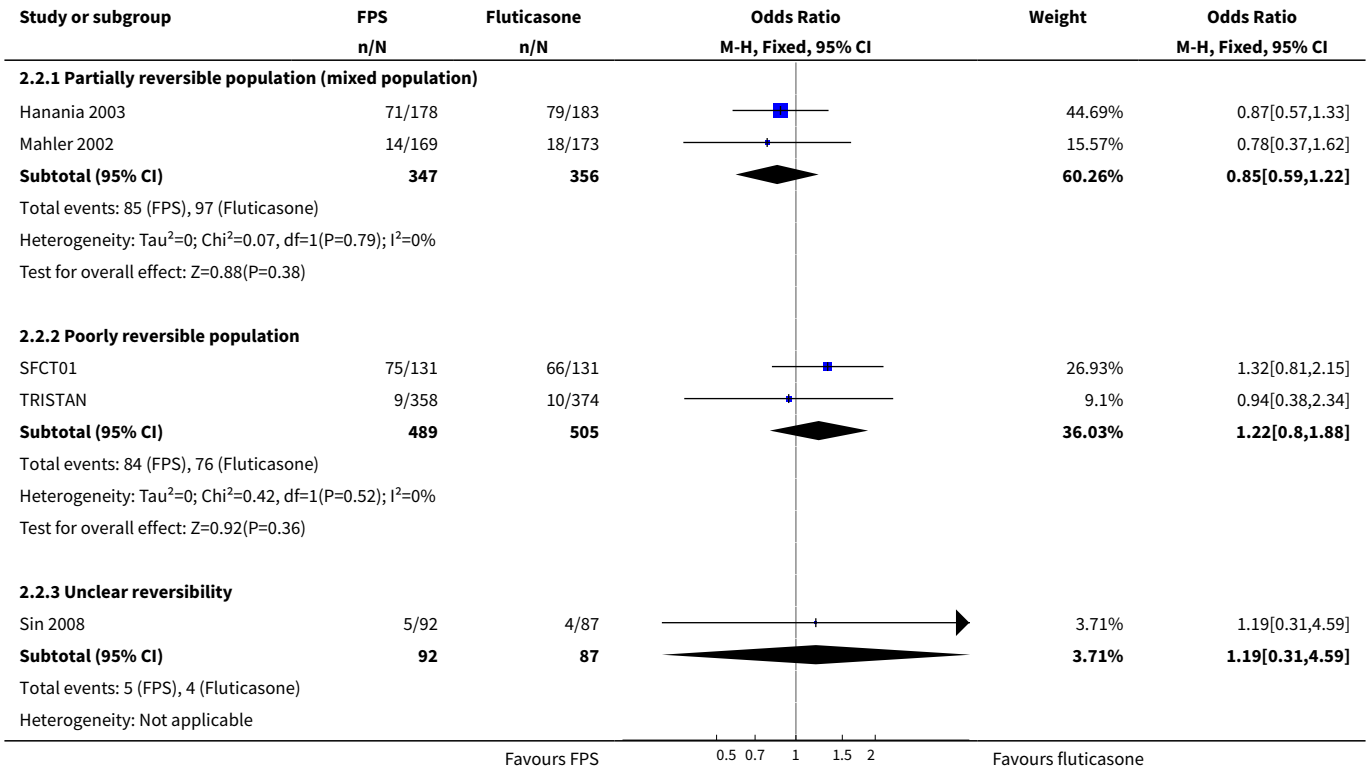
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Partially reversible population (mixed population)	2	703	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.66, 1.30]
19.2 Poorly reversible population	3	4092	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.13]
19.3 Unclear reversibility	3	299	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.49, 1.54]
20 Adverse events—serious	7	5055	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.82, 1.34]
20.1 Partially reversible population (mixed population)	2	703	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.39, 1.50]
20.2 Poorly reversible population	3	4092	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.84, 1.45]
20.3 Unclear reversibility	2	260	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.41, 2.85]
21 Adverse events (specific adverse events)	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 Pneumonia	7	5044	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.89, 1.27]
21.2 Candidiasis	6	1817	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.70, 1.48]
21.3 Hoarseness	1	262	Odds Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.14]
21.4 Palpitations	1	262	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.5 Upper respiratory tract infection	5	4717	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.96, 1.36]
21.6 Bronchitis	3	3441	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.94, 1.61]
21.7 Nasopharyngitis	2	3179	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.86, 1.29]
21.8 Cough	1	342	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.32, 3.24]
21.9 Dyspnoea	1	262	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.16]
21.10 Headache	6	4881	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.77, 1.17]

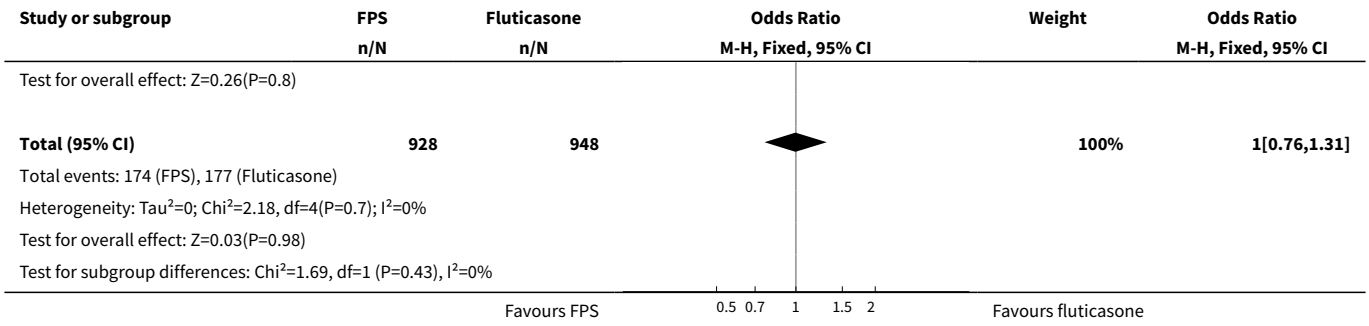
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.11 Urinary tract infection	2	343	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 2.02]

Analysis 2.1. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 1 Exacerbation rates.

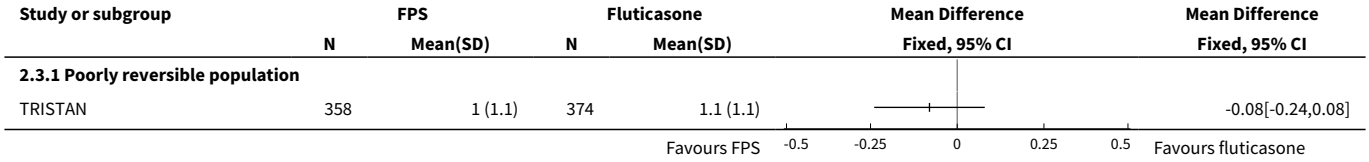


Analysis 2.2. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 2 Number of participants with one or more exacerbation.

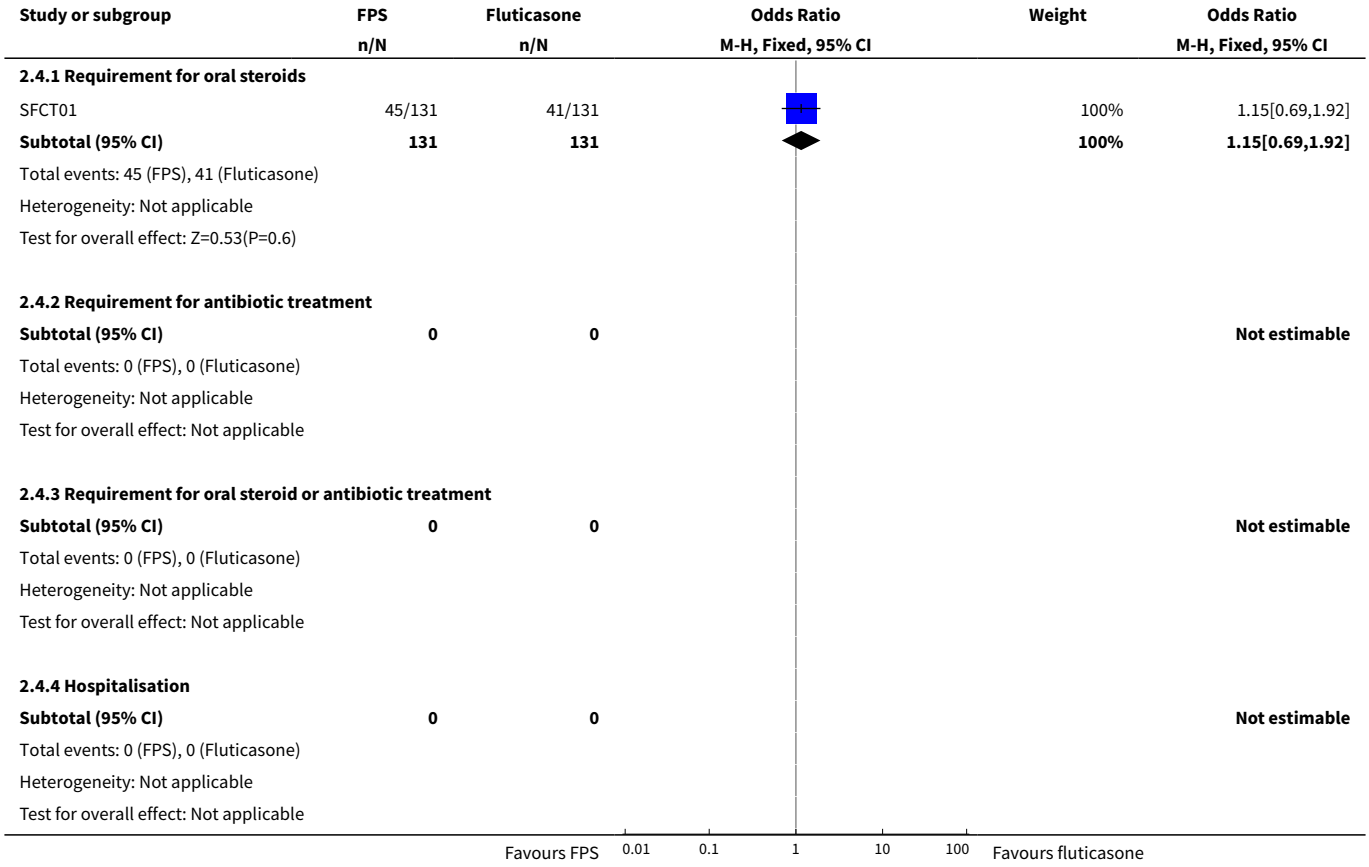


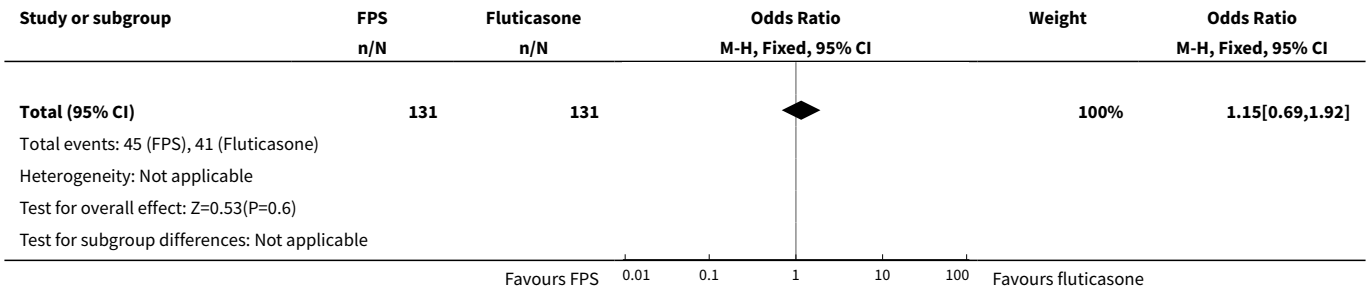


Analysis 2.3. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 3 End of treatment mean number of exacerbations per participant.

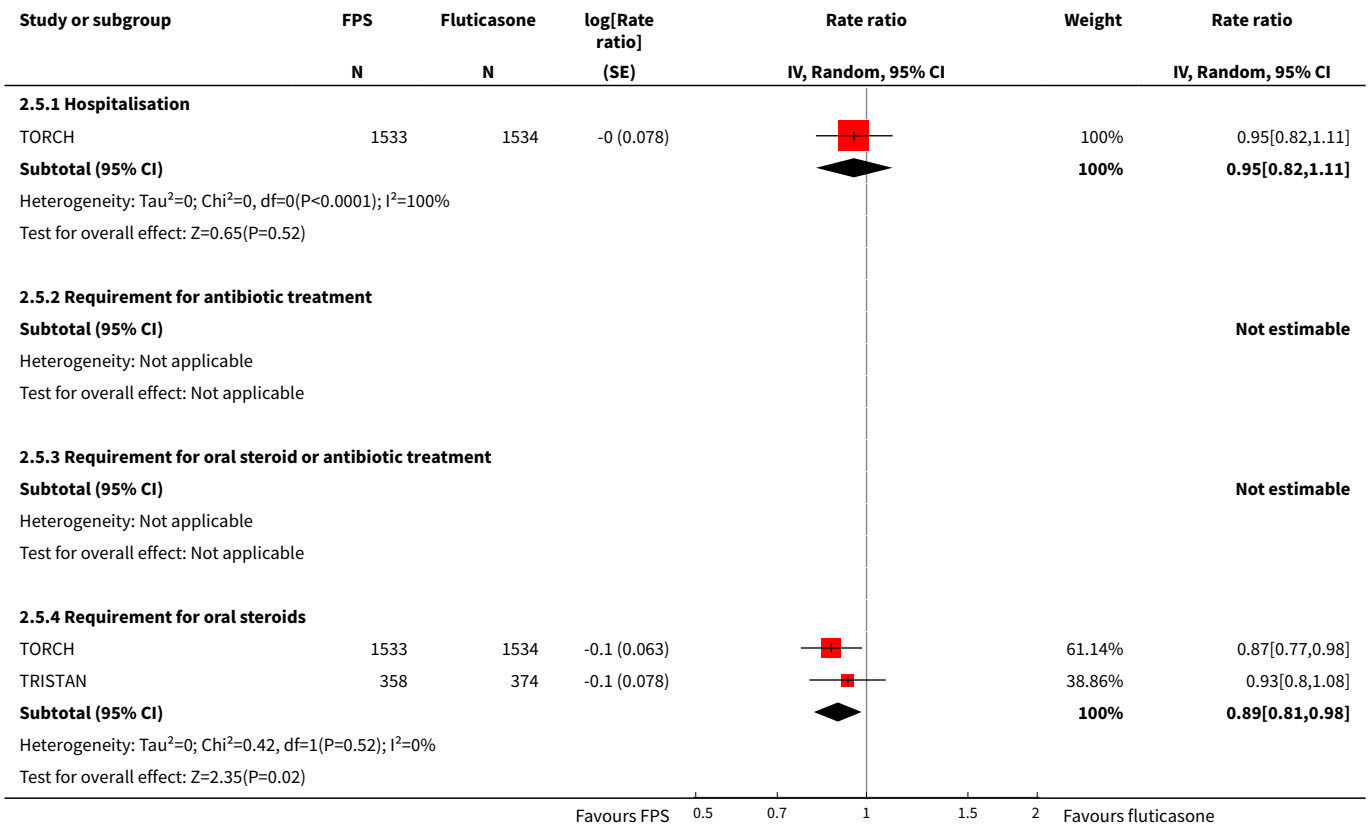


Analysis 2.4. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 4 Number of participants with one or more exacerbations by type.

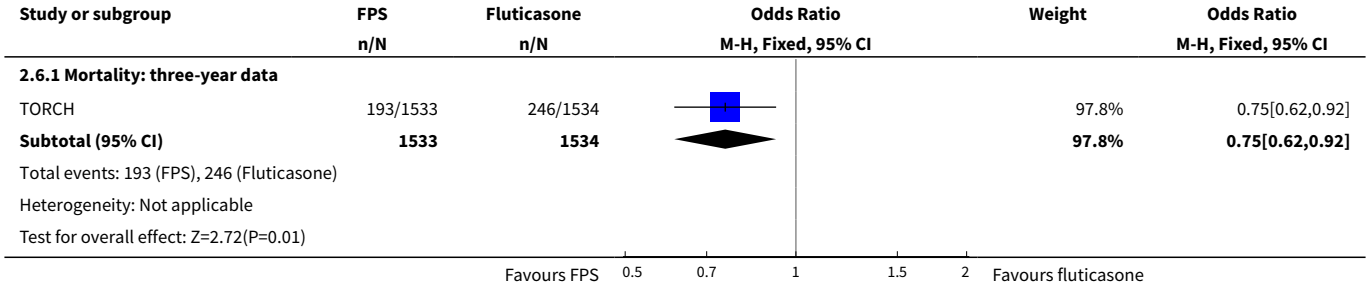


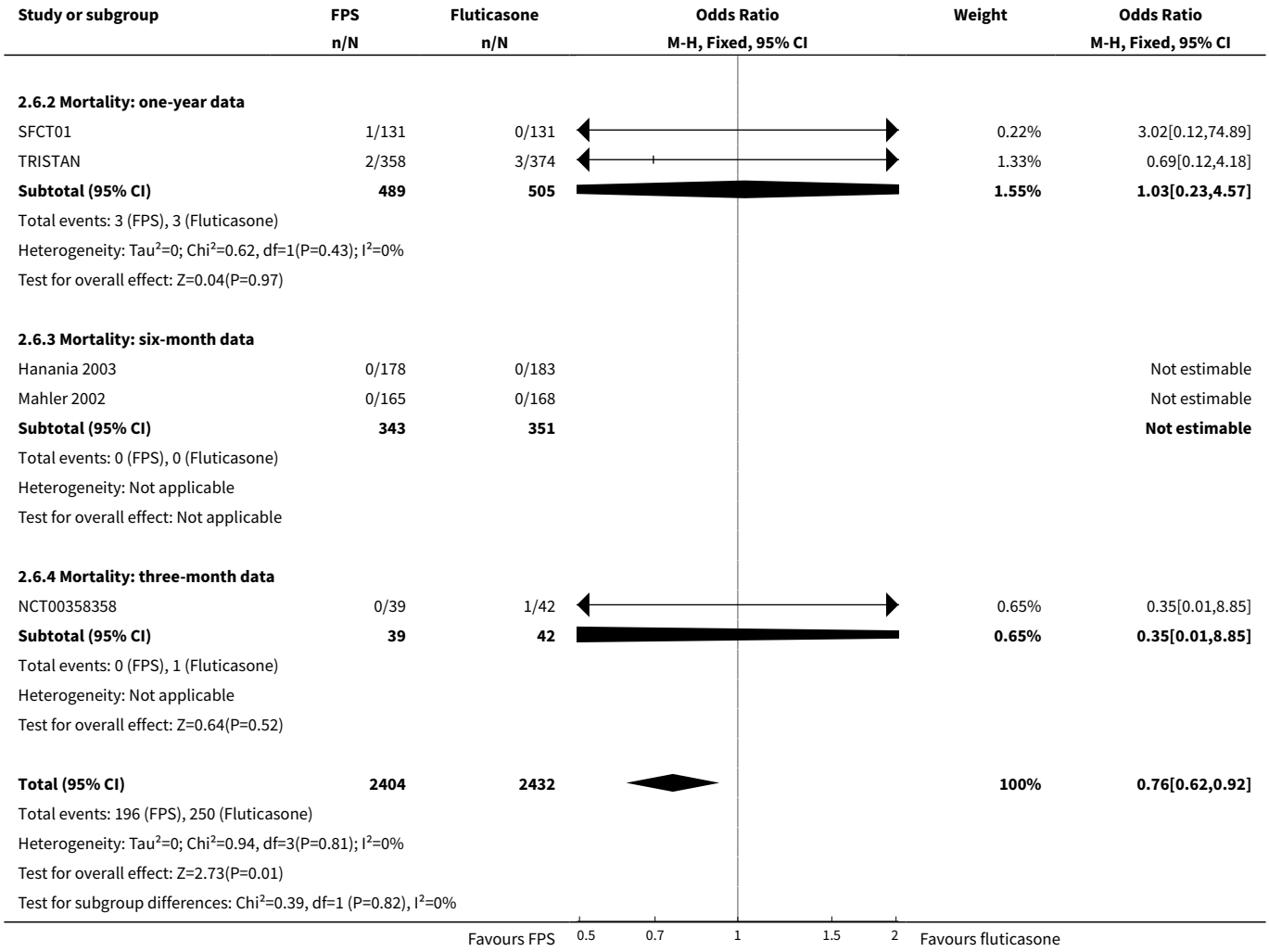


Analysis 2.5. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 5 Exacerbations by type.

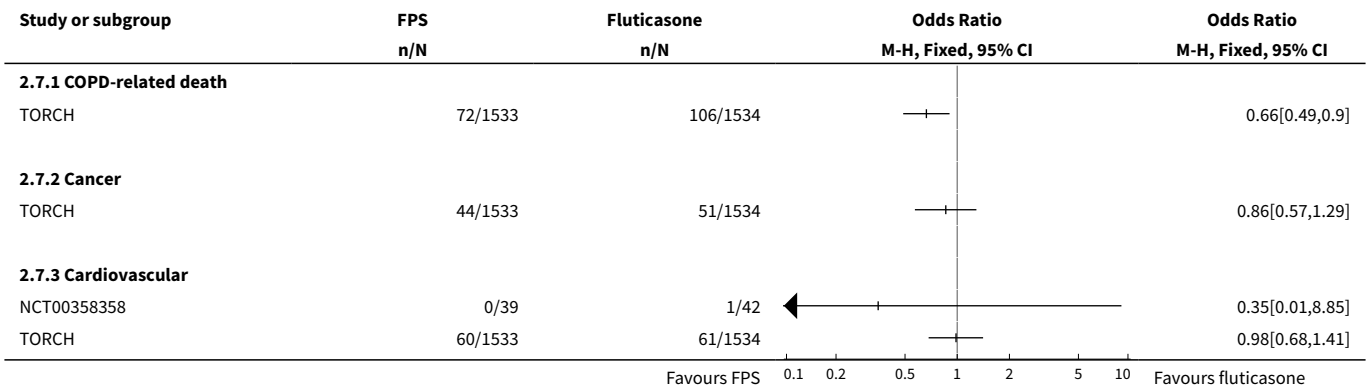


Analysis 2.6. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 6 Mortality.





Analysis 2.7. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 7 Mortality—cause specific.



Analysis 2.8. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 8 Change from baseline in St George's Respiratory Questionnaire (total score).

Study or subgroup	FPS N	Fluticasone N	SGRQ units (SE)	SGRQ units IV, Fixed, 95% CI	Weight	SGRQ units IV, Fixed, 95% CI
2.8.1 Poorly reversible population						
SFCT01	131	131	-3.1 (1.862)		4.03%	-3.15[-6.8,0.5]
TORCH	1002	1005	-1.1 (0.5)		55.86%	-1.1[-2.08,-0.12]
TRISTAN	358	374	-1.4 (0.59)		40.12%	-1.4[-2.56,-0.24]
Subtotal (95% CI)					**100%**	**-1.3[-2.04,-0.57]**
Heterogeneity: Tau²=0; Chi²=1.18, df=2(P=0.56); I²=0%						
Test for overall effect: Z=3.49(P=0)						
Total (95% CI)					**100%**	**-1.3[-2.04,-0.57]**
Heterogeneity: Tau²=0; Chi²=1.18, df=2(P=0.56); I²=0%						
Test for overall effect: Z=3.49(P=0)						

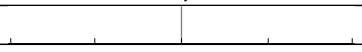
Analysis 2.9. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 9 Change from baseline in Transitional Dyspnoea Index (TDI).

Study or subgroup	FPS N	FPS Mean(SD)	Fluticasone N	Fluticasone Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.9.1 Partially reversible population (mixed population)							
Hanania 2003	178	1.7 (2.9)	183	1.7 (2.9)		60.72%	0[-0.6,0.6]
Mahler 2002	163	2.1 (4.3)	166	1.3 (4.4)		39.28%	0.8[-0.14,1.74]
Subtotal ***	**341**		**349**			**100%**	**0.31[-0.45,1.08]**
Heterogeneity: Tau²=0.16; Chi²=1.97, df=1(P=0.16); I²=49.22%							
Test for overall effect: Z=0.8(P=0.42)							
Total ***	**341**		**349**			**100%**	**0.31[-0.45,1.08]**
Heterogeneity: Tau²=0.16; Chi²=1.97, df=1(P=0.16); I²=49.22%							
Test for overall effect: Z=0.8(P=0.42)							

Analysis 2.10. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 10 Change from baseline in Chronic Respiratory Disease Questionnaire scores.

Study or subgroup	FPS N	FPS Mean(SD)	Fluticasone N	Fluticasone Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.10.1 Partially reversible population (mixed population)							
Hanania 2003	178	10 (17.2)	185	10.4 (17.2)		51.14%	-0.4[-3.94,3.14]
Mahler 2002	165	10 (18.2)	168	4.8 (18.2)		48.86%	5.2[1.29,9.11]
Subtotal ***	**343**		**353**			**100%**	**2.34[-3.15,7.82]**
Heterogeneity: Tau²=12.06; Chi²=4.33, df=1(P=0.04); I²=76.93%							
Test for overall effect: Z=0.83(P=0.4)							
Total ***	**343**		**353**			**100%**	**2.34[-3.15,7.82]**
Heterogeneity: Tau²=12.06; Chi²=4.33, df=1(P=0.04); I²=76.93%							

Study or subgroup	FPS N	FPS Mean(SD)	Fluticasone N	Fluticasone Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=0.83(P=0.4)							



Favours FPS | Favours fluticasone

Analysis 2.11. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 11 Change from baseline in predose FEV_1.

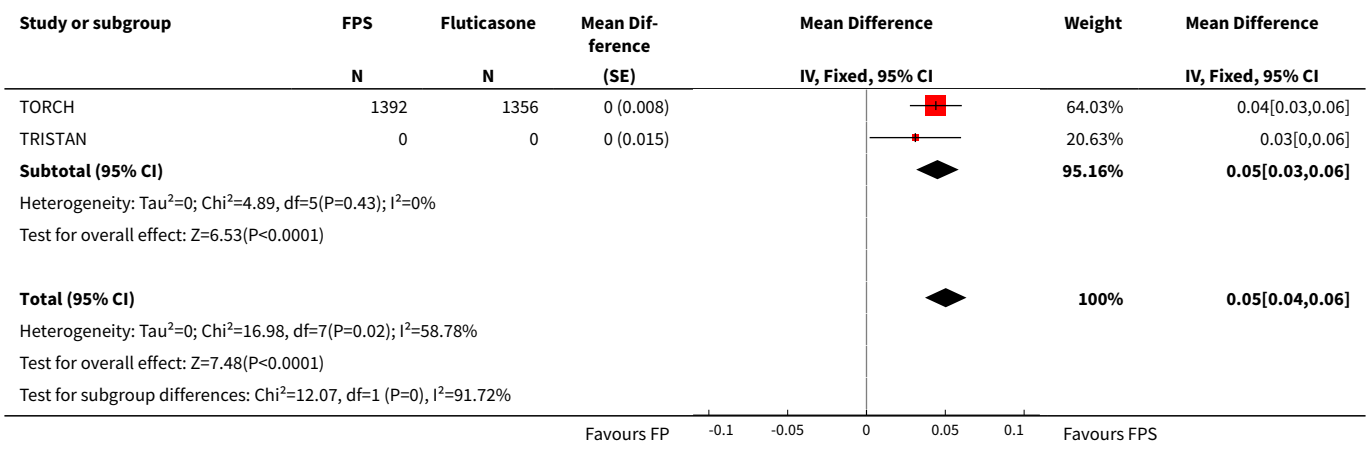
Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
2.11.1 Reversible population						
Hanania 2003	0	0	0.1 (0.04)		23.14%	0.06[-0.02,0.14]
Mahler 2002	0	0	0.1 (0.04)		23.73%	0.07[-0.01,0.15]
Subtotal (95% CI)					**46.87%**	**0.07[0.01,0.12]**
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.86); I^2=0%						
Test for overall effect: Z=2.3(P=0.02)						
2.11.2 Poorly reversible population						
Hanania 2003	0	0	0.1 (0.042)		21.71%	0.06[-0.02,0.14]
Mahler 2002	0	0	0 (0.035)		31.42%	0.03[-0.04,0.1]
Subtotal (95% CI)					**53.13%**	**0.04[-0.01,0.09]**
Heterogeneity: Tau^2=0; Chi^2=0.31, df=1(P=0.58); I^2=0%						
Test for overall effect: Z=1.59(P=0.11)						
Total (95% CI)					**100%**	**0.05[0.02,0.09]**
Heterogeneity: Tau^2=0; Chi^2=0.69, df=3(P=0.88); I^2=0%						
Test for overall effect: Z=2.74(P=0.01)						
Test for subgroup differences: Chi^2=0.35, df=1 (P=0.56), I^2=0%						

Favours FP | Favours FPS

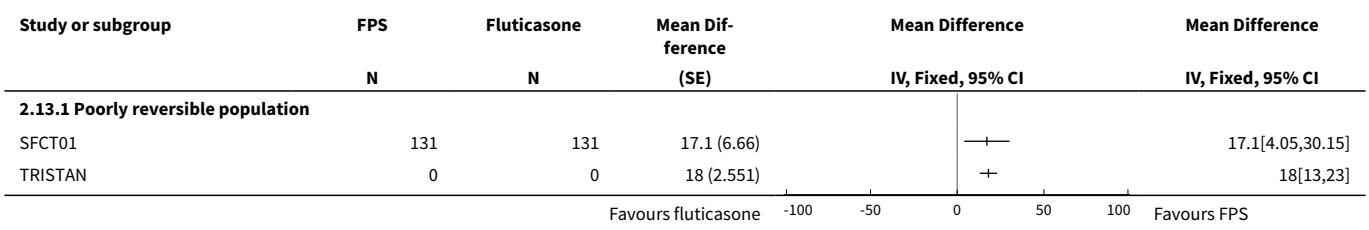
Analysis 2.12. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 12 Change from baseline in post-dose FEV_1.

Study or subgroup	FPS N	Fluticasone N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
2.12.1 Reversible population						
Hanania 2003	0	0	0.1 (0.045)		2.27%	0.15[0.06,0.24]
Mahler 2002	0	0	0.2 (0.042)		2.57%	0.16[0.08,0.24]
Subtotal (95% CI)					**4.84%**	**0.15[0.09,0.21]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%						
Test for overall effect: Z=5.04(P<0.0001)						
2.12.2 Poorly reversible population						
Hanania 2003	0	0	0.1 (0.042)		2.51%	0.11[0.03,0.2]
Lapperre 2009	0	0	0.1 (0.052)		1.68%	0.05[-0.05,0.15]
Mahler 2002	0	0	0.1 (0.035)		3.75%	0.08[0.02,0.15]
SFCT01	0	0	0.1 (0.042)		2.56%	0.06[-0.03,0.14]

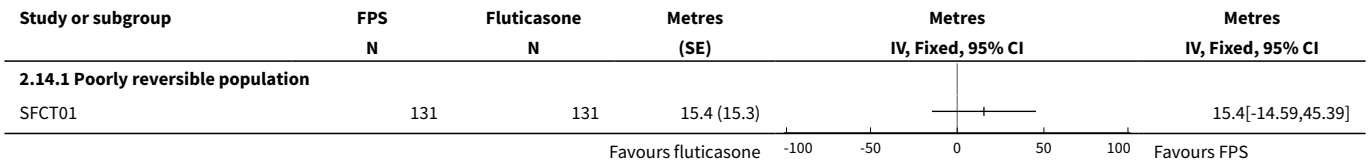
Favours FP | Favours FPS



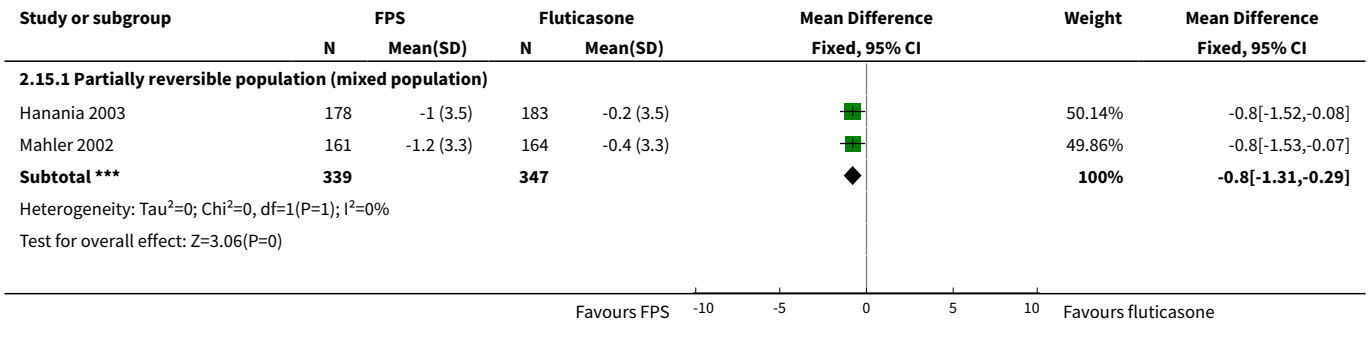
Analysis 2.13. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 13 End of treatment am PEF (L/min).

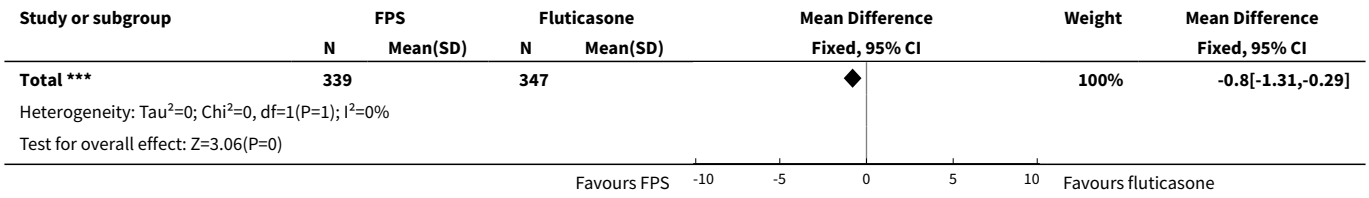


Analysis 2.14. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 14 Absolute shuttle walk test.

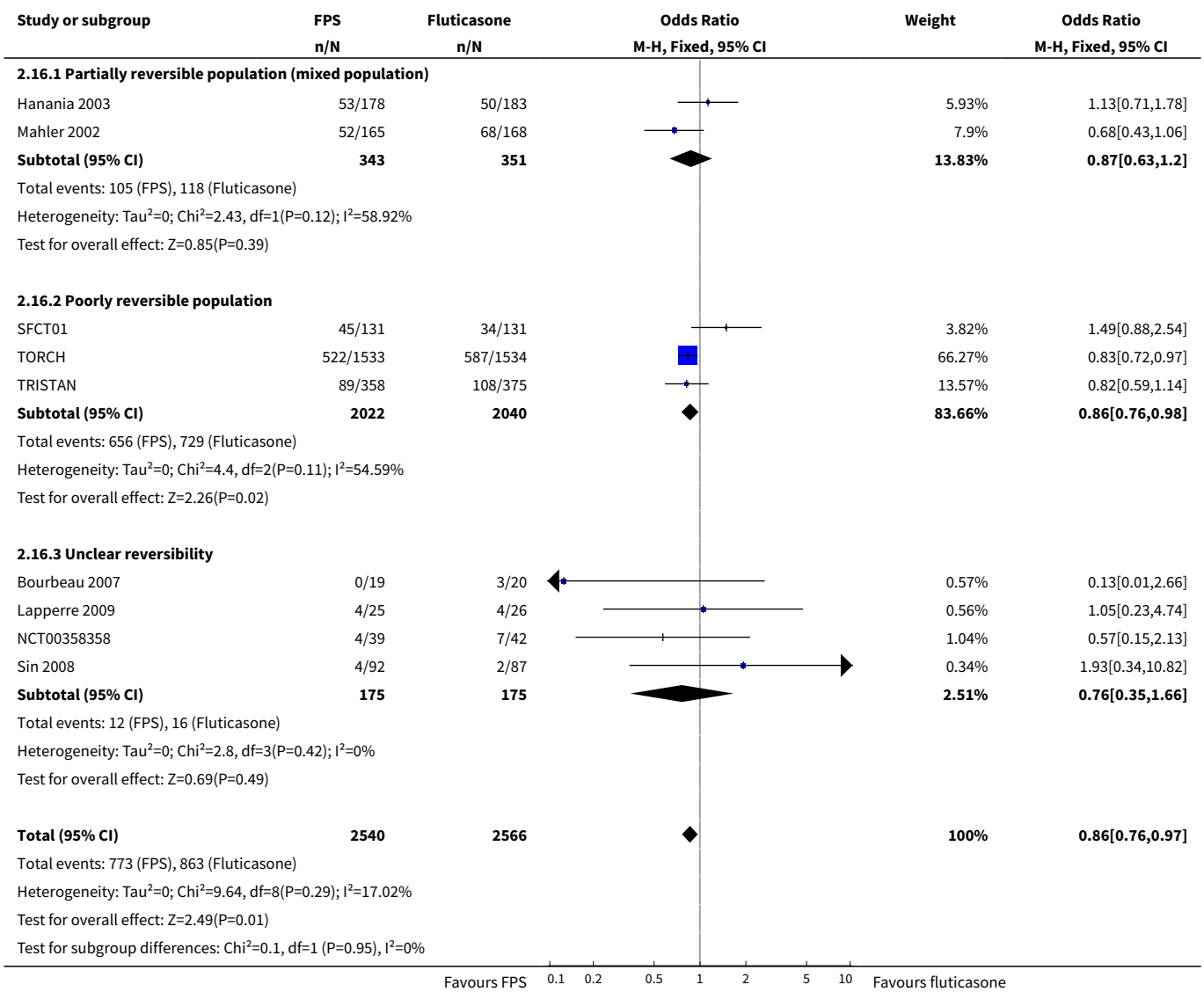


Analysis 2.15. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 15 Change from baseline in rescue medication usage (puffs/d).



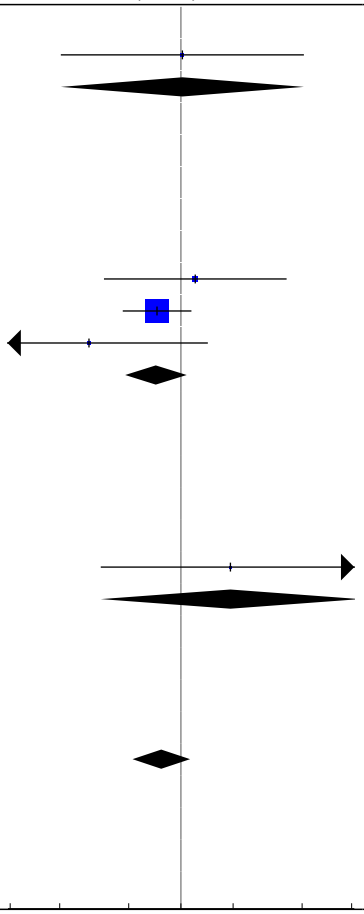


Analysis 2.16. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 16 Withdrawals.



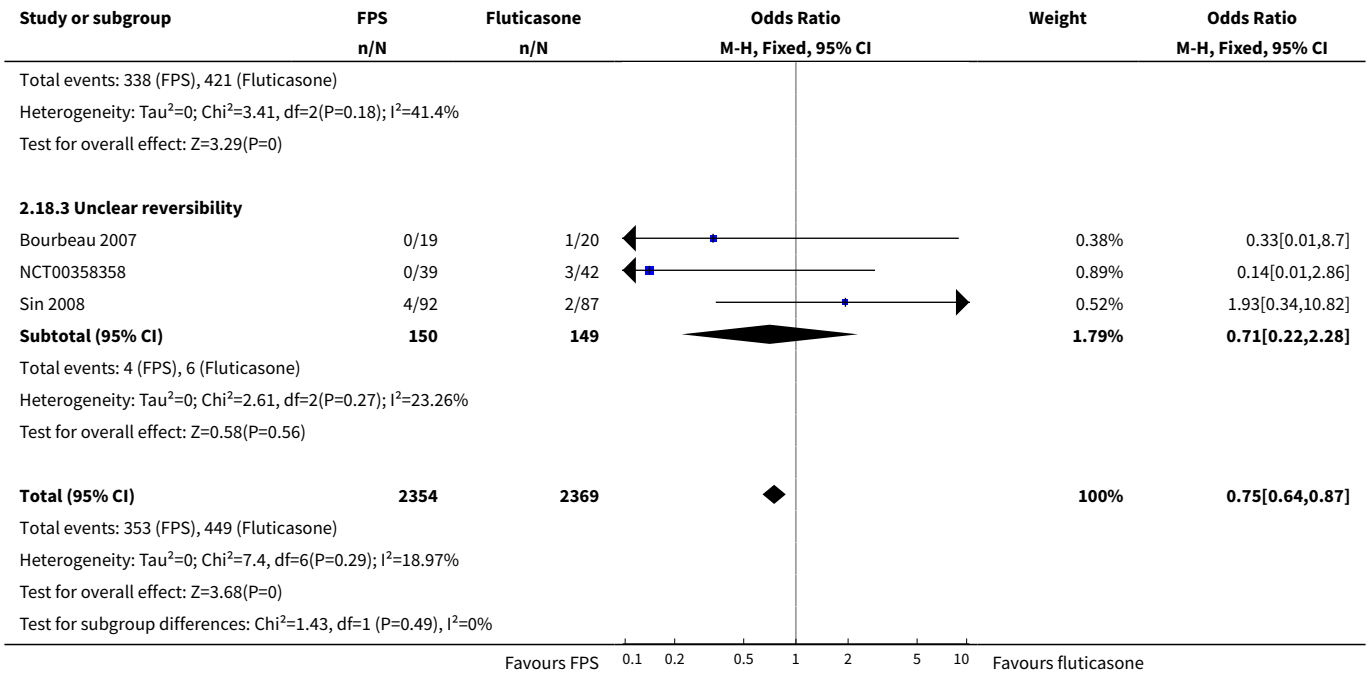
Analysis 2.17. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 17 Withdrawal due to lack of efficacy/exacerbation.

Study or subgroup	FPS n/N	Fluticasone n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.17.1 Partially reversible population (mixed population)					
Mahler 2002	3/165	3/168		4.83%	1.02[0.2,5.12]
Subtotal (95% CI)	**165**	**168**		**4.83%**	**1.02[0.2,5.12]**
Total events: 3 (FPS), 3 (Fluticasone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.02(P=0.98)					
2.17.2 Poorly reversible population					
SFCT01	6/131	5/131		7.89%	1.21[0.36,4.07]
TORCH	33/1533	45/1534		72.79%	0.73[0.46,1.15]
TRISTAN	2/358	7/375		11.24%	0.3[0.06,1.43]
Subtotal (95% CI)	**2022**	**2040**		**91.92%**	**0.72[0.48,1.08]**
Total events: 41 (FPS), 57 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=1.93, df=2(P=0.38); I^2=0%					
Test for overall effect: Z=1.61(P=0.11)					
2.17.3 Unclear reversibility					
Sin 2008	4/92	2/87		3.25%	1.93[0.34,10.82]
Subtotal (95% CI)	**92**	**87**		**3.25%**	**1.93[0.34,10.82]**
Total events: 4 (FPS), 2 (Fluticasone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.75(P=0.45)					
Total (95% CI)	**2279**	**2295**		**100%**	**0.77[0.53,1.13]**
Total events: 48 (FPS), 62 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=3.22, df=4(P=0.52); I^2=0%					
Test for overall effect: Z=1.34(P=0.18)					
Test for subgroup differences: Chi^2=1.33, df=1 (P=0.51), I^2=0%					

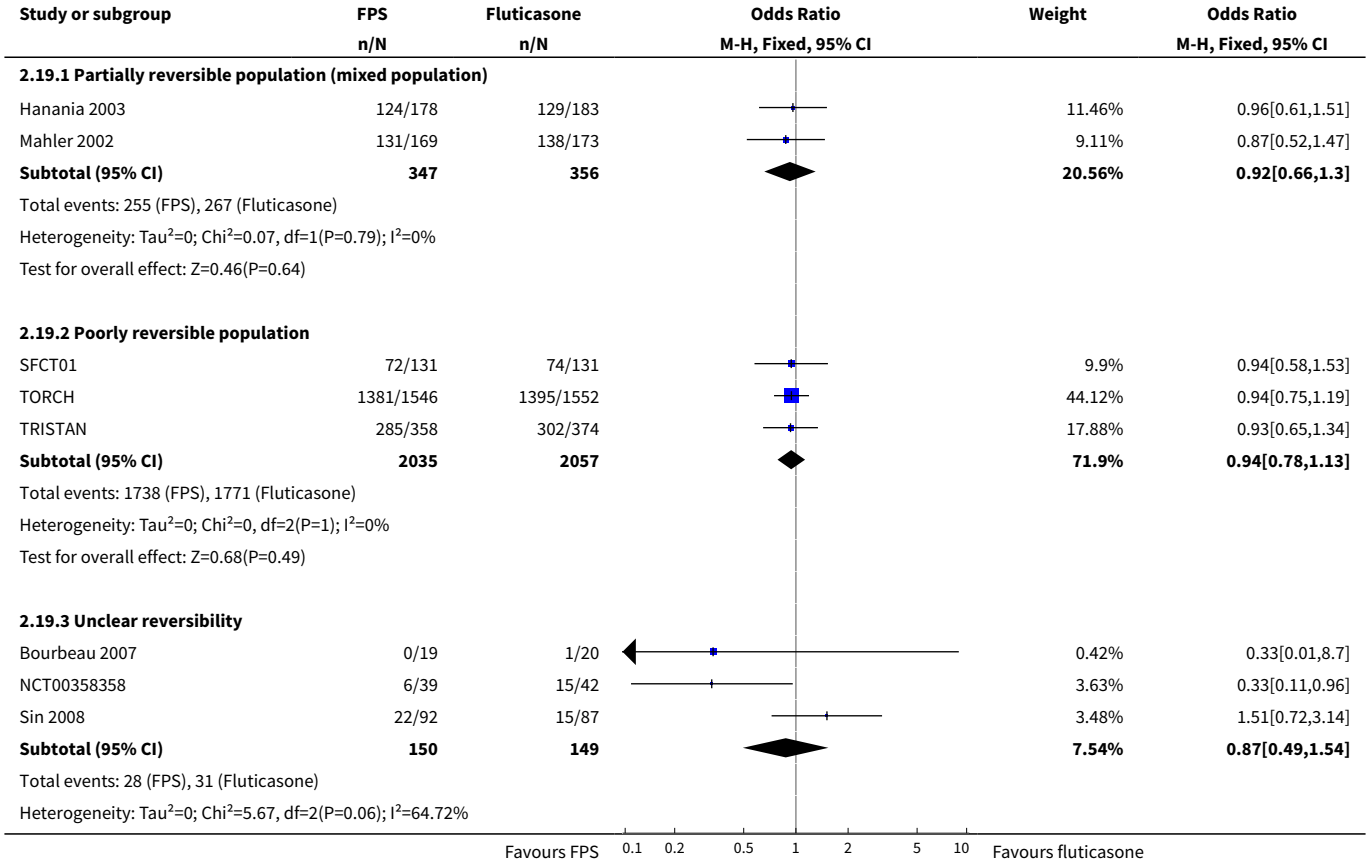


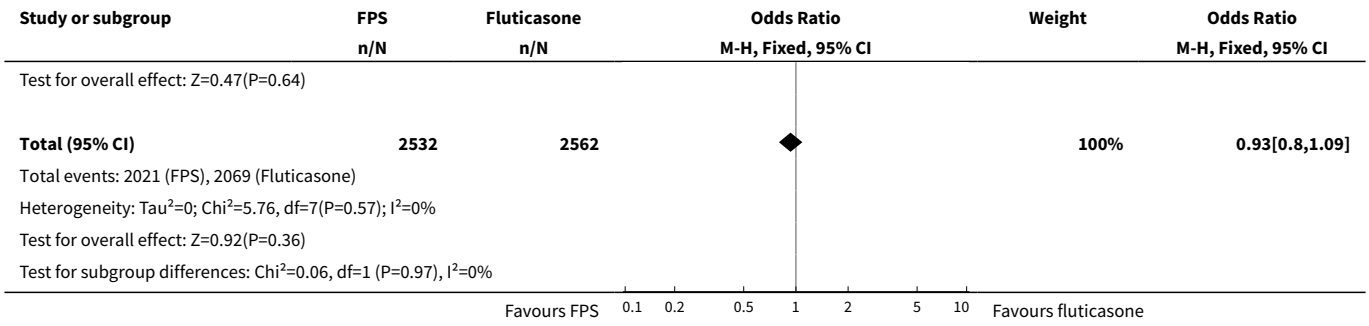
Analysis 2.18. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 18 Withdrawals due to adverse events.

Study or subgroup	FPS n/N	Fluticasone n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.18.1 Partially reversible population (mixed population)					
Mahler 2002	11/169	22/173		5.42%	0.48[0.22,1.02]
Subtotal (95% CI)	**169**	**173**		**5.42%**	**0.48[0.22,1.02]**
Total events: 11 (FPS), 22 (Fluticasone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.91(P=0.06)					
2.18.2 Poorly reversible population					
SFCT01	14/131	9/131		2.14%	1.62[0.68,3.89]
TORCH	278/1546	357/1542		78.15%	0.73[0.61,0.87]
TRISTAN	46/358	55/374		12.5%	0.86[0.56,1.3]
Subtotal (95% CI)	**2035**	**2047**		**92.79%**	**0.77[0.65,0.9]**

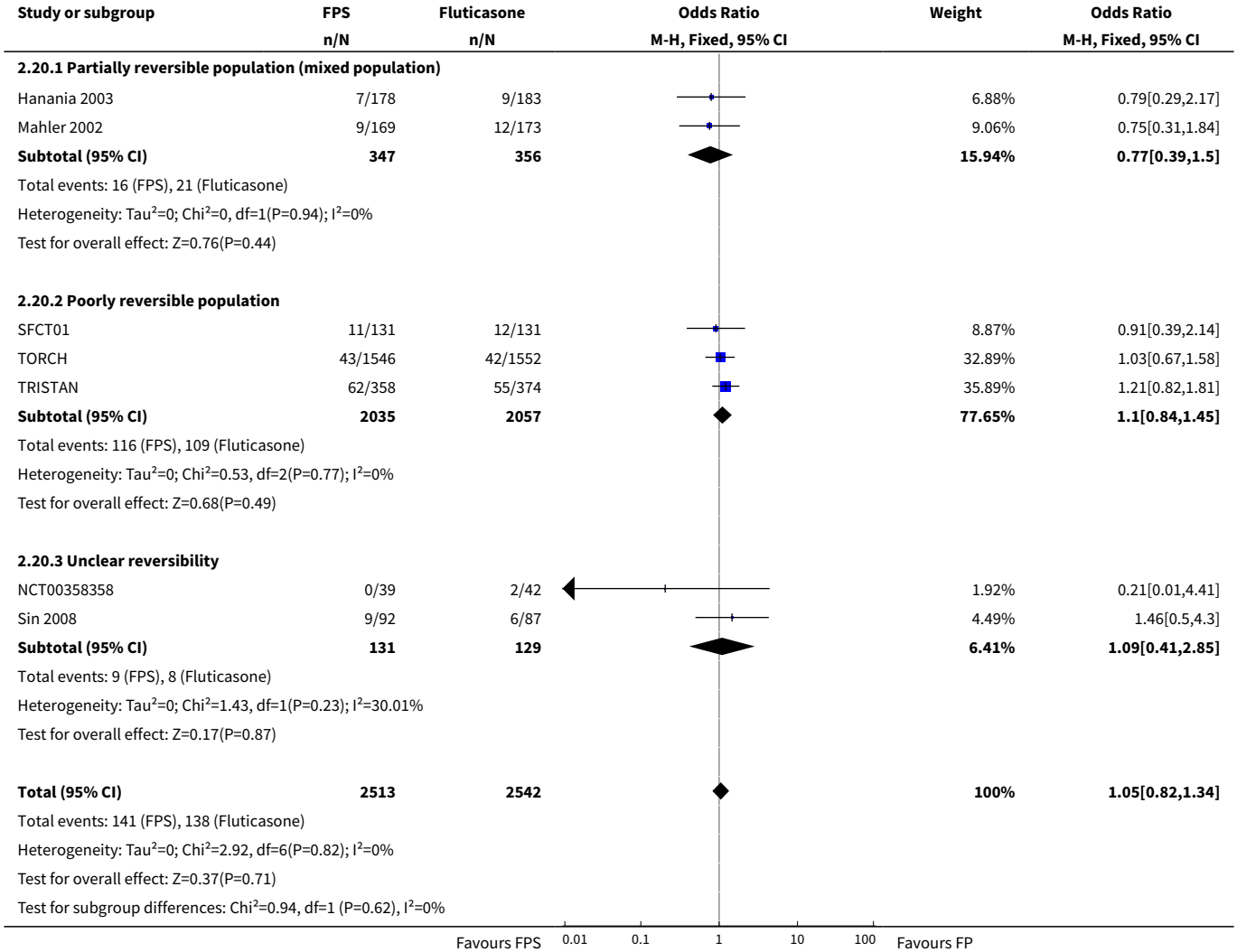


Analysis 2.19. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 19 Adverse events — any event.



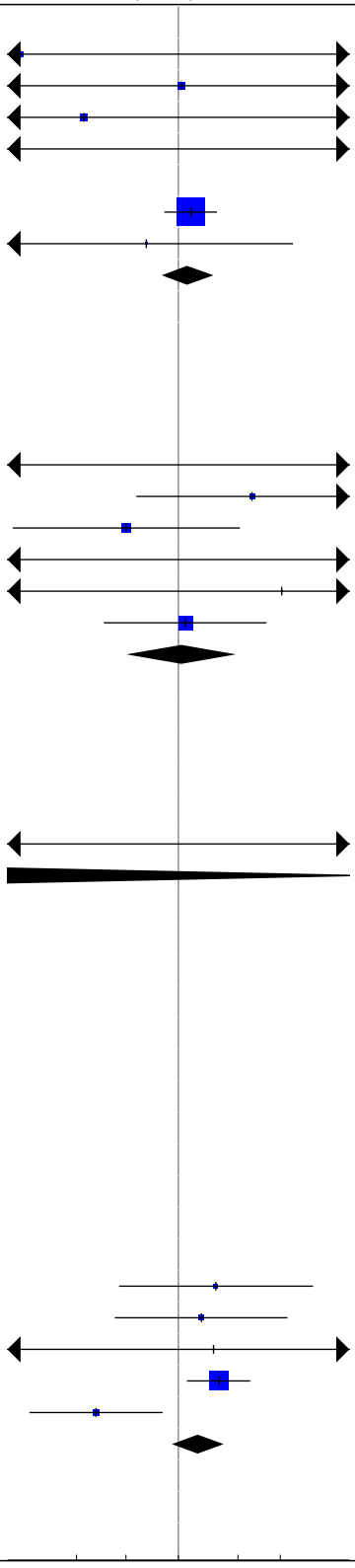


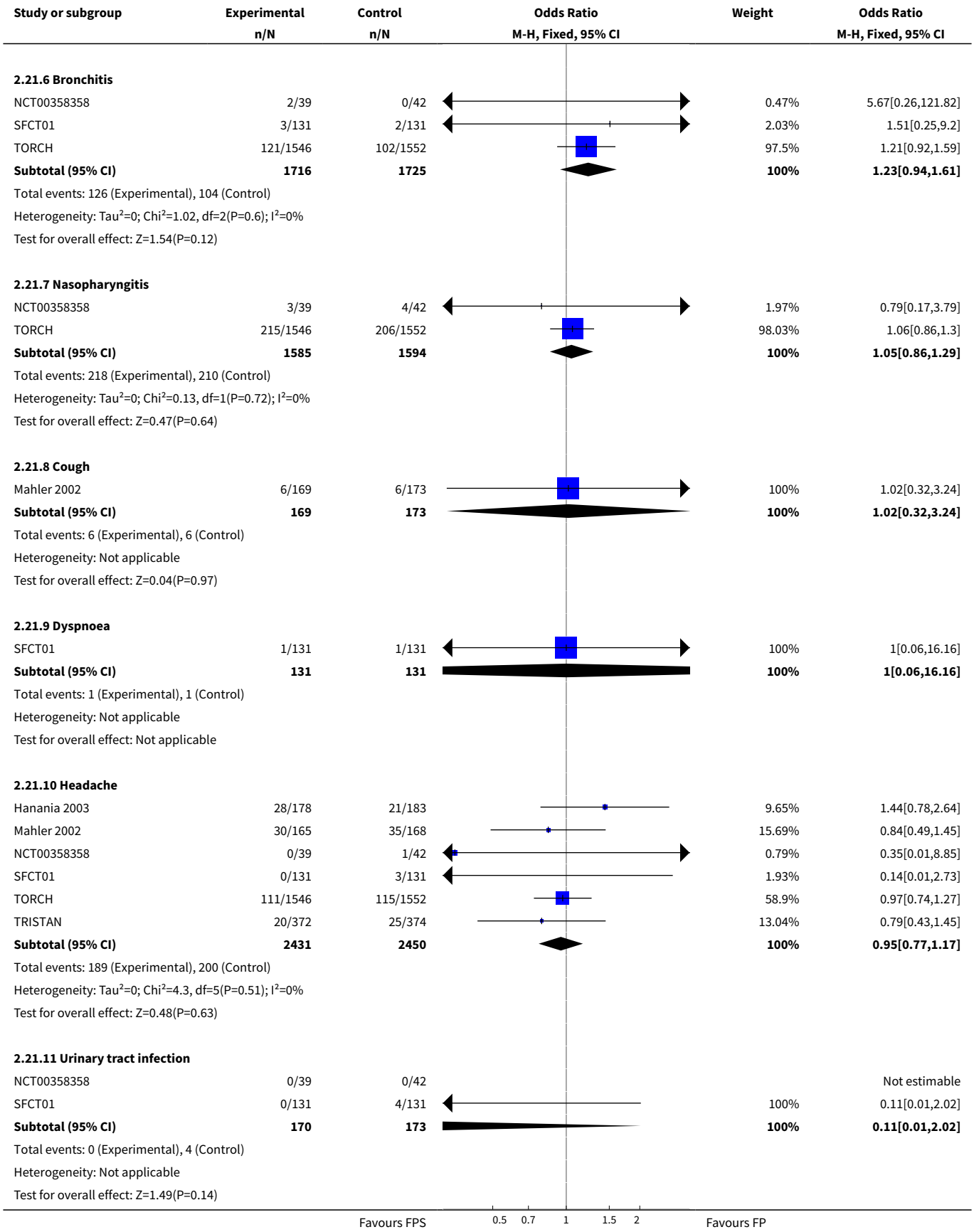
Analysis 2.20. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 20 Adverse events—serious.



Analysis 2.21. Comparison 2 Fluticasone/salmeterol (FPS) versus fluticasone (FP), Outcome 21 Adverse events (specific adverse events).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.21.1 Pneumonia					
Hanania 2003	0/178	1/183		0.61%	0.34[0.01,8.42]
Mahler 2002	2/165	2/168		0.8%	1.02[0.14,7.32]
NCT00358358	1/39	2/42		0.77%	0.53[0.05,6.05]
SFCT01	0/131	1/131		0.61%	0.33[0.01,8.19]
Sin 2008	0/92	0/87			Not estimable
TORCH	303/1546	284/1552		93.65%	1.09[0.91,1.3]
TRISTAN	7/358	9/372		3.56%	0.8[0.3,2.18]
Subtotal (95% CI)	**2509**	**2535**		**100%**	**1.06[0.89,1.27]**
Total events: 313 (Experimental), 299 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.68, df=5(P=0.89); I^2=0%					
Test for overall effect: Z=0.7(P=0.49)					
2.21.2 Candidiasis					
Bourbeau 2007	0/19	1/20		2.61%	0.33[0.01,8.7]
Hanania 2003	17/178	11/183		17.96%	1.65[0.75,3.63]
Mahler 2002	12/169	17/173		28.57%	0.7[0.32,1.52]
NCT00358358	0/39	2/42		4.36%	0.21[0.01,4.41]
SFCT01	2/131	1/131		1.8%	2.02[0.18,22.5]
TRISTAN	27/358	27/374		44.7%	1.05[0.6,1.82]
Subtotal (95% CI)	**894**	**923**		**100%**	**1.02[0.7,1.48]**
Total events: 58 (Experimental), 59 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.16, df=5(P=0.53); I^2=0%					
Test for overall effect: Z=0.1(P=0.92)					
2.21.3 Hoarseness					
SFCT01	0/131	2/131		100%	0.2[0.01,4.14]
Subtotal (95% CI)	**131**	**131**		**100%**	**0.2[0.01,4.14]**
Total events: 0 (Experimental), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.3)					
2.21.4 Palpitations					
SFCT01	0/131	0/131			Not estimable
Subtotal (95% CI)	**131**	**131**			**Not estimable**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.21.5 Upper respiratory tract infection					
Hanania 2003	22/178	18/183		6.64%	1.29[0.67,2.5]
Mahler 2002	28/165	25/168		8.78%	1.17[0.65,2.1]
Sin 2008	4/92	3/87		1.26%	1.27[0.28,5.86]
TORCH	213/1546	168/1552		61.68%	1.32[1.06,1.63]
TRISTAN	34/372	56/374		21.65%	0.57[0.36,0.9]
Subtotal (95% CI)	**2353**	**2364**		**100%**	**1.14[0.96,1.36]**
Total events: 301 (Experimental), 270 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.82, df=4(P=0.03); I^2=63.03%					
Test for overall effect: Z=1.46(P=0.14)					





Comparison 3. Budesonide/formoterol (BDF) versus budesonide (BD)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations	4		Rate Ratio (Fixed, 95% CI)	0.84 [0.73, 0.97]
1.1 Partially reversible	1		Rate Ratio (Fixed, 95% CI)	1.00 [0.76, 1.31]
1.2 Poorly reversible	3		Rate Ratio (Fixed, 95% CI)	0.79 [0.67, 0.93]
2 Mean exacerbation rates per participant per year	3		Rate Ratio (Fixed, 95% CI)	0.84 [0.72, 0.99]
2.1 Poorly reversible population	3		Rate Ratio (Fixed, 95% CI)	0.84 [0.72, 0.99]
3 Mortality	4	1777	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.54, 2.37]
3.1 Mortality as primary outcome	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Mortality data collected as secondary/unpublished outcome	4	1777	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.54, 2.37]
4 Quality of life—SGRQ total (change scores)	4		Mean Difference (Fixed, 95% CI)	-2.80 [-3.99, -1.61]
4.1 Partially reversible population (mixed population)	1		Mean Difference (Fixed, 95% CI)	-2.57 [-4.68, -0.46]
4.2 Poorly reversible population	3		Mean Difference (Fixed, 95% CI)	-2.91 [-4.35, -1.47]
5 Symptoms (change scores)	3		Mean Difference (Fixed, 95% CI)	-0.45 [-0.67, -0.22]
5.1 Poorly reversible	3		Mean Difference (Fixed, 95% CI)	-0.45 [-0.67, -0.22]
6 Breathlessness, cough and sputum score (BCSS) change from baseline—average over treatment period	1		Mean Difference (Fixed, 95% CI)	-0.11 [-0.38, 0.16]
6.1 Partially reversible (mixed population)	1		Mean Difference (Fixed, 95% CI)	-0.11 [-0.38, 0.16]
7 Awakening-free nights, percentage change from baseline	2		Mean Difference (Fixed, 95% CI)	-0.05 [-0.16, 0.06]
7.1 Partially reversible (mixed population)	1		Mean Difference (Fixed, 95% CI)	1.98 [-3.17, 7.13]
7.2 Poorly reversible population	1		Mean Difference (Fixed, 95% CI)	-0.05 [-0.16, 0.06]

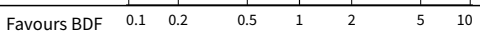
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Mean FEV_1 (% increase from baseline)	2		% increase (Fixed, 95% CI)	10.17 [7.71, 12.62]
8.1 Poorly reversible	2		% increase (Fixed, 95% CI)	10.17 [7.71, 12.62]
9 Pre-dose FEV_1 [L] change from baseline to the average over the randomised treatment period	1		Mean Difference (Fixed, 95% CI)	0.08 [0.05, 0.11]
9.1 Partially reversible population (mixed population)	1		Mean Difference (Fixed, 95% CI)	0.08 [0.05, 0.11]
10 1-Hour post-dose FEV_1 [L] change from baseline to the average over the randomised treatment period	1		Mean Difference (Fixed, 95% CI)	0.17 [0.14, 0.20]
10.1 Partially reversible population (mixed population)	1		Mean Difference (Fixed, 95% CI)	0.17 [0.14, 0.20]
11 Morning PEFR change from baseline, average over treatment period (L/min)	1		Mean Difference (Fixed, 95% CI)	14.08 [8.64, 19.52]
11.1 Poorly reversible population	1		Mean Difference (Fixed, 95% CI)	14.08 [8.64, 19.52]
12 Evening PEFR mean change from baseline, average over treatment period (L/min)	1		Mean Difference (Fixed, 95% CI)	12.59 [7.21, 17.97]
12.1 Partially reversible population (mixed population)	1		Mean Difference (Fixed, 95% CI)	12.59 [7.21, 17.97]
13 Rescue medication use	4		Mean Difference (Fixed, 95% CI)	-0.72 [-0.92, -0.52]
13.1 Partially reversible population (mixed population)	1		Mean Difference (Fixed, 95% CI)	-0.65 [-1.09, -0.21]
13.2 Poorly reversible	3		Mean Difference (Fixed, 95% CI)	-0.73 [-0.96, -0.51]
14 Sleep score (0 to 4) — change from baseline	1		Mean Difference (Fixed, 95% CI)	-0.04 [-0.14, 0.06]
14.1 Partially reversible population (mixed population)	1		Mean Difference (Fixed, 95% CI)	-0.04 [-0.14, 0.06]
15 Dyspnoea score (0 to 4) — change from baseline	2		Mean Difference (Fixed, 95% CI)	-0.12 [-0.20, -0.04]
15.1 Partially reversible population (mixed population)	1		Mean Difference (Fixed, 95% CI)	-0.12 [-0.22, -0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.2 Poorly reversible population	1		Mean Difference (Fixed, 95% CI)	-0.12 [-0.23, -0.01]
16 Cough score (0 to 4) — change from baseline	2		Mean Difference (Fixed, 95% CI)	-0.01 [-0.08, 0.06]
16.1 Partially reversible population (mixed population)	1		Mean Difference (Fixed, 95% CI)	0.0 [-0.11, 0.11]
16.2 Poorly reversible population	1		Mean Difference (Fixed, 95% CI)	-0.02 [-0.12, 0.08]
17 Sputum score (0 to 4) — change from baseline	1		Mean Difference (Fixed, 95% CI)	0.02 [-0.09, 0.13]
17.1 Partially reversible population (mixed population)	1		Mean Difference (Fixed, 95% CI)	0.02 [-0.09, 0.13]
18 Withdrawals due to worsening COPD symptoms	3	1225	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.46, 0.99]
18.1 Poorly reversible population	3	1225	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.46, 0.99]
19 Withdrawals due to adverse events	4	1777	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.66, 1.37]
19.1 Partially reversible population (mixed population)	1	552	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.43, 1.43]
19.2 Poorly reversible population	3	1225	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.68, 1.69]
20 Adverse event — any (one or more)	2	860	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.68, 1.19]
20.1 Partially reversible population (mixed population)	1	552	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.71, 1.40]
20.2 Poorly reversible population	1	308	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.44, 1.19]
21 Adverse events — serious events	3	1469	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.21]
21.1 Partially reversible population (mixed population)	1	552	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.70, 2.03]
21.2 Poorly reversible population	2	917	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.64, 1.16]
22 Adverse events (specific adverse events)	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 Pneumonia	3	1371	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.47, 2.63]
22.2 Candidiasis	2	1063	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.42, 1.80]
22.3 Dysphonia	2	1063	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.48, 3.51]
22.4 Palpitations	1	552	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.06, 15.95]
22.5 Laryngeal pharyngitis	2	819	Odds Ratio (M-H, Fixed, 95% CI)	2.05 [0.98, 4.29]
22.6 Bronchitis	1	552	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.49, 3.22]
22.7 Sinusitis	1	552	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [0.60, 6.77]
22.8 Diarrhoea	1	552	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.20, 4.96]
22.9 Upper airway infection	1	308	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.10, 1.08]
22.10 Nasopharyngitis	1	552	Odds Ratio (M-H, Fixed, 95% CI)	2.42 [1.09, 5.39]
22.11 Hypertension	1	511	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.23, 1.90]
22.12 Back pain	1	511	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [0.61, 6.92]
22.13 Chest pain	1	511	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [0.61, 6.92]
22.14 Headache	1	552	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.06, 15.95]
22.15 Dyspnoea	2	1063	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.32, 3.16]
22.16 Cough	1	552	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

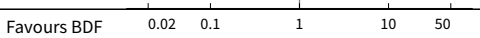
Analysis 3.1. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 1 Exacerbations.

Study or subgroup	BDF N	Budesonide N	log[Rate Ratio] (SE)	Rate Ratio IV, Fixed, 95% CI	Weight	Rate Ratio IV, Fixed, 95% CI
3.1.1 Partially reversible						
Tashkin 2008	0	0	-0 (0.14)		26.19%	1[0.76,1.31]
Subtotal (95% CI)					**26.19%**	**1[0.76,1.31]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.03(P=0.97)						
3.1.2 Poorly reversible						
Calverley 2003	1	1	-0.3 (0.142)		25.35%	0.72[0.54,0.95]
Szafranski 2003	1	1	-0.1 (0.135)		28.16%	0.89[0.69,1.17]
Zhong 2012	0	0	-0.3 (0.159)		20.3%	0.75[0.55,1.02]
Subtotal (95% CI)					**73.81%**	**0.79[0.67,0.93]**
Heterogeneity: Tau^2=0; Chi^2=1.41, df=2(P=0.49); I^2=0%						
Test for overall effect: Z=2.82(P=0)						
Total (95% CI)					**100%**	**0.84[0.73,0.97]**
Heterogeneity: Tau^2=0; Chi^2=3.41, df=3(P=0.33); I^2=12.06%						
Test for overall effect: Z=2.44(P=0.01)						
Test for subgroup differences: Chi^2=2, df=1 (P=0.16), I^2=50%						



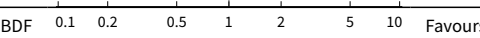
Analysis 3.2. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 2 Mean exacerbation rates per participant per year.

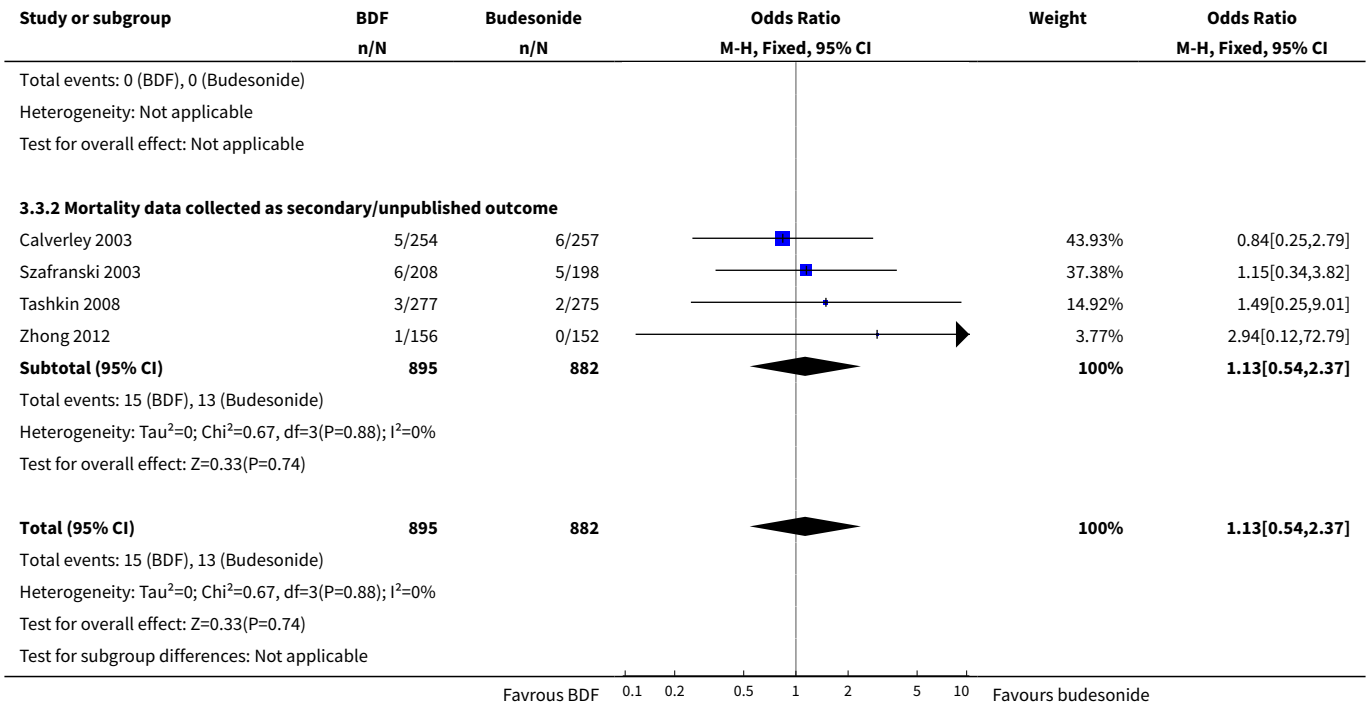
Study or subgroup	Experimental N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Fixed, 95% CI	Weight	Rate Ratio IV, Fixed, 95% CI
3.2.1 Poorly reversible population						
Calverley 2003	0	0	-0.1 (0.123)		41.65%	0.86[0.68,1.1]
Szafranski 2003	0	0	-0.1 (0.136)		34.32%	0.89[0.68,1.16]
Zhong 2012	0	0	-0.3 (0.162)		24.04%	0.75[0.55,1.03]
Subtotal (95% CI)					**100%**	**0.84[0.72,0.99]**
Heterogeneity: Tau^2=0; Chi^2=0.71, df=2(P=0.7); I^2=0%						
Test for overall effect: Z=2.15(P=0.03)						
Total (95% CI)					**100%**	**0.84[0.72,0.99]**
Heterogeneity: Tau^2=0; Chi^2=0.71, df=2(P=0.7); I^2=0%						
Test for overall effect: Z=2.15(P=0.03)						



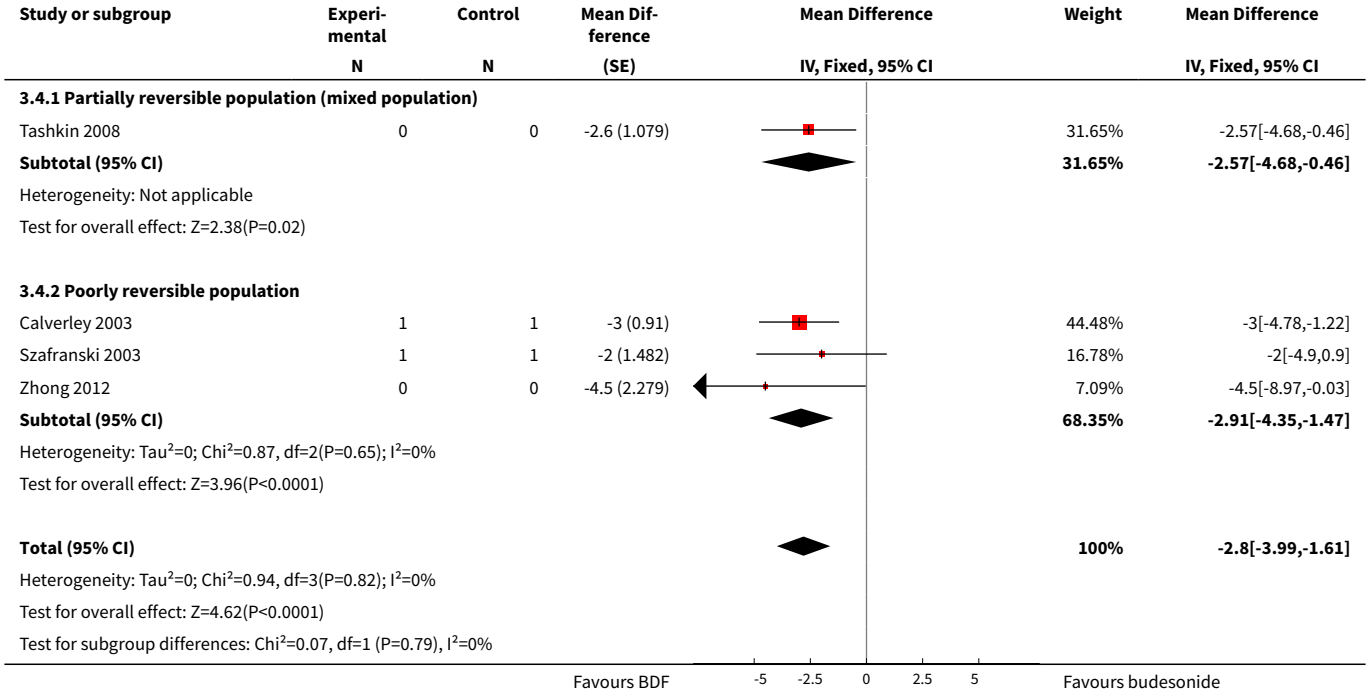
Analysis 3.3. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 3 Mortality.

Study or subgroup	BDF n/N	Budesonide n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.3.1 Mortality as primary outcome					
Subtotal (95% CI)	**0**	**0**			**Not estimable**





Analysis 3.4. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 4 Quality of life—SGRQ total (change scores).

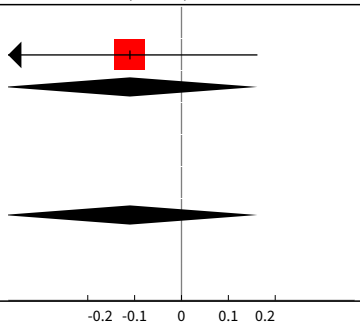


Analysis 3.5. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 5 Symptoms (change scores).

Study or subgroup	BDF N	Budesonide N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.5.1 Poorly reversible						
Calverley 2003	1	1	-0.3 (0.17)		45.76%	-0.26[-0.59,0.07]
Szafranski 2003	1	1	-0.7 (0.21)		29.99%	-0.7[-1.11,-0.29]
Zhong 2012	0	0	-0.5 (0.234)		24.25%	-0.49[-0.95,-0.03]
Subtotal (95% CI)					**100%**	**-0.45[-0.67,-0.22]**
Heterogeneity: Tau^2=0; Chi^2=2.7, df=2(P=0.26); I^2=25.8%						
Test for overall effect: Z=3.89(P<0.0001)						
Total (95% CI)					**100%**	**-0.45[-0.67,-0.22]**
Heterogeneity: Tau^2=0; Chi^2=2.7, df=2(P=0.26); I^2=25.8%						
Test for overall effect: Z=3.89(P<0.0001)						

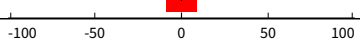
Analysis 3.6. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 6 Breathlessness, cough and sputum score (BCSS) change from baseline—average over treatment period.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.6.1 Partially reversible (mixed population)						
Tashkin 2008	0	0	-0.1 (0.139)		100%	-0.11[-0.38,0.16]
Subtotal (95% CI)					**100%**	**-0.11[-0.38,0.16]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.79(P=0.43)						
Total (95% CI)					**100%**	**-0.11[-0.38,0.16]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.79(P=0.43)						



Analysis 3.7. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 7 Awakening-free nights, percentage change from baseline.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.7.1 Partially reversible (mixed population)						
Tashkin 2008	0	0	2 (2.627)		0.05%	1.98[-3.17,7.13]
Subtotal (95% CI)					**0.05%**	**1.98[-3.17,7.13]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.75(P=0.45)						
3.7.2 Poorly reversible population						
Calverley 2003	0	0	-0 (0.056)		99.95%	-0.05[-0.16,0.06]



Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Subtotal (95% CI)					**99.95%**	**-0.05[-0.16,0.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.89(P=0.37)						
Total (95% CI)					**100%**	**-0.05[-0.16,0.06]**
Heterogeneity: Tau²=0; Chi²=0.6, df=1(P=0.44); I²=0%						
Test for overall effect: Z=0.87(P=0.38)						
Test for subgroup differences: Chi²=0.6, df=1 (P=0.44), I²=0%						

Favours BDF -100 -50 0 50 100 Favours budesonide

Analysis 3.8. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 8 Mean FEV_1 (% increase from baseline).

Study or subgroup	BDF N	Budesonide N	% increase (SE)	% increase IV, Fixed, 95% CI	Weight	% increase IV, Fixed, 95% CI
3.8.1 Poorly reversible						
Calverley 2003	1	1	11 (1.64)		58.32%	11[7.79,14.21]
Szafranski 2003	1	1	9 (1.94)		41.68%	9[5.2,12.8]
Subtotal (95% CI)					**100%**	**10.17[7.71,12.62]**
Heterogeneity: Tau²=0; Chi²=0.62, df=1(P=0.43); I²=0%						
Test for overall effect: Z=8.12(P<0.0001)						
Total (95% CI)					**100%**	**10.17[7.71,12.62]**
Heterogeneity: Tau²=0; Chi²=0.62, df=1(P=0.43); I²=0%						
Test for overall effect: Z=8.12(P<0.0001)						

Favours budesonide -100 -50 0 50 100 Favours BDF

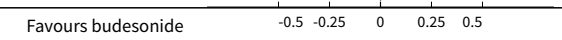
Analysis 3.9. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 9 Pre-dose FEV_1 [L] change from baseline to the average over the randomised treatment period.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.9.1 Partially reversible population (mixed population)						
Tashkin 2008	0	0	0.1 (0.018)		100%	0.08[0.05,0.11]
Subtotal (95% CI)					**100%**	**0.08[0.05,0.11]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%						
Test for overall effect: Z=4.57(P<0.0001)						
Total (95% CI)					**100%**	**0.08[0.05,0.11]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%						
Test for overall effect: Z=4.57(P<0.0001)						

Favours budesonide -0.2 -0.1 0 0.1 0.2 Favours BDF

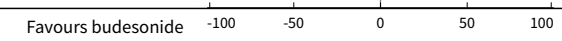
Analysis 3.10. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 10 1-Hour post-dose FEV_1 [L] change from baseline to the average over the randomised treatment period.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.10.1 Partially reversible population (mixed population)						
Tashkin 2008	0	0	0.2 (0.017)		100%	0.17[0.14,0.2]
Subtotal (95% CI)					**100%**	**0.17[0.14,0.2]**
Heterogeneity: Not applicable						
Test for overall effect: Z=10(P<0.0001)						
Total (95% CI)					**100%**	**0.17[0.14,0.2]**
Heterogeneity: Not applicable						
Test for overall effect: Z=10(P<0.0001)						



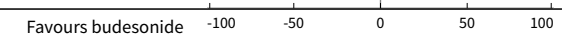
Analysis 3.11. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 11 Morning PEFR change from baseline, average over treatment period (L/min).

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.11.1 Poorly reversible population						
Tashkin 2008	0	0	14.1 (2.775)		100%	14.08[8.64,19.52]
Subtotal (95% CI)					**100%**	**14.08[8.64,19.52]**
Heterogeneity: Not applicable						
Test for overall effect: Z=5.07(P<0.0001)						
Total (95% CI)					**100%**	**14.08[8.64,19.52]**
Heterogeneity: Not applicable						
Test for overall effect: Z=5.07(P<0.0001)						



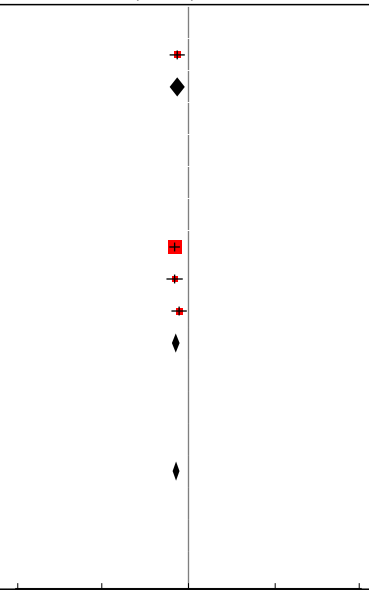
Analysis 3.12. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 12 Evening PEFR mean change from baseline, average over treatment period (L/min).

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.12.1 Partially reversible population (mixed population)						
Tashkin 2008	0	0	12.6 (2.745)		100%	12.59[7.21,17.97]
Subtotal (95% CI)					**100%**	**12.59[7.21,17.97]**
Heterogeneity: Not applicable						
Test for overall effect: Z=4.59(P<0.0001)						
Total (95% CI)					**100%**	**12.59[7.21,17.97]**
Heterogeneity: Not applicable						
Test for overall effect: Z=4.59(P<0.0001)						



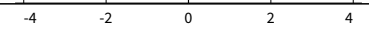
Analysis 3.13. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 13 Rescue medication use.

Study or subgroup	BDF N	Budesonide N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.13.1 Partially reversible population (mixed population)						
Tashkin 2008	0	0	-0.6 (0.223)		20.49%	-0.65[-1.09,-0.21]
Subtotal (95% CI)					**20.49%**	**-0.65[-1.09,-0.21]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.91(P=0)						
3.13.2 Poorly reversible						
Calverley 2003	1	1	-0.8 (0.156)		41.9%	-0.8[-1.11,-0.49]
Szafranski 2003	1	1	-0.8 (0.24)		17.7%	-0.8[-1.27,-0.33]
Zhong 2012	0	0	-0.5 (0.226)		19.91%	-0.54[-0.98,-0.1]
Subtotal (95% CI)					**79.51%**	**-0.73[-0.96,-0.51]**
Heterogeneity: Tau^2=0; Chi^2=0.99, df=2(P=0.61); I^2=0%						
Test for overall effect: Z=6.49(P<0.0001)						
Total (95% CI)					**100%**	**-0.72[-0.92,-0.52]**
Heterogeneity: Tau^2=0; Chi^2=1.1, df=3(P=0.78); I^2=0%						
Test for overall effect: Z=7.11(P<0.0001)						
Test for subgroup differences: Chi^2=0.12, df=1 (P=0.73), I^2=0%						



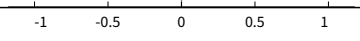
Analysis 3.14. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 14 Sleep score (0 to 4) — change from baseline.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.14.1 Partially reversible population (mixed population)						
Tashkin 2008	0	0	-0 (0.053)		100%	-0.04[-0.14,0.06]
Subtotal (95% CI)					**100%**	**-0.04[-0.14,0.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.76(P=0.45)						
Total (95% CI)					**100%**	**-0.04[-0.14,0.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.76(P=0.45)						



Analysis 3.15. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 15 Dyspnoea score (0 to 4) — change from baseline.

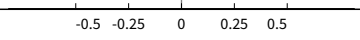
Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.15.1 Partially reversible population (mixed population)						
Tashkin 2008	0	0	-0.1 (0.053)		52.46%	-0.12[-0.22,-0.02]
Subtotal (95% CI)					**52.46%**	**-0.12[-0.22,-0.02]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.25(P=0.02)						
3.15.2 Poorly reversible population						
Calverley 2003	0	0	-0.1 (0.056)		47.54%	-0.12[-0.23,-0.01]
Subtotal (95% CI)					**47.54%**	**-0.12[-0.23,-0.01]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%						
Test for overall effect: Z=2.14(P=0.03)						
Total (95% CI)					**100%**	**-0.12[-0.2,-0.04]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%						
Test for overall effect: Z=3.1(P=0)						
Test for subgroup differences: Chi^2=0, df=1 (P=1), I^2=0%						



Favours BDF — Favours budesonide

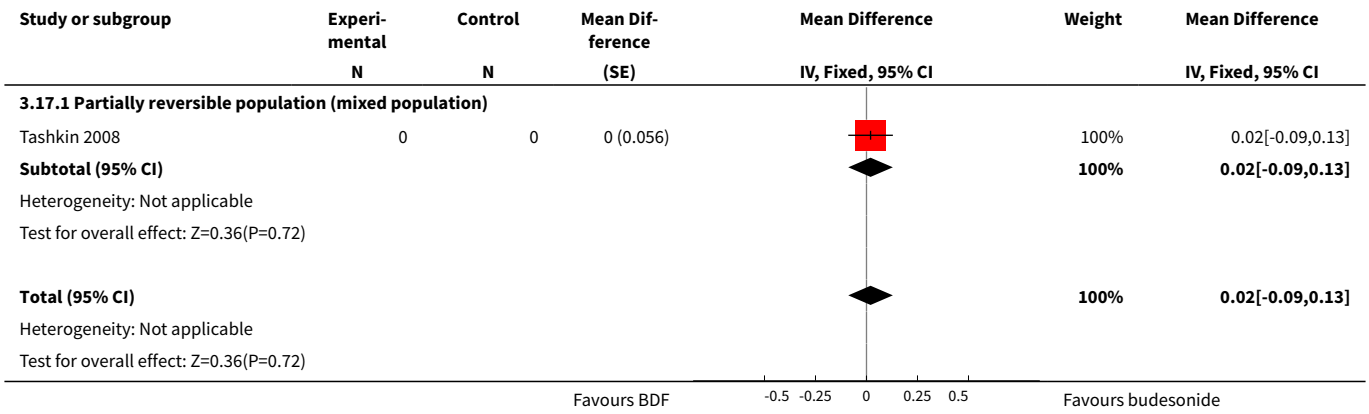
Analysis 3.16. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 16 Cough score (0 to 4) — change from baseline.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
3.16.1 Partially reversible population (mixed population)						
Tashkin 2008	0	0	0 (0.056)		45.51%	0[-0.11,0.11]
Subtotal (95% CI)					**45.51%**	**0[-0.11,0.11]**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.16.2 Poorly reversible population						
Calverley 2003	0	0	-0 (0.051)		54.49%	-0.02[-0.12,0.08]
Subtotal (95% CI)					**54.49%**	**-0.02[-0.12,0.08]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.39(P=0.69)						
Total (95% CI)					**100%**	**-0.01[-0.08,0.06]**
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.79); I^2=0%						
Test for overall effect: Z=0.29(P=0.77)						
Test for subgroup differences: Chi^2=0.07, df=1 (P=0.79), I^2=0%						

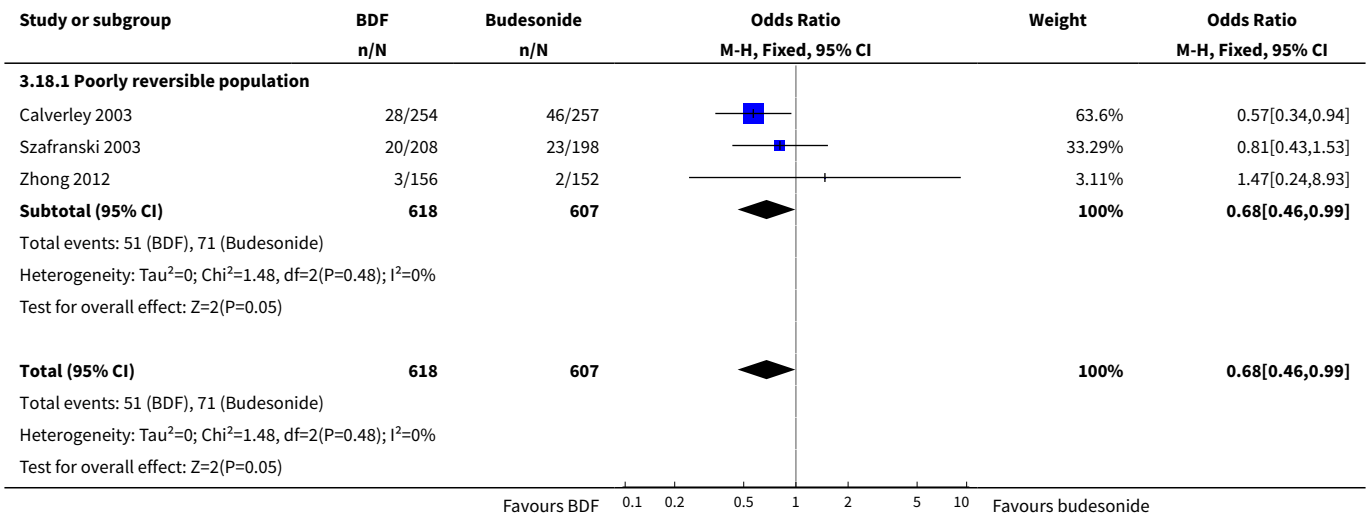


Favours BDF — Favours budesonide

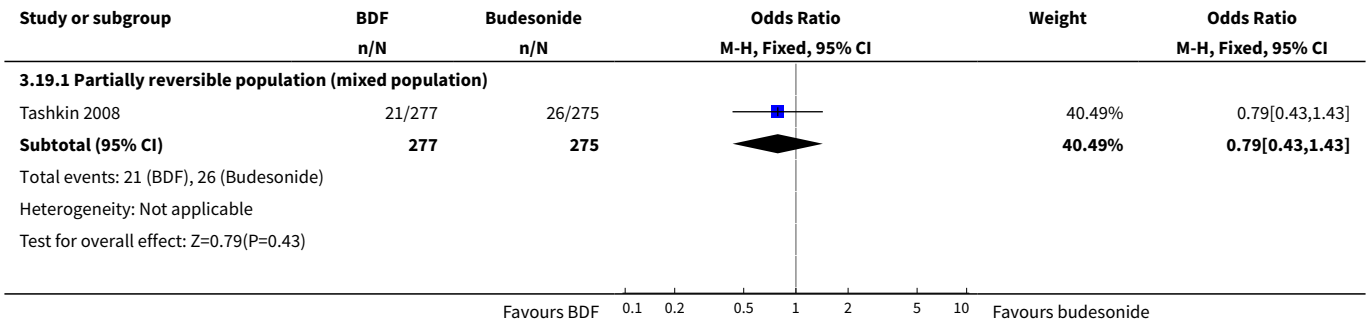
Analysis 3.17. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 17 Sputum score (0 to 4) — change from baseline.

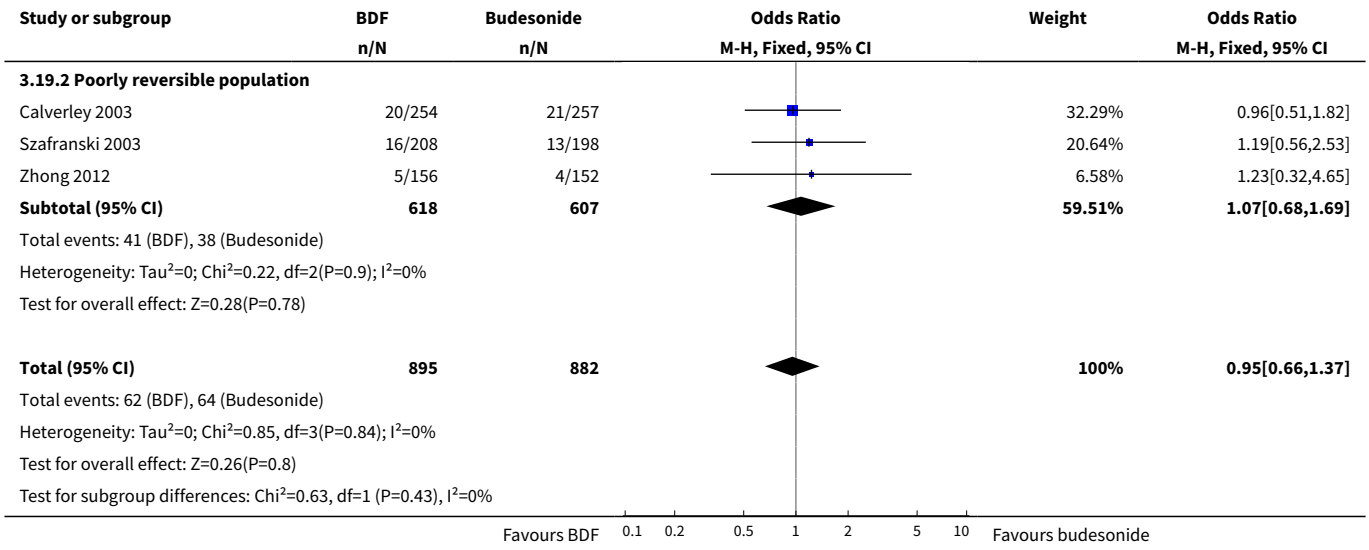


Analysis 3.18. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 18 Withdrawals due to worsening COPD symptoms.

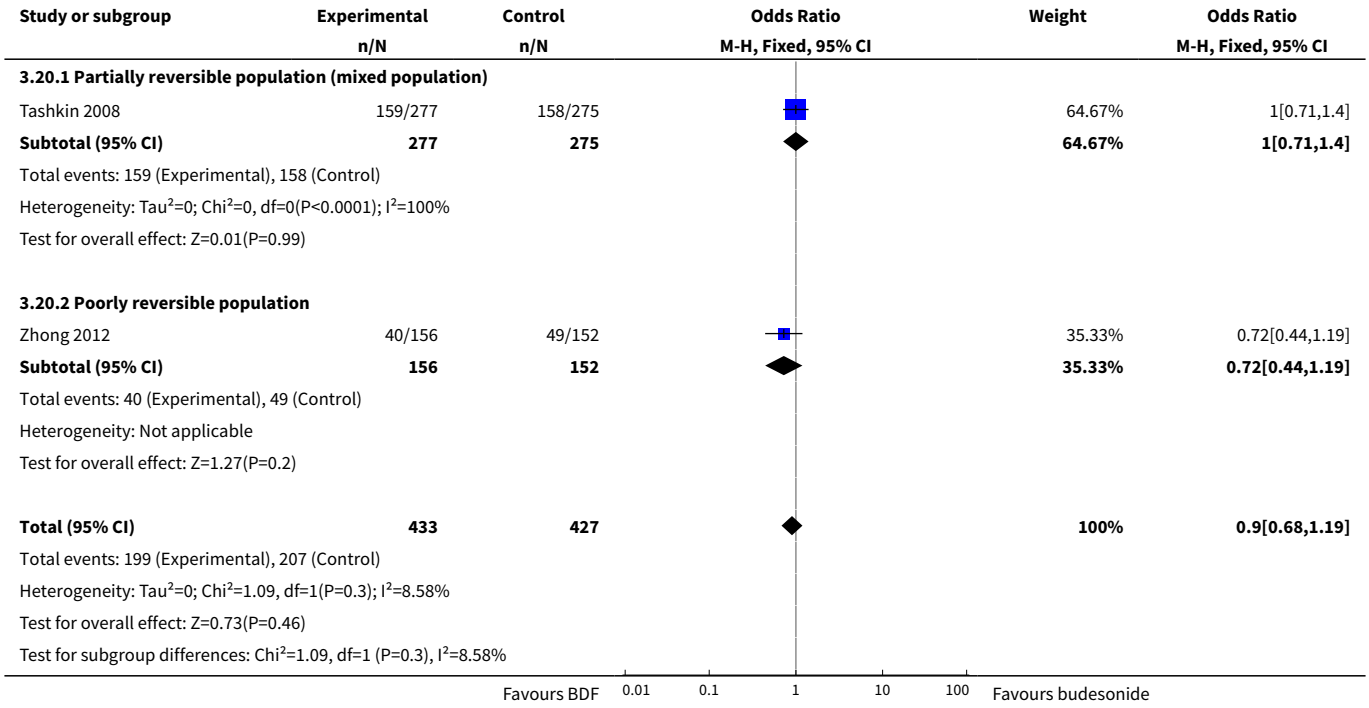


Analysis 3.19. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 19 Withdrawals due to adverse events.





Analysis 3.20. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 20 Adverse event—any (one or more).

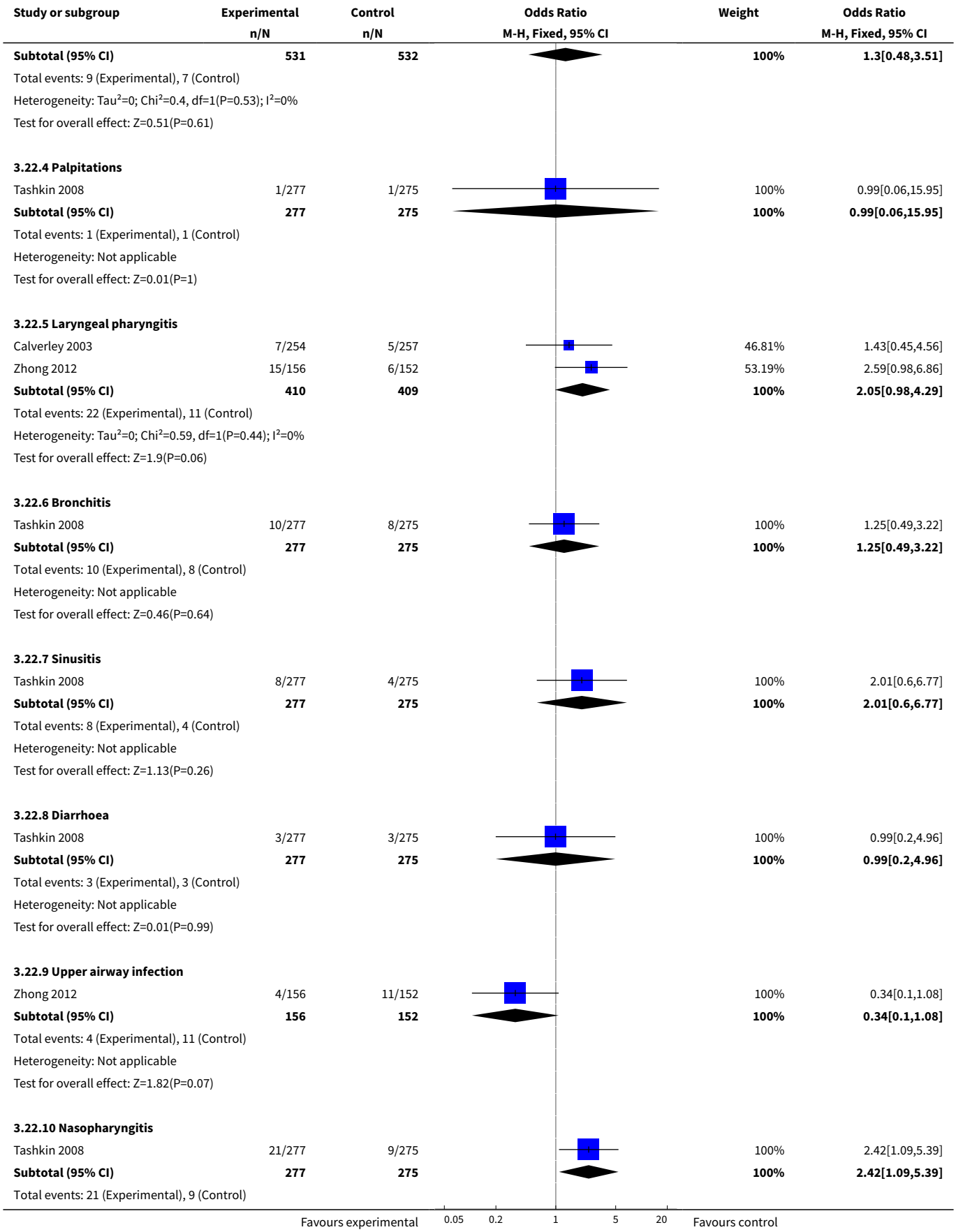


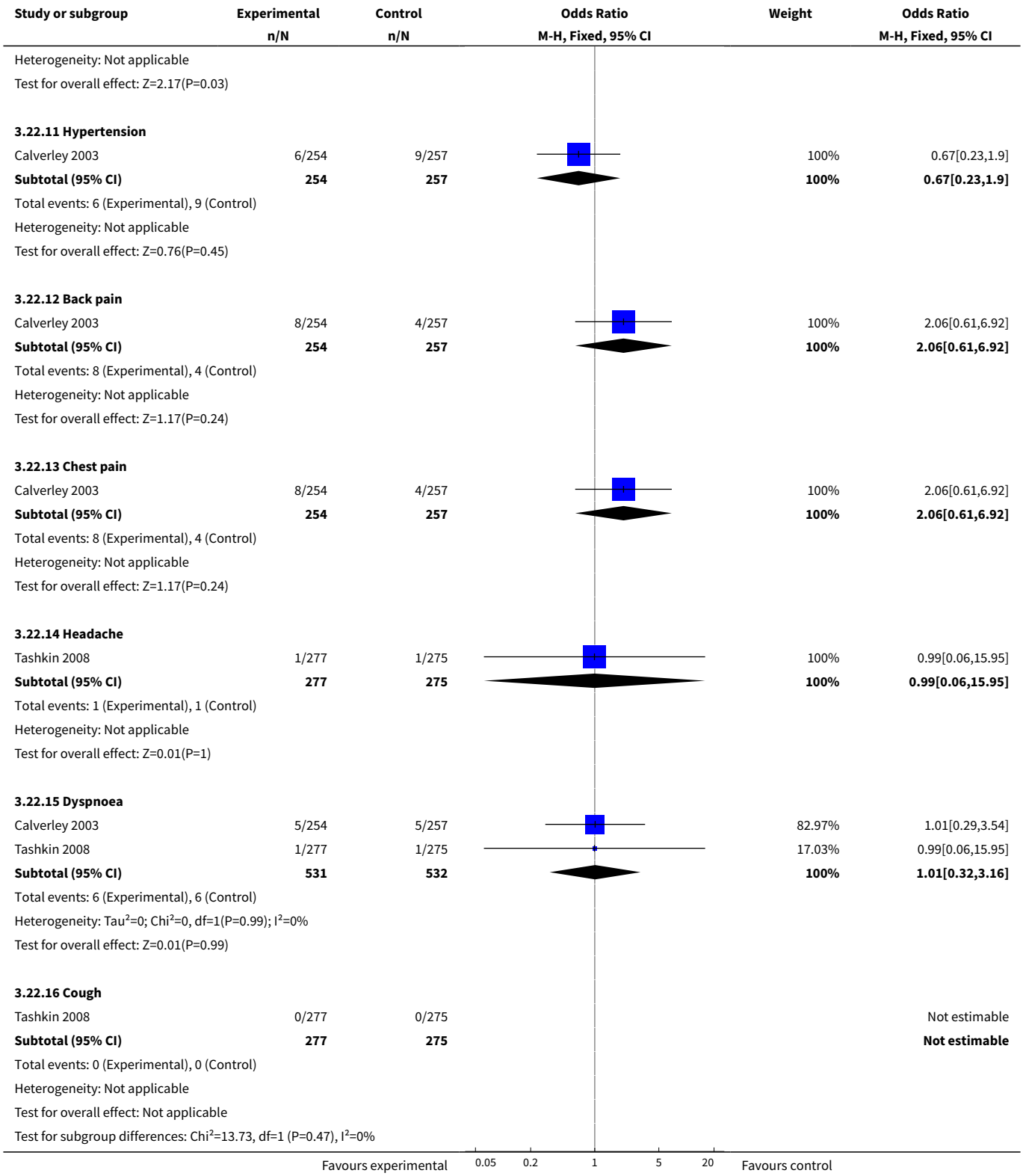
Analysis 3.21. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 21 Adverse events — serious events.

Study or subgroup	BDF n/N	Budesonide n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.21.1 Partially reversible population (mixed population)					
Tashkin 2008	33/277	28/275		21.02%	1.19[0.7,2.03]
Subtotal (95% CI)	**277**	**275**		**21.02%**	**1.19[0.7,2.03]**
Total events: 33 (BDF), 28 (Budesonide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.52)					
3.21.2 Poorly reversible population					
Calverley 2003	65/254	88/257		55.27%	0.66[0.45,0.97]
Szafranski 2003	46/208	35/198		23.71%	1.32[0.81,2.16]
Subtotal (95% CI)	**462**	**455**		**78.98%**	**0.86[0.64,1.16]**
Total events: 111 (BDF), 123 (Budesonide)					
Heterogeneity: Tau^2=0; Chi^2=4.79, df=1(P=0.03); I^2=79.13%					
Test for overall effect: Z=1(P=0.32)					
Total (95% CI)	**739**	**730**		**100%**	**0.93[0.72,1.21]**
Total events: 144 (BDF), 151 (Budesonide)					
Heterogeneity: Tau^2=0; Chi^2=5.9, df=2(P=0.05); I^2=66.11%					
Test for overall effect: Z=0.55(P=0.58)					
Test for subgroup differences: Chi^2=1.11, df=1 (P=0.29), I^2=9.65%					

Analysis 3.22. Comparison 3 Budesonide/formoterol (BDF) versus budesonide (BD), Outcome 22 Adverse events (specific adverse events).

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.22.1 Pneumonia					
Calverley 2003	8/254	5/257		49.23%	1.64[0.53,5.08]
Tashkin 2008	3/277	5/275		50.77%	0.59[0.14,2.5]
Zhong 2012	0/156	0/152			Not estimable
Subtotal (95% CI)	**687**	**684**		**100%**	**1.11[0.47,2.63]**
Total events: 11 (Experimental), 10 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.19, df=1(P=0.28); I^2=15.96%					
Test for overall effect: Z=0.23(P=0.82)					
3.22.2 Candidiasis					
Calverley 2003	4/254	4/257		25.21%	1.01[0.25,4.09]
Tashkin 2008	10/277	12/275		74.79%	0.82[0.35,1.93]
Subtotal (95% CI)	**531**	**532**		**100%**	**0.87[0.42,1.8]**
Total events: 14 (Experimental), 16 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.8); I^2=0%					
Test for overall effect: Z=0.38(P=0.71)					
3.22.3 Dysphonia					
Calverley 2003	5/254	5/257		71.12%	1.01[0.29,3.54]
Tashkin 2008	4/277	2/275		28.88%	2[0.36,11.01]





Comparison 4. Mometasone/formoterol (MF/F) versus Mometasone (MF)

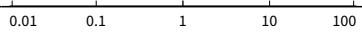
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with one or more exacerbation	2	905	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.45, 0.98]
1.1 Poorly reversible population	1	478	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.53, 1.42]
1.2 Unclear reversibility	1	427	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.22, 0.82]
2 Mortality	2	905	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.27, 2.91]
2.1 Poorly reversible population	1	478	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.33, 6.81]
2.2 Unclear reversibility	1	427	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.03, 3.10]
3 Change from baseline in SGRQ (total score)	2		Mean Difference (Fixed, 95% CI)	-0.29 [-2.16, 1.57]
3.1 Poorly reversible population	1		Mean Difference (Fixed, 95% CI)	-0.17 [-2.68, 2.34]
3.2 Unclear reversibility	1		Mean Difference (Fixed, 95% CI)	-0.44 [-3.23, 2.35]
4 Change from baseline in FEV_1 $AUC_{0\text{-}12\ h}$ (mL) week 26	2		Mean Difference (Fixed, 95% CI)	109.34 [57.87, 160.81]
4.1 Poorly reversible population	1		Mean Difference (Fixed, 95% CI)	119.0 [48.96, 189.04]
4.2 Unclear reversibility	1		Mean Difference (Fixed, 95% CI)	98.0 [22.11, 173.89]
5 Change from baseline in FEV_1 $AUC_{0\text{-}12\ h}$ (mL) week 13	2		Mean Difference (Fixed, 95% CI)	116.59 [68.59, 164.59]
5.1 Poorly reversible population	1		Mean Difference (Fixed, 95% CI)	126.0 [54.16, 197.84]
5.2 Unclear reversibility	1		Mean Difference (Fixed, 95% CI)	109.0 [44.49, 173.51]
6 Mean change from baseline AM pre-dose FEV_1 at 13 weeks (mL)	2		Mean Difference (Fixed, 95% CI)	0.08 [0.04, 0.11]
6.1 Poorly reversible population	1		Mean Difference (Fixed, 95% CI)	0.07 [0.02, 0.12]
6.2 Unclear reversibility	1		Mean Difference (Fixed, 95% CI)	0.08 [0.03, 0.14]
7 Withdrawals — total	2	905	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.56, 1.09]
7.1 Poorly reversible population	1	478	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.45, 1.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Unclear reversibility	1	427	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.52, 1.33]
8 Withdrawals due to adverse event	2	905	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [0.71, 2.68]
8.1 Poorly reversible population	1	478	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [0.69, 4.74]
8.2 Unclear reversibility	1	427	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.43, 2.71]
9 Withdrawal due to treatment failure	2	905	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.19, 2.44]
9.1 Poorly reversible population	1	478	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.04, 3.60]
9.2 Unclear reversibility	1	427	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.19, 4.85]
10 Adverse event—any	2	905	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.84, 1.46]
10.1 Poorly reversible population	1	478	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.94, 1.95]
10.2 Unclear reversibility	1	427	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.56, 1.30]
11 Adverse event—serious	2	905	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.63, 1.67]
11.1 Poorly reversible population	1	478	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.53, 1.95]
11.2 Unclear reversibility	1	427	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.50, 2.15]
12 Adverse events (specific adverse events)	2	12823	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.75, 1.25]
12.1 Cataract	2	905	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.05, 2.20]
12.2 COPD requiring hospitalisation	2	905	Odds Ratio (M-H, Fixed, 95% CI)	1.46 [0.66, 3.21]
12.3 Pneumonia	2	905	Odds Ratio (M-H, Fixed, 95% CI)	1.92 [0.66, 5.57]
12.4 Candidiasis	2	905	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.16, 1.36]
12.5 Lenticular opacities	1	478	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.05, 6.22]
12.6 Upper respiratory tract infection	2	905	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [0.77, 3.84]
12.7 Headache	2	905	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.39, 1.70]
12.8 Cough	2	905	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.15, 1.73]
12.9 Hypertension	2	905	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.34, 2.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.10 Chest pain	1	427	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.93]
12.11 Influenza	2	905	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.14, 1.55]
12.12 Nasopharyngitis	2	905	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.49, 1.99]
12.13 Bronchitis	1	478	Odds Ratio (M-H, Fixed, 95% CI)	5.73 [0.66, 49.40]
12.14 Pyrexia	1	478	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.32, 3.95]
12.15 Back pain	2	956	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.21, 2.67]
12.16 Peripheral oedema	1	478	Odds Ratio (M-H, Fixed, 95% CI)	2.26 [0.20, 25.09]
12.17 Dysphonia	1	478	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.09, 2.32]

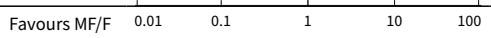
Analysis 4.1. Comparison 4 Mometasone/formoterol (MF/F) versus Mometasone (MF), Outcome 1 Patients with one or more exacerbation.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.1.1 Poorly reversible population					
Doherty 2012	34/225	43/253		53.95%	0.87[0.53,1.42]
Subtotal (95% CI)	**225**	**253**		**53.95%**	**0.87[0.53,1.42]**
Total events: 34 (Experimental), 43 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.56(P=0.58)					
4.1.2 Unclear reversibility					
Tashkin 2012	15/217	31/210		46.05%	0.43[0.22,0.82]
Subtotal (95% CI)	**217**	**210**		**46.05%**	**0.43[0.22,0.82]**
Total events: 15 (Experimental), 31 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=2.56(P=0.01)					
Total (95% CI)	**442**	**463**		**100%**	**0.67[0.45,0.98]**
Total events: 49 (Experimental), 74 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.9, df=1(P=0.09); I^2=65.57%					
Test for overall effect: Z=2.05(P=0.04)					
Test for subgroup differences: Chi^2=2.9, df=1 (P=0.09), I^2=65.55%					



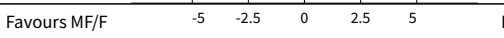
Analysis 4.2. Comparison 4 Mometasone/formoterol (MF/F) versus Mometasone (MF), Outcome 2 Mortality.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.2.1 Poorly reversible population					
Doherty 2012	4/225	3/253		47.75%	1.51[0.33,6.81]
Subtotal (95% CI)	**225**	**253**		**47.75%**	**1.51[0.33,6.81]**
Total events: 4 (Experimental), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.53(P=0.59)					
4.2.2 Unclear reversibility					
Tashkin 2012	1/217	3/210		52.25%	0.32[0.03,3.1]
Subtotal (95% CI)	**217**	**210**		**52.25%**	**0.32[0.03,3.1]**
Total events: 1 (Experimental), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.98(P=0.32)					
Total (95% CI)	**442**	**463**		**100%**	**0.89[0.27,2.91]**
Total events: 5 (Experimental), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.25, df=1(P=0.26); I^2=20.18%					
Test for overall effect: Z=0.2(P=0.84)					
Test for subgroup differences: Chi^2=1.25, df=1 (P=0.26), I^2=19.7%					



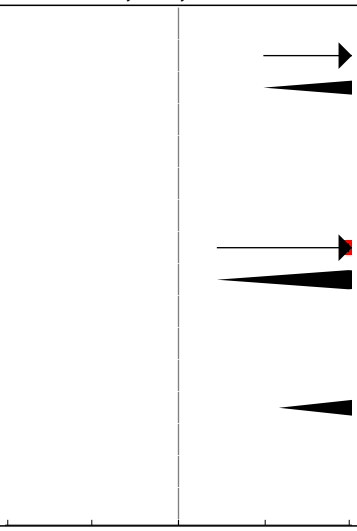
Analysis 4.3. Comparison 4 Mometasone/formoterol (MF/F) versus Mometasone (MF), Outcome 3 Change from baseline in SGRQ (total score).

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
4.3.1 Poorly reversible population						
Doherty 2012	0	0	-0.2 (1.278)		55.41%	-0.17[-2.68,2.34]
Subtotal (95% CI)					**55.41%**	**-0.17[-2.68,2.34]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.13(P=0.89)						
4.3.2 Unclear reversibility						
Tashkin 2012	0	0	-0.4 (1.425)		44.59%	-0.44[-3.23,2.35]
Subtotal (95% CI)					**44.59%**	**-0.44[-3.23,2.35]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.31(P=0.76)						
Total (95% CI)					**100%**	**-0.29[-2.16,1.57]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%						
Test for overall effect: Z=0.31(P=0.76)						
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.89), I^2=0%						



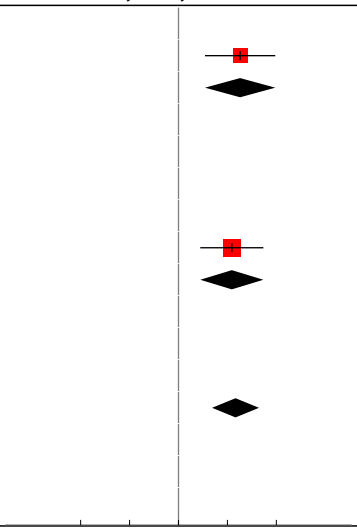
Analysis 4.4. Comparison 4 Mometasone/formoterol (MF/F) versus Mometasone (MF), Outcome 4 Change from baseline in FEV_1 $AUC_{0\text{-}12\ h}$ (mL) week 26.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
4.4.1 Poorly reversible population						
Doherty 2012	0	0	119 (35.738)		54%	119[48.96,189.04]
Subtotal (95% CI)					**54%**	**119[48.96,189.04]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.33(P=0)						
4.4.2 Unclear reversibility						
Tashkin 2012	0	0	98 (38.72)		46%	98[22.11,173.89]
Subtotal (95% CI)					**46%**	**98[22.11,173.89]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.53(P=0.01)						
Total (95% CI)					**100%**	**109.34[57.87,160.81]**
Heterogeneity: Tau^2=0; Chi^2=0.16, df=1(P=0.69); I^2=0%						
Test for overall effect: Z=4.16(P<0.0001)						
Test for subgroup differences: Chi^2=0.16, df=1 (P=0.69), I^2=0%						



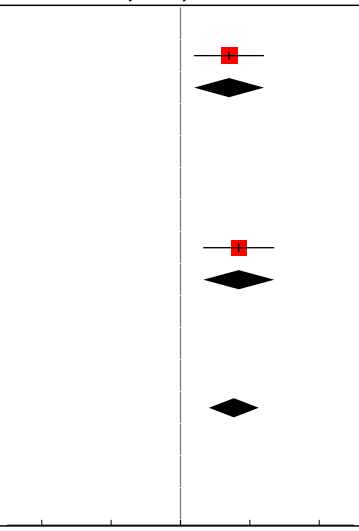
Analysis 4.5. Comparison 4 Mometasone/formoterol (MF/F) versus Mometasone (MF), Outcome 5 Change from baseline in FEV_1 $AUC_{0\text{-}12\ h}$ (mL) week 13.

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
4.5.1 Poorly reversible population						
Doherty 2012	0	0	126 (36.654)		44.64%	126[54.16,197.84]
Subtotal (95% CI)					**44.64%**	**126[54.16,197.84]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.44(P=0)						
4.5.2 Unclear reversibility						
Tashkin 2012	0	0	109 (32.912)		55.36%	109[44.49,173.51]
Subtotal (95% CI)					**55.36%**	**109[44.49,173.51]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.31(P=0)						
Total (95% CI)					**100%**	**116.59[68.59,164.59]**
Heterogeneity: Tau^2=0; Chi^2=0.12, df=1(P=0.73); I^2=0%						
Test for overall effect: Z=4.76(P<0.0001)						
Test for subgroup differences: Chi^2=0.12, df=1 (P=0.73), I^2=0%						



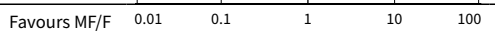
Analysis 4.6. Comparison 4 Mometasone/formoterol (MF/F) versus Mometasone (MF), Outcome 6 Mean change from baseline AM pre-dose FEV_1 at 13 weeks (mL).

Study or subgroup	Experimental N	Control N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
4.6.1 Poorly reversible population						
Doherty 2012	0	0	0.1 (0.026)		50.77%	0.07[0.02,0.12]
Subtotal (95% CI)					**50.77%**	**0.07[0.02,0.12]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.72(P=0.01)						
4.6.2 Unclear reversibility						
Tashkin 2012	0	0	0.1 (0.026)		49.23%	0.08[0.03,0.14]
Subtotal (95% CI)					**49.23%**	**0.08[0.03,0.14]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.22(P=0)						
Total (95% CI)					**100%**	**0.08[0.04,0.11]**
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.7); I^2=0%						
Test for overall effect: Z=4.2(P<0.0001)						
Test for subgroup differences: Chi^2=0.15, df=1 (P=0.7), I^2=0%						

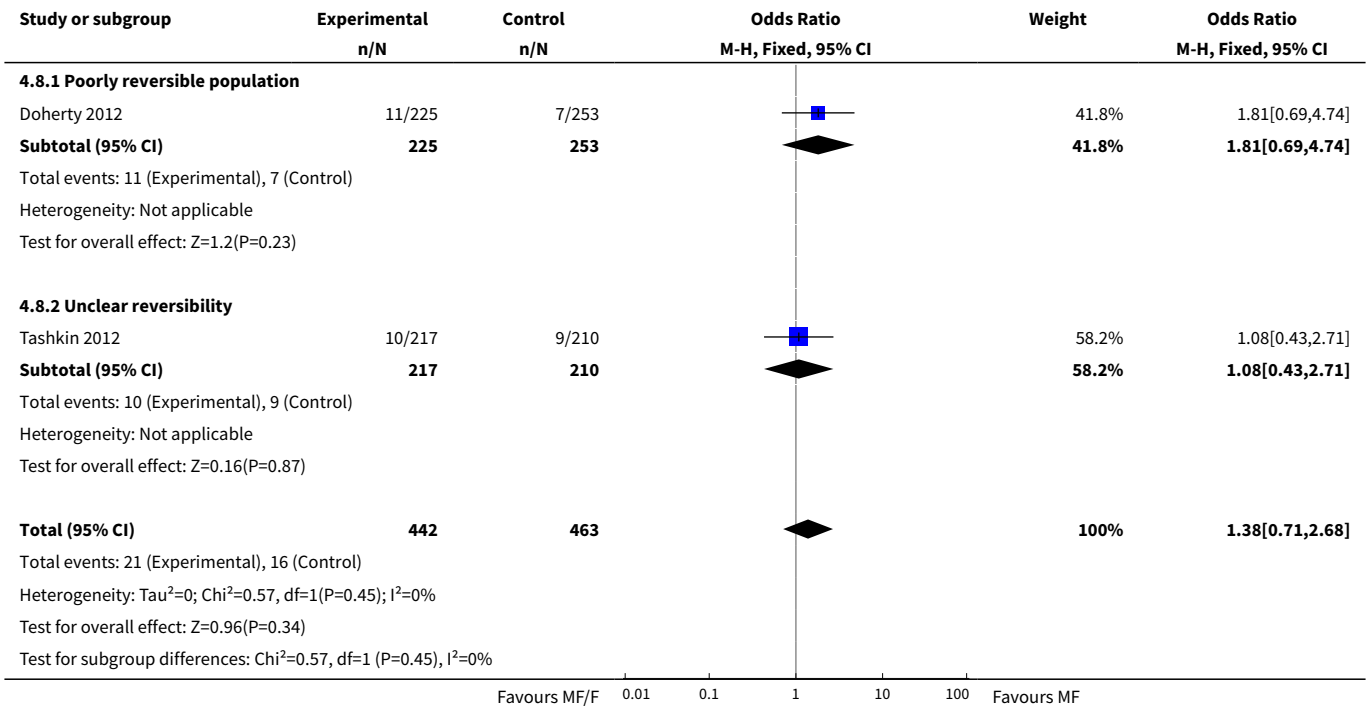


Analysis 4.7. Comparison 4 Mometasone/formoterol (MF/F) versus Mometasone (MF), Outcome 7 Withdrawals—total.

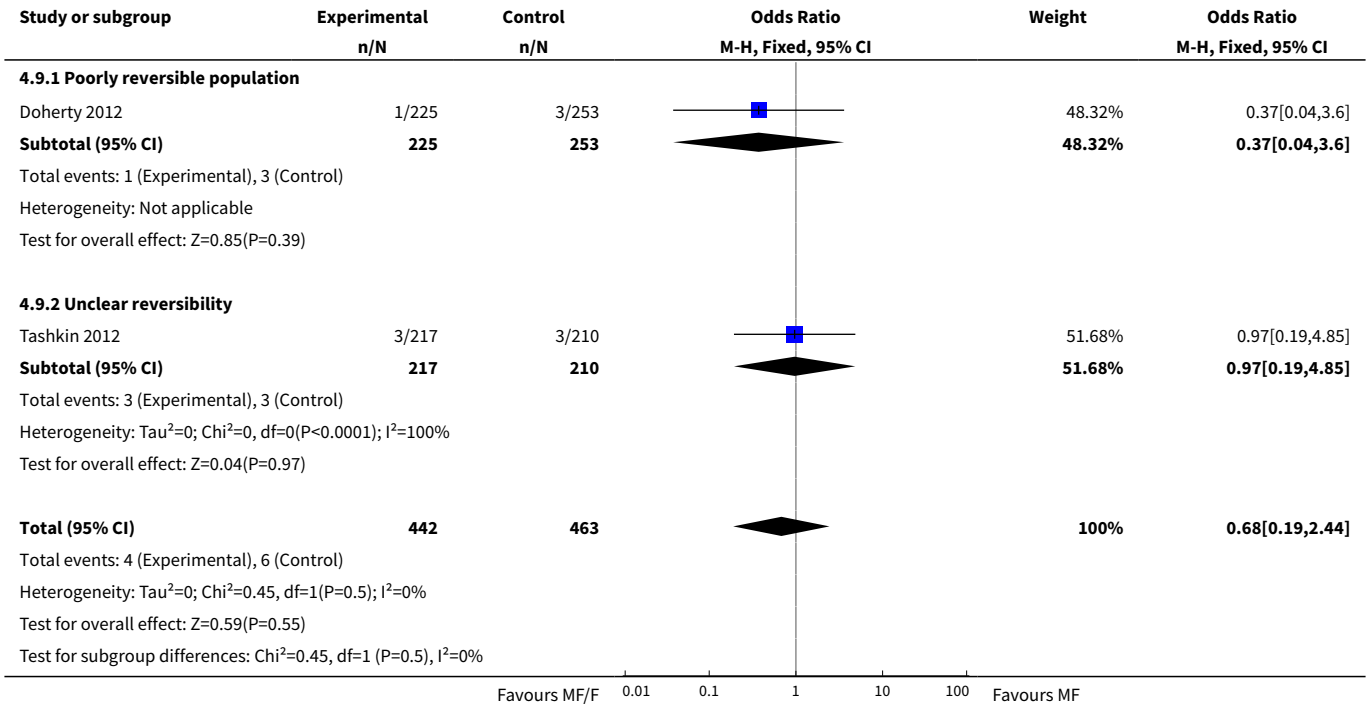
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.7.1 Poorly reversible population					
Doherty 2012	35/225	51/253		51.67%	0.73[0.45,1.17]
Subtotal (95% CI)	**225**	**253**		**51.67%**	**0.73[0.45,1.17]**
Total events: 35 (Experimental), 51 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.3(P=0.19)					
4.7.2 Unclear reversibility					
Tashkin 2012	41/217	46/210		48.33%	0.83[0.52,1.33]
Subtotal (95% CI)	**217**	**210**		**48.33%**	**0.83[0.52,1.33]**
Total events: 41 (Experimental), 46 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.77(P=0.44)					
Total (95% CI)	**442**	**463**		**100%**	**0.78[0.56,1.09]**
Total events: 76 (Experimental), 97 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.7); I^2=0%					
Test for overall effect: Z=1.47(P=0.14)					
Test for subgroup differences: Chi^2=0.14, df=1 (P=0.7), I^2=0%					



Analysis 4.8. Comparison 4 Mometasone/formoterol (MF/F) versus Mometasone (MF), Outcome 8 Withdrawals due to adverse event.

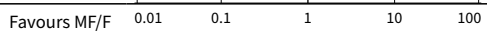


Analysis 4.9. Comparison 4 Mometasone/formoterol (MF/F) versus Mometasone (MF), Outcome 9 Withdrawal due to treatment failure.



Analysis 4.10. Comparison 4 Mometasone/formoterol (MF/F) versus Mometasone (MF), Outcome 10 Adverse event — any.

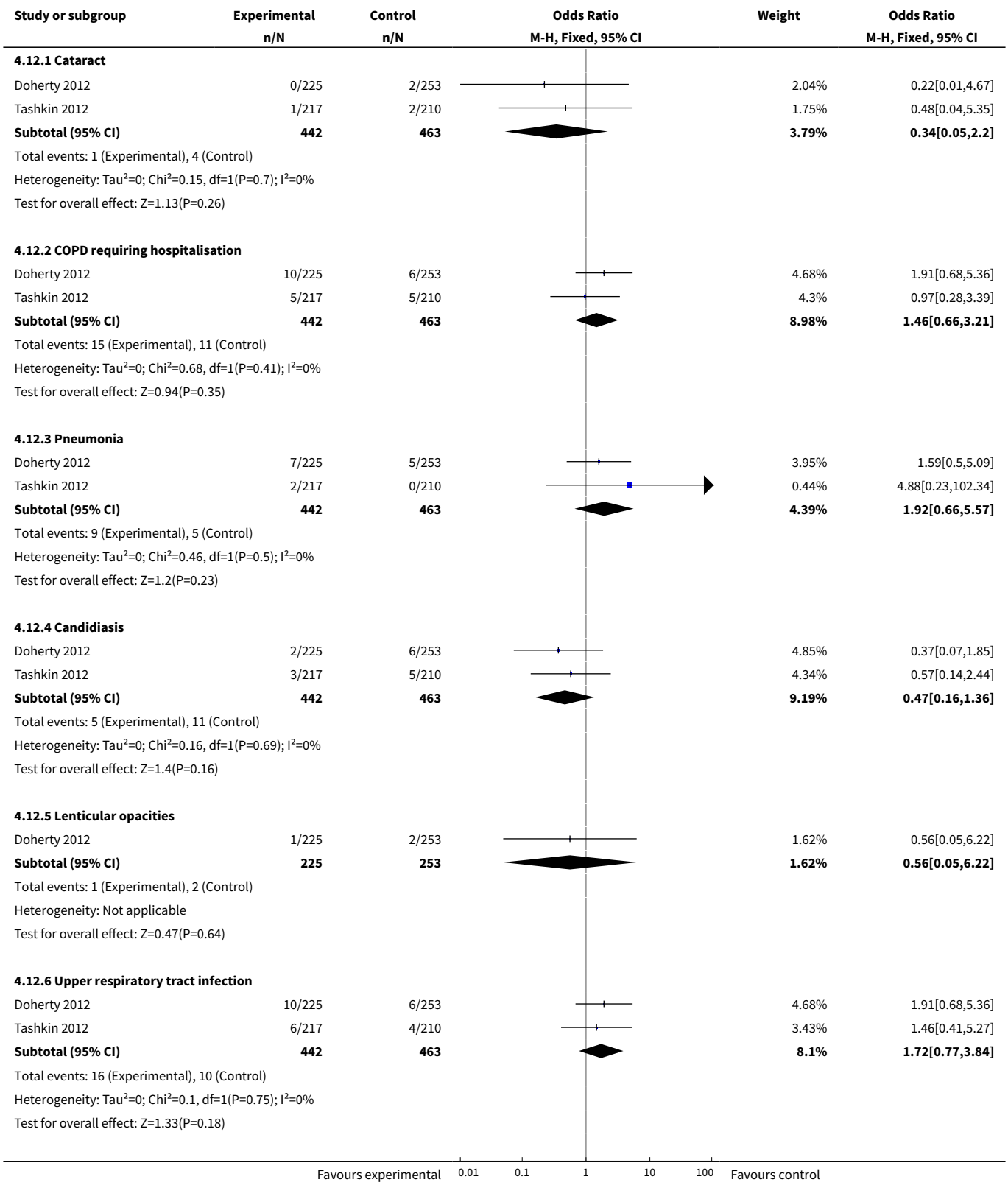
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.10.1 Poorly reversible population					
Doherty 2012	100/225	94/253		51.41%	1.35[0.94,1.95]
Subtotal (95% CI)	**225**	**253**		**51.41%**	**1.35[0.94,1.95]**
Total events: 100 (Experimental), 94 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.62(P=0.11)					
4.10.2 Unclear reversibility					
Tashkin 2012	57/217	62/210		48.59%	0.85[0.56,1.3]
Subtotal (95% CI)	**217**	**210**		**48.59%**	**0.85[0.56,1.3]**
Total events: 57 (Experimental), 62 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.75(P=0.45)					
Total (95% CI)	**442**	**463**		**100%**	**1.11[0.84,1.46]**
Total events: 157 (Experimental), 156 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.64, df=1(P=0.1); I^2=62.18%					
Test for overall effect: Z=0.73(P=0.46)					
Test for subgroup differences: Chi^2=2.64, df=1 (P=0.1), I^2=62.18%					

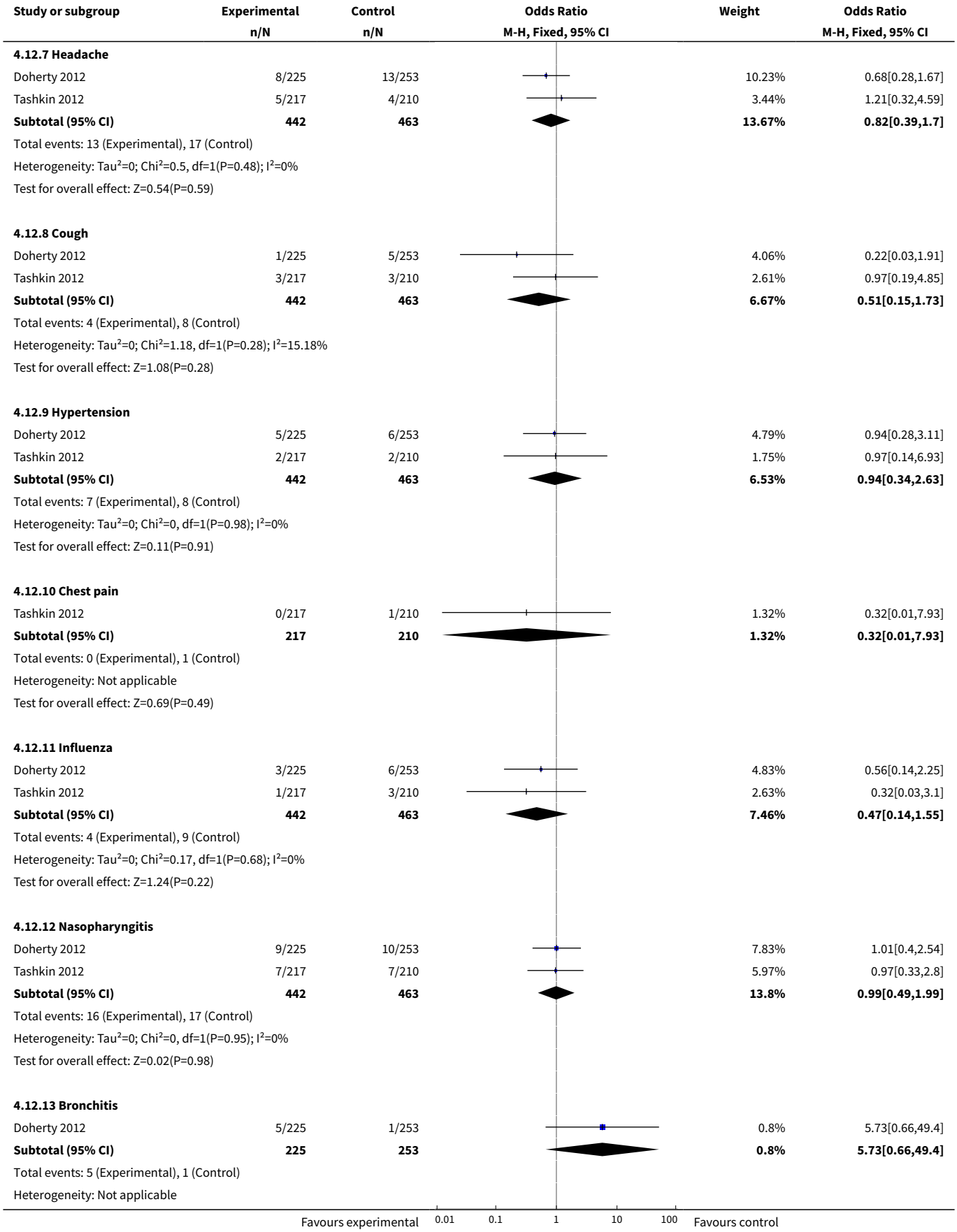


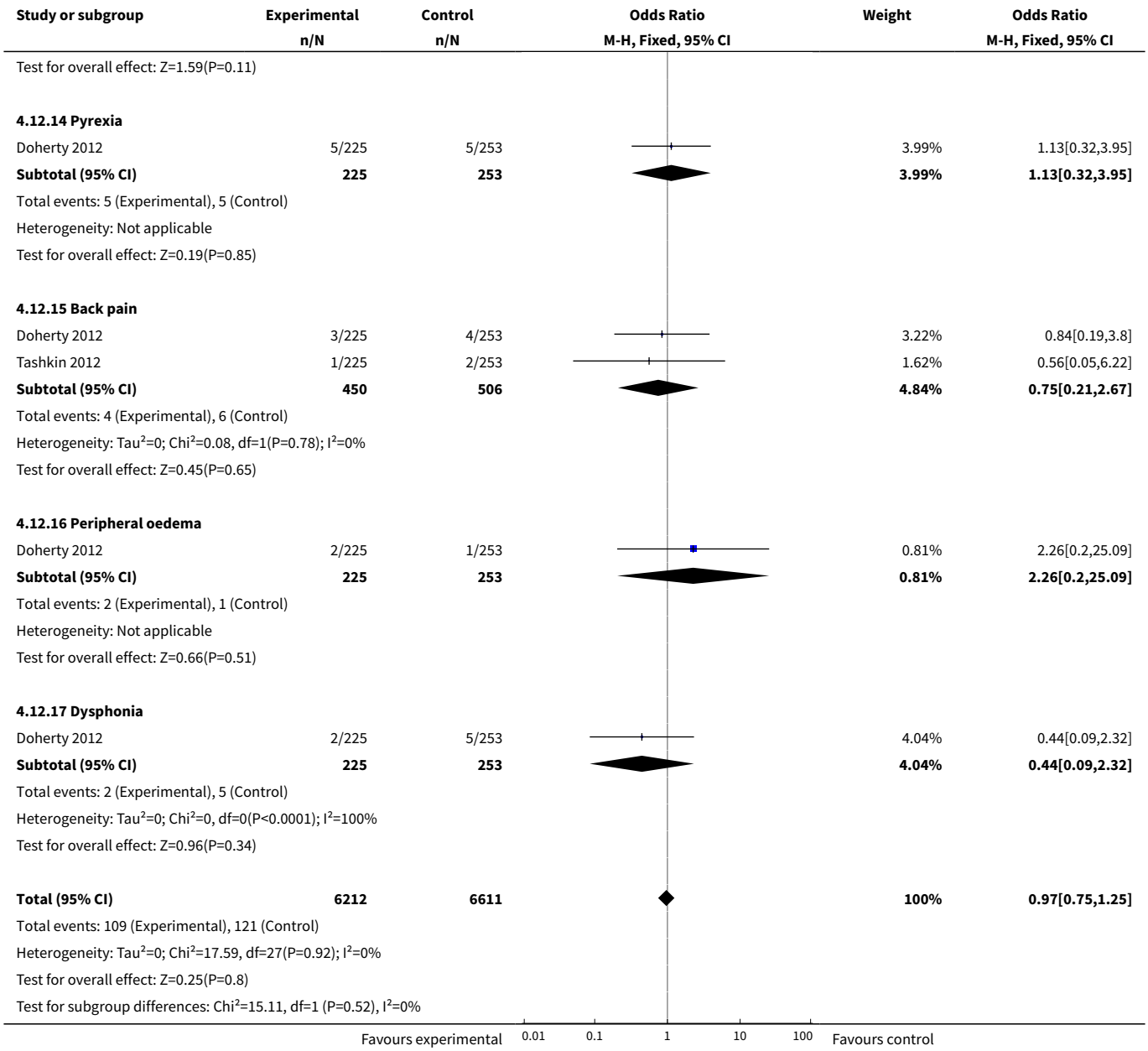
Analysis 4.11. Comparison 4 Mometasone/formoterol (MF/F) versus Mometasone (MF), Outcome 11 Adverse event — serious.

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.11.1 Poorly reversible population					
Doherty 2012	19/225	21/253		56.17%	1.02[0.53,1.95]
Subtotal (95% CI)	**225**	**253**		**56.17%**	**1.02[0.53,1.95]**
Total events: 19 (Experimental), 21 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.06(P=0.95)					
4.11.2 Unclear reversibility					
Tashkin 2012	16/217	15/210		43.83%	1.03[0.5,2.15]
Subtotal (95% CI)	**217**	**210**		**43.83%**	**1.03[0.5,2.15]**
Total events: 16 (Experimental), 15 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.09(P=0.93)					
Total (95% CI)	**442**	**463**		**100%**	**1.03[0.63,1.67]**
Total events: 35 (Experimental), 36 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.98); I^2=0%					
Test for overall effect: Z=0.1(P=0.92)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.98), I^2=0%					

Analysis 4.12. Comparison 4 Mometasone/formoterol (MF/F) versus Mometasone (MF), Outcome 12 Adverse events (specific adverse events).







ADDITIONAL TABLES

Table 1. Search history

Version	Detail
1st published version — Issue 4, 2003 (all years to April 2002)	References identified: 34 References retrieved: 7 Studies excluded: 3 (Cazzola 2000; Chapman 2002; Soriano 2002) Studies identified from supplementary searching: 4 (Dal Negro 2003; Hanania 2003 — both included; Cazzola 2002a; Cazzola 2004 — both excluded) Studies included: 4

Table 1. Search history *(Continued)*

2nd published version — Issue 3, 2004 (April 2003 to April 2004)	References identified: 12 References retrieved: 3 (2 papers full publication of a previously included or cited studies study (Dal Negro 2003; Hanania 2003)). Handsearching identified two further references to the COSMIC 2003 study Studies identified from supplementary searching: 1 (TRISTAN) New studies included: 2 Total studies included: 6
3rd published version — Issue 3, 2005 (April 2004 to April 2005)	References identified: 52 References retrieved: 46 (references to studies already included/excluded/ongoing: 24) New unique studies identified: 10 (ongoing studies: 2) New studies included: 0 Total studies included: 6
4th published version — April 2005 to April 2007	References identified: 66 References retrieved: 27 (references to studies already included/excluded/ongoing) New unique studies identified: 8 (ongoing studies: 0) New studies included: 1 Total studies included: 7
Present version — April 2007 to June 2013	References identified: 209 References retrieved: 63 (references to studies already included/excluded/ongoing: 6) New unique studies identified: 57 (ongoing studies: 0) New studies included: 8 Total studies included: 15

Table 2. Exacerbations

Trial	COPD exacerbation definition
Bourbeau 2007	Exacerbations not reported
Calverley 2003	**Mild exacerbations** = number of days with intake of 4 or more puffs of rescue medication **Severe exacerbation** = intake of a course of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms
Doherty 2012 / Tashkin 2012	**Mild exacerbation** = clinically judged deterioration of COPD symptoms (managed with increased short-acting bronchodilator use: ≥ 12 inhalations/d of SABA/short-acting anticholinergic, or ≥ 2 nebulised treatments/d of 2.5 mg SABA/short-acting anticholinergic) on any two consecutive days **Moderate exacerbation** = clinically judged deterioration of COPD with an acute change in symptoms that required antibiotic and/or oral steroid treatment for lower airway disease **Severe exacerbation** = deterioration of COPD that resulted in emergency treatment or hospitalisation due to COPD
Lapperre 2009	Exacerbations not reported
NCT00358358	Exacerbations not reported
SFCT01	No definition found
Sin 2008	"Exacerbations were defined as worsening of COPD symptoms leading to hospitalisation, a visit to the emergency room, or use of an antimicrobial agent and/or systemic corticosteroids as an outpatient"

Table 2. Exacerbations *(Continued)*

Szafranski 2003	**Mild exacerbations** = a day with ≥ 4 inhalations of reliever medication above the mean run-in use **Severe exacerbation** = use of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms
Tashkin 2008	"Worsening of COPD symptoms that required treatment with oral corticosteroids and/or hospitalisation"
TORCH	"A symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalisation, or a combination of these"
TRISTAN	"Exacerbations were defined a priori as a worsening of COPD symptoms that required treatment with antibiotics, oral corticosteroids, or both. Episodes that required corticosteroid treatment or hospital admission were noted separately"
Zhong 2012	"An exacerbation was defined as use of oral/IV corticosteroids and/or antibiotics and/or emergency room treatment/hospitalisation due to respiratory symptoms"

Table 3. Rates of NNT and mortality

Study ID	Study duration	ICS rate (%)	NNT *
Calverley 2003	52 weeks	2.3	202 (123 to 741)
SFCT01	52 weeks	0	NA
NCT00358358	12 weeks	2.38	195 (119 to 717)
Hanania 2003	24 weeks	0	NA
Mahler 2002	24 weeks	0	NA
Zhong 2012	24 weeks	0	NA
Szafranski 2003	52 weeks	2.5	186 (113 to 683)
TORCH	156 weeks	16	33 (20 to 123)
Doherty 2012	52 weeks	1.19	386 (236 to 1417)
TRISTAN	52 weeks	0.8	572 (350 to 2100)
Tashkin 2008	26 weeks	0.73	627 (383 to 2299)
Tashkin 2012	26 weeks	1.43	322 (197 to 1182)

*Number needed to treat to prevent one death.

Table 4. Included studies

Study ID	No. of participants randomised	Study duration (weeks)	Intervention	Control
Bourbeau 2007	39	16	FPS (50/500 mcg bid)	FP (500 mg bid)
Calverley 2003	511	52	BDF (320/9 mcg bid)	BUD (400 mcg bid)
Doherty 2012	478	26	MF/F (200/5 mcg bid)	MF (200 mcg bid)
Hanania 2003	366	24	FPS (50/250 mcg bid)	FP (250 mcg bid)
Lapperre 2009	54	130	FPS (50/500 mcg bid)	FP (500 mcg bid)
Mahler 2002	333	24	FPS (50/500 mcg bid)	FP (500 mcg bid)
NCT00358358	81	12	FPS (50/500 mcg bid)	FP (500 mcg bid)
SFCT01	256	52	FPS (50/500 mcg bid)	FP (500 mcg bid)
Sin 2008	179	4	FPS (50/500 mcg bid)	FP (500 mcg bid)
Szafranski 2003	406	52	BDF (320/9 mcg bid)	BUD (400 mcg bid)
Tashkin 2008	552	26	BDF (160/4.5 mcg) 2 inhalations bid	BUD (160 mcg) 2 inhalations bid
Tashkin 2012	427	26	MF/F (400/10 mcg bid)	MF (400 mcg bid)
TORCH	3091	156	FPS (50/500 mcg bid)	FP (500 mcg bid)
TRISTAN	733	52	FPS (50/500 mcg bid)	FP (500 mcg bid)
Zhong 2012	308	24	BDF (160/4.5 mcg) 2 inhalations bid	BUD (200 mcg) 2 inhalations bid

FPS = fluticasone/salmeterol;
FP = fluticasone;
BDF = budesonide/formoterol;
BUD = budesonide;
MF/F = mometasone/formoterol;
MF = mometasone.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*The Cochrane Library*)	Monthly

(Continued)

MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

WHAT'S NEW

Date	Event	Description
4 June 2014	Amended	PLS title amended

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 4, 2007

Date	Event	Description
27 June 2013	New search has been performed	Literature search run
27 June 2013	New citation required and conclusions have changed	Eight new studies for budesonide/formoterol and two studies for a new combined therapy, mometasone furoate/formoterol. New author team. Summary of findings table added, new methods applied; see differences between protocol and review.
11 November 2009	Amended	Spelling mistakes corrected and minor changes to wording. Changes made to formatting.
8 April 2008	Amended	Converted to new review format.
21 August 2007	New citation required and conclusions have changed	This review contains evidence from 5 studies previously included in a review of combination therapy in COPD (Nannini L, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler for chronic obstructive pulmonary

Date	Event	Description
		disease. Cochrane Database of Systematic Reviews 2004, Issue 3), with new data from two studies (TORCH; SFCT01). *New findings* There is a significant reduction on mortality with combination therapy compared with ICS alone. Exacerbation rates are lower with combination therapy compared with ICS. Additional work should focus on budesonide and formoterol, and the collection of data on pneumonia.

CONTRIBUTIONS OF AUTHORS

LJN and PP developed the protocol. Studies were assessed by LJN and TJL (an author on the previous version of the review). TJL and LJN checked data and entered them into RevMan 5.2. TJL and LJN conducted the analysis. TJL and LJN developed the discussion with input from PP. CJC participated in the 2004 and 2007 updates of the review and offered statistical advice and input with calculating SEMs and SDs for the included studies where appropriate.

In the 2012 update, LJN and PP updated the background section with input from SJM, and SJM updated the methods section. Studies were selected and appraised by LJN and PP, and data were extracted by SJM and AK and then were entered by SJM and checked by AK. SJM conducted the analysis with input from AK, LJN and PP. The results section was written by SJM with input from AK, LJN and PP. The discussion and conclusions were written by LJN and PP with input from SJM and AK.

DECLARATIONS OF INTEREST

The review authors who have been involved in this review have done so with no known conflicts of interest. None of the authors is considered a paid consultant by any pharmaceutical company that produces agents discussed in this review.

SOURCES OF SUPPORT

Internal sources

- St George's University of London, UK.

External sources

- NIHR, UK.

  Program grant for Stephen Milan and Annabel Kesterton

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have now included estimates of mortality from all included studies.

Since the time that the protocol of this Cochrane Review was published, several aspects of review methodology have changed in light of recent recommendations regarding the methodology of Cochrane Reviews.

- Risk of bias assessment (*Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 8). This has now displaced the Jadad scores that we generated previously in determining study quality.
- Generic inverse variance (*Cochrane Handbook for Systematic Reviews of Interventions*, Chapters 7 and 9). This method of meta-analysing adjusted effect estimates from clinical trials has enabled us to measure exacerbation outcomes as rate ratios.
- Summary of findings tables. We have adopted the GRADE methodology for assessing strength evidence and determining effect size in absolute terms for key outcomes in this review (GRADE working group).
- In 2012 the inclusion criteria were clarified as *randomised, double-blind, parallel-group clinical trials of at least 4 weeks' duration.* This was done to bring consistency to the inclusion criteria of the three Cochrane reviews considering combined corticosteroid and long-acting beta$_2$-agonist in one inhaler for chronic obstructive pulmonary disease.
- In 2012 we added the comparison of mometasone furoate/formoterol versus mometasone furoate.
- Studies in which the ICS dose in the ICS/LABA condition was < 80% of the ICS dose in the ICS-only condition were excluded.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*administration & dosage] [adverse effects]; Adrenergic beta-2 Receptor Agonists [*administration & dosage] [adverse effects]; Albuterol [administration & dosage] [adverse effects] [analogs & derivatives]; Androstadienes [administration & dosage] [adverse effects]; Bronchodilator Agents [administration & dosage] [adverse effects]; Budesonide [administration & dosage] [adverse effects]; Drug Combinations; Drug Therapy, Combination [adverse effects] [methods]; Ethanolamines [administration & dosage] [adverse effects]; Fluticasone-Salmeterol Drug Combination; Formoterol Fumarate; Nebulizers and Vaporizers; Pneumonia [chemically induced]; Pulmonary Disease, Chronic Obstructive [*drug therapy] [mortality]; Randomized Controlled Trials as Topic; Steroids [*administration & dosage] [adverse effects]

MeSH check words

Humans