Cochrane Library

Cochrane Database of Systematic Reviews

Beta$_2$-agonists for exercise-induced asthma (Review)

Bonini M, Di Mambro C, Calderon MA, Compalati E, Schünemann H, Durham S, Canonica GW

Bonini M, Di Mambro C, Calderon MA, Compalati E, Schünemann H, Durham S, Canonica GW.
Beta$_2$-agonists for exercise-induced asthma.
Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD003564.
DOI: 10.1002/14651858.CD003564.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Beta$_2$-agonists for exercise-induced asthma

Matteo Bonini[1,2,3], Corrado Di Mambro[4], Moises A Calderon[3], Enrico Compalati[5], Holger Schünemann[6], Stephen Durham[3], Giorgio W Canonica[5]

[1]Department of Public Health and Infectious Diseases, "Sapienza" University, Rome, Italy. [2]Institute of Translational Pharmacology (IFT), CNR, Rome, Italy. [3]Section of Allergy and Clinical Immunology, National Heart and Lung Institute, Imperial College London and Royal Brompton Hospital, London, UK. [4]Department of Medical and Surgical Pediatric Cardiology - UOC Arrhythmology, Children's Hospital "Bambino Gesù", Rome, Italy. [5]Allergy and Respiratory Diseases Clinic, Department of Internal Medicine (DIMI), University of Genoa, Genoa, Italy. [6]Departments of Clinical Epidemiology and Biostatistics and of Medicine, McMaster University, Hamilton, Canada

Contact: Matteo Bonini, Department of Public Health and Infectious Diseases, "Sapienza" University, Rome, Italy. matte.bonini@gmail.com.

Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 10, 2013.

Citation: Bonini M, Di Mambro C, Calderon MA, Compalati E, Schünemann H, Durham S, Canonica GW. Beta$_2$-agonists for exercise-induced asthma. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No.: CD003564. DOI: 10.1002/14651858.CD003564.pub3.

ABSTRACT

Background

It is well known that physical exercise can trigger asthma symptoms and can induce bronchial obstruction in people without clinical asthma. International guidelines on asthma management recommend the use of beta$_2$-agonists at any stage of the disease. At present, however, no consensus has been reached about the efficacy and safety of beta$_2$-agonists in the pretreatment of exercise-induced asthma and exercise-induced bronchoconstriction. For the purpose of the present review, both of these conditions are referred to by the acronymous EIA, independently from the presence of an underlying chronic clinical disease.

Objectives

To assess the effects of inhaled short- and long-acting beta$_2$-agonists, compared with placebo, in the pretreatment of children and adults with exercise-induced asthma (or exercise-induced bronchoconstriction).

Search methods

Trials were identified by electronic searching of the Cochrane Airways Group Specialised Register of Trials and by handsearching of respiratory journals and meetings. Searches are current as of August 2013.

Selection criteria

We included randomised, double-blind, placebo-controlled trials of any study design, published in full text, that assessed the effects of inhaled beta$_2$-agonists on EIA in adults and children. We excluded studies that did not clearly state diagnostic criteria for EIA.

Data collection and analysis

We used standard methodological procedures as expected by The Cochrane Collaboration.

Main results

We included 53 trials consisting of 1139 participants. Forty-eight studies used a cross-over design, and five were performed in accordance with a parallel-group design. Forty-five studies addressed the effect of a single beta$_2$-agonist administration, and eight focused on long-term treatment. We addressed these two different intervention regimens as different comparisons.

Among primary outcomes for short-term administration, data on maximum fall in forced expiratory volume in 1 second (FEV_1) showed a significant protective effect for both short-acting beta-agonists (SABA) and long-acting beta-agonists (LABA) compared with placebo, with a mean difference of -17.67% (95% confidence interval (CI) -19.51% to -15.84%, P = 0.00001, 799 participants from 72 studies). The subgroup analysis of studies performed in adults compared with those performed in children showed high heterogeneity confined to children, despite the comparable mean bronchoprotective effect.

Secondary outcomes on other pulmonary function parameters confirmed a more positive and protective effect of $beta_2$-agonists on EIA compared with placebo. Occurrence of side effects was not significantly different between $beta_2$-agonists and placebo.

Overall evaluation of the included long-term studies suggests a $beta_2$-agonist bronchoprotective effect for the first dose of treatment. However, long-term use of both SABA and LABA induced the onset of tolerance and decreased the duration of drug effect, even after a short treatment period.

Authors' conclusions

Evidence of low to moderate quality shows that $beta_2$-agonists, both SABA and LABA, when administered in a single dose, are effective and safe in preventing EIA.

Long-term regular administration of inhaled $beta_2$-agonists induces tolerance and lacks sufficient safety data. This finding appears to be of particular clinical relevance in view of the potential for prolonged regular use of $beta_2$-agonists as monotherapy in the pretreatment of EIA, despite the warnings of drug agencies (FDA, EMA) regarding LABA.

PLAIN LANGUAGE SUMMARY

Asthma reliever inhalers ($beta_2$-agonists) used for exercise-induced asthma and exercise-induced bronchoconstriction

Review question

Physical exercise may trigger symptoms such as cough, chest tightness and shortness of breath in people with asthma that is not adequately treated (exercise-induced asthma). Sometimes people who do not have asthma still experience asthma-like symptoms during exercise; this is called *exercise-induced bronchoconstriction*. We looked at both types of people in this review. The treatments we were interested in are called *$beta_2$-agonists*. These are drugs that are known to open up the airways (small tubes in the lungs), making it easier for people to breathe. Two kinds of $beta_2$-agonists are available: short-acting (SABA, e.g. salbutamol and terbutaline) and long-acting (LABA, e.g. formoterol and salmeterol).

What evidence did we find?

We found 53 trials consisting of 1139 participants. Forty-eight studies used a cross-over design, which meant that each person in the trial received two or more treatments — one or more active treatments, the beta-agonist and a placebo in random order. The rest were parallel-group trials, meaning that people received either the active treatment or a placebo. Most of the studies addressed the effect of a giving a single $beta_2$-agonist treatment before exercise and recorded the effect on lung function following exercise. Only eight focused on longer treatment — longer treatments would be needed to assess whether these treatments were harmful over the longer term.

Results

Studies in which people received a single administration of a beta-agonist showed that FEV_1 (a measure of lung function) fell significantly less for people taking SABA or LABA compared with placebo (mean difference (MD) -17.67%; 95% confidence interval (CI) -19.51% to -15.84%). Other lung function measures confirmed that $beta_2$-agonists were more beneficial compared with placebo. No significant difference in the number of side effects was noted in people taking SABA or LABA compared with people taking placebo. However, it is unlikely that people would be prescribed an inhaler for a single treatment, so we must consider longer-term studies to get a true measure of the side effects that inhalers can cause.

We found that included longer-term studies showed that $beta_2$-agonists were helpful in terms of lung function for the first dose of treatment. However, studies that provided longer-term treatment with SABA or LABA showed that over time, people built up a tolerance to the effects of treatments, and the beneficial effects lasted for shorter periods of time.

Quality of the evidence

Overall, we believe that the evidence was of low to moderate quality.

Conclusions

This review shows that beta$_2$-agonists — both SABA and LABA — when administered in a single dose, are effective and safe in preventing the symptoms of EIA. Longer-term administration of inhaled beta$_2$-agonists induces tolerance and lacks sufficient safety data. It is important to note that taking LABA without background inhaled steroids is considered unsafe and is not currently recommended in most of the clinical guidelines for asthma. We recommend that more studies are needed to determine whether it is safe to administer inhaled beta$_2$-agonists alone to people who experience asthma symptoms when exercising.

This review is current as of August 2013.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Beta$_2$-agonists compared with placebo (single administration) for exercise-induced asthma

Beta$_2$-agonists compared with placebo (single administration) for exercise-induced asthma

Patient or population: exercise-induced asthma
Intervention: beta$_2$-agonists
Comparison: placebo (single administration)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo (single administration)	Beta$_2$-agonists				
Maximal percentage fall in FEV_1	The mean fall in FEV_1 in the intervention group was MD 17.67 lower (19.51 lower to 15.84 lower)[a]		—	799 (72 studies)[a,b,c]	⊕⊕⊕⊖ **moderate** [d,e,f]	The results in the subgroup of LABA and SABA were similar: MD 15.6 lower (18.29 lower to 12.92 lower) and MD 18.99 lower (21.38 lower to 16.6 lower) in 44 and 28 studies, respectively
Number of participants with an FEV_1 fall > 10%	843 per 1000 (84.3)%	300 per 1000 (243 to 410)	**OR 0.08** (0.06 to 0.13)	773 (19 studies)	⊕⊕⊕⊖ **moderate** [d,e]	
Maximal percentage fall in PEF	The mean maximal percentage fall in PEF in the intervention group was MD 24.61 lower (37.57 lower to 11.65 lower)[1]		—	92 (14 studies)[b]	⊕⊕⊖⊖ **low** [d,e,g]	
Maximal percentage fall in $FEF_{25-75\%}$	The mean maximal percentage fall in $FEF_{25-75\%}$ in the intervention group was MD 20.75 lower (27.17 lower to 14.32 lower)[1]		—	106 (8 studies)[b]	⊕⊕⊖⊖ **low** [d,e,g]	
Side effects	50 per 1000 (5.0)%	42 per 1000 (22 to 77)	**OR 0.83** (0.43 to 1.59)	2165 (55 studies)[h]	⊕⊕⊖⊖ **low** [e,g,l]	

*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; $FEF_{25-75\%}$: forced expiratory flow 25–75%; FEV1: forced expiratory volume in 1 minute; LABA: long-acting $beta_2$-agonist; MD: mean difference; OR: odds ratio; peak expiratory flow (PEF); SABA: short-acting $beta_2$-agonist.

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.

[a]Lower indicates that $beta_2$-agonists are better than placebo.
[b]In 51 studies that provided data for subgroup analysis, no difference was observed in the maximal percentage fall in FEV_1, but the heterogeneity of the effect was seen primarily in the paediatric population.
[c]These represent 72 study arms from 53 studies.
[d]It is unclear how directly pulmonary function measures relate to what participants feel.
[e]There was concern about lack of concealment, loss to follow-up and reporting bias.
[f]Inconsistency was moderate to high and was explained in part by subgroup analyses of adults and children.
[g]Small numbers of participants were included with resulting wide confidence intervals.
[h]These represent 55 study arms rather than studies.
[i]This represents a mix of outcomes, and not all of them are of equal importance to patients.

BACKGROUND

Exercise-induced asthma (EIA) is the term commonly used to describe the transient increase in airway resistance that follows vigorous exercise (Anderson 1997). However a recent position paper suggested a preferred definition of exercise-induced bronchoconstriction (EIB) with or without asthma, depending on the presence of underlying clinical asthma (Weiler 2010). Despite this new nomenclature, most of the relevant studies were published before these terms were proposed and often do not provide sufficient information to distinguish between the two conditions. We therefore decided to adopt the term *exercise-induced asthma* (EIA) throughout the review for the sake of better consistency and clarity.

The prevalence of EIA ranges from 5% to 20% in the general population, to even 100% in people with uncontrolled asthma. This huge variability depends not only on the criteria used for diagnosis, but also on the population samples studied. EIA is, in fact, reported to be particularly frequent in children (Randolph 2008), in people with rhinitis (Brozek 2010) and in athletes, with percentages varying according to different sport disciplines (Carlsen 2008).

The diagnosis of EIA is usually made by exercise testing, either in the field or in the laboratory; this second option allows more standardised procedures (Rundell 2000). An individual's response to exercise is generally expressed by the maximal percent fall in forced expiratory volume in one second (FEV_1). The maximal percent fall is considered an expression of severity of EIA and is calculated by subtracting the lowest FEV_1 value from the pre-exercise value and expressing it as a percentage of the pre-exercise value. Both European Respiratory Society (ERS) and American Respiratory Society (ATS) recommendations set a fall threshold of 10% as a diagnostic criterion for EIA and a value greater than 30% as a marker of severe bronchial hyperreactivity, particularly if the person is treated with inhaled steroids (Sterk 1993). Other indirect tests such as eucapnic voluntary hyperpnoea (EVH) and mannitol challenge are usually considered surrogate tests for the diagnosis of EIA because they induce similar pathophysiological changes in the airways (Anderson 2003).

The main principle of treating EIA involves reversing the bronchial obstruction induced by exercise with bronchodilators or preventing it with daily use of either controller drugs in people with asthma (Koh 2007; Bateman 2008) or drugs that inhibit symptoms and improve pulmonary function immediately before exercise. Pretreatment before exercise includes mast cell stabilisers (Kelly 2000; Spooner 2003), leukotriene antagonists (Peroni 2011), short-acting beta$_2$-agonists (SABA) and, more recently, long-acting beta$_2$-agonists (LABA), especially in endurance athletes (Shapiro 2002).

Both SABA and LABA, administered at standard doses immediately before exercise, have been shown to reduce the fall in FEV_1 by 70% to 80% in most people with EIA (Anderson 2006). The mechanism of this protection is believed to be related to beta$_2$-receptor—induced relaxation of bronchial smooth muscle, which opposes the contractile effects of the various mediators of bronchoconstriction. Protection from EIA is also afforded by beta$_2$-receptor—induced inhibition of mediator release from mast cells.

At present, however, no consensus has been reached about the efficacy and safety of beta$_2$-agonists in the pretreatment of EIA. The role of these molecules in preventing EIA was questioned when patients taking beta$_2$-agonists daily reported breakthrough EIA within a dosing period. Several negative findings have been reported regarding the efficacy of daily treatment with beta$_2$-agonists in controlling the severity of bronchoconstriction and recovery from EIA. In fact, in a significant minority of people, EIA is not prevented by beta$_2$-agonists administered at the recommended dose (Anderson 1991; Weiler 2005). Furthermore, it has been reported how daily treatment with beta$_2$-agonists can enhance the severity of EIA (Hancox 2002) and decrease the duration of their protective effect, especially for LABA (Ramage 1994). In addition, recovery from EIA after a standard dose of beta$_2$-agonists is slower, and additional doses are often required when SABA or LABA are used daily (Hancox 2002).

On the other hand, the reported association between administration of LABA, not in combination with inhaled corticosteroids, and increased numbers of severe cardiovascular side effects and sudden deaths (Nelson 2006; Salpeter 2010) induced the U.S. Food and Drug Administration (FDA) to set a "black box" on these drugs, highlighting the urgent need to promote clear studies of pharmacovigilance (Martinez 2005).

OBJECTIVES

To assess the effects of inhaled short- and long-acting beta$_2$-agonists, compared with placebo, in the pretreatment of children and adults with exercise-induced asthma (or exercise-induced bronchoconstriction).

METHODS

Criteria for considering studies for this review

Types of studies

We included double-blind, randomised controlled trials (RCTs) of any study design. Data published in abstract form only were excluded. At least one primary outcome of this systematic review had to be reported for a study to be considered eligible.

Types of participants

We included children and adults (aged 18 years or older) with a clear history of exercise-induced asthma and/or a positive response to a standardised exercise challenge, defined according to ERS and ATS guidelines as a fall in $FEV_1 \geq 10\%$. Studies that did not clearly state criteria for EIA diagnosis were excluded.

Types of interventions

Eligible interventions included inhaled beta$_2$-agonists administered, at any dose, as short-term or long-term prophylactic treatment before participants underwent a standardised exercise challenge. SABA and LABA had to be administered within a time period before exercise challenge that did not exceed their pharmacological half-life (arbitrarily set at 1 hour for SABA, and at 12 hours for LABA). For studies with more than one drug arm, only the comparison with placebo was considered. Studies with more than one drug arm that evaluated different beta$_2$-agonist molecules were considered as separate trials.

Types of outcome measures

Primary outcomes

- Mean max % fall in FEV_1 (100 × (baseline pre-exercise value — lowest postexercise value)/baseline pre-exercise value) in people treated with a $beta_2$-agonist versus mean max % fall in FEV_1 in people treated with placebo
- Mean % protection afforded by $beta_2$-agonists (% protection = 100 × (max % fall FEV_1 placebo — max % fall FEV_1 $beta_2$-agonist)/ max % fall FEV_1 placebo)
- Mean area under the curve (AUC) of time course changes in FEV_1 after exercise in people treated with a $beta_2$-agonist versus mean AUC of time course changes in FEV_1 after exercise in people treated with placebo

Secondary outcomes

- Number of people with a max % fall in FEV_1 < 10% (complete protection), < 15% and < 20%
- Changes from baseline in symptom and sign scores
- Mean max % fall in other pulmonary function parameters (peak expiratory flow (PEF), forced expiratory flow 25–75% (FEF), maximal expiratory flow at 50% (MEF) etc.)
- Onset of tolerance (considered for long-term administration studies and in relation to concomitant treatment with inhaled corticosteroids)
- Outcomes of physical performance
- Side/adverse effects

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of Trials, which is derived from systematic searches of bibliographic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL, as well as handsearching of respiratory journals and meeting abstracts (see Appendix 1 for additional details). The Register was searched using the terms in Appendix 2 from the date of inception up to August 2013. No restriction was placed on language of publication.

Searching other resources

We screened reference lists of included studies, recent reviews and textbooks for relevant citations. We contacted authors of unpublished or 'in-progress' studies and selected manufacturers of $beta_2$-agonists to identify additional studies. Furthermore, we searched national and international clinical trial websites (www.clinicalstudyresults.org; www.clinicaltrials.gov; www.fda.gov) for additional trials. Personal contacts with colleagues, collaborators and other trialists working in the field of asthma were at last made to identify further potentially relevant studies. No language or publication restrictions were applied to these searches.

Data collection and analysis

Selection of studies

Titles and abstracts of papers identified in the search were reviewed independently by two review authors (MB, CDM), and articles that appeared to fulfil the inclusion criteria were retrieved. From the full text of these papers, two review authors (MB, EC) independently established whether studies met the inclusion criteria. Studies that did not fulfil all of the inclusion criteria were excluded, and reasons for exclusion were reported. The percentage of agreement was recorded, and any disagreement was solved by consensus. If the two review authors did not reach an agreement, a third review author adjudication (MC) was used to resolve disagreements. In case of further uncertainty, study authors were contacted. Review authors were not blinded to authors, journals, results, etc.

Data extraction and management

Data extraction was performed independently by two review authors (MB, EC). Full texts were screened, and bibliographic details, as well as data regarding study design, participants, disease severity, intervention and outcomes, were recorded in predefined forms and entered into RevMan 5.2. All data, numerical calculations and graphic extrapolations were independently confirmed. We did not deal with missing data.

Assessment of risk of bias in included studies

We assessed the risk of bias in included studies as high, low or unclear using The Cochrane Collaboration's 'Risk of bias' tool (Higgins 2011) and the following headings.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other bias.

Discussion or third party adjudication was used to resolve disagreements when necessary.

Measures of treatment effect

Treatment effects were measured as mean differences (MDs) for continuous outcomes and odds ratios (ORs) for dichotomous outcomes.

Unit of analysis issues

Many included studies were of cross-over design, but many did not report the results of paired *t*-tests for continuous outcomes in this review. Some studies provided raw data that allowed a calculation of the correlation between treatment periods on $beta_2$-agonists and placebo on maximum percentage fall in FEV_1 (see Appendix 3 for the raw data). We used the average correlation from these studies (0.36) to impute an appropriate standard error for within--participant differences (as described in Section 16.4.6.4 of the *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins 2011). We carried out a meta-analysis of the mean differences and their standard errors for this outcome using the Generic Inverse Variance method in RevMan 5.2.

Dealing with missing data

Missing data on the correlation between results from participants in the cross-over studies were imputed using the average correlation from studies that reported appropriate raw data. Cross-over studies provided information on the number of participants in each arm who experienced a given drop in FEV_1, but not the number of participants whose FEV_1 dropped on both interventions (active treatment and placebo). We were able to calculate marginal odds ratios for these outcomes but could not adjust the standard error to take advantage of the cross-over design.

Assessment of heterogeneity

To assess the level of heterogeneity, the Chi^2 test and the I^2 statistic were used. In establishing the level of heterogeneity, we considered the following rules for interpretation of results (Higgins 2011).

- 0 to 30% as low heterogeneity.
- 30% to 60% as moderate heterogeneity worthy of investigation.
- 60% to 90% as severe heterogeneity worthy of understanding.
- 90% to 100% as allowing aggregation only with major caution.

Assessment of reporting biases

Funnel plots were used to investigate the possibility of publication bias.

Data synthesis

Data were entered into RevMan 5.2. For continuous measures, individual and pooled statistics were reported as mean difference (MD) of treatment effect with 95% confidence intervals (95% CIs) using the fixed-effect model.

Subgroup analysis and investigation of heterogeneity

Heterogeneity worthy of investigation was examined using the following predefined subgroup analyses.

- Type of $beta_2$-agonist (SABA vs LABA).
- Molecule of $beta_2$-agonist (formoterol vs salmeterol).
- Age of participants (children vs adults).
- Concomitant treatments ($beta_2$-agonist monotherapy vs concomitant inhaled corticosteroid treatment).

RESULTS

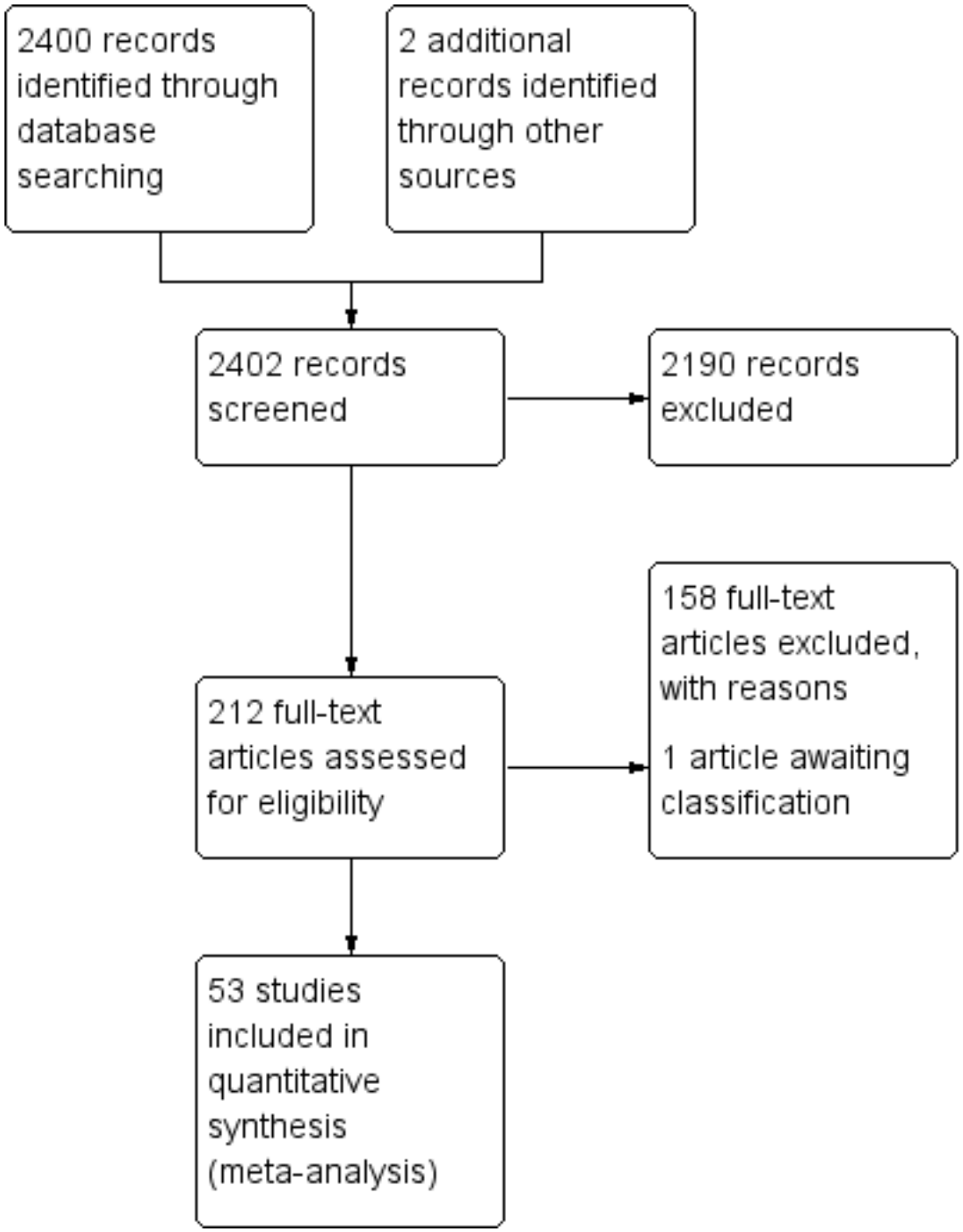
Description of studies

See:Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The search identified 2400 articles, and from these, 289 papers were independently selected by two review authors (k = 0.95) as being of potential interest on the basis of titles and abstracts. After non-interventional studies (n = 27) and articles published as abstract only (n = 52) were removed, we retrieved the remaining articles in full text and from these identified 51 studies for inclusion in the meta-analysis (Figure 1). Two further articles were added through the cross-checking reference process. We excluded 158 studies with reasons provided in Characteristics of excluded studies; one study is listed under Studies awaiting classification to be considered for inclusion when the review is next updated.

Figure 1. Study flow diagram.



Included studies

Full details can be found in the Characteristics of included studies tables.

Study features and design

All 53 included studies were double-blind, placebo-controlled, randomised trials. Forty-eight studies used a cross-over design, and five were performed in a parallel -group design. In the cross-over studies, washout periods ranged between 1 and 21 days. Nine studies did not mention duration of washout, and in two papers, no washout was performed. The exercise challenges involved treadmill (n = 35), cycle ergometer (n = 13) and free running (n = 5). All challenges were standardised and met recommended testing criteria. Trials were conducted between 1976 and 2010 in 12 different countries: Europe (N = 27), United States/Canada (N = 22) and Australia (N = 4). All articles except one (in Spanish) were written in English.

Population

Collectively, included studies reported data on 1139 participants. Population sample size ranged from 10 to 161 participants (55

in a single drug arm of parallel-group studies and 46 in cross-over studies—the highest number of enrolled participants). Studies included children and adults (age range 4 to 64 years). A total of 20 studies were performed in children, 18 in adults and 12 in both children and adults. Three papers did not provide sufficient information to allocate people according to age. Nine studies provided only information about ethnicity, and Caucasian was the most represented race.

Interventions

Of 53 included studies, 45 addressed beta$_2$-agonist short-term administration, and eight focused on long-term treatment. Articles were grouped on the basis of the type of beta$_2$-agonist drugs evaluated: SABA (N = 42; short-term administration n = 40 and long-term administration n = 2) and LABA (N = 27, short-term administration n = 21 and long-term administration n = 6). Among different beta$_2$-agonists, salbutamol (n = 27), salmeterol (n = 14), formoterol (n = 13) and terbutaline (n = 6) represented the molecules most frequently investigated. Beta$_2$-agonists were delivered through different devices (nebulisers, metered-dose inhalers (MDIs) and inhalers).

Details on dosage and types of beta$_2$-agonist administration are summarised in Table 1, together with timing in relation to exercise.

Outcomes

As per inclusion criteria, all 53 included studies reported data on at least one primary outcome of this review.

Excluded studies

See Characteristics of excluded studies.

Risk of bias in included studies

An assessment of the risk of bias is presented in the Characteristics of included studies tables and is summarised in a risk of bias figure (Figure 2).

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

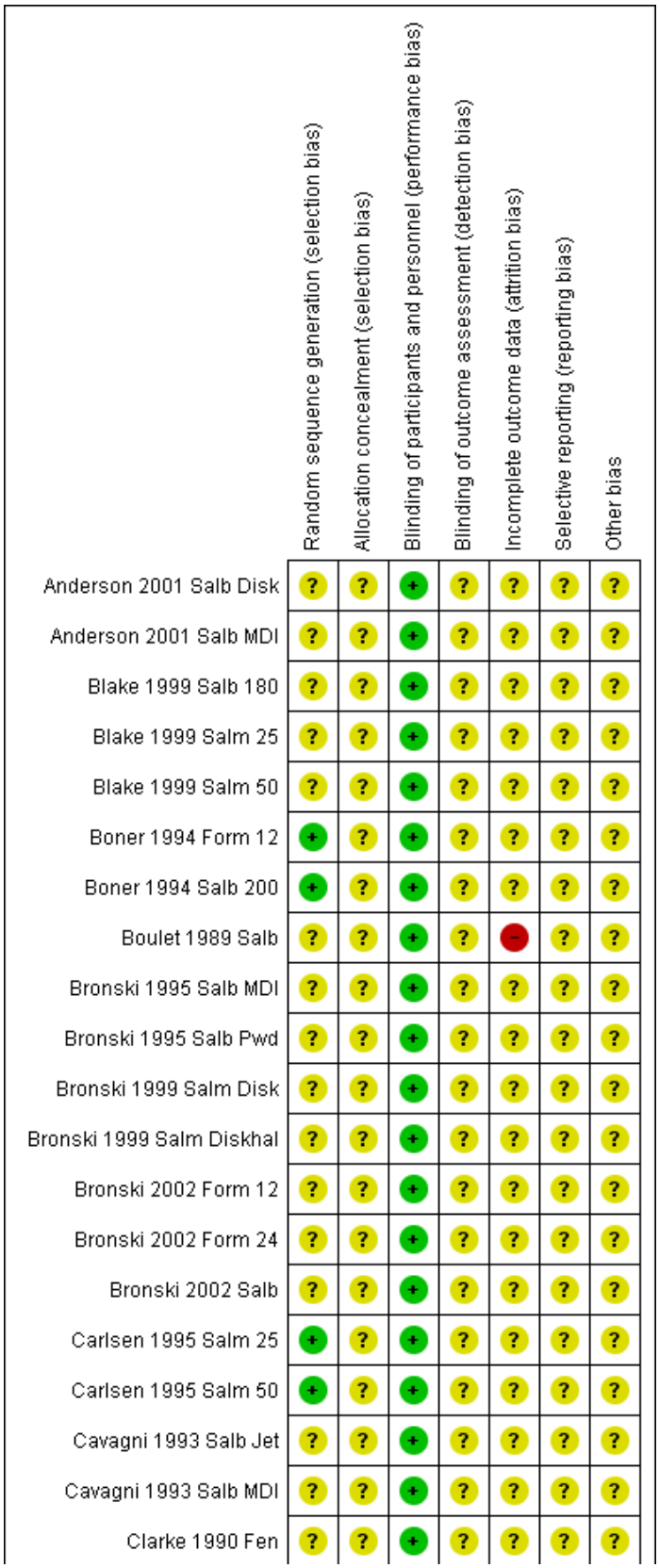


Figure 2. (Continued)

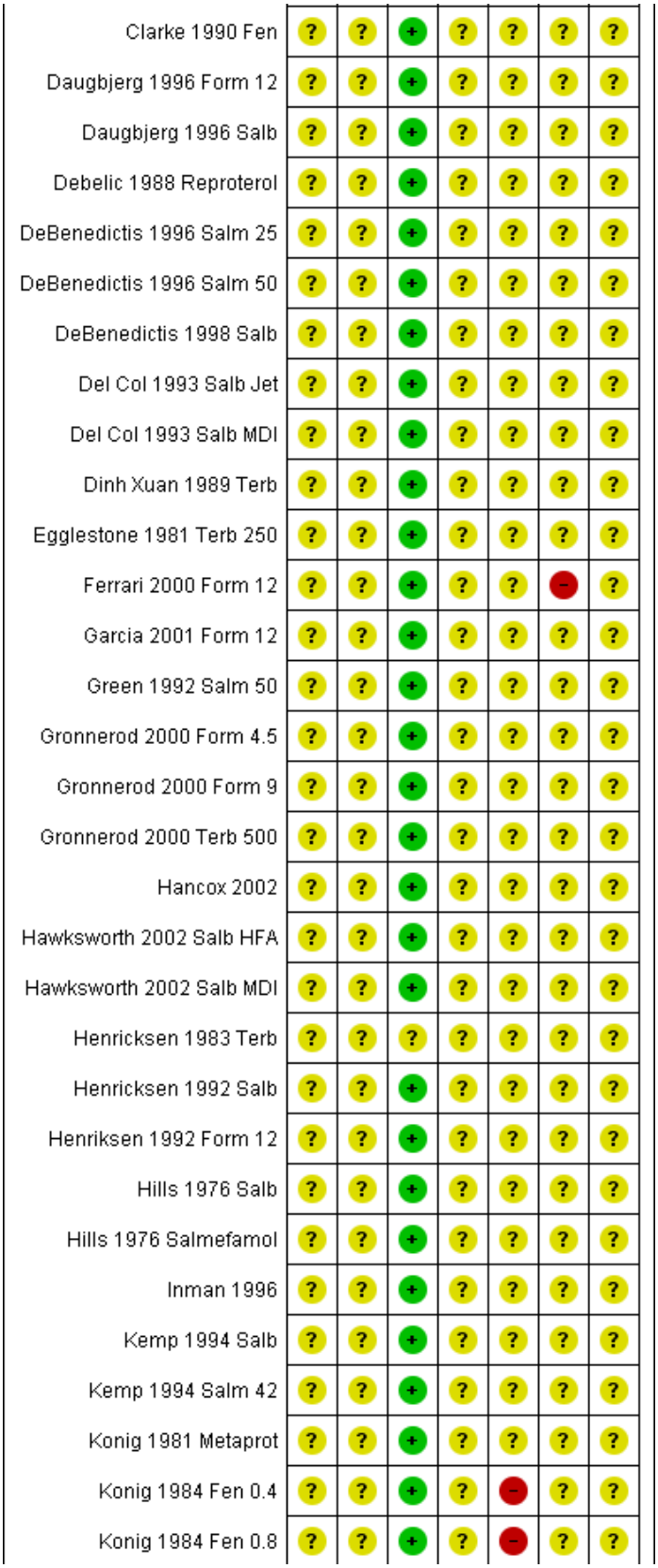


Figure 2. (Continued)

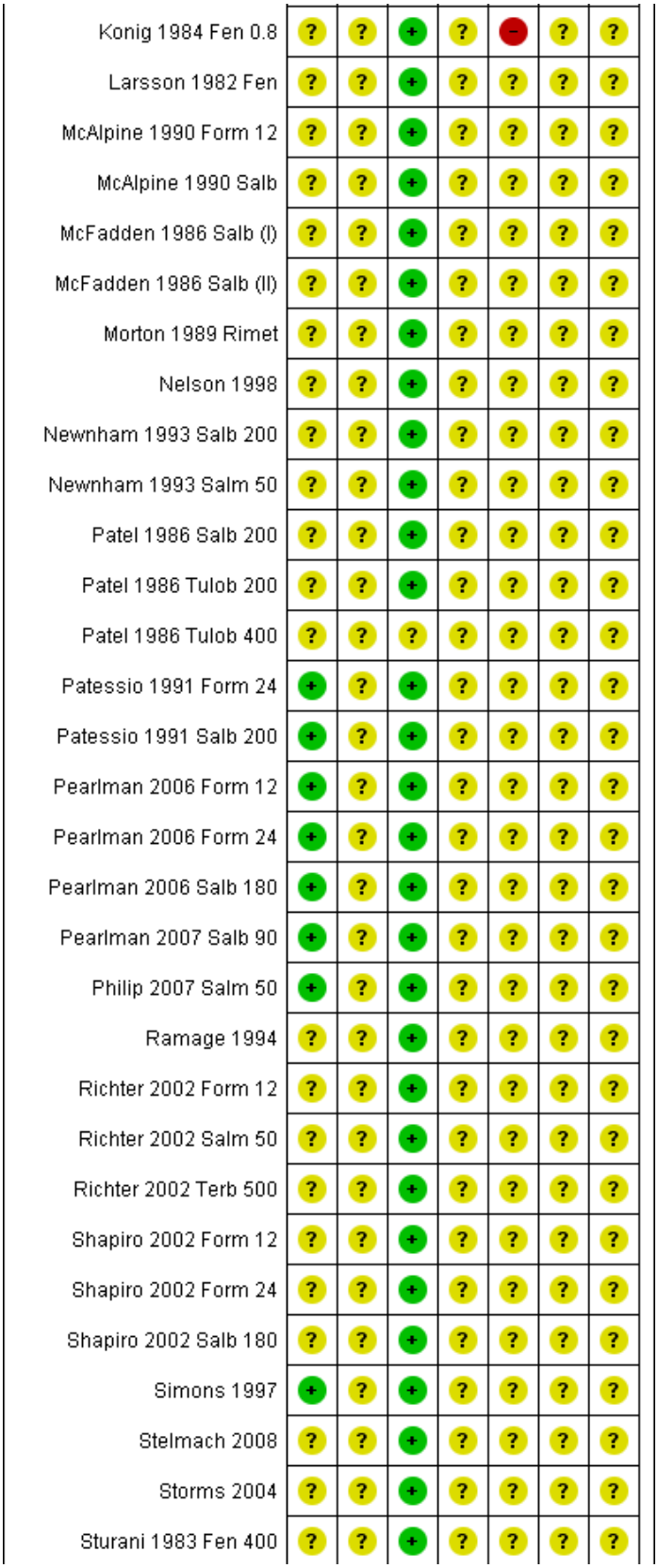


Figure 2. (Continued)

Allocation

Most of the included studies were judged at unclear risk for selection bias. Lack of information provided on random sequence generation and on allocation concealment may be explained by the high number of papers (40/53) conducted before 2000, when reporting of these risk of bias criteria was less common.

Blinding

Risks of performance and detection bias were minimised by the narrow inclusion criteria adopted, which allow inclusion in the systematic review of only randomised, at least double-blind, placebo-controlled trials.

Incomplete outcome data

Three drug arms (Konig 1984 Fen 0.4; Konig 1984 Fen 0.8; Boulet 1989 Salb) reported incomplete data on outcomes as specified in this systematic review and were therefore assigned a high risk of bias.

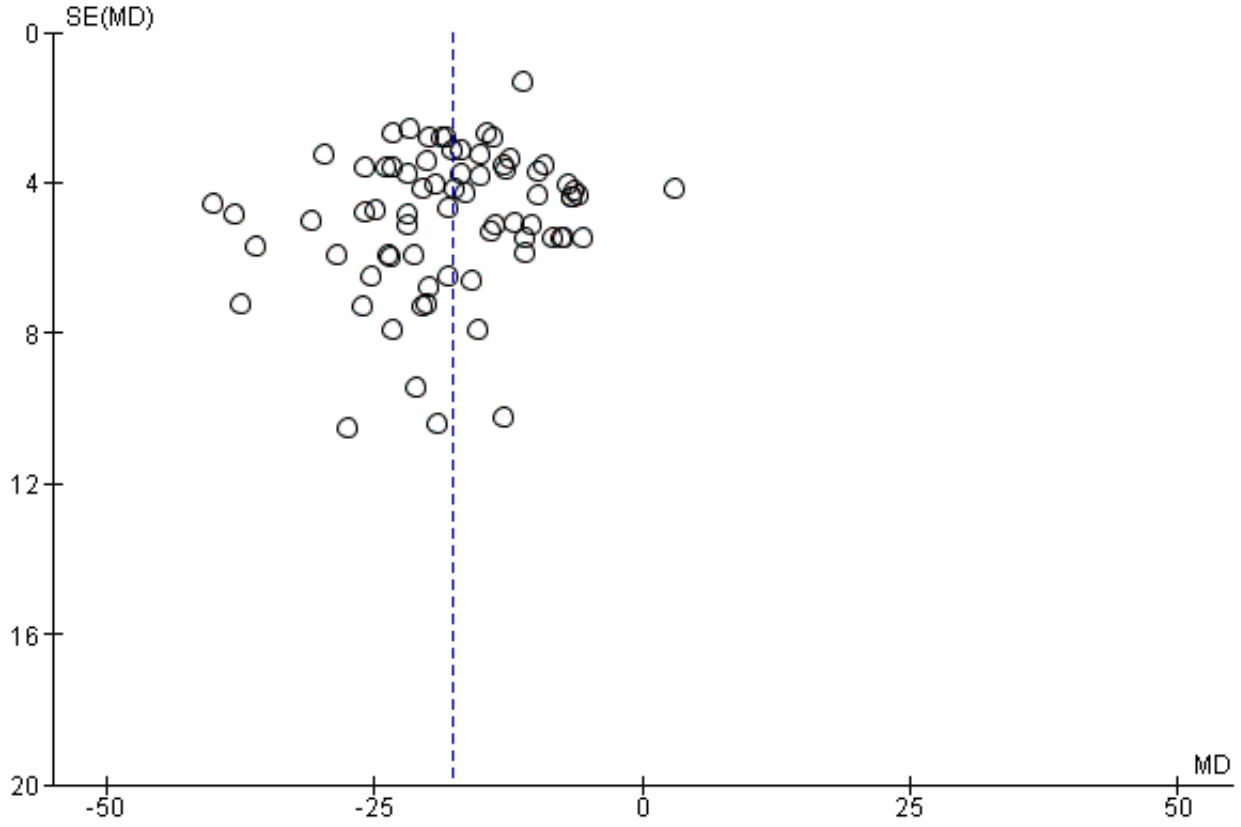
Selective reporting

All studies except one (Ferrari 2000 Form 12) were rated as having unclear risk for reporting bias.

Other potential sources of bias

The possibility of publication bias was investigated in the funnel plot shown in Figure 3. The presence of other potential sources of bias was rated as unclear risk because of the scarce information provided.

Figure 3. Funnel plot of comparison: 1 Beta$_2$-agonists versus placebo (single administration), outcome: 1.1 Maximal percentage fall in FEV$_1$.



Several papers reported data derived from industry-funded studies.

Effects of interventions

See: **Summary of findings for the main comparison** Beta$_2$-agonists compared with placebo (single administration) for exercise-induced asthma

Effects of intervention were separately assessed for short-term (single administration) and long-term beta$_2$-agonist administration.

Short-term administration

The 45 studies evaluating short-term beta$_2$-agonist administration included 77 arms of active treatment (49 SABA and 28 LABA) in comparison with placebo.

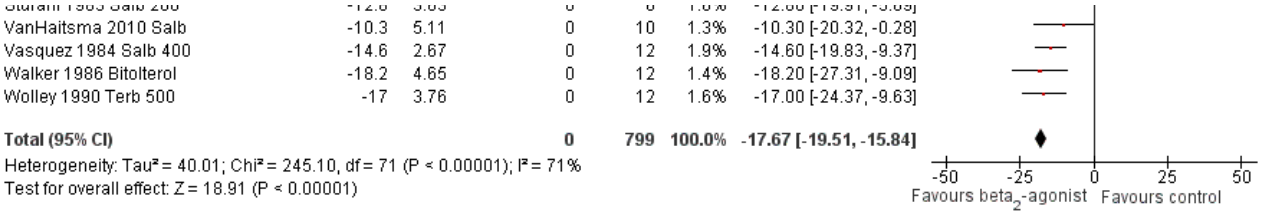
Primary outcomes

Data on max % fall in FEV$_1$ were provided by 77 arms. Effects of SABA short-term administration were evaluated beyond the pharmacological half-life (1 hour) in five studies, which were therefore excluded. Analysis of the remaining 72 arms, including 799 participants (Figure 4), showed a significant protective effect of beta$_2$-agonists compared with placebo (MD -17.67%, 95% CI -19.51% to -15.84%; P = 0.00001). In particular, 58 study arms favoured the active treatment, and 14 trial arms reported no significant difference. Heterogeneity was, however, high (I^2 = 71%).

Figure 4. Forest plot of comparison: 1 beta$_2$-agonists versus placebo (single administration), outcome: 1.1 Maximal percentage fall in FEV1.

Study or Subgroup	Mean Difference	SE	Beta$_2$-agonist Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Anderson 2001 Salb Disk	-25.98	4.76	0	14	1.4%	-25.98 [-35.31, -16.65]
Anderson 2001 Salb MDI	-30.89	4.99	0	13	1.3%	-30.89 [-40.67, -21.11]
Blake 1999 Salb 180	-9.7	4.32	0	8	1.5%	-9.70 [-18.17, -1.23]
Blake 1999 Salm 25	-6.01	4.36	0	8	1.5%	-6.01 [-14.56, 2.54]
Blake 1999 Salm 50	-6.66	4.37	0	8	1.5%	-6.66 [-15.23, 1.91]
Boner 1994 Form 12	-12.3	3.35	0	15	1.7%	-12.30 [-18.87, -5.73]
Bronski 1995 Salb MDI	-7	4.06	0	22	1.5%	-7.00 [-14.96, 0.96]
Bronski 1995 Salb Pwd	3	4.17	0	22	1.5%	3.00 [-5.17, 11.17]
Bronski 1999 Salm Disk	-6.5	4.4	0	12	1.5%	-6.50 [-15.12, 2.12]
Bronski 1999 Salm Diskhal	-6.4	4.21	0	12	1.5%	-6.40 [-14.65, 1.85]
Bronski 2002 Form 12	-21.3	5.9	0	6	1.2%	-21.30 [-32.86, -9.74]
Bronski 2002 Form 24	-23.7	5.9	0	6	1.2%	-23.70 [-35.26, -12.14]
Bronski 2002 Salb	-28.5	5.9	0	6	1.2%	-28.50 [-40.06, -16.94]
Carlsen 1995 Salm 25	-11	5.45	0	12	1.3%	-11.00 [-21.68, -0.32]
Carlsen 1995 Salm 50	-12	5.09	0	12	1.3%	-12.00 [-21.98, -2.02]
Cavagni 1993 Salb Jet	-27.55	10.52	0	4	0.6%	-27.55 [-48.17, -6.93]
Cavagni 1993 Salb MDI	-13	10.2	0	4	0.6%	-13.00 [-32.99, 6.99]
Clarke 1990 Fen	-29.7	3.23	0	20	1.7%	-29.70 [-36.03, -23.37]
Daugbjerg 1996 Form 12	-24	3.61	0	16	1.6%	-24.00 [-31.08, -16.92]
Debelic 1988 Reproterol	-25.9	3.61	0	16	1.6%	-25.90 [-32.98, -18.82]
DeBenedictis 1996 Salm 25	-16	6.61	0	6	1.0%	-16.00 [-28.96, -3.04]
DeBenedictis 1996 Salm 50	-20	6.77	0	6	1.0%	-20.00 [-33.27, -6.73]
DeBenedictis 1998 Salb	-22	5.14	0	12	1.3%	-22.00 [-32.07, -11.93]
Del Col 1993 Salb Jet	-8.38	5.47	0	7	1.2%	-8.38 [-19.10, 2.34]
Del Col 1993 Salb MDI	-14.23	5.32	0	8	1.3%	-14.23 [-24.66, -3.80]
Dinh Xuan 1989 Terb	-37.44	7.21	0	10	0.9%	-37.44 [-51.57, -23.31]
Egglestone 1981 Terb 250	-22	3.77	0	17	1.6%	-22.00 [-29.39, -14.61]
Ferrari 2000 Form 12	-23.4	3.61	0	14	1.6%	-23.40 [-30.48, -16.32]
Green 1992 Salm 50	-23.4	2.67	0	13	1.9%	-23.40 [-28.63, -18.17]
Gronnerod 2000 Form 4.5	-9.2	3.53	0	9	1.7%	-9.20 [-16.12, -2.28]
Gronnerod 2000 Form 9	-13	3.53	0	9	1.7%	-13.00 [-19.92, -6.08]
Gronnerod 2000 Terb 500	-15.1	3.83	0	9	1.6%	-15.10 [-22.61, -7.59]
Hawksworth 2002 Salb HFA	-18.3	2.83	0	12	1.8%	-18.30 [-23.85, -12.75]
Hawksworth 2002 Salb MDI	-18.8	2.83	0	12	1.8%	-18.80 [-24.35, -13.25]
Henricksen 1983 Terb	-11	5.88	0	14	1.2%	-11.00 [-22.52, 0.52]
Henricksen 1992 Salb	-26	7.28	0	6	0.9%	-26.00 [-40.27, -11.73]
Henriksen 1992 Form 12	-36	5.7	0	6	1.2%	-36.00 [-47.17, -24.83]
Hills 1976 Salb	-40.1	4.57	0	10	1.4%	-40.10 [-49.06, -31.14]
Hills 1976 Salmefamol	-38.1	4.82	0	9	1.4%	-38.10 [-47.55, -28.65]
Kemp 1994 Salb	-20	2.83	0	26	1.8%	-20.00 [-25.55, -14.45]
Kemp 1994 Salm 42	-14	2.83	0	26	1.8%	-14.00 [-19.55, -8.45]
Konig 1981 Metaprot	-17	3.16	0	24	1.7%	-17.00 [-23.19, -10.81]
Konig 1984 Fen 0.4	-23.5	6	0	6	1.1%	-23.50 [-35.26, -11.74]
Konig 1984 Fen 0.8	-25.3	6.47	0	6	1.1%	-25.30 [-37.98, -12.62]
Larsson 1982 Fen	-13.7	5.11	0	8	1.3%	-13.70 [-23.72, -3.68]
McAlpine 1990 Form 12	-25	4.71	0	11	1.4%	-25.00 [-34.23, -15.77]
McFadden 1986 Salb (I)	-9.7	3.73	0	15	1.6%	-9.70 [-17.01, -2.39]
McFadden 1986 Salb (II)	-15.2	3.23	0	20	1.7%	-15.20 [-21.53, -8.87]
Morton 1989 Rimet	-21.7	2.6	0	10	1.9%	-21.70 [-26.80, -16.60]
Newnham 1993 Salb 200	-23.3	7.91	0	6	0.9%	-23.30 [-38.80, -7.80]
Newnham 1993 Salm 50	-19.2	10.41	0	5	0.6%	-19.20 [-39.60, 1.20]
Patel 1986 Salb 200	-21.9	4.82	0	9	1.4%	-21.90 [-31.35, -12.45]
Patel 1986 Tulob 200	-18.2	6.46	0	5	1.1%	-18.20 [-30.86, -5.54]
Patel 1986 Tulob 400	-20.2	7.23	0	4	0.9%	-20.20 [-34.37, -6.03]
Patessio 1991 Form 24	-20.5	4.17	0	12	1.5%	-20.50 [-28.67, -12.33]
Pearlman 2006 Form 12	-5.6	5.46	0	7	1.3%	-5.60 [-16.30, 5.10]
Pearlman 2006 Form 24	-7.3	5.46	0	7	1.3%	-7.30 [-18.00, 3.40]
Pearlman 2006 Salb 180	-7.6	5.46	0	7	1.3%	-7.60 [-18.30, 3.10]
Pearlman 2007 Salb 90	-17.7	3.15	0	15	1.7%	-17.70 [-23.87, -11.53]
Philip 2007 Salm 50	-11.1	1.35	0	46	2.1%	-11.10 [-13.75, -8.45]
Richter 2002 Form 12	-19.4	4.04	0	8	1.6%	-19.40 [-27.32, -11.48]
Richter 2002 Salm 50	-17.5	4.17	0	8	1.5%	-17.50 [-25.67, -9.33]
Richter 2002 Terb 500	-16.6	4.25	0	8	1.5%	-16.60 [-24.93, -8.27]
Shapiro 2002 Form 12	-20.5	7.29	0	6	0.9%	-20.50 [-34.79, -6.21]
Shapiro 2002 Form 24	-15.4	7.92	0	6	0.9%	-15.40 [-30.92, 0.12]
Shapiro 2002 Salb 180	-21.1	9.44	0	5	0.7%	-21.10 [-39.60, -2.60]
Sturani 1983 Fen 400	-20.2	3.43	0	6	1.7%	-20.20 [-26.92, -13.48]
Sturani 1983 Salb 200	-12.8	3.63	0	6	1.6%	-12.80 [-19.91, -5.69]
VanHaitsma 2010 Salb	-10.3	5.11	0	10	1.3%	-10.30 [-20.32, -0.28]
Vasquez 1984 Salb 400	-14.6	2.67	0	12	1.9%	-14.60 [-19.83, -9.37]

Figure 4. (Continued)



Mean % protection was 66% (range 29% to 91%). In seven studies, beta$_2$-agonist administration not only completely protected participants from EIA but also induced a bronchodilator effect compared with baseline values. In only one case (Bronski 1995 Salb Pwd), placebo offered greater protection compared with the active treatment.

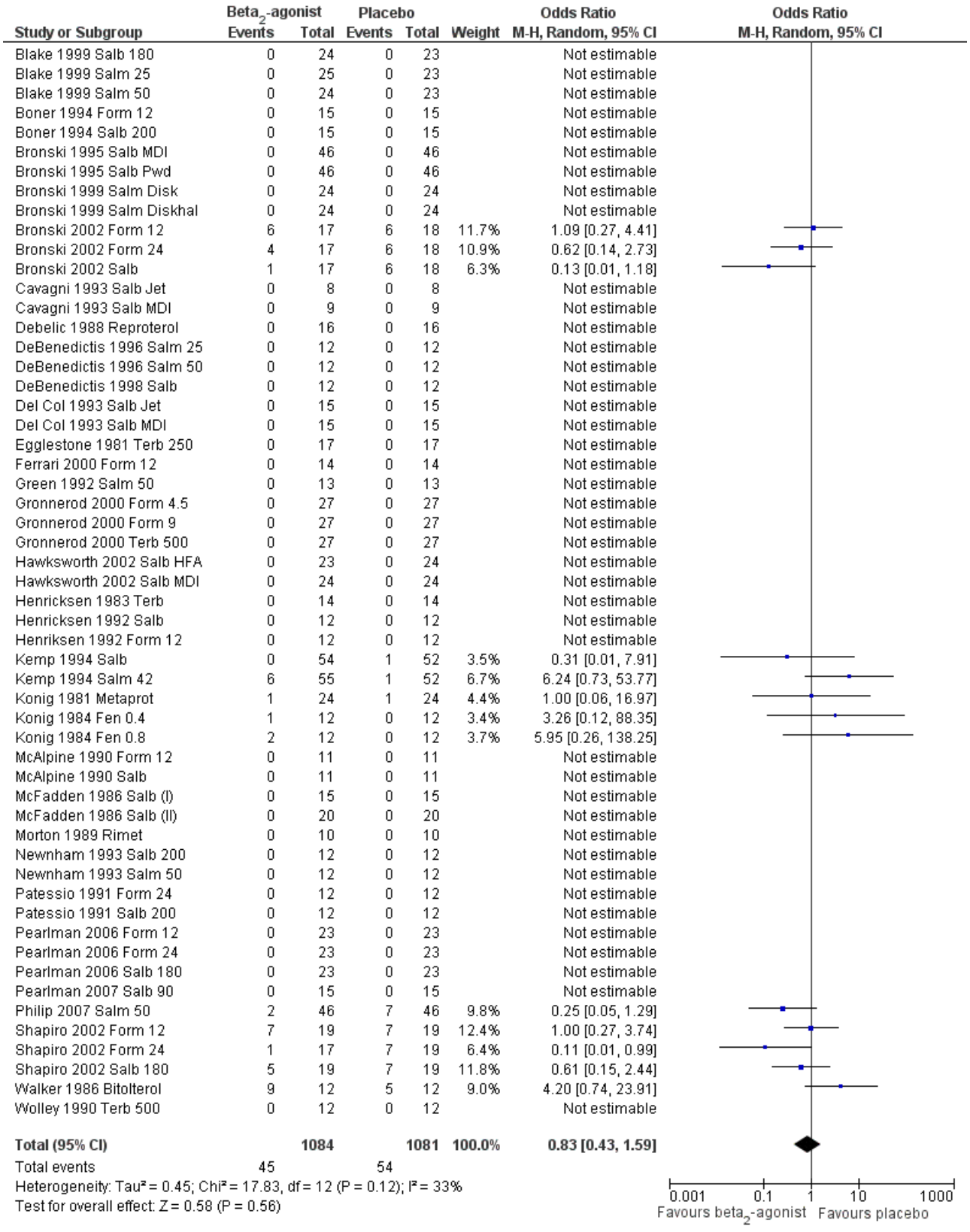
Seventeen studies evaluating LABA short-term administration at different time points showed an FEV$_1$ % fall AUC that favoured the active treatment. Different study designs prevented merging of the data in a unique comprehensive analysis.

Secondary outcomes

Secondary outcomes on pulmonary function parameters confirmed a positive protective effect of beta$_2$-agonists on EIA compared with placebo. Complete protection from EIA as assessed by numbers of participants with an FEV$_1$ % fall < 10% was evaluated in 19 studies (Analysis 1.2). A significant difference was noted in the number of participants completely protected (OR 0.08, 95% CI 0.06 to 0.13; P = 0.00001). Similar results were obtained for thresholds of FEV$_1$ fall set at 15% (OR 0.06, 95% CI 0.03 to 0.15) and 20% (OR 0.09, 95% CI 0.06 to 0.14) (Analysis 1.3; Analysis 1.4). Max PEF and FEF25-75 % fall were assessed, respectively, in 14 and in 8 studies (Analysis 1.5; Analysis 1.6). However, statistical analysis for these two outcomes was based on a limited number of trials because dispersion data were lacking in most of the studies considered. Only three arms (Vasquez 1984 Salb 400; Carlsen 1995 Salm 25; Carlsen 1995 Salm 50) reported data on max MEF25-50 % fall. No study provided information on changes in symptoms and sign scores and effects on physical performance.

As far as they concern secondary outcomes related to safety, side effects were assessed in 55 trials (Figure 5). Among these, 42 arms reported no adverse event for either active or placebo treatment. Analysis of the remaining 13 trials showed no significant difference between beta$_2$-agonists and placebo.

Figure 5. Forest plot of comparison: 1 Beta$_2$-agonists versus placebo (single administration), outcome: 1.1 Side effects.



Subgroup analysis

The high heterogeneity (I^2 = 71%) found for the primary outcome max FEV_1 % fall was investigated through the preplanned subgroup analysis.

We performed a subgroup analysis according to types of $beta_2$-agonists (SABA vs LABA; Figure 6). Although subgroup analysis confirmed a significant bronchoprotective effect against EIA for both classes compared with placebo, it was not able to explain the marked heterogeneity observed in the entire population sample: SABA (I^2 = 71%) and LABA (I^2 = 67%). Accordingly, non-significant differences emerged from the analysis of the different $beta_2$-agonist molecules administered (Figure 7). This evaluation was plotted only for the comparison between formoterol and salmeterol, because the number of studies evaluating different SABA molecules, apart from salbutamol, appeared to be too small for a reliable investigation. It is interesting to note that analysis of studies performed only in adults (n = 19) compared with those performed only in children (n = 32) showed that high heterogeneity was largely confined to studies in children (I^2 = 11% and 80%, respectively), despite the comparable mean bronchoprotective effect (Figure 8). Furthermore all studies that failed to show a positive protective effect against EIA of $beta_2$-agonists compared with placebo dealt with the paediatric population.

Figure 6. Forest plot of comparison: 1 Beta$_2$-agonists versus placebo (single administration), outcome: 1.8 Subgroup analysis: maximal percentage fall in FEV$_1$ SABA versus LABA.

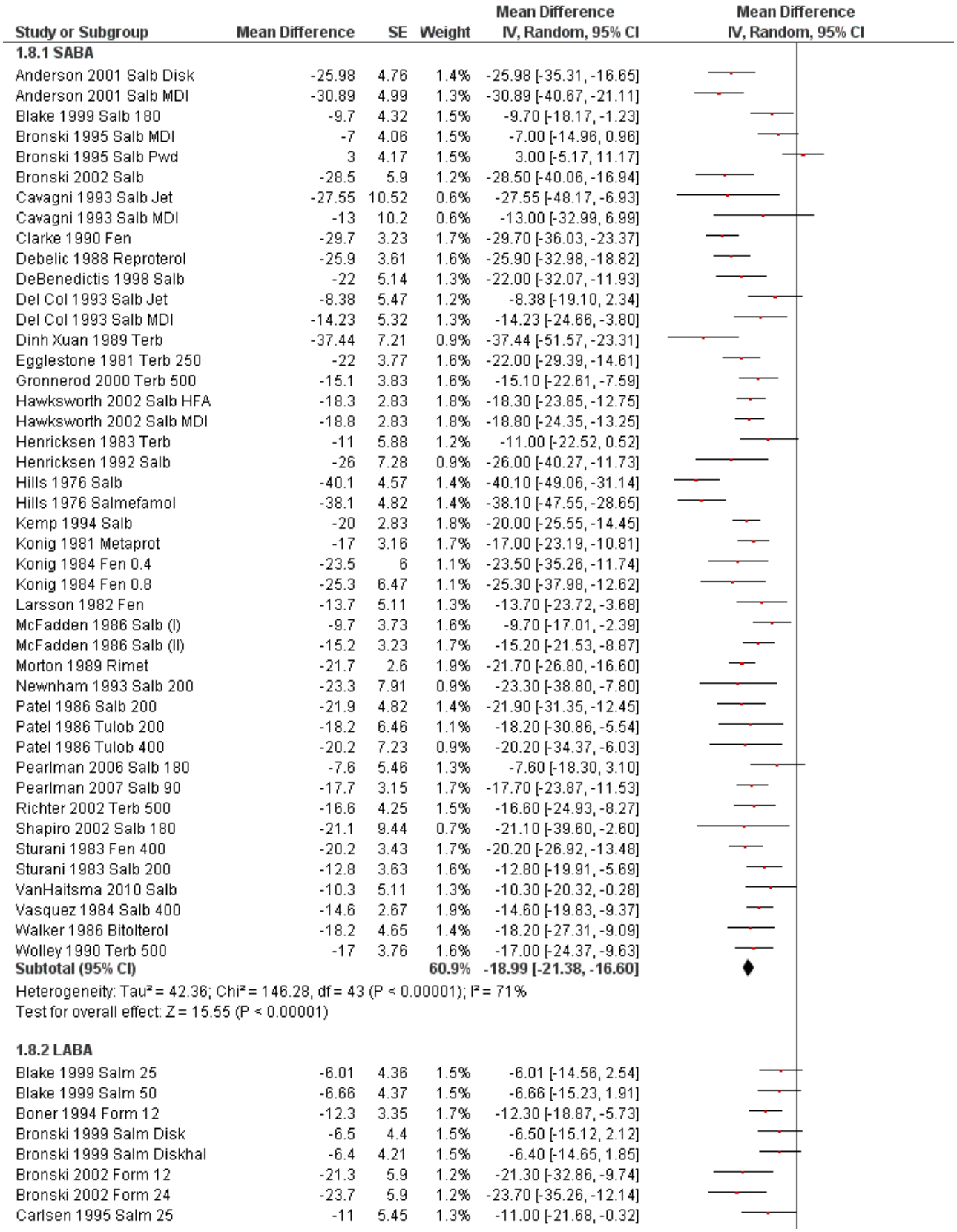


Figure 6. (Continued)

Bronski 2002 Form 24	-23.7	5.9	1.2%	-23.70 [-35.26, -12.14]
Carlsen 1995 Salm 25	-11	5.45	1.3%	-11.00 [-21.68, -0.32]
Carlsen 1995 Salm 50	-12	5.09	1.3%	-12.00 [-21.98, -2.02]
Daugbjerg 1996 Form 12	-24	3.61	1.6%	-24.00 [-31.08, -16.92]
DeBenedictis 1996 Salm 25	-16	6.61	1.0%	-16.00 [-28.96, -3.04]
DeBenedictis 1996 Salm 50	-20	6.77	1.0%	-20.00 [-33.27, -6.73]
Ferrari 2000 Form 12	-23.4	3.61	1.6%	-23.40 [-30.48, -16.32]
Green 1992 Salm 50	-23.4	2.67	1.9%	-23.40 [-28.63, -18.17]
Gronnerod 2000 Form 4.5	-9.2	3.53	1.7%	-9.20 [-16.12, -2.28]
Gronnerod 2000 Form 9	-13	3.53	1.7%	-13.00 [-19.92, -6.08]
Henriksen 1992 Form 12	-36	5.7	1.2%	-36.00 [-47.17, -24.83]
Kemp 1994 Salm 42	-14	2.83	1.8%	-14.00 [-19.55, -8.45]
McAlpine 1990 Form 12	-25	4.71	1.4%	-25.00 [-34.23, -15.77]
Newnham 1993 Salm 50	-19.2	10.41	0.6%	-19.20 [-39.60, 1.20]
Patessio 1991 Form 24	-20.5	4.17	1.5%	-20.50 [-28.67, -12.33]
Pearlman 2006 Form 12	-5.6	5.46	1.3%	-5.60 [-16.30, 5.10]
Pearlman 2006 Form 24	-7.3	5.46	1.3%	-7.30 [-18.00, 3.40]
Philip 2007 Salm 50	-11.1	1.35	2.1%	-11.10 [-13.75, -8.45]
Richter 2002 Form 12	-19.4	4.04	1.6%	-19.40 [-27.32, -11.48]
Richter 2002 Salm 50	-17.5	4.17	1.5%	-17.50 [-25.67, -9.33]
Shapiro 2002 Form 12	-20.5	7.29	0.9%	-20.50 [-34.79, -6.21]
Shapiro 2002 Form 24	-15.4	7.92	0.9%	-15.40 [-30.92, 0.12]
Subtotal (95% CI)			**39.1%**	**-15.60 [-18.29, -12.92]**

Heterogeneity: Tau² = 30.63; Chi² = 81.01, df = 27 (P < 0.00001); I² = 67%
Test for overall effect: Z = 11.38 (P < 0.00001)

Total (95% CI)			**100.0%**	**-17.67 [-19.51, -15.84]**

Heterogeneity: Tau² = 40.01; Chi² = 245.10, df = 71 (P < 0.00001); I² = 71%
Test for overall effect: Z = 18.91 (P < 0.00001)
Test for subgroup differences: Chi² = 3.40, df = 1 (P = 0.07), I² = 70.6%

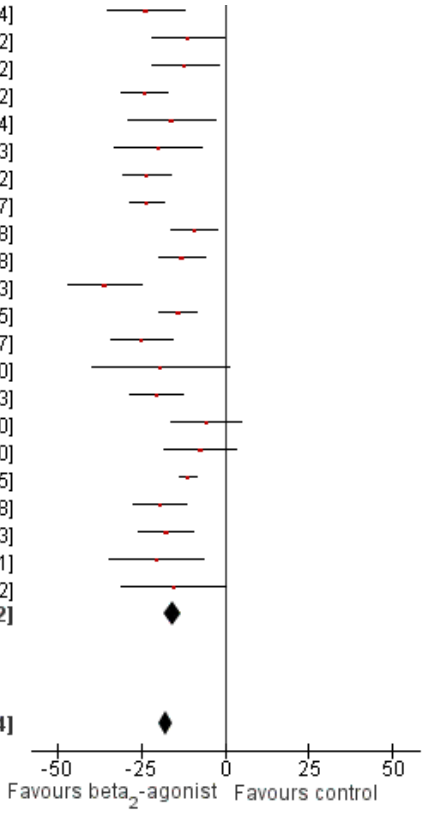


Figure 7. Forest plot of comparison: 1 Beta$_2$-agonists versus placebo (single administration), outcome: 1.9 Subgroup analysis: maximal percentage fall in FEV$_1$: salmeterol versus formoterol.

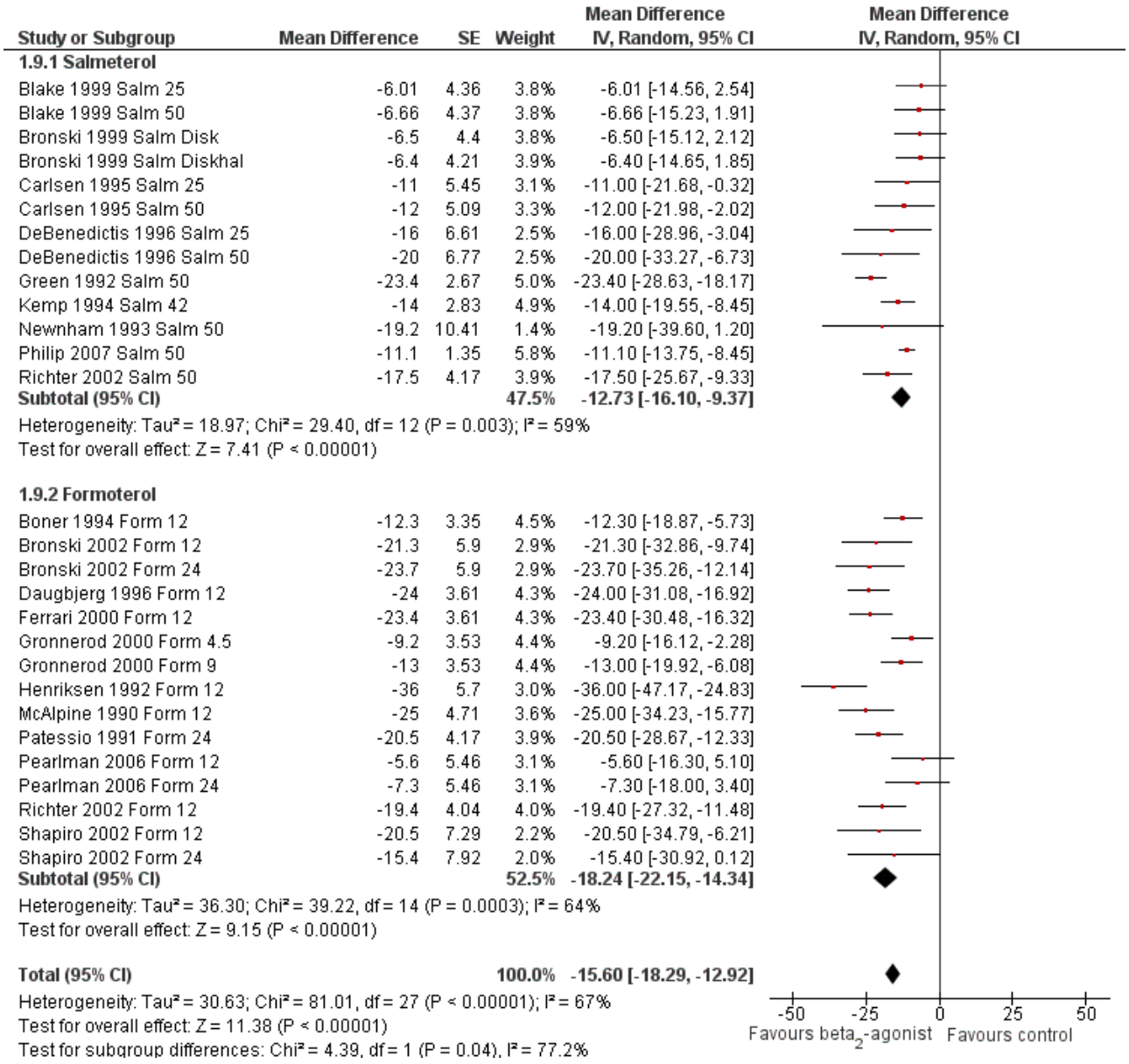


Figure 8. Forest plot of comparison: 1 Beta$_2$-agonists versus placebo (single administration), outcome: 1.10 Subgroup analysis: maximal percentage fall in FEV$_1$: adults versus children.

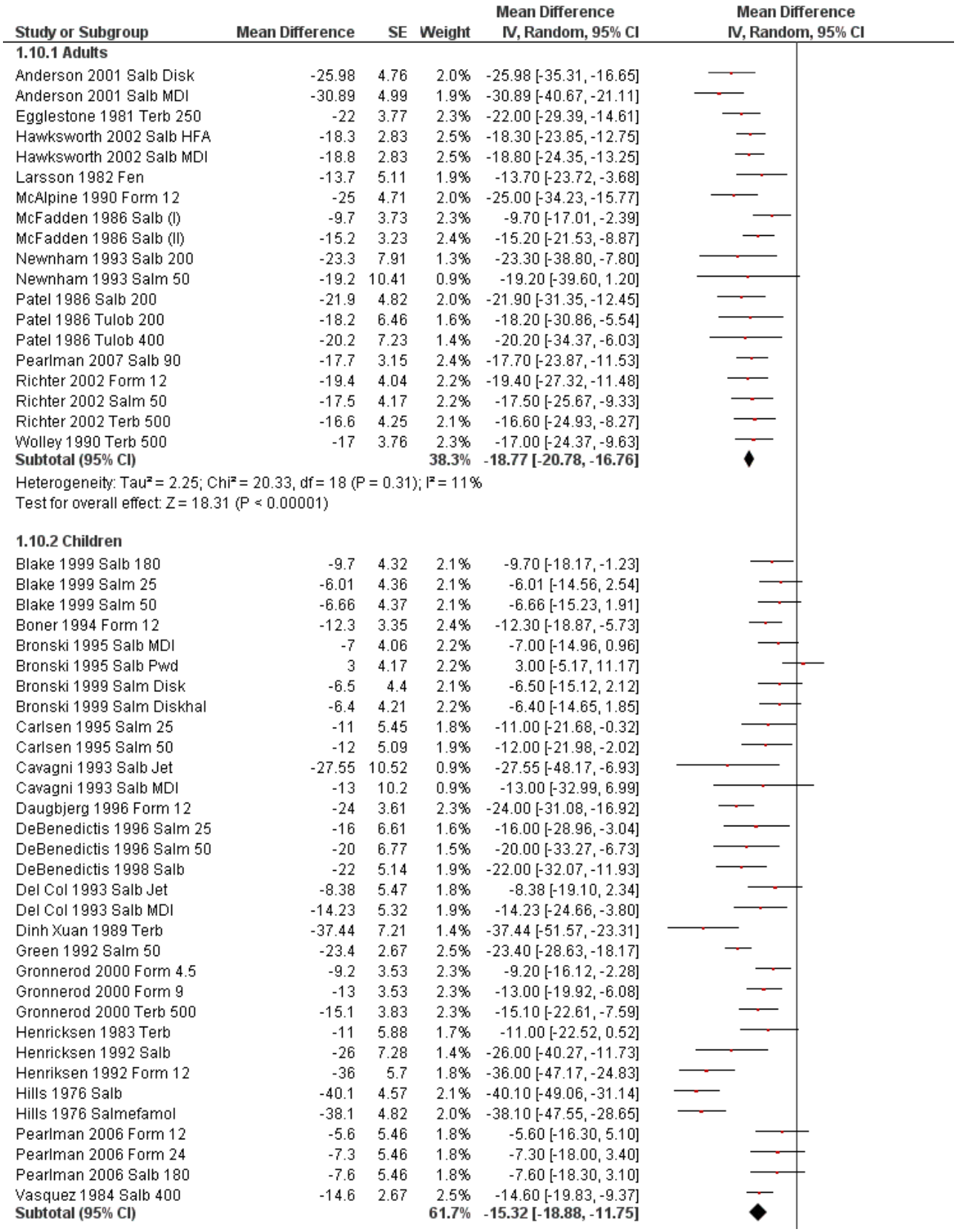
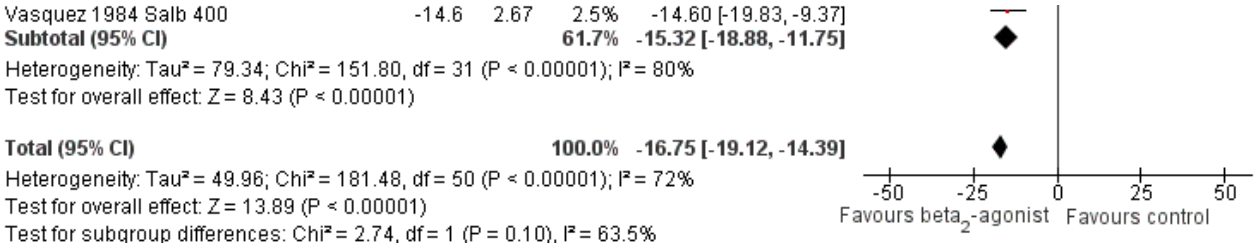


Figure 8. (Continued)



The different study designs used and the limited information provided prevented assessment of the potential role of concomitant treatment with inhaled corticosteroids.

Long-term administration

Long-term beta$_2$-agonist administration was addressed in only eight papers. Five trials were performed with a cross-over design in a total of 64 people (50 adults and 14 children). Three studies adopted a parallel-group design and included 69 people (49 adults and 20 children) in the active arms and 73 (53 adults and 20 children) placebo controls. Treatment periods range from 7 to 29 days. Effects of SABA were evaluated in two protocols, and LABA administration was assessed in six studies. The limited number of trials, the small population samples and the different study designs and drugs tested allow only a descriptive approach and prevent plotting of data in a meta-analysis.

Garcia and coauthors (Garcia 2001 Form 12) evaluated the effects of 28-day formoterol administration in a parallel-group design (10 people in the beta$_2$-agonist arm and 9 people in the placebo arm). The protective effect of salmeterol 12 mcg twice daily was assessed on the 1st, 14th and 28th study days, and results were not significantly greater than those provided by placebo at any time point. Furthermore, tachyphylaxis to the beta$_2$-agonist effect was developed already after two weeks of treatment, although it was not progressive.

Hancox (Hancox 2002) studied the effect of 200 mcg once daily of salbutamol in eight adults treated for seven days in a cross-over study. Results showed not only an increased max FEV_1 % fall after the exercise challenge, but also a sub-optimal bronchodilator response to further beta$_2$-agonist administration at the end of the treatment period in the active group.

Ten adults who inhaled 200 mcg of salbutamol or placebo four times a day for seven days were studied by Inman and O'Byrne (Inman 1996) in a cross-over study. One week of regular inhaled salbutamol resulted in worsening of EIA.

A cross-over design was also adopted by Nelson (Nelson 1998) in 20 adults treated for a month with inhaled salmeterol 42 mcg twice a day. Significant beta$_2$-agonist protection against EIA was maintained for the entire study period. However, the length of time that the drug remained active after a single dose significantly decreased. Furthermore, the number of participants for whom salmeterol did not offer complete protection against EIA (FEV_1 % fall < 10%) increased from two on study day 1 to 11 on day 29 (P = 0.02)

Ramage and coworkers (Ramage 1994) studied 12 adults treated with inhaled salmeterol 50 mcg twice daily for 4 weeks in a cross-over manner. The significant protection provided by the first dose of salmeterol against EIA at 6 and 12 hours was no longer present at the end of the treatment period.

Fourteen children were studied by Simons (Simons 1997) in a four-week cross-over study. The first dose of salmeterol had an excellent bronchoprotective effect against EIA at 1 and 9 hours. At the end of the study, however, the bronchoprotective effect was significantly greater than that of placebo only at 1 hour.

A parallel-group study design was adopted by Stelmach (Stelmach 2008) to compare the effects of formoterol 9 mcg daily against placebo in two arms, each consisting of 20 children. Both groups of people were receiving concomitant inhaled corticosteroid (ICS) treatment with budesonide 100 mcg daily. At the end of the four-week treatment period, bronchoconstriction induced by a standardised treadmill exercise challenge was significantly diminished in the active group compared with the placebo group,

At last, Storms (Storms 2004) in a four-week parallel-group study compared the protective effect of salmeterol 50 mcg twice daily against placebo. All enrolled people were receiving concomitant 100 mcg twice-daily fluticasone treatment. The protective effect against EIA was evaluated at weeks 1 and 4 and was not different between the two groups.

Only one study (Simons 1997) took into consideration safety aspects of long-term beta$_2$-adrenergic administration. Reported side effects were minor, were poorly related to study drug and anyway were not different between active and placebo groups.

The overall evaluation of presented studies seems to confirm the beta$_2$-agonist bronchoprotective effect for the first dose of treatment. However, long-term use of both SABA and LABA induced the development of tolerance and decreased the duration of drug effect, even after short-term treatment. The few available data on concomitant therapy with inhaled corticosteroids did not allow a firm statement about their potential influence on the response to beta$_2$-agonists.

DISCUSSION

Summary of main results

Evidence emerging from the meta-analysis of 45 short-term (single administration) studies shows that both short- and long-acting beta$_2$-agonists administered as preventive treatment (within the time-effect period set at one hour for SABA and at 12 hours for LABA) prevent exercise-induced asthma, as shown by the

primary outcomes related to the FEV_1 fall. This pharmacological effect appears to be clinically relevant and independent of the exercise challenge adopted (treadmill, cycle ergometer, free run). The assessment of secondary outcomes considered shows that the $beta_2$-agonist preventive effect is also documented by the number of participants protected (complete protection detectable in 68% of participants) and by other pulmonary function variables (PEF, FEF 25%-75%, MEF 50%) and $beta_2$-agonists did not cause side effects.

Overall completeness and applicability of evidence

The choice to include only double-blind randomised trials may influence the completeness of the present review but was thought to reinforce the quality of evidence.

Quality of the evidence

The quality of the evidence gathered for the primary outcome of maximal percentage fall in FEV_1 and the number of participants with a fall in FEV_1 greater than 10% were moderate owing to some concerns about risk of bias (unclear allocation concealment) and detected and not completely explained inconsistency and indirectness (relation of FEV_1 to patient-important outcomes). The same concerns apply to all other outcomes reported in the 'Summary of findings' (SoF) Table. In addition, for the outcomes of maximal percentage fall in PEF, maximal percentage fall in FEF 25-75 and side effects, the quality was lowered further by the small numbers of participants for these outcomes and the resulting wide confidence intervals. It can be argued that this review started with the premise that pulmonary function measures are patient-important outcomes and that, therefore, the quality of evidence should not be lowered for indirectness because the primary outcome was measured in these studies. However, despite these considerations, the meaning of the degree of change in FEV_1 for patients remains unclear (as well as how it relates to their well-being). Furthermore, (small) concerns about inconsistency and risk of bias justify an overall rating of quality as presented in the SoF Table. Further research should focus on patient-important outcomes and the imprecision that was encountered for many of the secondary outcomes.

Potential biases in the review process

The review process was protected from bias by adherence to a prepublished protocol. We tried to prevent bias in our search process by using comprehensive search terms and by asking study authors to identify other published and non-published studies. We minimised bias by assessing studies independently and resolving differences of opinion by discussion. Extraction of data and assessment of risk of bias were performed in duplicate as well. We performed only subgroup analyses that were specified a priori in the protocol.

Agreements and disagreements with other studies or reviews

Our results appear to be in agreement with those obtained by Spooner and coworkers in a Cochrane review and meta-analysis published in 2009 and focused on quantitative comparison of the effects of inhaling mast cell stabilisers (nedocromil sodium or sodium cromoglycate) versus $beta_2$-agonists (Spooner 2003). However, the review authors confined their review to single-dose administration and to short-acting $beta_2$-agonist molecules. As far as we know, no recent systematic reviews have specifically addressed the efficacy and safety of both SABA and LABA, in short-term and long-term administration, for prevention of exercise-induced asthma.

AUTHORS' CONCLUSIONS

Implications for practice

$Beta_2$-agonists, both SABA and LABA, when administered in a single dose before exercise is undertaken, are effective and safe in preventing exercise-induced asthma. Long-term regular administration of inhaled $beta_2$-agonists induces tolerance and lacks sufficient safety data. This finding appears to be of particular clinical relevance in view of the potential for regular prolonged use of $beta_2$-agonists as monotherapy in the pretreatment of EIA, despite the drug agencies' warning on LABA.

Implications for research

Further research should focus on the following.

- Distinguishing between EIA (exercise-induced bronchoconstriction with asthma) from exercise-induced bronchoconstriction without coexisting asthma as different phenotypes, in relation to clinical features, pathophysiological mechanisms, patterns of inflammation and response to treatments, including $beta_2$-agonists.
- Evaluating the potential influence of different genotypes (i.e. $beta_2$-adrenergic receptor polymorphisms) and phenotypes on exercise-induced bronchoconstriction severity and response to $beta_2$-adrenergic treatment.
- Better defining response to therapy, not only according to functional parameters, but also on the basis of clinical endpoints (symptoms, disease control and patient-related outcomes), markers of inflammation and omic approaches.
- Defining standardised operational procedures (i.e. exercise challenges, diagnostic thresholds, outcome measures) for clinical trials in EIA.
- Performing additional independent trials to address long-term $beta_2$-agonist administration in EIA, with special reference to concomitant inhaled corticosteroid treatment, to better assess the risk/benefit ratio between drug efficacy and potential cardiovascular side effects and onset of tolerance.
- Establishing whether pretreatment of EIA with $beta_2$-agonists may exert, beyond the bronchodilator effect, an anti-inflammatory action, as suggested by recent findings on the role of mechanical factors in inflammation and airways remodelling.
- Designing protocols specifically addressed to clarify the potential role of generics and different devices in influencing the efficacy and safety of $beta_2$-agonist prevention of EIA.
- Developing systematic reviews and meta-analyses to assess which is the most appropriate and effective treatment strategy, among those available, for prevention of exercise-induced asthma.

ACKNOWLEDGEMENTS

We thank Brian Rowe for conceiving the original idea for this review and drafting the first version of the protocol.

The authors would like to thank the staff of the Cochrane Airways Group, especially Toby Lasserson and Emma Welsh, who provided invaluable assistance in developing and refining the systematic review. Special thanks to Chris Cates for statistical support, Elizabeth Stovold for her precious assistance in the electronic search and retrieval of papers and Barbara Prediger for her kind help with the SoF Tables.

REFERENCES

References to studies included in this review

Anderson 2001 Salb Disk *{published data only}*

Anderson SD, Lambert S, Brannan JD, Wood RJ, Koskela H, Morton AR, et al. Laboratory protocol for exercise asthma to evaluate salbutamol given by two devices. *Medicine & Science in Sports & Exercise* 2001;**33**(6):893-900.

Anderson 2001 Salb MDI *{published data only}*

Anderson SD, Lambert S, Brannan JD, Wood RJ, Koskela H, Morton AR, et al. Laboratory protocol for exercise asthma to evaluate salbutamol given by two devices. *Medicine & Science in Sports & Exercise* 2001;**33**(6):893-900.

Blake 1999 Salb 180 *{published data only}*

Blake K, Pearlman DS, Scott C, Wang Y, Stahl E, Arledge T. Prevention of exercise-induced bronchospasm in pediatric asthma patients: a comparison of salmeterol powder with albuterol. *Annals of Allergy, Asthma & Immunology* 1999;**82**(2):205-11.

Blake 1999 Salm 25 *{published data only}*

Blake K, Pearlman DS, Scott C, Wang Y, Stahl E, Arledge T. Prevention of exercise-induced bronchospasm in pediatric asthma patients: a comparison of salmeterol powder with albuterol. *Annals of Allergy, Asthma & Immunology* 1999;**82**(2):205-11.

Blake 1999 Salm 50 *{published data only}*

Blake K, Pearlman DS, Scott C, Wang Y, Stahl E, Arledge T. Prevention of exercise-induced bronchospasm in pediatric asthma patients: a comparison of salmeterol powder with albuterol. *Annals of Allergy, Asthma & Immunology* 1999;**82**(2):205-11.

Boner 1994 Form 12 *{published data only}*

Boner AL, Spezia E, Piovesan P, Chiocca E, Maiocchi G. Inhaled formoterol in the prevention of exercise-induced bronchoconstriction in asthmatic children. *American Journal of Respiratory and Critical Care Medicine* 1994;**149**(4):935-9.

Boner 1994 Salb 200 *{published data only}*

Boner AL, Spezia E, Piovesan P, Chiocca E, Maiocchi G. Inhaled formoterol in the prevention of exercise-induced bronchoconstriction in asthmatic children. *American Journal of Respiratory and Critical Care Medicine* 1994;**149**(4):935-9.

Boulet 1989 Salb *{published data only}*

Boulet LP, Turcotte H, Tennina S. Comparative efficacy of salbutamol, ipratropium, and cromoglycate in the prevention of bronchospasm induced by exercise and hyperosmolar challenges. *Journal of Allergy and Clinical Immunology* 1989;**83**(5):882-7.

Bronski 1995 Salb MDI *{published data only}*

Bronsky EA, Spector SL, Pearlman DS, Justus SE, Bishop AL. Albuterol aerosol versus albuterol Rotacaps in exercise-induced bronchospasm in children. *Journal of Asthma* 1995;**32**(3):207-14.

Bronski 1995 Salb Pwd *{published data only}*

Bronsky EA, Spector SL, Pearlman DS, Justus SE, Bishop AL. Albuterol aerosol versus albuterol Rotacaps in exercise-induced bronchospasm in children. *Journal of Asthma* 1995;**32**(3):207-14.

Bronski 1999 Salm Disk *{published data only}*

Bronsky EA, Pearlman DS, Pobiner BF, Scott C, Wang Y, Stahl E. Prevention of exercise-induced bronchospasm in pediatric asthma patients: a comparison of two salmeterol powder delivery devices. *Pediatrics* 1999;**104**:501-6.

Bronski 1999 Salm Diskhal *{published data only}*

Bronsky EA, Pearlman DS, Pobiner BF, Scott C, Wang Y, Stahl E. Prevention of exercise-induced bronchospasm in pediatric asthma patients: a comparison of two salmeterol powder delivery devices. *Pediatrics* 1999;**104**:501-6.

Bronski 2002 Form 12 *{published data only}*

Bronsky EA, Yegen U, Yeh CM, Larsen LV, Della Cioppa G. Formoterol provides long-lasting protection against exercise-induced bronchospasm. *Annals of Allergy, Asthma & Immunology* 2002;**89**(4):407-12.

Bronski 2002 Form 24 *{published data only}*

Bronsky EA, Yegen U, Yeh CM, Larsen LV, Della Cioppa G. Formoterol provides long-lasting protection against exercise-induced bronchospasm. *Annals of Allergy, Asthma & Immunology* 2002;**89**(4):407-12.

Bronski 2002 Salb *{published data only}*

Bronsky EA, Yegen U, Yeh CM, Larsen LV, Della Cioppa G. Formoterol provides long-lasting protection against exercise-induced bronchospasm. *Annals of Allergy, Asthma & Immunology* 2002;**89**(4):407-12.

Carlsen 1995 Salm 25 *{published data only}*

Carlsen KH, Roksund O, Olsholt K, Njå F, Leegaard J, Bratten G. Overnight protection by inhaled salmeterol on exercise-induced asthma in children. *European Respiratory Journal* 1995;**8**(11):1852-5.

Carlsen 1995 Salm 50 *{published data only}*

Carlsen KH, Roksund O, Olsholt K, Njå F, Leegaard J, Bratten G. Overnight protection by inhaled salmeterol on exercise-induced asthma in children. *European Respiratory Journal* 1995;**8**(11):1852-5.

Cavagni 1993 Salb Jet *{published data only}*

Cavagni G, Caffarelli C, Manni PL, Stapane I, Preti PAM, Cantini L. Salbutamol administered through a new spacer device to prevent exercise-induced asthma. *Advanced Therapy* 1993;**10**(5):207-16.

Cavagni 1993 Salb MDI *{published data only}*

Cavagni G, Caffarelli C, Manni PL, Stapane I, Preti PAM, Cantini L. Salbutamol administered through a new spacer device to prevent exercise-induced asthma. *Advanced Therapy* 1993;**10**(5):207-16.

Clarke 1990 Fen *{published data only}*

Clarke PS, Ratowsky DA. Effect of fenoterol hydrobromide and sodium cromoglycate individually and in combination on postexercise asthma. *Annals of Allergy* 1990;**64**:187-90.

Daugbjerg 1996 Form 12 *{published data only}*

Daugbjerg P, Nielsen KG, Skov M, Bisgaard H. Duration of action of formoterol and salbutamol dry-powder inhalation in prevention of exercise-induced asthma in children. *Acta Paediatrica* 1996;**85**(6):684-7.

Daugbjerg 1996 Salb *{published data only}*

Daugbjerg P, Nielsen KG, Skov M, Bisgaard H. Duration of action of formoterol and salbutamol dry-powder inhalation in prevention of exercise-induced asthma in children. *Acta Paediatrica* 1996;**85**(6):684-7.

Debelic 1988 Reproterol *{published data only}*

Debelic M, Hertel G, Konig J. Double-blind crossover study comparing sodium cromoglycate, reproterol, reproterol plus sodium cromoglycate, and placebo in exercise-induced asthma. *Annals of Allergy* 1988;**61**(1):25-9.

DeBenedictis 1996 Salm 25 *{published data only}*

de Benedictis FM, Tuteri G, Pazzelli P, Niccoli A, Mezzetti D, Vaccaro R. Salmeterol in exercise-induced bronchoconstriction in asthmatic children: comparison of two doses. *European Respiratory Journal* 1996;**9**(10):2099-103.

DeBenedictis 1996 Salm 50 *{published data only}*

De Benedictis FM, Tuteri G, Pazzelli P, Niccoli A, Mezzetti D, Vaccaro R. Salmeterol in exercise-induced bronchoconstriction in asthmatic children: comparison of two doses. *European Respiratory Journal* 1996;**9**(10):2099-103.

DeBenedictis 1998 Salb *{published data only}*

De Benedictis FM, Tuteri G, Pazzelli P, Solinas LF, Niccoli A, Parente C. Combination drug therapy for the prevention of exercise-induced bronchoconstriction in children. *Annals of Allergy, Asthma & Immunology* 1998;**80**(4):352-6.

Del Col 1993 Salb Jet *{published data only}*

Del Col G, Spezia E, Richelli C, Piovesan P, Cantini L, Boner AL. Assessment of a new space device (Jet) for use with inhaled beta2-agonists in children with exercise-induced asthma. *Pediatric Allergy and Immunology* 1993;**7**(2):119-26.

Del Col 1993 Salb MDI *{published data only}*

Del Col G, Spezia E, Richelli C, Piovesan P, Cantini L, Boner AL. Assessment of a new space device (Jet) for use with inhaled beta2-agonists in children with exercise-induced asthma. *Pediatric Allergy and Immunology* 1993;**7**(2):119-26.

Dinh Xuan 1989 Terb *{published data only}*

Dinh Xuan AT, Lebeau C, Roche R, Ferriere A, Chaussain M. Inhaled terbutaline administered via a spacer fully prevents exercise-induced asthma in young asthmatic subjects: a double-blind, randomized, placebo-controlled study. *Journal of International Medical Research* 1989;**17**(6):506-13.

Egglestone 1981 Terb 250 *{published data only}*

Eggleston PA, Beasley PP. Bronchodilation and inhibition of induced asthma by adrenergic agonists. *Clinical Pharmacology & Therapeutics* 1981;**29**(4):505-510.

Ferrari 2000 Form 12 *{published data only}*

Ferrari M, Balestreri F, Baratieri S, Biasin C, Oldani V, Lo Cascio V. Evidence of the rapid protective effect of formoterol dry-powder inhalation against exercise-induced bronchospasm in athletes with asthma. *Respiration* 2000;**67**(5):510-3.

Garcia 2001 Form 12 *{published data only}*

Garcia R, Guerra P, Feo F, Galindo PA, Gómez E, Borja J, et al. Tachyphylaxis following regular use of formoterol in exercise-induced bronchospasm. *Journal of Investigational Allergology and Clinical Immunology* 2001;**11**(3):176-82.

Green 1992 Salm 50 *{published data only}*

Green CP, Price JF. Prevention of exercise induced asthma by inhaled salmeterol xinafoate. *Archives of Disease in Childhood* 1992;**67**(8):1014-7.

Gronnerod 2000 Form 4.5 *{published data only}*

Gronnerod TA, von Berg A, Schwabe G, Soliman S. Formoterol via Turbuhaler gave better protection than terbutaline against repeated exercise challenge for up to 12 hours in children and adolescents. *Respiratory Medicine* 2000;**94**(7):661-7.

Gronnerod 2000 Form 9 *{published data only}*

Gronnerod TA, von Berg A, Schwabe G, Soliman S. Formoterol via Turbuhaler gave better protection than terbutaline against repeated exercise challenge for up to 12 hours in children and adolescents. *Respiratory Medicine* 2000;**94**(7):661-7.

Gronnerod 2000 Terb 500 *{published data only}*

Gronnerod TA, von Berg A, Schwabe G, Soliman S. Formoterol via Turbuhaler gave better protection than terbutaline against repeated exercise challenge for up to 12 hours in children and adolescents. *Respiratory Medicine* 2000;**94**(7):661-7.

Hancox 2002 *{published data only}*

Hancox RJ, Subbarao P, Kamada D, Watson RM, Hargreave FE, Inman MD. Beta2-agonist tolerance and exercise-induced bronchospasm. *American Journal of Respiratory and Critical Care Medicine* 2002;**165**(8):1068-70.

Hawksworth 2002 Salb HFA *{published data only}*

Hawksworth RJ, Sykes AP, Faris M, Mant T, Lee TH. Albuterol HFA is as effective as albuterol CFC in preventing exercise-induced bronchoconstriction. *Annals of Allergy, Asthma & Immunology* 2002;**88**(5):473-7.

Hawksworth 2002 Salb MDI *{published data only}*

Hawksworth RJ, Sykes AP, Faris M, Mant T, Lee TH. Albuterol HFA is as effective as albuterol CFC in preventing exercise-induced bronchoconstriction. *Annals of Allergy, Asthma & Immunology* 2002;**88**(5):473-7.

Henricksen 1983 Terb *{published data only}*

Henriksen JM, Dahl R. Effects of inhaled budesonide alone and in combination with low-dose terbutaline in children

with exercise-induced asthma. *American Review of Respiratory Disease* 1983;**128**(6):993-7.

Henricksen 1992 Salb *{published data only}*

Henriksen JM, Agertoft L, Pedersen S. Protective effect and duration of action of inhaled formoterol and salbutamol on exercise-induced asthma in children. *Journal of Allergy and Clinical Immunology* 1992;**89**(6):1176-82.

Henriksen 1992 Form 12 *{published data only}*

Henriksen JM, Agertoft L, Pedersen S. Protective effect and duration of action of inhaled formoterol and salbutamol on exercise-induced asthma in children. *Journal of Allergy and Clinical Immunology* 1992;**89**(6):1176-82.

Hills 1976 Salb *{published data only}*

Hills EA, Davies S, Geary M. Salmefamol and salbutamol in exercise-induced asthma in children. *British Journal of Diseases of the Chest* 1976;**70**(2):78-82.

Hills 1976 Salmefamol *{published data only}*

Hills EA, Davies S, Geary M. Salmefamol and salbutamol in exercise-induced asthma in children. *British Journal of Diseases of the Chest* 1976;**70**(2):78-82.

Inman 1996 *{published data only}*

Inman MD, O'Byrne PM. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. *American Journal of Respiratory and Critical Care Medicine* 1996;**153**(1):65-9.

Kemp 1994 Salb *{published data only}*

Kemp JP, Dockhorn RJ, Busse WW, Bleecker ER, Van As A. Prolonged effect of inhaled salmeterol against exercise-induced bronchospasm. *American Journal of Respiratory and Critical Care Medicine* 94;**150**:1612-5.

Kemp 1994 Salm 42 *{published data only}*

Kemp JP, Dockhorn RJ, Busse WW, Bleecker ER, Van As A. Prolonged effect of inhaled salmeterol against exercise-induced bronchospasm. *American Journal of Respiratory and Critical Care Medicine* 94;**150**:1612-5.

Konig 1981 Metaprot *{published data only}*

Konig P, Eggleston PA, Serby CW. Comparison of oral and inhaled metaproterenol for prevention of exercise-induced asthma. *Clinical Allergy* 1981;**11**(6):597-604.

Konig 1984 Fen 0.4 *{published data only}*

Konig P, Hordvik NL, Serby CW. Fenoterol in exercise-induced asthma: effect of dose on efficacy and duration of action. *Chest* 1984;**85**:462-4.

Konig 1984 Fen 0.8 *{published data only}*

Konig P, Hordvik NL, Serby CW. Fenoterol in exercise-induced asthma: effect of dose on efficacy and duration of action. *Chest* 1984;**85**:462-4.

Larsson 1982 Fen *{published data only}*

Larsson K. Oxitropium bromide, ipratropium bromide and fenoterol in exercise-induced asthma. *Respiration* 1982;**43**(1):57-63.

McAlpine 1990 Form 12 *{published data only}*

McAlpine LG, Thomson NC. Prophylaxis of exercise-induced asthma with inhaled formoterol, a long-acting beta 2-adrenergic agonist. *Respiratory Medicine* 1990;**84**(4):293-5.

McAlpine 1990 Salb *{published data only}*

McAlpine LG, Thomson NC. Prophylaxis of exercise-induced asthma with inhaled formoterol, a long-acting beta 2-adrenergic agonist. *Respiratory Medicine* 1990;**84**(4):293-5.

McFadden 1986 Salb (I) *{published data only}*

McFadden ER Jr, Mills R. Prevention of exercise-induced bronchospasm with aerosolized albuterol. *Current Therapeutic Research, Clinical and Experimental* 1986;**39**(1):112-8.

McFadden 1986 Salb (II) *{published data only}*

McFadden ER, Mills R. Inhaled albuterol powder for the prevention of exercise-induced bronchospasm. *Immunology and Allergy Practice* 1986;**8**(6):199-203.

Morton 1989 Rimet *{published data only}*

Morton AR, Scott CA, Fitch KD. Rimiterol and the prevention of exercise-induced asthma. *Journal of Allergy and Clinical Immunology* 1989;**83**(1):61-5.

Nelson 1998 *{published data only}*

Nelson JA, Strauss L, Skowronski M, Ciufo R, Novak R, McFadden ER Jr. Effect of long-term salmeterol treatment on exercise-induced asthma. *New England Journal of Medicine* 1998;**339**(3):141-6.

Newnham 1993 Salb 200 *{published data only}*

Newnham DM, Ingram CG, Earnshaw J, Palmer JB, Dhillon DP. Salmeterol provides prolonged protection against exercise-induced bronchoconstriction in a majority of subjects with mild, stable asthma. *Respiratory Medicine* 1993;**87**(6):439-4.

Newnham 1993 Salm 50 *{published data only}*

Newnham DM, Ingram CG, Earnshaw J, Palmer JB, Dhillon DP. Salmeterol provides prolonged protection against exercise-induced bronchoconstriction in a majority of subjects with mild, stable asthma. *Respiratory Medicine* 1993;**87**(6):439-4.

Patel 1986 Salb 200 *{published data only}*

Patel KR. Bronchodilator activity of a new inhaled beta$_2$-adrenoceptor agonist, tulobuterol, and its protective effect in exercise-induced asthma. *British Journal of Clinical Pharmacology* 1986;**21**(2):234-7.

Patel 1986 Tulob 200 *{published data only}*

Patel KR. Bronchodilator activity of a new inhaled beta$_2$-adrenoceptor agonist, tulobuterol, and its protective effect in exercise-induced asthma. *British Journal of Clinical Pharmacology* 1986;**21**(2):234-7.

Patel 1986 Tulob 400 *{published data only}*

Patel KR. Bronchodilator activity of a new inhaled beta$_2$-adrenoceptor agonist, tulobuterol, and its protective effect in exercise-induced asthma. *British Journal of Clinical Pharmacology* 1986;**21**(2):234-7.

Patessio 1991 Form 24 *{published data only}*

Patessio A, Podda A, Carone M, Trombetta N, Donner CF. Protective effect and duration of action of formoterol aerosol on exercise-induced asthma. *European Respiratory Journal* 1991;**4**(3):296-300.

Patessio 1991 Salb 200 *{published data only}*

Patessio A, Podda A, Carone M, Trombetta N, Donner CF. Protective effect and duration of action of formoterol aerosol on exercise-induced asthma. *European Respiratory Journal* 1991;**4**(3):296-300.

Pearlman 2006 Form 12 *{published data only}*

Pearlman D, Milgrom H, Till D, Ziehmer B. Effect of formoterol fumarate treatment on exercise-induced bronchoconstriction in children. *Annals of Allergy, Asthma & Immunology* 2006;**97**(3):382-8.

Pearlman 2006 Form 24 *{published data only}*

Pearlman D, Milgrom H, Till D, Ziehmer B. Effect of formoterol fumarate treatment on exercise-induced bronchoconstriction in children. *Annals of Allergy, Asthma & Immunology* 2006;**97**(3):382-8.

Pearlman 2006 Salb 180 *{published data only}*

Pearlman D, Milgrom H, Till D, Ziehmer B. Effect of formoterol fumarate treatment on exercise-induced bronchoconstriction in children. *Annals of Allergy, Asthma & Immunology* 2006;**97**(3):382-8.

Pearlman 2007 Salb 90 *{published data only}*

Pearlman DS, Rees W, Schaefer K, Huang H, Andrews WT. An evaluation of levalbuterol HFA in the prevention of exercise-induced bronchospasm. *Journal of Asthma* 2007;**44**(9):729-33.

Philip 2007 Salm 50 *{published data only}*

Philip G, Pearlman DS, Villarán C, Legrand C, Loeys T, Langdon RB, et al. Single-dose montelukast or salmeterol as protection against exercise-induced bronchoconstriction. *Chest* 2007;**132**(3):875-83.

Ramage 1994 *{published data only}*

Ramage L, Lipworth BJ, Ingram CG, Cree IA, Dhillon DP. Reduced protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. *Respiratory Medicine* 1994;**88**(5):363-8.

Richter 2002 Form 12 *{published data only}*

Richter K, Janicki S, Jorres RA, Magnussen H. Acute protection against exercise-induced bronchoconstriction by formoterol, salmeterol and terbutaline. *European Respiratory Journal* 2002;**19**(5):865-71.

Richter 2002 Salm 50 *{published data only}*

Richter K, Janicki S, Jorres RA, Magnussen H. Acute protection against exercise-induced bronchoconstriction by formoterol, salmeterol and terbutaline. *European Respiratory Journal* 2002;**19**(5):865-71.

Richter 2002 Terb 500 *{published data only}*

Richter K, Janicki S, Jorres RA, Magnussen H. Acute protection against exercise-induced bronchoconstriction by formoterol, salmeterol and terbutaline. *European Respiratory Journal* 2002;**19**(5):865-71.

Shapiro 2002 Form 12 *{published data only}*

Shapiro GG, Kemp JP, DeJong R, Chapko M, Bierman CW, Altman LC, et al. Effects of albuterol and procaterol on exercise-induced asthma. *Annals of Allergy* 1990;**65**(4):273-6.

Shapiro 2002 Form 24 *{published data only}*

Shapiro GG, Kemp JP, DeJong R, Chapko M, Bierman CW, Altman LC, et al. Effects of albuterol and procaterol on exercise-induced asthma. *Annals of Allergy* 1990;**65**(4):273-6.

Shapiro 2002 Salb 180 *{published data only}*

Shapiro GG, Kemp JP, DeJong R, Chapko M, Bierman CW, Altman LC, et al. Effects of albuterol and procaterol on exercise-induced asthma. *Annals of Allergy* 1990;**65**(4):273-6.

Simons 1997 *{published data only}*

Simons FE, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* 1997;**99**(5):655-9.

Stelmach 2008 *{published data only}*

Stelmach I, Grzelewski T, Majak P, Jerzynska J, Stelmach W, Kuna P. Effect of different antiasthmatic treatments on exercise-induced bronchoconstriction in children with asthma. *Journal of Allergy and Clinical Immunology* 2008;**121**(2):383-9.

Storms 2004 *{published data only}*

Storms W, Chervinsky P, Ghannam AF, Bird S, Hustad CM, Edelman JM, et al. A comparison of the effects of oral montelukast and inhaled salmeterol on response to rescue bronchodilation after challenge. *Respiratory Medicine* 2004;**98**(11):1051-62.

Sturani 1983 Fen 400 *{published data only}*

Sturani C, Schiavina M, Tosi I, Gunella G. Comparison of inhaled fenoterol and salbutamol in the prevention of exercise-induced asthma. *European Journal of Respiratory Diseases* 1983;**128(Suppl)**:526-8.

Sturani 1983 Salb 200 *{published data only}*

Sturani C, Schiavina M, Tosi I, Gunella G. Comparison of inhaled fenoterol and salbutamol in the prevention of exercise-induced asthma. *European Journal of Respiratory Diseases* 1983;**128**:526-8.

VanHaitsma 2010 Salb *{published data only}*

VanHaitsma TA, Mickleborough T, Stager JM, Koceja DM, Lindley MR, Chapman R. Comparative effects of caffeine and albuterol on the bronchoconstrictor response to exercise in asthmatic athletes. *International Journal of Sports Medicine* 2010;**31**(4):231-6.

Vasquez 1984 Salb 400 *{published data only}*

Vazquez C, Fidalgo I, Virto MC, Labayru MT, Casas C. Efficacy of disodium chromoglycate, salbutamol and ipratroprium bromide on inhibition of exercise induced bronchospasm. *Anales Espanoles de Pediatria* 1984;**20**(8):756-62.

Walker 1986 Bitolterol *{published data only}*

Walker SB, Bierman CW, Pierson WE, Shapiro GG, Furukawa CT, Mingo TS. Bitolterol mesylate in exercise-induced asthma. *Journal of Allergy and Clinical Immunology* 1986;**77**:32-6.

Wolley 1990 Terb 500 *{published data only}*

Woolley M, Anderson SD, Quigley BM. Duration of protective effect of terbutaline sulfate and cromolyn sodium alone and in combination on exercise-induced asthma. *Chest* 1990;**97**(1):39-45.

References to studies excluded from this review

Aebischer 1984 *{published data only}*

Aebischer JC, Benoit RC, Scherrer M. Pirbuterol and salbutamol aerosol for exercise-induced bronchoconstriction. *Journal Suisse de Medecine* 1984;**114**(46):1660-4.

Agostini 1983 I *{published data only}*

Agostini M, Barlocco G, Mastella G. Protective effect of fenoterol spray, ipratropium bromide plus fenoterol spray, and oral clenbuterol, on exercise-induced asthma in children. Double blind controlled and randomized clinical trial. *European Journal of Respiratory Diseases* 1983;**128**(2):529-32.

Agostini 1983 II *{published data only}*

Agostini M, Barlocco G, Mastella G. Protection against exercise induced asthma in children. Double blind controlled clinical trial with fenoterol spray, fenoterol plus ipratropium and oral clenbuterol. *Rivista Italiana di Pediatria* 1983;**9**(4):347-52.

Allegra 1976 *{published data only}*

Allegra J, Field J, Trautlein J, Gillin M, Zelis R. The pharmacologic effect of aerosolized terbutaline sulfate in exercise-induced bronchospasm. *Journal of Clinical Pharmacology* 1976;**16**(8-9):444-7.

Anderson 1975 *{published data only}*

Anderson SD, Rozea PJ, Dolton R, Lindsay DA. Inhaled and oral bronchodilator therapy in exercise induced asthma. *Australian and New Zealand Journal of Medicine* 1975;**5**(6):544-50.

Anderson 1976 *{published data only}*

Anderson SD, Seale JP, Rozea P, Bandler L, Theobald G, Lindsay D. Inhaled and oral salbutamol in exercise-induced asthma. *American Review of Respiratory Disease* 1976;**114**(3):493-500.

Anderson 1991 *{published data only}*

Anderson SD, Rodwell LT, Du Toit J, Young IH. Duration of protection by inhaled salmeterol in exercise-induced asthma. *Chest* 1991;**100**(5):1254-60.

Aranda 1992 *{published data only}*

Aranda PC, Merello AM, Power A, Reus M, Astudillo P. Prevention of exercise induced asthma by bronchodilator drug aerosol. *Revista Chilena de Pediatria* 1992;**63**(4):202-5.

Bakran 1980 *{published data only}*

Bakran I, Vrhovac B, Plavsić F. Aminophylline vs. salbutamol in exercise-induced asthma. *International Journal of Clinical Pharmacology, Therapy and Toxicology* 1980;**18**(10):442-6.

Battistini 1980 *{published data only}*

Battistini A, Grzincich GL, Gorni A, Baroni AL. Asthma and bronchodilator drugs. Evaluation of a newly developed beta$_2$-agonist: clenbuterol. *Rivista Italiana di Pediatria* 1980;**6**(3):313-9.

Baur 1979 *{published data only}*

Baur X. Concerning the therapy of exercise-induced asthma. *Praxis und Klinik der Pneumologie* 1979;**33**(6):791-5.

Berkowitz 1986 *{published data only}*

Berkowitz R, Schwartz E, Bukstein D, Grunstein M, Chai H. Albuterol protects against exercise-induced asthma longer than metaproterenol sulfate. *Pediatrics* 1986;**77**(2):173-8.

Boner 1984 *{published data only}*

Boner AL, Zamo CR, Marchiori MM, Biancotto R, Antolini I, Vallone G. Comparison of nebulized ipratropium, salbutamol and cromoglicate solutions, cromoglicate inhaled powder, theophylline elixir and placebo in exercise induced asthma of the children. *Giornale Italiano delle Malattie del Torace* 1984;**38**(6):395-9.

Boner 1987 *{published data only}*

Boner AL, De Stefano G, Niero E, Vallone G, Gaburro D. Salbutamol and ipratropium bromide solution in the treatment of bronchospasm in asthmatic children. *Annals of Allergy* 1987;**58**(1):54-8.

Boner 1988 *{published data only}*

Boner AL, Vallone G, Brighenti C, Schiassi M, Miglioranzi P, Richelli C. Comparison of the protective effect and duration of action of orally administered clenbuterol and salbutamol on exercise-induced asthma in children. *Pediatric Pulmonology* 1988;**4**(4):197-200.

Bratteby 1986 *{published data only}*

Bratteby LE, Foucard T, Lönnerholm G. Combined treatment with ipratropium bromide and beta-2-adrenoceptor agonists in childhood asthma. *European Journal of Respiratory Diseases* 1986;**68**(4):239-47.

Bundgaard 1980 *{published data only}*

Bundgaard AF, Rasmussen FV, Madsen L. Pretreatment of exercise-induced asthma in adults with aerosols and pulverized tablets. *Allergy* 1980;**35**(8):639-45.

Bundgaard 1983 I *{published data only}*

Bundgaard AF. Pretreatment of exercise-induced asthma with beta-2 agonists inhaled from RV to TLC or at TLC. A

preliminary report. *European Journal of Respiratory Diseases* 1983;**128**(2):518-20.

Bundgaard 1983 II *{published data only}*

Bundgaard AF, Buch D, Schmidt A, Bach-Mortensen N. Pretreatment of exercise-induced asthma in children using disodium cromoglycate and fenoterol inhalation powder. *European Journal of Respiratory Diseases* 1983;**130**:36-41.

Bundgaard 1983 III *{published data only}*

Bundgaard A, Schmidt A. Double-blind pretreatment of exercise-induced asthma with sequential inhalations of fenoterol from an aerosol and as a powder; second of two parts. *European Journal of Respiratory Diseases* 1983;**130**:67-72.

Bye 1980 *{published data only}*

Bye PT, Anderson SD, Daviskas E, Marty JJ, Sampson D. Plasma cyclic AMP levels in response to exercise and terbutaline sulphate aerosol in normal and asthmatic subjects. *European Journal of Respiratory Diseases* 1980;**61**(5):287-97.

Ceugniet 1997 *{published data only}*

Ceugniet F, Cauchefer F, Fragneaud C, Evano-Celli I. Prophylactic treatment of exercise-induced asthma in children: salmeterol or sodium cromoglycate single dose before exercise?. *Annales De Pediatrie* 1997;**44**(9):625-34.

Colice 1999 *{published data only}*

Colice GL, Klinger NM, Ekholm BP, Dockhorn RJ. Proventil HFA prevents exercise-induced bronchoconstriction in children. *Journal of Asthma* 1999;**36**(8):671-6.

Coreno 2000 *{published data only}*

Coreno A, Skowronski M, Kotaru C, McFadden ER Jr. Comparative effects of long-acting beta2-agonists, leukotriene receptor antagonists, and a 5-lipoxygenase inhibitor on exercise-induced asthma. *Journal of Allergy and Clinical Immunology* 2000;**106**(3):500-6.

Corrias 1989 *{published data only}*

Corrias A, Pelosi U, Corona GB, Minelli R, Peri M, Corda R. Efficacy of broxaterol vs salbutamol in asthma induced by physical exercise in children. *Pediatria Medica e Chirurgica* 1989;**11**:161-3.

Dal Col 1995 *{published data only}*

Dal Col G, Martinati L, Mingoni S, Boner A, Cantini L. Salbutamol powder, administered via a multidose and a single-dose powder inhaler, in the prevention of exercise-induced asthma in children. *Pediatric Asthma, Allergy and Immunology* 1995;**9**(3):165-71.

Del Bono 1979 *{published data only}*

Del Bono N, Quartieri F, Vibelli C. Aerosolized clenbuterol NAB 365 and salbutamol in exercise-induced asthma. *Current Medical Research & Opinion* 1979;**6**(4):237-43.

Di Gioacchino 1987 *{published data only}*

Di Gioacchino M, Mezzetti A, Mancini M, Guglielmi MD, Lo Medico E, Proietti Franceschilli G, et al. Study of the cardiovascular effects of clenbuterol in exercise-induced asthma. *Respiration* 1987;**51**(3):205-13.

Dockhorn 1997 *{published data only}*

Dockhorn RJ, Wagner DE, Burgess GL, Hafner KB, Letourneau K, Colice GL, et al. Proventil HFA provides protection from exercise-induced bronchoconstriction comparable to proventil and ventolin. *Annals of Allergy* 1997;**79**(1):85-8.

Edelman 2000 *{published data only}*

Edelman JL, Turpin JA, Bronsky EA, Grossman J, Kemp JP, Ghannam AF, et al. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction. A randomized, double-blind trial. Exercise Study Group. *Annals of Internal Medicine* 2000;**132**(2):97-104.

Eggleston 1981 *{published data only}*

Eggleston PA, Beasley PP, Kindley RT. The effects of oral doses of theophylline and fenoterol on exercise-induced asthma. *Chest* 1981;**79**(4):399-405.

Ferrari 2002 *{published data only}*

Ferrari M, Segattini C, Zanon R, Bertaiola M, Balestreri F, Brotto E, et al. Comparison of the protective effect of formoterol and of salmeterol against exercise-induced bronchospasm when given immediately before a cycloergometric test. *Respiration* 2002;**69**(6):509-12.

Fogel 2010 *{published data only}*

Fogel BR, Rosario N, Aristizabal G, Loeys T, Noonan G, Gaile S, et al. Effect of montelukast or salmeterol added to inhaled fluticasone on exercise-induced bronchoconstriction in children. *Annals of Allergy, Asthma & Immunology* 2010;**104**:511-7.

Francis 1980 *{published data only}*

Francis PW, Krastins IR, Levison H. Oral and inhaled salbutamol in the prevention of exercise-induced bronchospasm. *Pediatrics* 1980;**66**(1):103-8.

Freeman 1989 *{published data only}*

Freeman W, Packe GE, Cayton RM. Effect of nebulised salbutamol on maximal exercise performance in men with mild asthma. *Thorax* 1989;**44**(11):942-7.

Gibson 1978 *{published data only}*

Gibson GJ, Greenacre JK, König P, Conolly ME, Pride NB. Use of exercise challenge to investigate possible tolerance to beta-adrenoceptor stimulation in asthma. *British Journal of Diseases of the Chest* 1978;**72**(3):199-206.

Gimeno 1985 *{published data only}*

Gimeno F, van Veenen R, Steenhuis EJ, Berg WC. Comparison of disodium cromoglycate, terbutaline and thiazinamium in the prevention of exercise-induced asthma and its relation to non-specific bronchial responsiveness. *Respiration* 1985;**48**(2):108-15.

GlaxoSmithKline 2006 I *{unpublished data only}*

GlaxoSmithKline. A study measuring asthma control in pediatric and adolescent subjects whose asthma is worsened by activity or exercise. clinicaltrials.gov.

GlaxoSmithKline 2006 II *{unpublished data only}*

GlaxoSmithKline. A Stratified, Multicenter, Randomized, Double-Blind, Parallel Group, 4-Week Comparison of Fluticasone Propionate/Salmeterol DISKUS Combination Product 100/50 mcg BID versus Fluticasone Propionate DISKUS 100 mcg BID in Pediatric and in Adolescent Subjects With Activity-Induced Bronchospasm. GlaxoSmithKline Clinical Trial Register.

Godfrey 1975 *{published data only}*

Godfrey S, König P. Suppression of exercise-induced asthma by salbutamol, theophylline, atropine, cromolyn, and placebo in a group of asthmatic children. *Pediatrics* 1975;**56**(5 pt 2 suppl):930-4.

Godfrey 1976 *{published data only}*

Godfrey S, König P. Inhibition of exercise-induced asthma by different pharmacological pathways. *Thorax* 1976;**31**(2):137-43.

Guerin 1992 *{published data only}*

Guerin JC, Brambilla C, Godard P, de Muizon H, Aubert B, Bons J. Prolonged effect against exercise-induced bronchospasm: salmeterol versus sodium cromoglycate. *Revue des Maladies Respiratoires* 1992;**9**(1):27-30.

Gunawardena 2005 *{published data only}*

Gunawardena K, Palmer P, Das S, Hewitt A. Using exercise-induced bronchoconstriction as a method to compare formoterol inhalers in children. *Journal of Applied Therapeutic Research* 2005;**5**(3):16-23.

Hermansen 2006 *{published data only}*

Hermansen MN, Nielsen KG, Buchvald F, Jespersen JJ, Bengtsson T, Bisgaard H. Acute relief of exercise-induced bronchoconstriction by inhaled formoterol in children with persistent asthma. *Chest* 2006;**129**(5):1203-9.

Higgs 1983 *{published data only}*

Higgs CM, Laszlo G. The duration of protection from exercise-induced asthma by inhaled salbutamol, and a comparison with inhaled reproterol. *British Journal of Diseases of the Chest* 1983;**77**(3):262-9.

Ienna 1997 *{published data only}*

Ienna TM, McKenzie DC. The asthmatic athlete: metabolic and ventilatory responses to exercise with and without pre-exercise medication. *International Journal of Sports Medicine* 1997;**18**(2):142-8.

Iikura 1988 *{published data only}*

Iikura Y, Inui H, Obata T, Nagakura T, Sugimoto H, Lee TH, et al. Drug effects on exercise-induced late asthmatic responses. *New England and Regional Allergy Proceedings* 1988;**9**(3):203-7.

Ioli 1986 *{published data only}*

Ioli F, Donner CF, Fracchia C, Manini G, Patessio A, Spada EL, et al. A new bronchodilating agent, procaterol, in preventing exercise-induced asthma. *International Journal of Clinical Pharmacology Research* 1986;**6**(5):389-96.

Johnson 1986 *{published data only}*

Johnson CE, Belfield PW, Davis S, Cooke NJ, Spencer A, Davies JA. Platelet activation during exercise induced asthma: effect of prophylaxis with cromoglycate and salbutamol. *Thorax* 1986;**41**(4):290-4.

Koch 1972 *{published data only}*

Koch G. Terbutaline in bronchial asthma. Effect on lung volumes, ventilatory performance, pulmonary gas exchange and circulation at rest and during exercise. *Scandinavian Journal of Respiratory Diseases* 1972;**53**(4):187-95.

Kumar 1988 *{published data only}*

Kumar AS. Salmeterol in exercise induced asthma. *Indian Pediatrics* 1988;**35**(7):681-2.

Lopes Dos Santos 1991 *{published data only}*

dos Santos JM, Costa H, Ståhl E, Wirén JE. Bricanyl Turbuhaler and Ventolinrho Rotahaler in exercise-induced asthma in children. *Allergy* 1991;**46**(3):203-5.

Machado 2012 *{published data only}*

Machado D, Pereira G, Tavares B, Loureiro G, Segorbe-Luis A. Airways hyperresponsiveness to different inhaled combination therapies in adolescent asthmatics. *European Annals of Allergy and Clinical Immunology* 2012;**44**(1):12-7.

Macucci 2004 *{published data only}*

Macucci F, Guerrini L, Strambi M. Oral montelukast compared with inhaled salbutamol to prevent exercise-induced asthma in children. *Minerva Pneumologica* 2004;**43**(1):41-50.

Magnussen 1984 *{published data only}*

Magnussen H, Reuss G. Blockade of exercise-induced asthma by fenoterol. *Klinische Wochenschrift* 1984;**62**(4):168-74.

Makela 2012 *{published data only}*

Makela MJ, Malmberg LP, Csonka P, Klemola T, Kajosaari M, Pelkonen AS. Salmeterol and fluticasone in young children with multiple-trigger wheeze. *Annals of Allergy, Asthma & Immunology* 2012;**109**:65-70.

Martinsson 1985 *{published data only}*

Martinsson A, Larsson K, Hjemdahl P. Reduced beta 2-adrenoceptor responsiveness in exercise-induced asthma. *Chest* 1985;**88**(4):594-600.

Merck 2005 I *{unpublished data only}*

Merck. An investigational drug to prevent exercise-induced bronchospasm. clinicaltrials.gov.

Merck 2005 II *{unpublished data only}*

Merck. Two investigational drugs in the prevention of airway constriction brought on by exercise in asthmatic patients. clinicaltrials.gov.

Mickleborough 2007 *{published data only}*

Mickleborough TD, Lindley MR, Turner LA. Comparative effects of a high-intensity interval warm-up and salbutamol on the bronchoconstrictor response to exercise in asthmatic athletes. *International Journal of Sports Medicine* 2007;**28**(6):456-62.

Millqvist 2000 *{published data only}*

Millqvist EB, Bengtsson U, Löwhagen O. Combining a beta2-agonist with a face mask to prevent exercise-induced bronchoconstriction. *Allergy* 2000;**55**(7):672-5.

Morandini 1982 *{published data only}*

Morandini GC. Protection of exercise-induced asthma: comparative study of drugs with a different mechanism of action. *Minerva Pneumologica* 1982;**21**(2):75-85.

Morooka 1987 *{published data only}*

Morooka T, Nishima S, Ota S. Prevention of exercise-induced bronchospasm in asthmatic children. Effect of aerosol and oral procaterol hydrochloride. *Journal of Asthma* 1987;**24**(6):335-46.

Morse 1976 *{published data only}*

Morse J, Jones NL, Anderson GD. The effect of terbutaline in exercise-induced asthma. *American Review of Respiratory Disease* 1976;**113**(1):89-92.

Morton 1992 *{published data only}*

Morton AR, Papalia SM, Morton PS, Fitch KD. The efficacy of the nebuhaler method of administration of terbutaline sulphate in the prevention and amelioration of exercise induced asthma. *Australian Journal of Science and Medicine in Sport* 1992;**24**(4):103-6.

Murray 2011 *{published data only}*

Murray JJ, Waitkus-Edwards KR, Yancey SW. Evaluation of fluticasone propionate and fluticasone propionate/salmeterol combination on exercise in pediatric and adolescent patients with asthma. *The Open Respiratory Medicine Journal* 2011;**5**:11-8.

Pearlman 2009 *{published data only}*

Pearlman D, Qaqundah P, Matz J, Yancey SW, Stempel DA, Ortega HG. Fluticasone propionate/salmeterol and exercise-induced asthma in children with persistent asthma. *Pediatric Pulmonology* 2009;**44**(5):429-35.

Pfleger 2002 *{published data only}*

Pfleger A, Eber E, Weinhandl E, Zach MS. Effects of nedocromil and salbutamol on airway reactivity in children with asthma. *European Respiratory Journal* 2002;**20**(3):624-9.

Pichaipat 1995 *{published data only}*

Pichaipat V, Tongpenyai Y, Nerntong T, Sriprapachiranont C. The protective effect of inhaled terbutaline, sodium cromoglycate and budesonide on exercise-induced asthma in children. *Journal of the Medical Association of Thailand* 1995;**78**(10):505-8.

Pichon 2005 *{published data only}*

Pichon A, Roulaud M, Denjean A, de Bisschop C. Airway tone during exercise in healthy subjects: effects of salbutamol and ipratropium bromide. *International Journal of Sports Medicine* 2005;**26**(5):321-6.

Poppius 1973 *{published data only}*

Poppius H, Salorinne Y. Comparative trial of salbutamol and an anticholinergic drug, SCH 1000, in prevention of exercise-induced asthma. *Scandinavian Journal of Respiratory Diseases* 1973;**54**(3):142-7.

Rabe 1993 *{published data only}*

Rabe KF, Jörres R, Magnussen H. The effect of 10, 50 and 200 micrograms inhaled fenoterol on exercise induced asthma. *Clinical and Experimental Allergy* 1993;**23**(5):440-5.

Raissy 2006 *{unpublished data only}*

Raissy HH. Exercise induced bronchospasm in children. clinicaltrials.gov.

Raissy 2008 *{published data only}*

Raissy HH, Harkins M, Kelly F, Kelly HW. Pretreatment with albuterol versus montelukast for exercise-induced bronchospasm in children. *Pharmacotherapy* 2008;**28**(3):287-94.

Revill 1998 *{published data only}*

Revill SM, Morgan MD. The cardiorespiratory response to submaximal exercise in subjects with asthma following pretreatment with controlled release oral salbutamol and high-dose inhaled salmeterol. *Respiratory Medicine* 1998;**92**(8):1053-8.

Robertson 1994 *{published data only}*

Robertson W, Simkins J, O'Hickey SP, Freeman S, Cayton RM. Does single dose salmeterol affect exercise capacity in asthmatic men?. *European Respiratory Journal* 1994;**7**(11):1978-84.

Rohr 1987 *{published data only}*

Rohr AS, Siegel SC, Katz RM, Rachelefsky GS, Spector SL, Lanier R. A comparison of inhaled albuterol and cromolyn in the prophylaxis of exercise-induced bronchospasm. *Annals of Allergy* 1987;**59**(2):107-9.

Sanguinetti 1986 *{published data only}*

Sanguinetti CM, De Luca S, Gasparini S, Massei V. Evaluation of Duovent in the prevention of exercise-induced asthma. *Respiration* 1986;**50**(2):181-5.

Schaanning 1996 *{published data only}*

Schaanning J, Vilsvik J, Henriksen AH, Bratten G. Efficacy and duration of salmeterol powder inhalation in protecting against exercise-induced bronchoconstriction. *Annals of Allergy, Asthma & Immunology* 1996;**76**(1):57-60.

Shah 1983 *{published data only}*

Shah S, Johnston D, Woodcock AA, Johnson M, Geddes DM. Breathlessness and exercise tolerance in chronic airflow obstruction: 2-hourly versus 4-hourly salbutamol by inhalation. *Current Medical Research & Opinion* 1983;**8**(5):343-9.

Shapiro 1981 *{published data only}*

Shapiro GG, McPhillips JJ, Smith K, Furukawa CT, Pierson WE, Bierman CW. Effectiveness of terbutaline and theophylline alone and in combination in exercise-induced bronchospasm. *Pediatrics* 1981;**67**(4):508-13.

Shapiro 1990 *{published data only}*

Shapiro GG, Kemp JP, DeJong R, Chapko M, Bierman CW, Altman LC, et al. Effects of albuterol and procaterol on exercise-induced asthma. *Annals of Allergy* 1990;**65**(4):273-6.

Sichletidis 1993 *{published data only}*

Sichletidis L, Daskalopoulou E, Kyriazis G, Kosmidou I, Koupidou S, Pechlivanidis T, et al. Comparative efficacy of salbutamol and salmeterol in exercise-induced asthma. *Journal of International Medical Research* 1993;**21**(2):81-8.

Silverman 1973 *{published data only}*

Silverman M, Konig P, Godfrey S. Use of serial exercise tests to assess the efficacy and duration of action of drugs for asthma. *Thorax* 1973;**28**(5):574-8.

Singh 1992 *{published data only}*

Singh JP, Singh R, Gupta RC, Bharadwaja B. A comparative study of bronchodilator actions of ipratropium bromide (Atrovent) and salbutamol (Ventolin) on exercise induced bronchial asthma. *Journal of the Association of Physicians of India* 1992;**40**(8):545-7.

Sly 1968 *{published data only}*

Sly RM, Heimlich EM, Ginsburg J, Busser RJ, Strick L. Exercise-induced bronchospasm: evaluation of metaproterenol. *Annals of Allergy* 1968;**26**(5):253-8.

Sly 1975 *{published data only}*

Sly RM, Puapan P, Ghazanshahi S, Midha R. Exercise-induced bronchospasm: evaluation of albuterol aerosol. *Annals of Allergy* 1975;**34**(1):7-14.

Sly 1982 *{published data only}*

Sly RM, O'Brien SR. Effect of oral terbutaline on exercise-induced asthma. *Annals of Allergy* 1982;**48**(3):151-5.

Spada 1985 *{published data only}*

Spada EL, Donner CF, Meriggi A, Vecchio C. Pharmacologic prevention of exercise-induced asthma. *Minerva Pneumologica* 1985;**24**(2):159-64.

Stark 1981 *{published data only}*

Stark RD, Gambles SA. Effects of salbutamol, ipratropium bromide and disodium cromoglycate on breathlessness induced by exercise in normal subjects. *British Journal of Clinical Pharmacology* 1981;**12**(4):497-501.

Steinshamn 2004 *{published data only}*

Steinshamn S, Sandsund M, Sue-Chu M, Bjermer L. Effects of montelukast and salmeterol on physical performance and exercise economy in adult asthmatics with exercise-induced bronchoconstriction. *Chest* 2004;**126**(4):1154-60.

Svenonius 1983 *{published data only}*

Svenonius E, Kautto R, Arborelius M Jr. Improvement after training of children with exercise-induced asthma. *Acta Paediatrica Scandinavica* 1983;**72**(1):23-30.

Svenonius 1988 *{published data only}*

Svenonius E, Arborelius M Jr, Wiberg R, Ekberg P. Prevention of exercise-induced asthma by drugs inhaled from metered aerosols. *Allergy* 1988;**43**(4):252-7.

Svenonius 1994 *{published data only}*

Svenonius E, Arborelius M, Wiberg R, Ståhl E, Svensson M. A comparison of terbutaline inhaled by Turbuhaler and by a chlorofluorocarbon CFC inhaler in children with exercise-induced asthma. *Allergy* 1994;**49**(6):408-12.

Tabas 1985 *{published data only}*

Tabas A, Rodríguez A, Lobera T, Diéguez I, Oehling A. Carbuterol, salbutamol and DSCG in exercise-induced asthma. *Allergologia et Immunopathologia* 1985;**13**(6):493-500.

Tammivaara 1979 *{published data only}*

Tammivaara R. The efficacy of terbutaline and fenoterol aerosols on adult exercise-induced asthma. *Scandinavian Journal of Respiratory Diseases* 1979;**103**:212-3.

Unnithan 1994 *{published data only}*

Unnithan VB, Thomson KJ, Aitchison TC, Paton JY. Beta 2-agonists and running economy in prepubertal boys. *Pediatric Pulmonology* 1994;**17**(6):378-82.

Verini 1983 *{published data only}*

Verini M, Chiarelli F, Di Tullio A, Morgese G, Pallotta R. Pharmacological prevention of exercise-induced bronchospasm: review of the literature and trial of disodium cromoglycate, fenoterol and ipratropium bromide in a pediatric population. *Pediatria Medica e Chirurgica* 1983;**5**(6):501-9.

Verini 1985 *{published data only}*

Verini M, Ansaloni A, Di Vincenzo MG, Napoleone M, Morgese G. Evaluation of reproterol's effectiveness in preventing exercise-induced bronchospasm in children. *Journal of International Medical Research* 1985;**13**(1):19-23.

Verini 1999 *{published data only}*

Verini M, Verrotti A, Greco R, Chiarelli F. Functional effects of controlled physical activity in children and young adults affected by exercise-induced asthma treated with corticosteroids and beta-2 agonists. *Clinical Drug Investigation* 1999;**17**(6):467-73.

Villaran 1999 *{published data only}*

Villaran C, O'Neill SJ, Helbling A, van Noord JA, Lee TH, Chuchalin AG, et al. Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. *Journal of Allergy and Clinical Immunology* 1999;**104**(3):547-53.

Vilsvik 1991 *{published data only}*

Vilsvik J, Schaanning J, Ståhl E, Holthe S. Comparison between Bricanyl Turbuhaler and Ventolin metered dose inhaler in the

treatment of exercise-induced asthma in adults. *Annals of Allergy* 1991;**67**(3):315-8.

Vilsvik 2001 *{published data only}*

Vilsvik J, Ankerst J, Palmqvist M, Persson G, Schaanning J, Schwabe G, et al. Protection against cold air and exercise-induced bronchoconstriction while on regular treatment with Oxis. *Respiratory Medicine* 2001;**95**(6):484-90.

Von Berg 2002 *{published data only}*

Von Berg A, Albrecht B, Darlath W, Vo HW, Berdel D. Intraindividual, randomised, double-blind comparison between sodium cromoglycate and reproterol to assess the protective effect of the single drugs and their combination in children with exercise-induced asthma. *Allergologie* 2002;**25**(11):557-64.

Weiler 2005 *{published data only}*

Weiler JM, Nathan RA, Rupp NT, Kalberg CJ, Emmett A, Dorinsky PM. Effect of fluticasone/salmeterol administered via a single device on exercise-induced bronchospasm in patients with persistent asthma. *Annals of Allergy, Asthma & Immunology* 2005;**94**(1):65-72.

Weinberg 1982 *{published data only}*

Weinberg EG. The effect of terbutaline sulphate on exercise-induced asthma in children. *South African Medical Journal* 1982;**61**(16):587-9.

Yeung 1980 *{published data only}*

Yeung R, Nolan GM, Levison H. Comparison of the effects of inhaled SCH 1000 and fenoterol on exercise-induced bronchospasm in children. *Pediatrics* 1980;**66**(1):109-14.

Zanconato 1990 *{published data only}*

Zanconato S, Baraldi E, Santuz P, Magagnin G, Zacchello F. Effect of inhaled disodium cromoglycate and albuterol on energy: cost of running in asthmatic children. *Pediatric Pulmonology* 1990;**8**(4):240-4.

Zimmermann 2003 *{published data only}*

Zimmermann T, Gulyas A, Bauer CP, Steinkamp G, Trautmann M. Salmeterol versus sodium cromoglycate for the protection of exercise induced asthma in children—a randomised cross-over study. *European Journal of Medical Research* 2003;**8**(9):428-34.

References to studies awaiting assessment

Kupper 2012 *{published data only}*

Küpper T, Goebbels K, Kennes LN, Netzer NC. Cromoglycate, reproterol, or both—what's best for exercise-induced asthma?. *Sleep and Breathing* 2012;**16**(4):1229-35.

Additional references

Anderson 1997

Anderson SD. Exercise-induced asthma. In: Kay AB editor(s). Allergy and Allergic Disease. Oxford: Blackwell Scientific Publications, 1997:692-711.

Anderson 2003

Anderson SD, Brannan JD. Methods for "indirect" challenge tests including exercise, eucapnic voluntary hyperpnea, and hypertonic aerosols. *Clinical Reviews in Allergy & Immunology* 2003;**24**(1):27-54.

Anderson 2006

Anderson SD, Caillaud C, Brannan JD. Beta2-agonists and exercise-induced asthma. *Clinical Reviews in Allergy & Immunology* 2006;**31**(2-3):163-80.

Bateman 2008

Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *European Respiratory Journal* 2008;**31**(1):143-78.

Brozek 2010

Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *Journal of Allergy and Clinical Immunology* 2010;**126**(3):466-76.

Carlsen 2008

Carlsen KH, Anderson SD, Bjermer L, Bonini S, Brusasco V, Canonica W, et al. Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. *Allergy* 2008;**63**(4):387-403.

Higgins 2011

Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. www.cochranehandbook.org, 2011.

Kelly 2000

Kelly KD, Spooner CH, Rowe BH. Nedocromil sodium versus sodium cromoglycate for preventing exercise-induced bronchoconstriction. *Cochrane Database of Systematic Reviews* 2000, Issue 3. [DOI: 10.1002/14651858.CD002731]

Koh 2007

Koh MS, Tee A, Lasserson TJ, Irving LB. Inhaled corticosteroids compared to placebo for prevention of exercise induced bronchoconstriction. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD002739.pub3]

Martinez 2005

Martinez FD. Safety of long-acting beta-agonists—an urgent need to clear the air. *New England Journal of Medicine* 2005;**353**:2637-9.

Nelson 2006

Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, for the SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;**129**:15-26.

Peroni 2011

Peroni DG, Pescollderungg L, Sandri M, Chinellato I, Boner AL, Piacentini GL. Time-effect of montelukast on protection against exercise-induced bronchoconstriction. *Respiratory Medicine* 2011;**105**(12):1790-7.

Randolph 2008

Randolph C. Exercise-induced bronchospasm in children. *Clinical Reviews in Allergy & Immunology* 2008;**34**(2):205-16.

RevMan 5.2 [Computer program]

The Cochrane Collaboration. Review Manager (RevMan) Version 5.2. The Cochrane Collaboration, 2012.

Rundell 2000

Rundell KW, Wilber RL, Szmedra L, Jenkinson DM, Mayers LB, Im J. Exercise-induced asthma screening of elite athletes: field versus laboratory exercise challenge. *Medicine & Science in Sports & Exercise* 2000;**32**(2):309-16.

Salpeter 2010

Salpeter SR, Wall AJ, Buckley NS. Long-acting beta-agonists with and without inhaled corticosteroids and catastrophic asthma events. *American Journal of Medicine* 2010;**123**(4):322-8.

Shapiro 2002

Shapiro GS, Yegen U, Xiang J, Kottakis J, Della Cioppa G. A randomized, double-blind, single-dose, crossover clinical trial of the onset and duration of protection from exercise-induced bronchoconstriction by formoterol and albuterol. *Clinical Therapeutics* 2002;**24**(12):2077-87.

Spooner 2003

Spooner CH, Spooner GR, Rowe BH. Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD002307]

Sterk 1993

Sterk PJ, Fabbri LM, Quanjer PH, Cockcroft DW, O'Byrne PM, Anderson SD, et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *European Respiratory Journal* 1993;**16**(Suppl):53-83.

Weiler 2010

Weiler JM, Anderson SD, Randolph C, Bonini S, Craig TJ, Pearlman DS, et al. Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: a practice parameter. *Annals of Allergy, Asthma & Immunology* 2010;**105**(6 suppl):1-47.

CHARACTERISTICS OF STUDIES

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

Anderson 2001 Salb Disk

Methods	Study design: Randomized, double blind, cross over
	Study location: 2 centres, Australia
	Wash-out: 1-14 days
	Exercise challenge: Cycle-ergometer for 8 min up to 50-60% of MVV
	Criteria for EIB diagnosis: Positive history, FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 29
	% of males: 40%
	Age range: 18-40 years
	Ethnicity: Not reported
	Withdrawal or drop out: 2
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 30 min.
	Intervention: Salbutamol MDI 200 mcg; Salbutamol diskus 200 mcg
	Control: Placebo

Anderson 2001 Salb Disk *(Continued)*

	Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Not allowed on the study day
Outcomes	Primary available: max FEV1 % fall, % protection Secondary available: Number of patients with a max FEV1 % fall <10%, <15%, <20%
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Anderson 2001 Salb MDI

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Anderson 2001 Salb Disk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information

Anderson 2001 Salb MDI *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Blake 1999 Salb 180

Methods	Study design: Randomized, double blind, cross over
	Study location: United States
	Wash-out: 3-14 days
	Exercise challenge: Treadmill for 6 min at 85% of max HR
	Criteria for EIB diagnosis: FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 26
	% of males: 65%
	Age range: 4-11 years
	Ethnicity: 81% Caucasians, 15% Blacks, 4% Hispanic
	Withdrawal or drop out: 3
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 30 min, 5:30 hours, 11:30 hours
	Intervention: Albuterol 180 mcg, Salmeterol 25 mcg Diskus, Salmeterol 50 mcg Diskus
	Control: Placebo
	Other drug arms: None
	Concomitant inhaled corticosteroid (ICS) treatment: Not allowed
Outcomes	Primary available: max FEV1 % fall, % protection, FEV1 fall AUC
	Secondary available: Side effects

Blake 1999 Salb 180 *(Continued)*

Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Blake 1999 Salm 25

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Blake 1999 Salb

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Low risk	Double blind study

Blake 1999 Salm 25 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Blake 1999 Salm 50

Methods		
Participants		
Interventions		
Outcomes		
Notes	See: Blake 1999 Salb	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Boner 1994 Form 12

Methods	Study design: Randomized, double blind, cross over Study location: Italy Wash-out: 2-10 days Exercise challenge: Treadmill for 6 min at 90±4% of max HR Criteria for EIB diagnosis: Positive history, asthma according to ATS, FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 16 % of males: 68% Age range: 6-12 years Ethnicity: Not reported Withdrawal or drop out: 1
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 3 hours, 12 hours Intervention: Salbutamol 200 mcg, Formoterol 12 mcg Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Not allowed
Outcomes	Primary available: max FEV1 % fall, % protection, FEV1 fall AUC Secondary available: Side effects
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization described explicitly
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient information

Boner 1994 Form 12 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Boner 1994 Salb 200

Methods		
Participants		
Interventions		
Outcomes		
Notes	See: Boner 1994 Form	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization described explicitly
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Boulet 1989 Salb

Methods	Study design: Randomized, double blind, cross over Study location: Canada Wash-out: >2 days

Boulet 1989 Salb *(Continued)*

	Exercise challenge: Ergometer for 6 min at 80% of VO2 max Criteria for EIB diagnosis: Positive history, asthma according to ATS, FEV1 fall >10% after exercise challenge
Participants	Number of subjects: 12 % of males: 36% Age range: 19-49 years Ethnicity: Not reported Withdrawal or drop out: 1
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 30 min. Intervention: Salbutamol 200 mcg Control: Placebo Other drug arms: Ipratroprium bromide, Sodium cromoglycate Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: % protection Secondary available: None
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	Data on primary and secondary outcomes are reported incompletely
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Bronski 1995 Salb MDI

Methods	Study design: Randomized, double blind, cross over Study location: United States Wash-out: 2-7 days Exercise challenge: Treadmill for 6 min at 85% of max HR Criteria for EIB diagnosis: FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 46 % of males: 59% Age range: 4-11 years Ethnicity: 87% Caucasians, 13% Others Withdrawal or drop out: 2
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 15 min. Intervention: Albuterol MDI 180 mcg, Albuterol rotacaps 200 mcg Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Not allowed
Outcomes	Primary available: max FEV1 % fall, % protection Secondary available: Side effects, Number of patients with a max FEV1 % fall <20%
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient information

Bronski 1995 Salb MDI *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Bronski 1995 Salb Pwd

Methods		
Participants		
Interventions		
Outcomes		
Notes	See: Bronski 1995 Salb MDI	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Bronski 1999 Salm Disk

Methods	Study design: Randomized, double blind, cross over Study location: United States Wash-out: 2-14 days

Bronski 1999 Salm Disk *(Continued)*

	Exercise challenge: Treadmill for 6 min at 85% of max HR Criteria for EIB diagnosis: FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 24 % of males: 58% Age range: 4-11 years Ethnicity: 91% Caucasians, 9% Blacks Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 30 min, 5:30 hours, 11:30 hours Intervention: Salmeterol 50 mcg Diskus, Salmeterol 50 mcg Diskhaler Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Not allowed
Outcomes	Primary available: max FEV1 % fall, % protection, FEV1 fall AUC Secondary available: Side effects, Number of patients with a max FEV1 % fall <15%, <20%
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Bronski 1999 Salm Diskhal

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Bronski 1999 Salm Disk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Bronski 2002 Form 12

Methods	Study design: Randomized, double blind, cross over Study location: United States Wash-out: 3-7 days Exercise challenge: Treadmill for 6 min at 90% of max HR Criteria for EIB diagnosis: FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 18 % of males: 78% Age range: 13-36 years

Bronski 2002 Form 12 *(Continued)*

	Ethnicity: 88% Caucasians, 12% Others
	Withdrawal or drop out: 1
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 15 min, 4 hours, 8 hours, 12 hours
	Intervention: Albuterol 180 mcg, Formoterol 12 mcg, Formoterol 24 mcg
	Control: Placebo
	Other drug arms: None
	Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: max FEV1 % fall; % protection; FEV1 fall AUC
	Secondary available: Side effects; Number of patients with a max FEV1 % fall <20%; Max PEF % fall
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Bronski 2002 Form 24

Methods
Participants
Interventions

Bronski 2002 Form 24 *(Continued)*

Outcomes	
Notes	See: Bronski 2002 Form 12

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Bronski 2002 Salb

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Bronski 2002 Form 12

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information

Bronski 2002 Salb *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Carlsen 1995 Salm 25

Methods	Study design: Randomized, double blind, cross over
	Study location: Norway
	Wash-out: 2-14 days
	Exercise challenge: Treadmill for 6 min up to 170-180 bpm
	Criteria for EIB diagnosis: Positive history, FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 23
	% of males: 47%
	Age range: 8-16 years
	Ethnicity: Not reported
	Withdrawal or drop out: 0
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: between 10-12 hours
	Intervention: Salmeterol diskhaler 25 mcg, Salmeterol diskhaler 50 mcg
	Control: Placebo
	Other drug arms: None
	Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection
	Secondary available: Number of patients with a max FEV1 % fall <15%; Max MEF25-50 % fall
Notes	
Risk of bias	

Carlsen 1995 Salm 25 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization described explicitly
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Carlsen 1995 Salm 50

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Carlsen Salm 25

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization described explicitly
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information

Carlsen 1995 Salm 50 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Cavagni 1993 Salb Jet

Methods	Study design: Randomized, double blind, cross over
	Study location: Italy
	Wash-out: Not reported
	Exercise challenge: Treadmill for 6 min up to 170-180 bpm
	Criteria for EIB diagnosis: Positive history, FEV1 fall >15% after exercise challenge, FEV1 >15% after bronchodilator
Participants	Number of subjects: 9
	% of males: 66%
	Age range: 5-9 years
	Ethnicity: Not reported
	Withdrawal or drop out: 1
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 10 min.
	Intervention: Salbutamol MDI 200 mcg, Salbutamol jet disposable 200 mcg
	Control: Placebo
	Other drug arms: None
	Concomitant inhaled corticosteroid (ICS) treatment: Not reported
Outcomes	Primary available: Max FEV1 % fall; % protection
	Secondary available: Side effects; Max PEF % fall; Max FEF25-75 % fall
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information

Cavagni 1993 Salb Jet *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Cavagni 1993 Salb MDI

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Cavagni 1993 Salb Jet

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information

Cavagni 1993 Salb MDI *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Clarke 1990 Fen

Methods	Study design: Randomized, double blind, cross over
	Study location: Australia
	Wash-out: <14 days
	Exercise challenge: Treadmill at 15° inclination for 6 min. up to 150 bpm
	Criteria for EIB diagnosis: FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 20
	% of males: 70%
	Age range: Not reported
	Ethnicity: Not reported
	Withdrawal or drop out: 0
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 10 min.
	Intervention: Fenoterol 100 mcg
	Control: Placebo
	Other drug arms: Sodim cromoglycate 20 mg; Sodium cromoglycate 20 mg + Fenoterol 100 mcg
	Concomitant inhaled corticosteroid (ICS) treatment: Not allowed
Outcomes	Primary available: Max FEV1 % fall; % protection
	Secondary available: None
Notes	Industry funded study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study

Clarke 1990 Fen *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Daugbjerg 1996 Form 12

Methods	Study design: Randomized, double blind, cross over
	Study location: Denmark
	Wash-out: Not reported
	Exercise challenge: Treadmill for 6 min. up to 150 bpm
	Criteria for EIB diagnosis: FEV1 fall >22% after exercise challenge
Participants	Number of subjects: 16
	% of males: 81%
	Age range: 10-14 years
	Ethnicity: Not reported
	Withdrawal or drop out: 0
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 3 hours, 12 hours
	Intervention: Salbutamol 400 mcg, Formoterol 12 mcg
	Control: Placebo
	Other drug arms: None
	Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC
	Secondary available: None
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information

Daugbjerg 1996 Form 12 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Daugbjerg 1996 Salb

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Daugbjerg 1996 Form 12

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information

Daugbjerg 1996 Salb *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Debelic 1988 Reproterol

Methods	Study design: Randomized, double blind, cross over Study location: Germany Wash-out: Not reported Exercise challenge: Free running for 6 min up to 160-180 bpm Criteria for EIB diagnosis: FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 16 % of males: Not reported Age range: 8-20 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 15 min. Intervention: Reproterol 1 mg Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Any drug suspended 12 hours before exercise challenge
Outcomes	Primary available: Max FEV1 % fall; % protection; Secondary available: Side effects; Number of patients with a max FEV1 % fall <10%
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Low risk	Double blind study

Debelic 1988 Reproterol *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

DeBenedictis 1996 Salm 25

Methods	Study design: Randomized, double blind, cross over
	Study location: Italy
	Wash-out: 2-10 days
	Exercise challenge: Treadmill for 6 min at 85% of max HR
	Criteria for EIB diagnosis: FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 12
	% of males: 83%
	Age range: 7-14 years
	Ethnicity: Not reported
	Withdrawal or drop out: 0
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 1 hour, 12 hours
	Intervention: Salmeterol 25 mcg, Salmeterol 50 mcg
	Control: Placebo
	Other drug arms: None
	Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC
	Secondary available: Side effects; Number of patients with a max FEV1 % fall <10%
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

DeBenedictis 1996 Salm 25 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

DeBenedictis 1996 Salm 50

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: De Benedictis 1996 Salm 25

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information

DeBenedictis 1996 Salm 50 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

DeBenedictis 1998 Salb

Methods	Study design: Randomized, double blind, cross over Study location: Italy Wash-out: <10 days Exercise challenge: Treadmill for 6 min at 85% of max HR Criteria for EIB diagnosis: FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 12 % of males: 66% Age range: 7-13 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 20 min. Intervention: Salbutamol 200 mcg Control: Placebo Other drug arms: Salbutamol 200 mcg + Nedocromil 4 mg Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; Secondary available: Side effects; Number of patients with a max FEV1 % fall <10%
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information

DeBenedictis 1998 Salb *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Del Col 1993 Salb Jet

Methods	Study design: Randomized, double blind, cross over
	Study location: Italy
	Wash-out: 2-6 days
	Exercise challenge: Treadmill for 6 min at 90±4% of max HR
	Criteria for EIB diagnosis: Positive history
Participants	Number of subjects: 15
	% of males: 60%
	Age range: 9-13 years
	Ethnicity: Not reported
	Withdrawal or drop out: 0
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 10 min.
	Intervention: Salbutamol MDI 200 mcg, Salbutamol Jet device 200 mcg
	Control: Placebo
	Other drug arms: None
	Concomitant inhaled corticosteroid (ICS) treatment: Not reported
Outcomes	Primary available: Max FEV1 % fall; % protection;
	Secondary available: Side effects; Max PEF % fall
Notes	
Risk of bias	

Del Col 1993 Salb Jet *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Del Col 1993 Salb MDI

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Del Col 1993 Salb Jet

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information

Del Col 1993 Salb MDI *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Dinh Xuan 1989 Terb

Methods	Study design: Randomized, double blind, cross over Study location: France Wash-out: Not reported Exercise challenge: Cycle-ergometer for 5 min at 90% of max HR Criteria for EIB diagnosis: FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 10 % of males: 70% Age range: 6-16 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 15 min. Intervention: Terbutaline 500 mcg Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Not reported
Outcomes	Primary available: Max FEV1 % fall; % protection; Secondary available: Number of patients with a max FEV1 % fall <10%, <15% and <20%
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information

Dinh Xuan 1989 Terb *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Egglestone 1981 Terb 250

Methods	Study design: Randomized, double blind, cross over Study location: United States Wash-out: ≧2 days Exercise challenge: Treadmill for 5 min at 90% of max HR Criteria for EIB diagnosis: Positive history; FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 17 % of males: Not reported Age range: 18-32 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 1 hour Intervention: Terbutaline 250 mcg Control: Placebo Other drug arms: Isoproterenol 100 mcg Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; Secondary available: Side effects; Max FEF25-75 % fall;

Egglestone 1981 Terb 250 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Ferrari 2000 Form 12

Methods	Study design: Randomized, double blind, cross over Study location: Italy Wash-out: ≧2 days Exercise challenge: Cycle-ergometer for 7 min at 85% of max HR Criteria for EIB diagnosis: FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 14 % of males: 92% Age range: 12-28 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 15 min, 4 hours Intervention: Formoterol 12 mcg Control: Placebo

Ferrari 2000 Form 12 *(Continued)*

	Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; Secondary available: Side effects; Number of patients with a max FEV1 % fall <10%
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	High risk	Statistical analysis and manuscript writing made by drug industry staff
Other bias	Unclear risk	Insufficient information

Garcia 2001 Form 12

Methods	Study design: Randomized, double blind, parallel groups Study location: Spain Wash-out: Not applicable Exercise challenge: Cycle-ergometer for 6 min at 85% of max HR Criteria for EIB diagnosis: FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 19 % of males: 42% Age range: Not reported Ethnicity: Not reported

Garcia 2001 Form 12 *(Continued)*

	Withdrawal or drop out: 0
Interventions	Drug administration: Chronic administration (4 weeks) Time of exercise challenge after drug administration: 30 min, 12 hours at day 1, 14 and 28 Intervention: Formoterol 12 mcg twice daily Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Onset of tolerance; Number of patients with a max FEV1 % fall <10%
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Green 1992 Salm 50

Methods	Study design: Randomized, double blind, cross over Study location: United Kingdom Wash-out: 4-10 days Exercise challenge: Treadmill for 8 min up to 170 bpm

Green 1992 Salm 50 *(Continued)*

	Criteria for EIB diagnosis: Positive history, FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 13 % of males: 61% Age range: 8-15 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 1 hour, 5 hours, 9 hours Intervention: Salmeterol 50 mcg Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Side effects; Number of patients with a max FEV1 % fall <15%
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Gronnerod 2000 Form 4.5

Methods	Study design: Randomized, double blind, cross over Study location: Germany and Norway Wash-out: ≧3 days Exercise challenge: Treadmill for 4-8 min up to 180 bpm Criteria for EIB diagnosis: Asthma according ATS; FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 27 % of males: 55% Age range: 8-17 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 15 min, 4 hours, 8 hours, 12 hours Intervention: Terbutaline 500 mcg; Formoterol 9 mcg; Formoterol 4.5 mcg Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information

Gronnerod 2000 Form 4.5 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Gronnerod 2000 Form 9

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Gronnerod 2000 Form 4.5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Gronnerod 2000 Terb 500

Methods	
Participants	
Interventions	

Gronnerod 2000 Terb 500 *(Continued)*

Outcomes	
Notes	See: Gronnerod 2000 Form 4.5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Hancox 2002

Methods	Study design: Randomized, double blind, cross over Study location: Canada Wash-out: No Exercise challenge: Cycle ergometer for 7 min at 80% of max work rate Criteria for EIB diagnosis: Positive history; FEV1 fall >15% after exercise challenge which was sustained >10% for at least 5 minutes
Participants	Number of subjects: 9 % of males: 11% Age range: 18-44 years Ethnicity: Not reported Withdrawal or drop out: 1
Interventions	Drug administration: Chronic administration (1 week) Time of exercise challenge after drug administration: 8 hours

Hancox 2002 *(Continued)*

	Intervention: Salbutamol 800 mcg daily
	Control: Placebo
	Other drug arms: None
	Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC
	Secondary available: Tolerance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Hawksworth 2002 Salb HFA

Methods	Study design: Randomized, double blind, cross over
	Study location: United Kingdom
	Wash-out: 1-14 days
	Exercise challenge: Treadmill for 6 min at >80% of max HR
	Criteria for EIB diagnosis: FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 24
	% of males: 75%
	Age range: 18-45 years

Hawksworth 2002 Salb HFA *(Continued)*

	Ethnicity: Caucasian 83%; Asian 17% Withdrawal or drop out: 1
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 30 min Intervention: Salbutamol 180 HFA; Salbutamol 180 mcg MDI Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; Secondary available: Side effects; Number of patients with a max FEV1 % fall <20%
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Hawksworth 2002 Salb MDI

Methods	
Participants	
Interventions	

Hawksworth 2002 Salb MDI *(Continued)*

Outcomes	
Notes	See: Hawksworth 2002 Salb HFA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Henricksen 1983 Terb

Methods	Study design: Randomized, double blind, cross over Study location: Denmark Wash-out: No Exercise challenge: Free running for 6 min at 80-85% of max work capacity Criteria for EIB diagnosis: PEF fall >20% after exercise challenge
Participants	Number of subjects: 14 % of males: Not reported Age range: 8-15 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 15 min

Henricksen 1983 Terb *(Continued)*

	Intervention: Terbutaline 32.5 mcg Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Not allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; Secondary available: Max PEF % fall; Side effects; Number of patients with a max FEV1 % fall <20%
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Henricksen 1992 Salb

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Henricksen 1992 Form 12

Risk of bias

Henricksen 1992 Salb *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Henriksen 1992 Form 12

Methods	Study design: Randomized, double blind, cross over
	Study location: Denmark
	Wash-out: Not reported
	Exercise challenge: Treadmill for 6 min up to 180 bpm
	Criteria for EIB diagnosis: PEF or FEV1 fall >25% after exercise challenge
Participants	Number of subjects: 12
	% of males: Not reported
	Age range: 8-15 years
	Ethnicity: Not reported
	Withdrawal or drop out: 0
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 30 min, 3 hours, 5.30 hours, 8 hours
	Intervention: Salbutamol 200 mcg; Formoterol 12 mcg
	Control: Placebo
	Other drug arms: None
	Concomitant inhaled corticosteroid (ICS) treatment: Allowed

Henriksen 1992 Form 12 *(Continued)*

Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Max PEF % fall; Side effects; Number of patients with a max FEV1 % fall <20%
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Hills 1976 Salb

Methods	Study design: Randomized, double blind, cross over Study location: United Kingdom Wash-out: < 7 days Exercise challenge: Free running for 8 min at max speed Criteria for EIB diagnosis: FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 19 % of males: 42% Age range: 5-15 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose

Hills 1976 Salb *(Continued)*

	Time of exercise challenge after drug administration: 20 min Intervention: Salbutamol 200 mcg; Salmefamol 200 mcg Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection Secondary available: None
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Hills 1976 Salmefamol

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Hills 1976 Salb

Risk of bias

Hills 1976 Salmefamol *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Inman 1996

Methods	Study design: Randomized, double blind, cross over
	Study location: Canada
	Wash-out: 7-21 days
	Exercise challenge: Cycle ergometer for 5 min at 80% of max work rate
	Criteria for EIB diagnosis: Positive history
Participants	Number of subjects: 10
	% of males: 70%
	Age range: 19-37 years
	Ethnicity: Not reported
	Withdrawal or drop out: 0
Interventions	Drug administration: Chronic administration 81 week)
	Time of exercise challenge after drug administration: 24 hours
	Intervention: Salbutamol 800 mcg daily
	Control: Placebo
	Other drug arms: None
	Concomitant inhaled corticosteroid (ICS) treatment: Not reported

Inman 1996 *(Continued)*

Outcomes	Primary available: Max FEV1 % fall; % protection Secondary available: Onset of tolerance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Kemp 1994 Salb

Methods	Study design: Randomized, double blind, parallel groups Study location: United States Wash-out: Not applicable Exercise challenge: Treadmill for 6 min at 80% of max HR Criteria for EIB diagnosis: Asthma according to ATS; FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 161 % of males: 42% Age range: 12-35 years Ethnicity: Not reported Withdrawal or drop out: 8
Interventions	Drug administration: Single dose

Kemp 1994 Salb *(Continued)*

	Time of exercise challenge after drug administration: 30 min, 5.30 hours, 11.30 hours Intervention: Salbutamol 180 mcg; Salmeterol 42 mcg Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Not allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Side effects; Number of patients with a max FEV1 % fall <10% and 20%
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Kemp 1994 Salm 42

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Kemp 1994 Salb

Risk of bias

Kemp 1994 Salm 42 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Konig 1981 Metaprot

Methods	Study design: Randomized, double blind, cross over
	Study location: United States
	Wash-out: Not reported
	Exercise challenge: Treadmill for 6 min at 90% of max HR
	Criteria for EIB diagnosis: Asthma according to ATS; FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 24
	% of males: 67%
	Age range: 17-34 years
	Ethnicity: Not reported
	Withdrawal or drop out: 0
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 10 min, 1 hour
	Intervention: Metaproterenol 130 mcg
	Control: Placebo
	Other drug arms: Oral metaproterenol
	Concomitant inhaled corticosteroid (ICS) treatment: Allowed

Konig 1981 Metaprot *(Continued)*

Outcomes	Primary available: Max FEV1 % fall; % protection Secondary available: Max FEF 25--75 % fall; Side effects; Number of patients with a max FEV1 % fall <10%;
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Konig 1984 Fen 0.4

Methods	Study design: Randomized, double blind, cross over Study location: United States Wash-out: Not reported Exercise challenge: Treadmill up to 90% of max HR Criteria for EIB diagnosis: Asthma according to ATS; FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 12 % of males: 100% Age range: 17-29 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose

Konig 1984 Fen 0.4 *(Continued)*

	Time of exercise challenge after drug administration: 10 min, 2 hours, 4 hours Intervention: Fenoterol 40 mcg; Fenoterol 80 mcg Control: Placebo Other drug arms: No Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection Secondary available: Max FEF 25--75 % fall; Side effects; Number of patients with a max FEV1 % fall <10%;
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	Data for max FEF 25--75 % fall not reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Konig 1984 Fen 0.8

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Konig 1984 Fen 0.4

Konig 1984 Fen 0.8 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	Data for max FEF 25--75 % fall not reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Larsson 1982 Fen

Methods	Study design: Randomized, double blind, cross over Study location: Sweden Wash-out: Not reported Exercise challenge: Cycle ergometer for 6-9 min till exhaustion Criteria for EIB diagnosis: FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 8 % of males: 69% Age range: 29-64 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 10 min Intervention: Fenoterol 400 mcg Control: Placebo Other drug arms: Oxitropium bromide; Ipratropium bromide

Larsson 1982 Fen *(Continued)*

	Concomitant inhaled corticosteroid (ICS) treatment: Any anti-asthmatic drug suspended 12 hours before the test
Outcomes	Primary available: Max FEV1 % fall; % protection Secondary available: Number of patients with a max FEV1 % fall <15%;
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

McAlpine 1990 Form 12

Methods	Study design: Randomized, double blind, cross over Study location: United Kingdom Wash-out: 1-7 days Exercise challenge: Treadmill for 5-8 min up to 90% of max HR Criteria for EIB diagnosis: Documented exercise-induced bronchoconstriction
Participants	Number of subjects: 12 % of males: 41% Age range: 19-41 years Ethnicity: Not reported Withdrawal or drop out: 1

McAlpine 1990 Form 12 *(Continued)*

Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 2 hours, 4 hours Intervention: Salbutamol 200 mcg; Formoterol 12 mcg Control: Placebo Other drug arms: No Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

McAlpine 1990 Salb

Methods	
Participants	
Interventions	
Outcomes	

McAlpine 1990 Salb *(Continued)*

Notes	See: McAlpine 1990 Form 12

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

McFadden 1986 Salb (I)

Methods	Study design: Randomized, double blind, cross over Study location: United States Wash-out: 1-15 days Exercise challenge: Cycle ergometer for 4-5 min till exhaustion Criteria for EIB diagnosis: Positive screening exercise challenge
Participants	Number of subjects: 20 % of males: 60% Age range: 21-42 years Ethnicity: Not reported Withdrawal or drop out: 5
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 15 min Intervention: Salbutamol 200 mcg Control: Placebo

McFadden 1986 Salb (I) *(Continued)*

	Other drug arms: No Concomitant inhaled corticosteroid (ICS) treatment: Not allowed
Outcomes	Primary available: Max FEV1 % fall; % protection Secondary available: Max FEF 25--75 % fall; Side effects; Number of patients with a max FEV1 % fall <20%;
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

McFadden 1986 Salb (II)

Methods	Study design: Randomized, double blind, cross over Study location: United States Wash-out: 1-10 days Exercise challenge: Cycle ergometer for 4-5 min till exhaustion Criteria for EIB diagnosis: Positive screening exercise challenge
Participants	Number of subjects: 20 % of males: 60% Age range: Not reported Ethnicity: Not reported

McFadden 1986 Salb (II) *(Continued)*

	Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 15 min Intervention: Salbutamol 180 mcg Control: Placebo Other drug arms: No Concomitant inhaled corticosteroid (ICS) treatment: Not allowed
Outcomes	Primary available: Max FEV1 % fall; % protection Secondary available: Max FEF 25--75 % fall; Side effects; Number of patients with a max FEV1 % fall <20%;
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Morton 1989 Rimet

Methods	Study design: Randomized, double blind, cross over Study location: Australia Wash-out: 2-7 days Exercise challenge: Treadmill for 8 min at 80% of anaerobic threshold

Morton 1989 Rimet *(Continued)*

	Criteria for EIB diagnosis: Asthma according to ATS; FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 10 % of males: 70% Age range: 15-30 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 2 min Intervention: Rimeterol 400 mcg Control: Placebo Other drug arms: No Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection Secondary available: Side effects; Number of patients with a max FEV1 % fall <15%;
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Nelson 1998

Methods	Study design: Randomized, double blind, cross over Study location: United States Wash-out: 7 days Exercise challenge: Cycle ergometer for 4 min at exhausting work Criteria for EIB diagnosis: FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 20 % of males: 45% Age range: Not reported Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Chronic administration (29 days) Time of exercise challenge after drug administration: 30 min, 9 hours Intervention: Salmeterol 84 mcg daily Control: Placebo Other drug arms: No Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Onset of tolerance; Number of patients with a max FEV1 % fall <10%;
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information

Nelson 1998 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Newnham 1993 Salb 200

Methods	Study design: Randomized, double blind, cross over Study location: United Kingdom Wash-out: ≥2 days Exercise challenge: Treadmill for 6 min up to 90% of max HR Criteria for EIB diagnosis: FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 12 % of males: 50% Age range: 21-33 years Ethnicity: Not reported Withdrawal or drop out: 1
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 1 hour, 6 hours, 12 hours Intervention: Salbutamol 200 mcg; Salmeterol 50 mcg Control: Placebo Other drug arms: No Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Side effects; Number of patients with a max FEV1 % fall <20%;
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study

Newnham 1993 Salb 200 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Newnham 1993 Salm 50

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Newnham 1993 Salb 200

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Patel 1986 Salb 200

Methods	Study design: Randomized, double blind, cross over Study location: United Kingdom Wash-out: Not reported Exercise challenge: Treadmill for 6-8 min Criteria for EIB diagnosis: Diagnosis of exercise-induced bronchoconstriction
Participants	Number of subjects: 9 % of males: Not reported Age range: 19-46 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 20 min Intervention: Salbutamol 200 mcg; Tolobuterol 200 mcg; Tolobuterol 400 mcg Control: Placebo Other drug arms: No Concomitant inhaled corticosteroid (ICS) treatment: Not allowed
Outcomes	Primary available: Max FEV1 % fall; % protection Secondary available: None
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information

Patel 1986 Salb 200 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Patel 1986 Tulob 200

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Patel 1986 Salb 200

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Patel 1986 Tulob 400

Methods	
Participants	
Interventions	

Patel 1986 Tulob 400 *(Continued)*

Outcomes	
Notes	See: Patel 1986 Salb 200

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Patessio 1991 Form 24

Methods	Study design: Randomized, double blind, cross over Study location: Italy Wash-out: 1 day Exercise challenge: Treadmill for 7 min up to 90% of max HR Criteria for EIB diagnosis: Asthma according to ATS; FEV1 fall >20% after exercise challenge
Participants	Number of subjects:12 % of males: 16% Age range: Not reported Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 2 hours, 8 hours

Patessio 1991 Form 24 *(Continued)*

	Intervention: Salbutamol 200 mcg; Formoterol 24 mcg Control: Placebo Other drug arms: No Concomitant inhaled corticosteroid (ICS) treatment: Not reported
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Side effects; Number of patients with a max FEV1 % fall <15%;
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization described explicitly
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Patessio 1991 Salb 200

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Patessio 1991 Form 24

Risk of bias

Patessio 1991 Salb 200 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization described explicitly
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Pearlman 2006 Form 12

Methods	Study design: Randomized, double blind, cross over
	Study location: United States
	Wash-out: ≥3 days
	Exercise challenge: Treadmill for 6 min up to 80-90% of max HR
	Criteria for EIB diagnosis: FEV1 fall >20% after exercise challenge
Participants	Number of subjects:23
	% of males: 30%
	Age range: 4-11 years
	Ethnicity: Not reported
	Withdrawal or drop out: 2
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 15 min, 4 hours, 8 hours, 12 hours
	Intervention: Salbutamol 180 mcg; Formoterol 12 mcg; Formoterol 24 mcg
	Control: Placebo
	Other drug arms: No
	Concomitant inhaled corticosteroid (ICS) treatment: Allowed

Pearlman 2006 Form 12 *(Continued)*

Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Side effects; Number of patients with a max FEV1 % fall <10% and <20%
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization described explicitly
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Pearlman 2006 Form 24

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Pearlman 2006 Form 12

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization described explicitly
Allocation concealment (selection bias)	Unclear risk	Insufficient information

Pearlman 2006 Form 24 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Pearlman 2006 Salb 180

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Pearlman 2006 Form 12

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization described explicitly
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Pearlman 2006 Salb 180 *(Continued)*

Other bias	Unclear risk	Insufficient information

Pearlman 2007 Salb 90

Methods	Study design: Randomized, double blind, cross over Study location: United States Wash-out: 3-7 days Exercise challenge: Treadmill for at least 4 min at 85% of max HR Criteria for EIB diagnosis: Exercise-induced bronchoconstriction for at least 6 months; FEV1 fall >20% and <50% after exercise challenge
Participants	Number of subjects:15 % of males: 86% Age range: Not reported Ethnicity: 100% Caucasian Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 20 min Intervention: Salbutamol 90 mcg Control: Placebo Other drug arms: No Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Side effects; Number of patients with a max FEV1 % fall <10%, <15% and <20%
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization described explicitly
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study

Pearlman 2007 Salb 90 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Philip 2007 Salm 50

Methods	Study design: Randomized, double blind, cross over
	Study location: South America
	Wash-out: 3-7 days
	Exercise challenge: Treadmill for 6 min up to 80-90% of max HR
	Criteria for EIB diagnosis: FEV1 fall >20% and <40% after exercise challenge
Participants	Number of subjects:47
	% of males: 49%
	Age range: 15-45 years
	Ethnicity: 55% Caucasian; 45% Others
	Withdrawal or drop out: 1
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 2 hours, 8.30 hours, 24 hours
	Intervention: Salmeterol 50 mcg
	Control: Placebo
	Other drug arms: Oral Montelukast 10 mg
	Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection
	Secondary available: Side effects
Notes	Industry funded study

Risk of bias

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

Philip 2007 Salm 50 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Ramage 1994

Methods	Study design: Randomized, double blind, cross over
	Study location: United Kingdom
	Wash-out: 7 days
	Exercise challenge: Treadmill for 6 min up to 80-90% of max HR
	Criteria for EIB diagnosis: FEV1 fall >20% and <40% after exercise challenge
Participants	Number of subjects: 12
	% of males: 66%
	Age range: 19-36 years
	Ethnicity: Not reported
	Withdrawal or drop out: 0
Interventions	Drug administration: Chronic administration (28 days)
	Time of exercise challenge after drug administration: 6 hours, 12 hours
	Intervention: Salmeterol 100 mcg daily
	Control: Placebo
	Other drug arms: No
	Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC
	Secondary available: Onset of tolerance

Ramage 1994 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Richter 2002 Form 12

Methods	Study design: Randomized, double blind, cross over Study location: Germany Wash-out: ≥2 days Exercise challenge: Cycle-ergometer for 6 min up to 85% of max HR Criteria for EIB diagnosis: Positive history; Positive methacholine test (PC20 <8mg/ml); Positive exercise challenge
Participants	Number of subjects: 25 % of males: 66% Age range: 19-36 years Ethnicity: Not reported Withdrawal or drop out: 1
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 5 min, 30 min, 1 hour Intervention: Terbutaline 500 mcg; Formoterol 12 mcg; Salmeterol 50 mcg

Richter 2002 Form 12 *(Continued)*

	Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: None
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Richter 2002 Salm 50

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Richter Form 12

Risk of bias

Bias	Authors' judgement	Support for judgement

Richter 2002 Salm 50 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Richter 2002 Terb 500

Methods		
Participants		
Interventions		
Outcomes		
Notes	See: Richter Form 12	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information

Richter 2002 Terb 500 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Shapiro 2002 Form 12

Methods	Study design: Randomized, double blind, cross over Study location: United States Wash-out: 3-7 days Exercise challenge: Treadmill for 6 min at 90% of max HR Criteria for EIB diagnosis: FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 20 % of males: 45% Age range: 13-41 years Ethnicity: Caucasians 90%; Others 10% Withdrawal or drop out: 3
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 15 min, 4 hours, 8 hours, 12 hours Intervention: Salbutamol 180 mcg; Formoterol 12 mcg; Formoterol 24 mcg Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Side effects; Number of patients with a max FEV1 % fall <20%; Max PEF % fall;
Notes	Industry funded study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information

Shapiro 2002 Form 12 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Shapiro 2002 Form 24

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Shapiro 2002 Form 12

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Shapiro 2002 Form 24 *(Continued)*

Other bias	Unclear risk	Insufficient information

Shapiro 2002 Salb 180

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Shapiro 2002 Form 12

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Simons 1997

Methods	Study design: Randomized, double blind, cross over Study location: Canada Wash-out: 14 days Exercise challenge: Treadmill for 8 min up to 90% of max HR or 180 bpm Criteria for EIB diagnosis: Asthma according to ATS; Positive exercise challenge

Simons 1997 *(Continued)*

Participants	Number of subjects: 16 % of males: 41% Age range: 12-16 years Ethnicity: Not reported Withdrawal or drop out: 2
Interventions	Drug administration: Chronic administration (28 weeks) Time of exercise challenge after drug administration: 1 hour, 9 hours Intervention: Salmeterol 50 mcg Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: None
Notes	Industry funded study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization described explicitly
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Stelmach 2008

Methods	Study design: Randomized, double blind, parallel groups Study location: Poland Wash-out: Not applicable Exercise challenge: Treadmill for six min at 95% of max HR Criteria for EIB diagnosis: FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 100 % of males: Not reported Age range: 6-18 years Ethnicity: Not reported Withdrawal or drop out: 9
Interventions	Drug administration: Chronic administration (28 weeks) Time of exercise challenge after drug administration: 1 hour, 9 hours Intervention: Formoterol 9 mcg daily Control: Placebo Other drug arms: Oral Montelukast Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Onset of tolerance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization described explicitly
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information

Stelmach 2008 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Storms 2004

Methods	Study design: Randomized, double blind, parallel groups Study location: United States Wash-out: Not applicable Exercise challenge: Treadmill for six min at 95% of max HR Criteria for EIB diagnosis: FEV1 fall >20% (or >15% if on ICS) after an exercise challenge in the last year
Participants	Number of subjects: 122 % of males: Not reported Age range: 15-58 years Ethnicity: Not reported Withdrawal or drop out: 13
Interventions	Drug administration: Chronic administration (28 weeks) Time of exercise challenge after drug administration: 1 hour, 9 hours Intervention: Salmeterol 100 mcg daily Control: Placebo Other drug arms: Oral Montelukast 10 mg Concomitant inhaled corticosteroid (ICS) treatment: Allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; FEV1 % fall AUC Secondary available: Onset of tolerance
Notes	Industry funded study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study

Storms 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Sturani 1983 Fen 400

Methods	Study design: Randomized, double blind, cross over
	Study location: Italy
	Wash-out: Not reported
	Exercise challenge: Free running for 6 min up to 85% of max HR
	Criteria for EIB diagnosis: FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 12
	% of males: 58%
	Age range: 16-42 years
	Ethnicity: Not reported
	Withdrawal or drop out: 0
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 30 min.
	Intervention: Fenoterol 400 mcg; Salbutamol 200 mcg
	Control: Placebo
	Other drug arms: None
	Concomitant inhaled corticosteroid (ICS) treatment: Not allowed
Outcomes	Primary available: Max FEV1 % fall; % protection
	Secondary available: None
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information

Sturani 1983 Fen 400 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Sturani 1983 Salb 200

Methods	
Participants	
Interventions	
Outcomes	
Notes	See: Sturani 1983 Fen 400

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information

Sturani 1983 Salb 200 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

VanHaitsma 2010 Salb

Methods	Study design: Randomized, double blind, cross-over Study location: United States Wash-out: ≥2 days Exercise challenge: Treadmill for at least 3 min at 85% of max HR Criteria for EIB diagnosis: Physician diagnosed asthma; FEV1 fall >10% after exercise challenge
Participants	Number of subjects: 10 % of males: 70% Age range: Not reported Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 15 min. Intervention: Salbutamol 180 mcg Control: Placebo Other drug arms: None Concomitant inhaled corticosteroid (ICS) treatment: Not reported
Outcomes	Primary available: Max FEV1 % fall; % protection; Secondary available: Max Pef % fall; Max FEF 25--75 % fall
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study

VanHaitsma 2010 Salb *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Vasquez 1984 Salb 400

Methods	Study design: Randomized, double blind, parallel groups
	Study location: Spain
	Wash-out: Not applicable
	Exercise challenge: Free running 5-8 min at max speed (around 170 bpm)
	Criteria for EIB diagnosis: FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 25
	% of males: Not reported
	Age range: Not reported
	Ethnicity: Not reported
	Withdrawal or drop out: 0
Interventions	Drug administration: Single dose
	Time of exercise challenge after drug administration: 15 min.
	Intervention: Salbutamol 400 mcg
	Control: Placebo
	Other drug arms: Disodium cromoglycate 200 mcg; Ipratropium bromide 40 mcg;
	Concomitant inhaled corticosteroid (ICS) treatment: Not reported
Outcomes	Primary available: Max FEV1 % fall; % protection;
	Secondary available: Number of patients with a max FEV1 % fall <15%; Max MEF50 % fall;
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information

Vasquez 1984 Salb 400 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Walker 1986 Bitolterol

Methods	Study design: Randomized, double blind, cross over Study location: United States Wash-out: Not reported Exercise challenge: Cycle-ergometer for 6 min at 80% of max HR Criteria for EIB diagnosis: FEV1 fall >15% after exercise challenge
Participants	Number of subjects: 12 % of males: 58% Age range: 14-25 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 45 min. Intervention: Bitolterol 1050 mcg Control: Placebo Other drug arms: Isoproterenol 255 mcg Concomitant inhaled corticosteroid (ICS) treatment: Not allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; Secondary available: Side effects; Number of patients with a max FEV1 % fall <10%; Max PEF % fall; Max FEF25-75 % fall;

Walker 1986 Bitolterol *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Wolley 1990 Terb 500

Methods	Study design: Randomized, double blind, cross over Study location: Australia Wash-out: Not reported Exercise challenge: Treadmill for 8 min at 60% of MVV Criteria for EIB diagnosis: Positive history, FEV1 fall >20% after exercise challenge
Participants	Number of subjects: 12 % of males: 58% Age range: 18-28 years Ethnicity: Not reported Withdrawal or drop out: 0
Interventions	Drug administration: Single dose Time of exercise challenge after drug administration: 25 min, 2 hours, 4 hours, 6 hours Intervention: Terbutaline 500 mcg Control: Placebo

Wolley 1990 Terb 500 *(Continued)*

	Other drug arms: Cromolyn sodium 2 mg; Cromolyn sodium 2 mg + Terbutaline 500 mcg Concomitant inhaled corticosteroid (ICS) treatment: Not allowed
Outcomes	Primary available: Max FEV1 % fall; % protection; Secondary available: Side effects; Number of patients with a max FEV1 % fall <10%
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

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

Study	Reason for exclusion
Aebischer 1984	No beta-2 agonist pretreatment
Agostini 1983 I	Duplicate
Agostini 1983 II	No systematic review primary outcomes
Allegra 1976	No clear diagnosi of exercise-induced bronchoconstriction
Anderson 1975	No double blind
Anderson 1976	No randomization
Anderson 1991	No randomization

Study	Reason for exclusion
Aranda 1992	No double blind
Bakran 1980	No placebo control
Battistini 1980	No inhaled beta-2 agonist administration
Baur 1979	No systematic review primary outcomes
Berkowitz 1986	No double blind
Boner 1984	No double blind
Boner 1987	No placebo control
Boner 1988	No inhaled beta-2 agonist administration
Bratteby 1986	No placebo control
Bundgaard 1980	No systematic review primary outcomes
Bundgaard 1983 I	No randomization
Bundgaard 1983 II	No systematic review primary outcomes
Bundgaard 1983 III	No systematic review primary outcomes
Bye 1980	No randomization
Ceugniet 1997	No placebo control
Colice 1999	No double blind
Coreno 2000	No double blind
Corrias 1989	No placebo control
Dal Col 1995	No double blind
Del Bono 1979	No double blind
Di Gioacchino 1987	No inhaled beta-2 agonist administration
Dockhorn 1997	No double blind
Edelman 2000	No placebo control
Eggleston 1981	No inhaled beta-2 agonist administration
Ferrari 2002	No placebo control
Fogel 2010	No placebo control
Francis 1980	No clear diagnosi of exercise-induced bronchoconstriction
Freeman 1989	No clear diagnosi of exercise-induced bronchoconstriction

Study	Reason for exclusion
Gibson 1978	No randomization
Gimeno 1985	No clear diagnosi of exercise-induced bronchoconstriction
GlaxoSmithKline 2006 I	No placebo control
GlaxoSmithKline 2006 II	Duplicate
Godfrey 1975	Duplicate
Godfrey 1976	No inhaled beta-2 agonist administration
Guerin 1992	No placebo control
Gunawardena 2005	No placebo control
Hermansen 2006	No beta-2 agonist pretreatment
Higgs 1983	No placebo control
Ienna 1997	No systematic review primary outcomes
Iikura 1988	No randomization
Ioli 1986	No double blind
Johnson 1986	No clear diagnosi of exercise-induced bronchoconstriction
Koch 1972	No randomization
Kumar 1988	No randomization
Lopes Dos Santos 1991	No beta-2 agonist pretreatment
Machado 2012	No placebo control
Macucci 2004	No randomization
Magnussen 1984	No double blind
Makela 2012	No placebo control
Martinsson 1985	No inhaled beta-2 agonist administration
Merck 2005 I	Duplicate
Merck 2005 II	No placebo control
Mickleborough 2007	No placebo control
Millqvist 2000	No randomization
Morandini 1982	No randomization
Morooka 1987	No clear diagnosi of exercise-induced bronchoconstriction

Study	Reason for exclusion
Morse 1976	No inhaled beta-2 agonist administration
Morton 1992	No double blind
Murray 2011	No placebo control
Pearlman 2009	No placebo control
Pfleger 2002	No exercise challenge
Pichaipat 1995	No randomization
Pichon 2005	No clear diagnosi of exercise-induced bronchoconstriction
Poppius 1973	No placebo control
Rabe 1993	No systematic review primary outcomes
Raissy 2006	No placebo control
Raissy 2008	No placebo control
Revill 1998	No placebo control
Robertson 1994	No clear diagnosi of exercise-induced bronchoconstriction
Rohr 1987	No placebo control
Sanguinetti 1986	Exercise challenge beyond beta-2 agonist pharmacological half-life
Schaanning 1996	No systematic review primary outcomes
Shah 1983	No clear diagnosi of exercise-induced bronchoconstriction
Shapiro 1981	No inhaled beta-2 agonist administration
Shapiro 1990	No double blind
Sichletidis 1993	No placebo control
Silverman 1973	No randomization
Singh 1992	No randomization
Sly 1968	No double blind
Sly 1975	No systematic review primary outcomes
Sly 1982	No inhaled beta-2 agonist administration
Spada 1985	No placebo control
Stark 1981	No clear diagnosi of exercise-induced bronchoconstriction
Steinshamn 2004	No placebo control

Study	Reason for exclusion
Svenonius 1983	No randomization
Svenonius 1988	No double blind
Svenonius 1994	No beta-2 agonist pretreatment
Tabas 1985	No inhaled beta-2 agonist administration
Tammivaara 1979	No randomization
Unnithan 1994	No clear diagnosi of exercise-induced bronchoconstriction
Verini 1983	No placebo control
Verini 1985	No inhaled beta-2 agonist administration
Verini 1999	No placebo control
Villaran 1999	No placebo control
Vilsvik 1991	No beta-2 agonist pretreatment
Vilsvik 2001	No placebo control
Von Berg 2002	No placebo control
Weiler 2005	No placebo control
Weinberg 1982	No double blind
Yeung 1980	No placebo control
Zanconato 1990	No placebo control
Zimmermann 2003	No placebo control

DATA AND ANALYSES

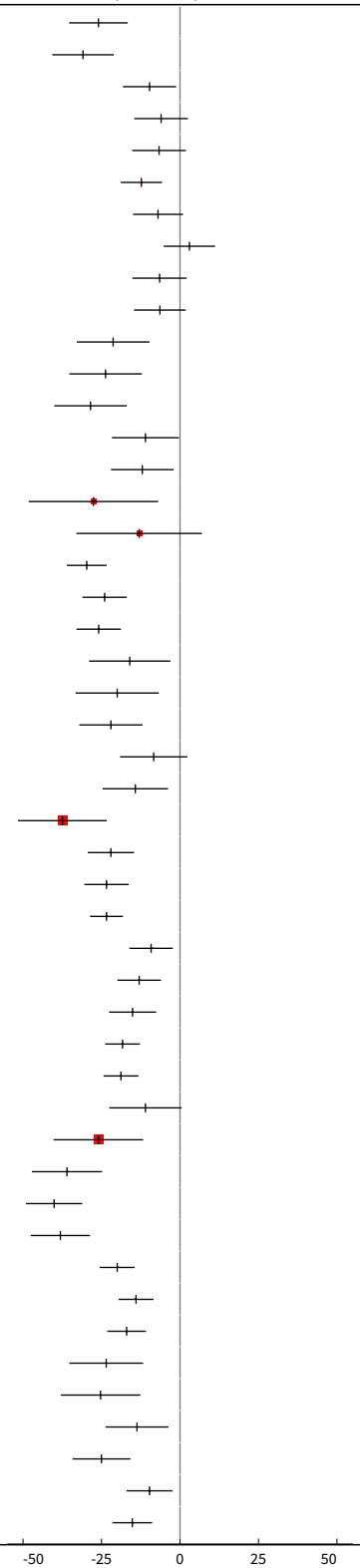
Comparison 1. Beta$_2$-agonists versus placebo (single administration)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maximal percentage fall in FEV_1	72	799	Mean Difference (Random, 95% CI)	-17.67 [-19.51, -15.84]
2 Number of participants with an FEV_1 fall > 10%	19	773	Odds Ratio (M-H, Random, 95% CI)	0.08 [0.06, 0.13]

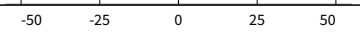
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Number of participants with an FEV_1 fall > 15%	13	457	Odds Ratio (M-H, Random, 95% CI)	0.06 [0.03, 0.15]
4 Number of participants with an FEV_1 fall > 20%	25	1021	Odds Ratio (M-H, Random, 95% CI)	0.09 [0.06, 0.14]
5 Maximal percentage fall in PEF	14	92	Mean Difference (Random, 95% CI)	-24.61 [-37.57, -11.65]
6 Maximal percentage fall in FEF 25-75	8	106	Mean Difference (Fixed, 95% CI)	-20.75 [-27.17, -14.32]
7 Side effects	55	2165	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.43, 1.59]
8 Subgroup analysis: maximal percentage fall in FEV_1 SABA vs LABA	72		Mean Difference (Random, 95% CI)	-17.67 [-19.51, -15.84]
8.1 SABA	44		Mean Difference (Random, 95% CI)	-18.99 [-21.38, -16.60]
8.2 LABA	28		Mean Difference (Random, 95% CI)	-15.60 [-18.29, -12.92]
9 Subgroup analysis: maximal percentage fall in FEV_1: salmeterol versus formoterol	28		Mean Difference (Random, 95% CI)	-15.60 [-18.29, -12.92]
9.1 Salmeterol	13		Mean Difference (Random, 95% CI)	-12.73 [-16.10, -9.37]
9.2 Formoterol	15		Mean Difference (Random, 95% CI)	-18.24 [-22.15, -14.34]
10 Subgroup analysis: maximal percentage fall in FEV_1: adults versus children	51		Mean Difference (Random, 95% CI)	-16.75 [-19.12, -14.39]
10.1 Adults	19		Mean Difference (Random, 95% CI)	-18.77 [-20.78, -16.76]
10.2 Children	32		Mean Difference (Random, 95% CI)	-15.32 [-18.88, -11.75]

Analysis 1.1. Comparison 1 Beta$_2$-agonists versus placebo (single administration), Outcome 1 Maximal percentage fall in FEV$_1$.

Study or subgroup	Beta2-agonist N	Placebo N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Anderson 2001 Salb Disk	0	14	-26 (4.76)		1.39%	-25.98[-35.31,-16.65]
Anderson 2001 Salb MDI	0	13	-30.9 (4.99)		1.35%	-30.89[-40.67,-21.11]
Blake 1999 Salb 180	0	8	-9.7 (4.32)		1.49%	-9.7[-18.17,-1.23]
Blake 1999 Salm 25	0	8	-6 (4.36)		1.48%	-6.01[-14.56,2.54]
Blake 1999 Salm 50	0	8	-6.7 (4.37)		1.48%	-6.66[-15.23,1.91]
Boner 1994 Form 12	0	15	-12.3 (3.35)		1.71%	-12.3[-18.87,-5.73]
Bronski 1995 Salb MDI	0	22	-7 (4.06)		1.55%	-7[-14.96,0.96]
Bronski 1995 Salb Pwd	0	22	3 (4.17)		1.52%	3[-5.17,11.17]
Bronski 1999 Salm Disk	0	12	-6.5 (4.4)		1.47%	-6.5[-15.12,2.12]
Bronski 1999 Salm Diskhal	0	12	-6.4 (4.21)		1.51%	-6.4[-14.65,1.85]
Bronski 2002 Form 12	0	6	-21.3 (5.9)		1.17%	-21.3[-32.86,-9.74]
Bronski 2002 Form 24	0	6	-23.7 (5.9)		1.17%	-23.7[-35.26,-12.14]
Bronski 2002 Salb	0	6	-28.5 (5.9)		1.17%	-28.5[-40.06,-16.94]
Carlsen 1995 Salm 25	0	12	-11 (5.45)		1.25%	-11[-21.68,-0.32]
Carlsen 1995 Salm 50	0	12	-12 (5.09)		1.33%	-12[-21.98,-2.02]
Cavagni 1993 Salb Jet	0	4	-27.5 (10.52)		0.58%	-27.55[-48.17,-6.93]
Cavagni 1993 Salb MDI	0	4	-13 (10.2)		0.61%	-13[-32.99,6.99]
Clarke 1990 Fen	0	20	-29.7 (3.23)		1.73%	-29.7[-36.03,-23.37]
Daugbjerg 1996 Form 12	0	16	-24 (3.61)		1.65%	-24[-31.08,-16.92]
Debelic 1988 Reproterol	0	16	-25.9 (3.61)		1.65%	-25.9[-32.98,-18.82]
DeBenedictis 1996 Salm 25	0	6	-16 (6.61)		1.04%	-16[-28.96,-3.04]
DeBenedictis 1996 Salm 50	0	6	-20 (6.77)		1.02%	-20[-33.27,-6.73]
DeBenedictis 1998 Salb	0	12	-22 (5.14)		1.32%	-22[-32.07,-11.93]
Del Col 1993 Salb Jet	0	7	-8.4 (5.47)		1.25%	-8.38[-19.1,2.34]
Del Col 1993 Salb MDI	0	8	-14.2 (5.32)		1.28%	-14.23[-24.66,-3.8]
Dinh Xuan 1989 Terb	0	10	-37.4 (7.21)		0.95%	-37.44[-51.57,-23.31]
Egglestone 1981 Terb 250	0	17	-22 (3.77)		1.61%	-22[-29.39,-14.61]
Ferrari 2000 Form 12	0	14	-23.4 (3.61)		1.65%	-23.4[-30.48,-16.32]
Green 1992 Salm 50	0	13	-23.4 (2.67)		1.85%	-23.4[-28.63,-18.17]
Gronnerod 2000 Form 4.5	0	9	-9.2 (3.53)		1.67%	-9.2[-16.12,-2.28]
Gronnerod 2000 Form 9	0	9	-13 (3.53)		1.67%	-13[-19.92,-6.08]
Gronnerod 2000 Terb 500	0	9	-15.1 (3.83)		1.6%	-15.1[-22.61,-7.59]
Hawksworth 2002 Salb HFA	0	12	-18.3 (2.83)		1.82%	-18.3[-23.85,-12.75]
Hawksworth 2002 Salb MDI	0	12	-18.8 (2.83)		1.82%	-18.8[-24.35,-13.25]
Henricksen 1983 Terb	0	14	-11 (5.88)		1.17%	-11[-22.52,0.52]
Henricksen 1992 Salb	0	6	-26 (7.28)		0.94%	-26[-40.27,-11.73]
Henriksen 1992 Form 12	0	6	-36 (5.7)		1.21%	-36[-47.17,-24.83]
Hills 1976 Salb	0	10	-40.1 (4.57)		1.43%	-40.1[-49.06,-31.14]
Hills 1976 Salmefamol	0	9	-38.1 (4.82)		1.38%	-38.1[-47.55,-28.65]
Kemp 1994 Salb	0	26	-20 (2.83)		1.82%	-20[-25.55,-14.45]
Kemp 1994 Salm 42	0	26	-14 (2.83)		1.82%	-14[-19.55,-8.45]
Konig 1981 Metaprot	0	24	-17 (3.16)		1.75%	-17[-23.19,-10.81]
Konig 1984 Fen 0.4	0	6	-23.5 (6)		1.15%	-23.5[-35.26,-11.74]
Konig 1984 Fen 0.8	0	6	-25.3 (6.47)		1.07%	-25.3[-37.98,-12.62]
Larsson 1982 Fen	0	8	-13.7 (5.11)		1.32%	-13.7[-23.72,-3.68]
McAlpine 1990 Form 12	0	11	-25 (4.71)		1.4%	-25[-34.23,-15.77]
McFadden 1986 Salb (I)	0	15	-9.7 (3.73)		1.62%	-9.7[-17.01,-2.39]
McFadden 1986 Salb (II)	0	20	-15.2 (3.23)		1.73%	-15.2[-21.53,-8.87]

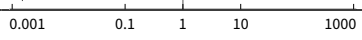


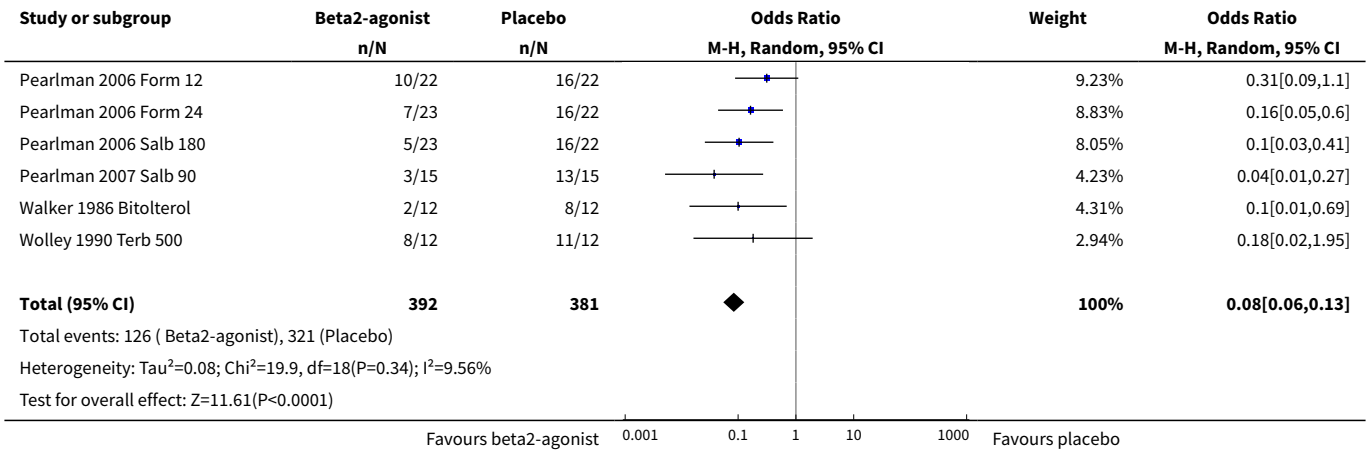
Study or subgroup	Beta2-agonist N	Placebo N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Morton 1989 Rimet	0	10	-21.7 (2.6)		1.87%	-21.7[-26.8,-16.6]
Newnham 1993 Salb 200	0	6	-23.3 (7.91)		0.85%	-23.3[-38.8,-7.8]
Newnham 1993 Salm 50	0	5	-19.2 (10.41)		0.59%	-19.2[-39.6,1.2]
Patel 1986 Salb 200	0	9	-21.9 (4.82)		1.38%	-21.9[-31.35,-12.45]
Patel 1986 Tulob 200	0	5	-18.2 (6.46)		1.07%	-18.2[-30.86,-5.54]
Patel 1986 Tulob 400	0	4	-20.2 (7.23)		0.95%	-20.2[-34.37,-6.03]
Patessio 1991 Form 24	0	12	-20.5 (4.17)		1.52%	-20.5[-28.67,-12.33]
Pearlman 2006 Form 12	0	7	-5.6 (5.46)		1.25%	-5.6[-16.3,5.1]
Pearlman 2006 Form 24	0	7	-7.3 (5.46)		1.25%	-7.3[-18,3.4]
Pearlman 2006 Salb 180	0	7	-7.6 (5.46)		1.25%	-7.6[-18.3,3.1]
Pearlman 2007 Salb 90	0	15	-17.7 (3.15)		1.75%	-17.7[-23.87,-11.53]
Philip 2007 Salm 50	0	46	-11.1 (1.35)		2.09%	-11.1[-13.75,-8.45]
Richter 2002 Form 12	0	8	-19.4 (4.04)		1.55%	-19.4[-27.32,-11.48]
Richter 2002 Salm 50	0	8	-17.5 (4.17)		1.52%	-17.5[-25.67,-9.33]
Richter 2002 Terb 500	0	8	-16.6 (4.25)		1.5%	-16.6[-24.93,-8.27]
Shapiro 2002 Form 12	0	6	-20.5 (7.29)		0.94%	-20.5[-34.79,-6.21]
Shapiro 2002 Form 24	0	6	-15.4 (7.92)		0.85%	-15.4[-30.92,0.12]
Shapiro 2002 Salb 180	0	5	-21.1 (9.44)		0.68%	-21.1[-39.6,-2.6]
Sturani 1983 Fen 400	0	6	-20.2 (3.43)		1.69%	-20.2[-26.92,-13.48]
Sturani 1983 Salb 200	0	6	-12.8 (3.63)		1.64%	-12.8[-19.91,-5.69]
VanHaitsma 2010 Salb	0	10	-10.3 (5.11)		1.32%	-10.3[-20.32,-0.28]
Vasquez 1984 Salb 400	0	12	-14.6 (2.67)		1.85%	-14.6[-19.83,-9.37]
Walker 1986 Bitolterol	0	12	-18.2 (4.65)		1.42%	-18.2[-27.31,-9.09]
Wolley 1990 Terb 500	0	12	-17 (3.76)		1.61%	-17[-24.37,-9.63]
Total (95% CI)					**100%**	**-17.67[-19.51,-15.84]**
Heterogeneity: Tau²=40.01; Chi²=245.1, df=71(P<0.0001); I²=71.03%						
Test for overall effect: Z=18.91(P<0.0001)						



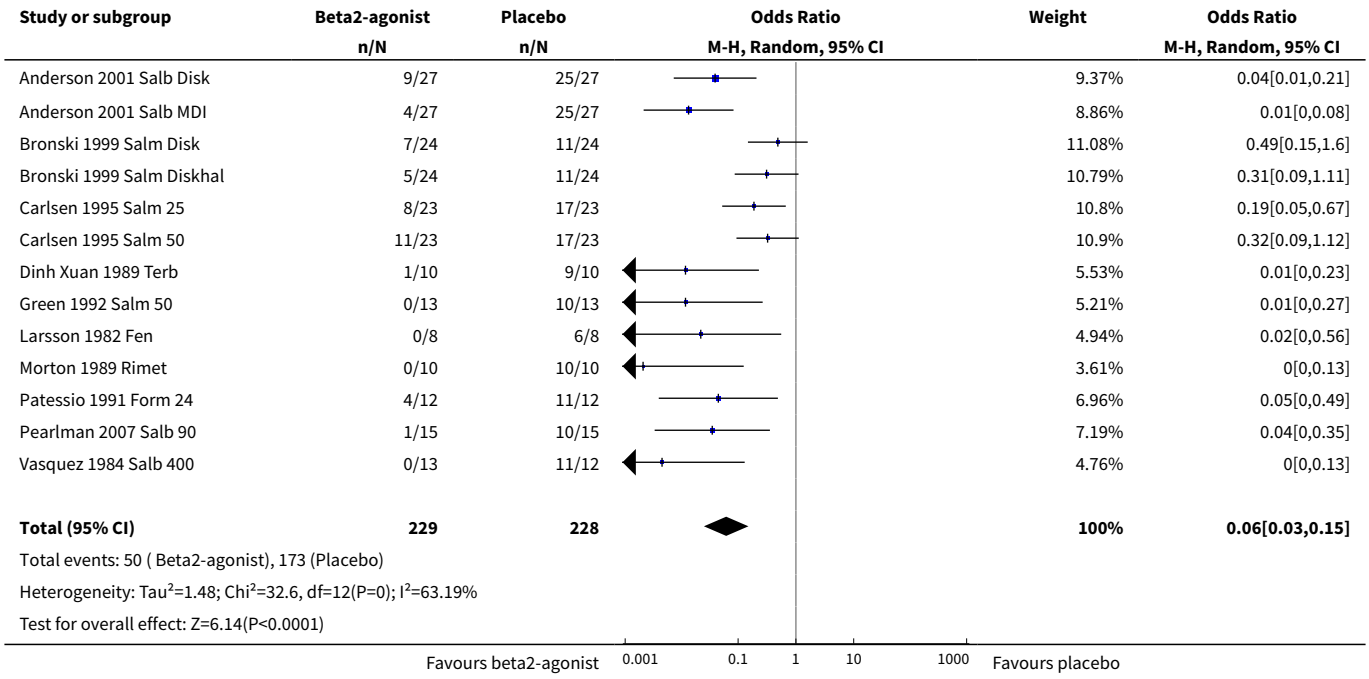
Analysis 1.2. Comparison 1 Beta$_2$-agonists versus placebo (single administration), Outcome 2 Number of participants with an FEV$_1$ fall > 10%.

Study or subgroup	Beta2-agonist n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Anderson 2001 Salb Disk	12/27	26/27		3.58%	0.03[0,0.26]
Anderson 2001 Salb MDI	9/27	26/27		3.54%	0.02[0,0.17]
Debelic 1988 Reproterol	8/16	14/16		5.04%	0.14[0.02,0.84]
DeBenedictis 1996 Salm 25	4/12	11/12		2.94%	0.05[0,0.49]
DeBenedictis 1996 Salm 50	0/12	11/12		1.56%	0.01[0,0.14]
DeBenedictis 1998 Salb	2/12	11/12		2.57%	0.02[0,0.23]
Dinh Xuan 1989 Terb	1/10	9/10		1.97%	0.01[0,0.23]
Ferrari 2000 Form 12	2/14	11/14		4.18%	0.05[0.01,0.33]
Kemp 1994 Salb	14/54	37/49		15.84%	0.11[0.05,0.28]
Kemp 1994 Salm 42	14/53	37/49		15.8%	0.12[0.05,0.28]
Konig 1981 Metaprot	20/24	24/24		1.9%	0.09[0,1.83]
Konig 1984 Fen 0.4	3/12	12/12		1.78%	0.01[0,0.32]
Konig 1984 Fen 0.8	2/12	12/12		1.71%	0.01[0,0.22]

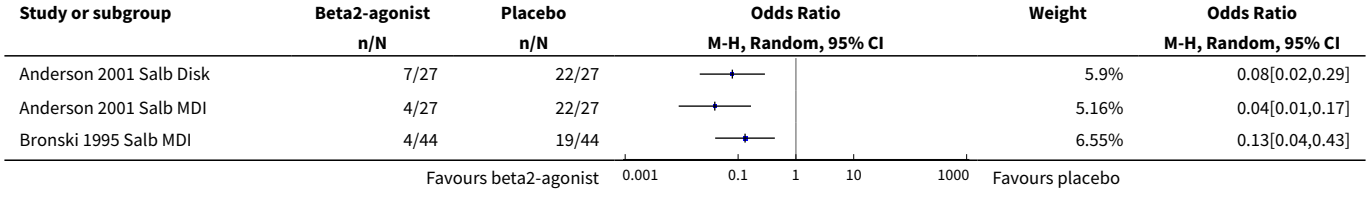




Analysis 1.3. Comparison 1 Beta$_2$-agonists versus placebo (single administration), Outcome 3 Number of participants with an FEV$_1$ fall > 15%.



Analysis 1.4. Comparison 1 Beta$_2$-agonists versus placebo (single administration), Outcome 4 Number of participants with an FEV$_1$ fall > 20%.



Study or subgroup	Beta2-agonist n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Bronski 1995 Salb Pwd	2/44	19/44		4.71%	0.06[0.01,0.29]
Bronski 1999 Salm Disk	6/24	8/24		6.15%	0.67[0.19,2.34]
Bronski 1999 Salm Diskhal	5/24	8/24		5.88%	0.53[0.14,1.93]
Bronski 2002 Form 12	3/17	15/17		3.37%	0.03[0,0.2]
Bronski 2002 Form 24	5/17	15/17		3.73%	0.06[0.01,0.34]
Bronski 2002 Salb	3/17	15/17		3.37%	0.03[0,0.2]
Dinh Xuan 1989 Terb	1/10	8/10		2.08%	0.03[0,0.37]
Hawksworth 2002 Salb HFA	9/23	21/24		5.01%	0.09[0.02,0.4]
Hawksworth 2002 Salb MDI	8/24	21/24		4.98%	0.07[0.02,0.31]
Henricksen 1983 Terb	8/14	13/14		2.55%	0.1[0.01,1.02]
Henricksen 1992 Salb	2/12	12/12		1.47%	0.01[0,0.22]
Henriksen 1992 Form 12	2/12	12/12		1.47%	0.01[0,0.22]
McFadden 1986 Salb (I)	0/15	7/15		1.62%	0.04[0,0.72]
Newnham 1993 Salb 200	4/12	12/12		1.55%	0.02[0,0.45]
Newnham 1993 Salm 50	2/12	12/12		1.47%	0.01[0,0.22]
Pearlman 2006 Form 12	5/22	16/22		5.51%	0.11[0.03,0.43]
Pearlman 2006 Form 24	6/23	16/22		5.76%	0.13[0.04,0.5]
Pearlman 2006 Salb 180	3/23	7/22		4.84%	0.32[0.07,1.45]
Pearlman 2007 Salb 90	1/15	7/15		2.6%	0.08[0.01,0.79]
Shapiro 2002 Form 12	4/19	13/17		4.57%	0.08[0.02,0.4]
Shapiro 2002 Form 24	5/17	13/17		4.75%	0.13[0.03,0.59]
Shapiro 2002 Salb 180	4/19	11/17		4.95%	0.15[0.03,0.64]
Total (95% CI)	**513**	**508**		**100%**	**0.09[0.06,0.14]**
Total events: 103 (Beta2-agonist), 344 (Placebo)					
Heterogeneity: Tau^2=0.27; Chi^2=32.96, df=24(P=0.11); I^2=27.18%					
Test for overall effect: Z=11.53(P<0.0001)					

Analysis 1.5. Comparison 1 Beta$_2$-agonists versus placebo (single administration), Outcome 5 Maximal percentage fall in PEF.

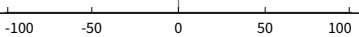
Study or subgroup	Beta2-agonist N	Placebo N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Bronski 2002 Form 12	0	6	-20 (0)			Not estimable
Bronski 2002 Form 24	0	6	-22 (0)			Not estimable
Bronski 2002 Salb	0	6	-19 (0)			Not estimable
Cavagni 1993 Salb Jet	0	4	-28.2 (0)			Not estimable
Cavagni 1993 Salb MDI	0	4	-22.3 (0)			Not estimable
Del Col 1993 Salb Jet	0	7	-12.4 (0)			Not estimable
Del Col 1993 Salb MDI	0	8	-9.8 (0)			Not estimable
Henricksen 1992 Salb	0	6	-30 (18.686)		12.52%	-30[-66.62,6.62]
Henriksen 1992 Form 12	0	6	-39 (16.8)		15.49%	-39[-71.93,-6.07]
Shapiro 2002 Form 12	0	6	-18.3 (17.328)		14.56%	-18.3[-52.26,15.66]
Shapiro 2002 Form 24	0	6	-15.5 (19.233)		11.82%	-15.5[-53.2,22.2]
Shapiro 2002 Salb 180	0	5	-14.6 (20.153)		10.76%	-14.6[-54.1,24.9]

Study or subgroup	Beta2-agonist N	Placebo N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
VanHaitsma 2010 Salb	0	10	-25.1 (11.202)		34.84%	-25.1[-47.06,-3.14]
Walker 1986 Bitolterol	0	12	-15.8 (0)			Not estimable
Total (95% CI)					**100%**	**-24.61[-37.57,-11.65]**
Heterogeneity: Tau²=0; Chi²=1.42, df=5(P=0.92); I²=0%						
Test for overall effect: Z=3.72(P=0)						

Favours beta2-agonist — Favours placebo

Analysis 1.6. Comparison 1 Beta$_2$-agonists versus placebo (single administration), Outcome 6 Maximal percentage fall in FEF 25-75.

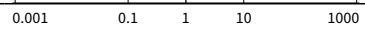
Study or subgroup	Beta2-agonist N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Cavagni 1993 Salb Jet	0	4	-35.6 (0)			Not estimable
Cavagni 1993 Salb MDI	0	4	-18.3 (0)			Not estimable
Egglestone 1981 Terb 250	0	17	-28 (5.16)		40.38%	-28[-38.11,-17.89]
Konig 1981 Metaprot	0	24	-12.1 (5.25)		39%	-12.1[-22.39,-1.81]
McFadden 1986 Salb (I)	0	15	-18 (0)			Not estimable
McFadden 1986 Salb (II)	0	20	-15.5 (0)			Not estimable
VanHaitsma 2010 Salb	0	10	-22.9 (7.22)		20.62%	-22.9[-37.05,-8.75]
Walker 1986 Bitolterol	0	12	-27.8 (0)			Not estimable
Total (95% CI)					**100%**	**-20.75[-27.17,-14.32]**
Heterogeneity: Tau²=0; Chi²=4.78, df=2(P=0.09); I²=58.14%						
Test for overall effect: Z=6.33(P<0.0001)						



Favours beta2-agonist — Favours placebo

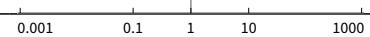
Analysis 1.7. Comparison 1 Beta$_2$-agonists versus placebo (single administration), Outcome 7 Side effects.

Study or subgroup	Beta2-agonist n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Blake 1999 Salb 180	0/24	0/23			Not estimable
Blake 1999 Salm 25	0/25	0/23			Not estimable
Blake 1999 Salm 50	0/24	0/23			Not estimable
Boner 1994 Form 12	0/15	0/15			Not estimable
Boner 1994 Salb 200	0/15	0/15			Not estimable
Bronski 1995 Salb MDI	0/46	0/46			Not estimable
Bronski 1995 Salb Pwd	0/46	0/46			Not estimable
Bronski 1999 Salm Disk	0/24	0/24			Not estimable
Bronski 1999 Salm Diskhal	0/24	0/24			Not estimable
Bronski 2002 Form 12	6/17	6/18		11.67%	1.09[0.27,4.41]
Bronski 2002 Form 24	4/17	6/18		10.88%	0.62[0.14,2.73]
Bronski 2002 Salb	1/17	6/18		6.33%	0.13[0.01,1.18]
Cavagni 1993 Salb Jet	0/8	0/8			Not estimable



Favours beta2-agonist — Favours placebo

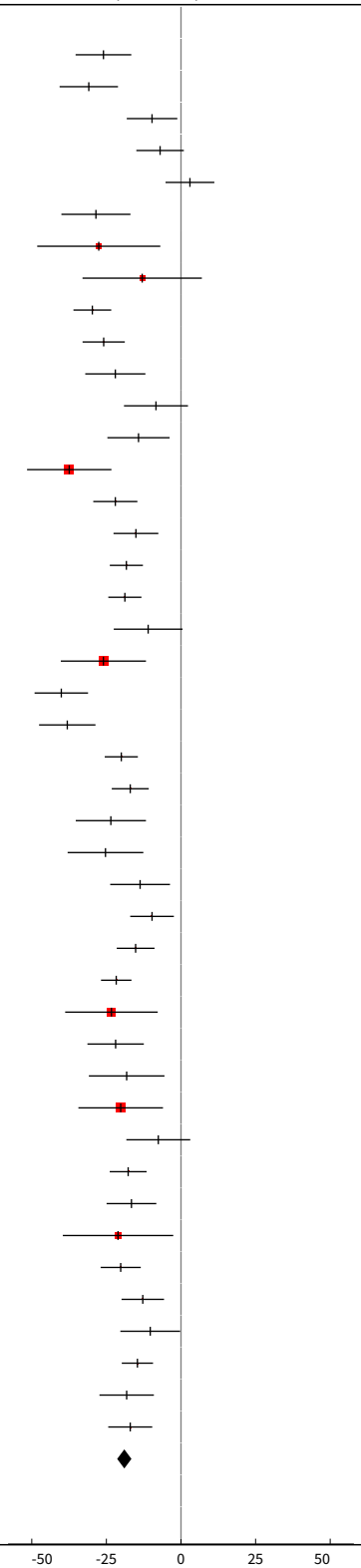
Study or subgroup	Beta2-agonist n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Cavagni 1993 Salb MDI	0/9	0/9			Not estimable
Debelic 1988 Reproterol	0/16	0/16			Not estimable
DeBenedictis 1996 Salm 25	0/12	0/12			Not estimable
DeBenedictis 1996 Salm 50	0/12	0/12			Not estimable
DeBenedictis 1998 Salb	0/12	0/12			Not estimable
Del Col 1993 Salb Jet	0/15	0/15			Not estimable
Del Col 1993 Salb MDI	0/15	0/15			Not estimable
Egglestone 1981 Terb 250	0/17	0/17			Not estimable
Ferrari 2000 Form 12	0/14	0/14			Not estimable
Green 1992 Salm 50	0/13	0/13			Not estimable
Gronnerod 2000 Form 4.5	0/27	0/27			Not estimable
Gronnerod 2000 Form 9	0/27	0/27			Not estimable
Gronnerod 2000 Terb 500	0/27	0/27			Not estimable
Hawksworth 2002 Salb HFA	0/23	0/24			Not estimable
Hawksworth 2002 Salb MDI	0/24	0/24			Not estimable
Henricksen 1983 Terb	0/14	0/14			Not estimable
Henricksen 1992 Salb	0/12	0/12			Not estimable
Henriksen 1992 Form 12	0/12	0/12			Not estimable
Kemp 1994 Salb	0/54	1/52		3.53%	0.31[0.01,7.91]
Kemp 1994 Salm 42	6/55	1/52		6.73%	6.24[0.73,53.77]
Konig 1981 Metaprot	1/24	1/24		4.39%	1[0.06,16.97]
Konig 1984 Fen 0.4	1/12	0/12		3.39%	3.26[0.12,88.35]
Konig 1984 Fen 0.8	2/12	0/12		3.68%	5.95[0.26,138.25]
McAlpine 1990 Form 12	0/11	0/11			Not estimable
McAlpine 1990 Salb	0/11	0/11			Not estimable
McFadden 1986 Salb (I)	0/15	0/15			Not estimable
McFadden 1986 Salb (II)	0/20	0/20			Not estimable
Morton 1989 Rimet	0/10	0/10			Not estimable
Newnham 1993 Salb 200	0/12	0/12			Not estimable
Newnham 1993 Salm 50	0/12	0/12			Not estimable
Patessio 1991 Form 24	0/12	0/12			Not estimable
Patessio 1991 Salb 200	0/12	0/12			Not estimable
Pearlman 2006 Form 12	0/23	0/23			Not estimable
Pearlman 2006 Form 24	0/23	0/23			Not estimable
Pearlman 2006 Salb 180	0/23	0/23			Not estimable
Pearlman 2007 Salb 90	0/15	0/15			Not estimable
Philip 2007 Salm 50	2/46	7/46		9.78%	0.25[0.05,1.29]
Shapiro 2002 Form 12	7/19	7/19		12.39%	1[0.27,3.74]
Shapiro 2002 Form 24	1/17	7/19		6.41%	0.11[0.01,0.99]
Shapiro 2002 Salb 180	5/19	7/19		11.79%	0.61[0.15,2.44]
Walker 1986 Bitolterol	9/12	5/12		9.02%	4.2[0.74,23.91]
Wolley 1990 Terb 500	0/12	0/12			Not estimable
Total (95% CI)	**1084**	**1081**		**100%**	**0.83[0.43,1.59]**
Total events: 45 (Beta2-agonist), 54 (Placebo)					
Heterogeneity: Tau^2=0.45; Chi^2=17.83, df=12(P=0.12); I^2=32.7%					
Test for overall effect: Z=0.58(P=0.56)					

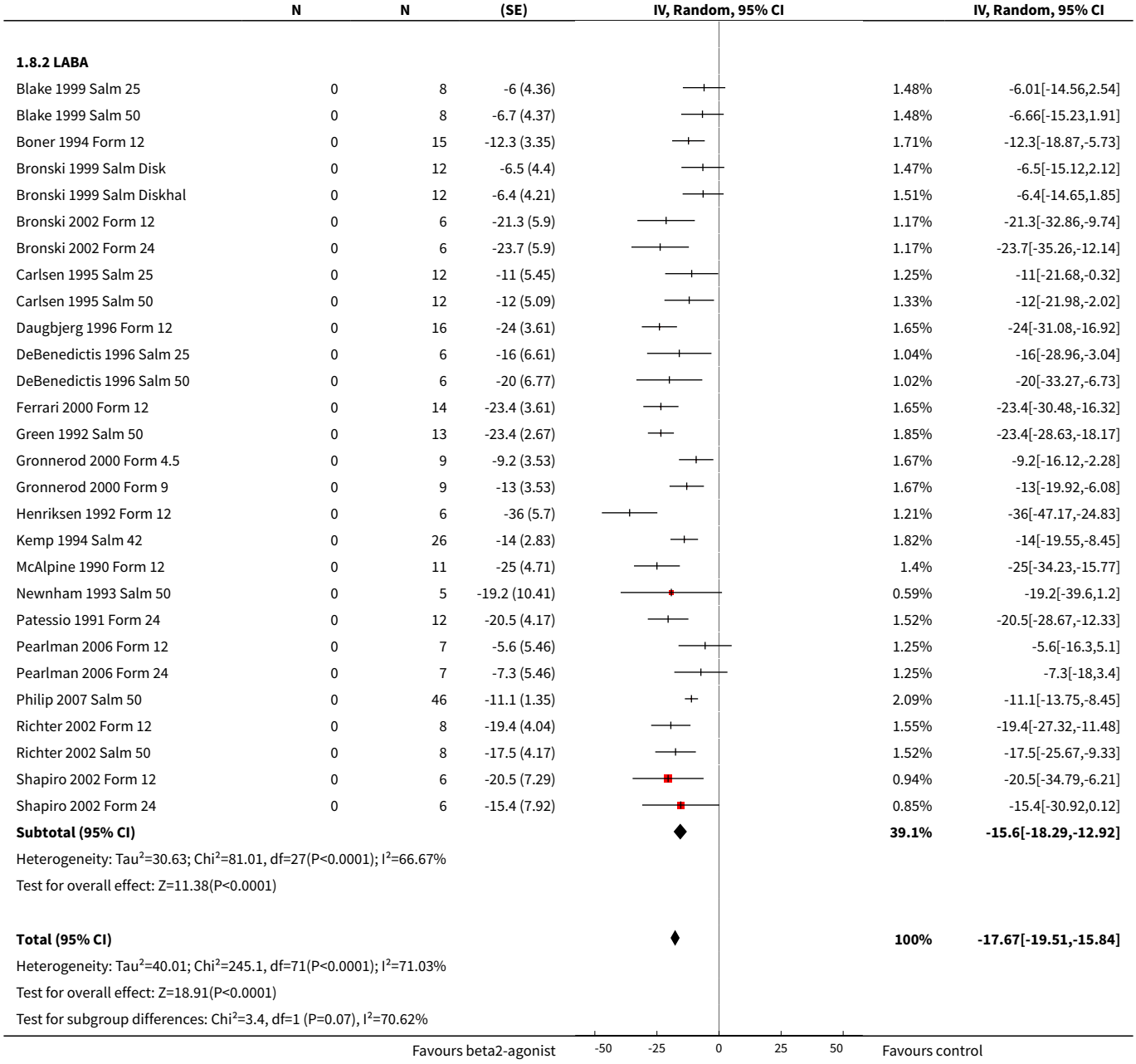


Favours beta2-agonist Favours placebo

Analysis 1.8. Comparison 1 Beta$_2$-agonists versus placebo (single administration), Outcome 8 Subgroup analysis: maximal percentage fall in FEV$_1$ SABA vs LABA.

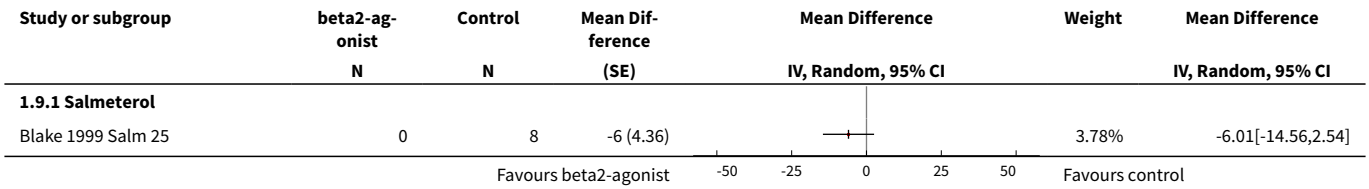
Study or subgroup	beta2-agonist N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.8.1 SABA						
Anderson 2001 Salb Disk	0	14	-26 (4.76)		1.39%	-25.98[-35.31,-16.65]
Anderson 2001 Salb MDI	0	13	-30.9 (4.99)		1.35%	-30.89[-40.67,-21.11]
Blake 1999 Salb 180	0	8	-9.7 (4.32)		1.49%	-9.7[-18.17,-1.23]
Bronski 1995 Salb MDI	0	22	-7 (4.06)		1.55%	-7[-14.96,0.96]
Bronski 1995 Salb Pwd	0	22	3 (4.17)		1.52%	3[-5.17,11.17]
Bronski 2002 Salb	0	6	-28.5 (5.9)		1.17%	-28.5[-40.06,-16.94]
Cavagni 1993 Salb Jet	0	4	-27.5 (10.52)		0.58%	-27.55[-48.17,-6.93]
Cavagni 1993 Salb MDI	0	4	-13 (10.2)		0.61%	-13[-32.99,6.99]
Clarke 1990 Fen	0	20	-29.7 (3.23)		1.73%	-29.7[-36.03,-23.37]
Debelic 1988 Reproterol	0	16	-25.9 (3.61)		1.65%	-25.9[-32.98,-18.82]
DeBenedictis 1998 Salb	0	12	-22 (5.14)		1.32%	-22[-32.07,-11.93]
Del Col 1993 Salb Jet	0	7	-8.4 (5.47)		1.25%	-8.38[-19.1,2.34]
Del Col 1993 Salb MDI	0	8	-14.2 (5.32)		1.28%	-14.23[-24.66,-3.8]
Dinh Xuan 1989 Terb	0	10	-37.4 (7.21)		0.95%	-37.44[-51.57,-23.31]
Egglestone 1981 Terb 250	0	17	-22 (3.77)		1.61%	-22[-29.39,-14.61]
Gronnerod 2000 Terb 500	0	9	-15.1 (3.83)		1.6%	-15.1[-22.61,-7.59]
Hawksworth 2002 Salb HFA	0	12	-18.3 (2.83)		1.82%	-18.3[-23.85,-12.75]
Hawksworth 2002 Salb MDI	0	12	-18.8 (2.83)		1.82%	-18.8[-24.35,-13.25]
Henricksen 1983 Terb	0	14	-11 (5.88)		1.17%	-11[-22.52,0.52]
Henricksen 1992 Salb	0	6	-26 (7.28)		0.94%	-26[-40.27,-11.73]
Hills 1976 Salb	0	10	-40.1 (4.57)		1.43%	-40.1[-49.06,-31.14]
Hills 1976 Salmefamol	0	9	-38.1 (4.82)		1.38%	-38.1[-47.55,-28.65]
Kemp 1994 Salb	0	26	-20 (2.83)		1.82%	-20[-25.55,-14.45]
Konig 1981 Metaprot	0	24	-17 (3.16)		1.75%	-17[-23.19,-10.81]
Konig 1984 Fen 0.4	0	6	-23.5 (6)		1.15%	-23.5[-35.26,-11.74]
Konig 1984 Fen 0.8	0	6	-25.3 (6.47)		1.07%	-25.3[-37.98,-12.62]
Larsson 1982 Fen	0	8	-13.7 (5.11)		1.32%	-13.7[-23.72,-3.68]
McFadden 1986 Salb (I)	0	15	-9.7 (3.73)		1.62%	-9.7[-17.01,-2.39]
McFadden 1986 Salb (II)	0	20	-15.2 (3.23)		1.73%	-15.2[-21.53,-8.87]
Morton 1989 Rimet	0	10	-21.7 (2.6)		1.87%	-21.7[-26.8,-16.6]
Newnham 1993 Salb 200	0	6	-23.3 (7.91)		0.85%	-23.3[-38.8,-7.8]
Patel 1986 Salb 200	0	9	-21.9 (4.82)		1.38%	-21.9[-31.35,-12.45]
Patel 1986 Tulob 200	0	5	-18.2 (6.46)		1.07%	-18.2[-30.86,-5.54]
Patel 1986 Tulob 400	0	4	-20.2 (7.23)		0.95%	-20.2[-34.37,-6.03]
Pearlman 2006 Salb 180	0	7	-7.6 (5.46)		1.25%	-7.6[-18.3,3.1]
Pearlman 2007 Salb 90	0	15	-17.7 (3.15)		1.75%	-17.7[-23.87,-11.53]
Richter 2002 Terb 500	0	8	-16.6 (4.25)		1.5%	-16.6[-24.93,-8.27]
Shapiro 2002 Salb 180	0	5	-21.1 (9.44)		0.68%	-21.1[-39.6,-2.6]
Sturani 1983 Fen 400	0	6	-20.2 (3.43)		1.69%	-20.2[-26.92,-13.48]
Sturani 1983 Salb 200	0	6	-12.8 (3.63)		1.64%	-12.8[-19.91,-5.69]
VanHaitsma 2010 Salb	0	10	-10.3 (5.11)		1.32%	-10.3[-20.32,-0.28]
Vasquez 1984 Salb 400	0	12	-14.6 (2.67)		1.85%	-14.6[-19.83,-9.37]
Walker 1986 Bitolterol	0	12	-18.2 (4.65)		1.42%	-18.2[-27.31,-9.09]
Wolley 1990 Terb 500	0	12	-17 (3.76)		1.61%	-17[-24.37,-9.63]
Subtotal (95% CI)					**60.9%**	**-18.99[-21.38,-16.6]**
Heterogeneity: Tau^2=42.36; Chi^2=146.28, df=43(P<0.0001); I^2=70.6%						
Test for overall effect: Z=15.55(P<0.0001)						





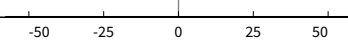
Study or subgroup	beta2-agonist N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.8.2 LABA						
Blake 1999 Salm 25	0	8	-6 (4.36)		1.48%	-6.01[-14.56,2.54]
Blake 1999 Salm 50	0	8	-6.7 (4.37)		1.48%	-6.66[-15.23,1.91]
Boner 1994 Form 12	0	15	-12.3 (3.35)		1.71%	-12.3[-18.87,-5.73]
Bronski 1999 Salm Disk	0	12	-6.5 (4.4)		1.47%	-6.5[-15.12,2.12]
Bronski 1999 Salm Diskhal	0	12	-6.4 (4.21)		1.51%	-6.4[-14.65,1.85]
Bronski 2002 Form 12	0	6	-21.3 (5.9)		1.17%	-21.3[-32.86,-9.74]
Bronski 2002 Form 24	0	6	-23.7 (5.9)		1.17%	-23.7[-35.26,-12.14]
Carlsen 1995 Salm 25	0	12	-11 (5.45)		1.25%	-11[-21.68,-0.32]
Carlsen 1995 Salm 50	0	12	-12 (5.09)		1.33%	-12[-21.98,-2.02]
Daugbjerg 1996 Form 12	0	16	-24 (3.61)		1.65%	-24[-31.08,-16.92]
DeBenedictis 1996 Salm 25	0	6	-16 (6.61)		1.04%	-16[-28.96,-3.04]
DeBenedictis 1996 Salm 50	0	6	-20 (6.77)		1.02%	-20[-33.27,-6.73]
Ferrari 2000 Form 12	0	14	-23.4 (3.61)		1.65%	-23.4[-30.48,-16.32]
Green 1992 Salm 50	0	13	-23.4 (2.67)		1.85%	-23.4[-28.63,-18.17]
Gronnerod 2000 Form 4.5	0	9	-9.2 (3.53)		1.67%	-9.2[-16.12,-2.28]
Gronnerod 2000 Form 9	0	9	-13 (3.53)		1.67%	-13[-19.92,-6.08]
Henriksen 1992 Form 12	0	6	-36 (5.7)		1.21%	-36[-47.17,-24.83]
Kemp 1994 Salm 42	0	26	-14 (2.83)		1.82%	-14[-19.55,-8.45]
McAlpine 1990 Form 12	0	11	-25 (4.71)		1.4%	-25[-34.23,-15.77]
Newnham 1993 Salm 50	0	5	-19.2 (10.41)		0.59%	-19.2[-39.6,1.2]
Patessio 1991 Form 24	0	12	-20.5 (4.17)		1.52%	-20.5[-28.67,-12.33]
Pearlman 2006 Form 12	0	7	-5.6 (5.46)		1.25%	-5.6[-16.3,5.1]
Pearlman 2006 Form 24	0	7	-7.3 (5.46)		1.25%	-7.3[-18,3.4]
Philip 2007 Salm 50	0	46	-11.1 (1.35)		2.09%	-11.1[-13.75,-8.45]
Richter 2002 Form 12	0	8	-19.4 (4.04)		1.55%	-19.4[-27.32,-11.48]
Richter 2002 Salm 50	0	8	-17.5 (4.17)		1.52%	-17.5[-25.67,-9.33]
Shapiro 2002 Form 12	0	6	-20.5 (7.29)		0.94%	-20.5[-34.79,-6.21]
Shapiro 2002 Form 24	0	6	-15.4 (7.92)		0.85%	-15.4[-30.92,0.12]
Subtotal (95% CI)					**39.1%**	**-15.6[-18.29,-12.92]**
Heterogeneity: Tau^2=30.63; Chi^2=81.01, df=27(P<0.0001); I^2=66.67%						
Test for overall effect: Z=11.38(P<0.0001)						
Total (95% CI)					**100%**	**-17.67[-19.51,-15.84]**
Heterogeneity: Tau^2=40.01; Chi^2=245.1, df=71(P<0.0001); I^2=71.03%						
Test for overall effect: Z=18.91(P<0.0001)						
Test for subgroup differences: Chi^2=3.4, df=1 (P=0.07), I^2=70.62%						

Analysis 1.9. Comparison 1 $Beta_2$-agonists versus placebo (single administration), Outcome 9 Subgroup analysis: maximal percentage fall in FEV_1: salmeterol versus formoterol.



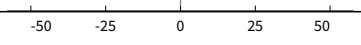
Study or subgroup	beta2-agonist N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.9.1 Salmeterol						
Blake 1999 Salm 25	0	8	-6 (4.36)		3.78%	-6.01[-14.56,2.54]

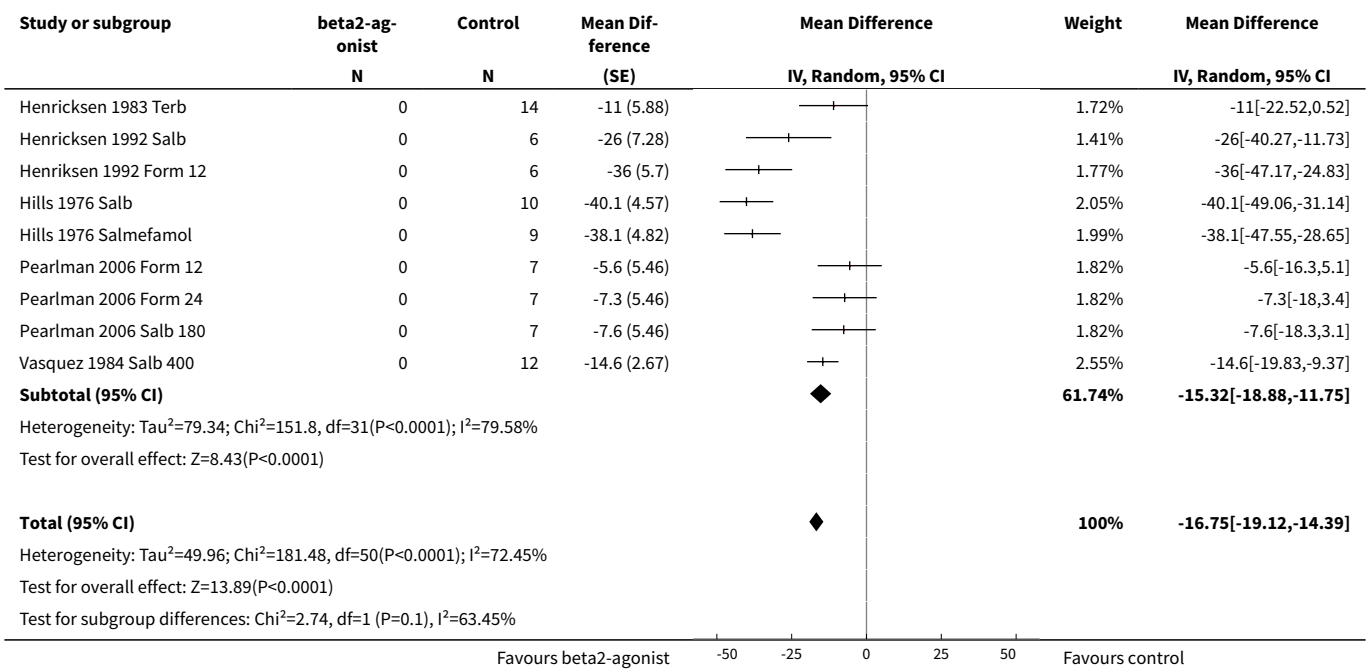
Study or subgroup	beta2-agonist N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Blake 1999 Salm 50	0	8	-6.7 (4.37)		3.78%	-6.66[-15.23,1.91]
Bronski 1999 Salm Disk	0	12	-6.5 (4.4)		3.76%	-6.5[-15.12,2.12]
Bronski 1999 Salm Diskhal	0	12	-6.4 (4.21)		3.89%	-6.4[-14.65,1.85]
Carlsen 1995 Salm 25	0	12	-11 (5.45)		3.11%	-11[-21.68,-0.32]
Carlsen 1995 Salm 50	0	12	-12 (5.09)		3.32%	-12[-21.98,-2.02]
DeBenedictis 1996 Salm 25	0	6	-16 (6.61)		2.53%	-16[-28.96,-3.04]
DeBenedictis 1996 Salm 50	0	6	-20 (6.77)		2.46%	-20[-33.27,-6.73]
Green 1992 Salm 50	0	13	-23.4 (2.67)		4.98%	-23.4[-28.63,-18.17]
Kemp 1994 Salm 42	0	26	-14 (2.83)		4.86%	-14[-19.55,-8.45]
Newnham 1993 Salm 50	0	5	-19.2 (10.41)		1.35%	-19.2[-39.6,1.2]
Philip 2007 Salm 50	0	46	-11.1 (1.35)		5.79%	-11.1[-13.75,-8.45]
Richter 2002 Salm 50	0	8	-17.5 (4.17)		3.91%	-17.5[-25.67,-9.33]
Subtotal (95% CI)					**47.52%**	**-12.73[-16.1,-9.37]**
Heterogeneity: Tau²=18.97; Chi²=29.4, df=12(P=0); I²=59.19%						
Test for overall effect: Z=7.41(P<0.0001)						
1.9.2 Formoterol						
Boner 1994 Form 12	0	15	-12.3 (3.35)		4.49%	-12.3[-18.87,-5.73]
Bronski 2002 Form 12	0	6	-21.3 (5.9)		2.87%	-21.3[-32.86,-9.74]
Bronski 2002 Form 24	0	6	-23.7 (5.9)		2.87%	-23.7[-35.26,-12.14]
Daugbjerg 1996 Form 12	0	16	-24 (3.61)		4.3%	-24[-31.08,-16.92]
Ferrari 2000 Form 12	0	14	-23.4 (3.61)		4.3%	-23.4[-30.48,-16.32]
Gronnerod 2000 Form 4.5	0	9	-9.2 (3.53)		4.36%	-9.2[-16.12,-2.28]
Gronnerod 2000 Form 9	0	9	-13 (3.53)		4.36%	-13[-19.92,-6.08]
Henriksen 1992 Form 12	0	6	-36 (5.7)		2.98%	-36[-47.17,-24.83]
McAlpine 1990 Form 12	0	11	-25 (4.71)		3.56%	-25[-34.23,-15.77]
Patessio 1991 Form 24	0	12	-20.5 (4.17)		3.91%	-20.5[-28.67,-12.33]
Pearlman 2006 Form 12	0	7	-5.6 (5.46)		3.11%	-5.6[-16.3,5.1]
Pearlman 2006 Form 24	0	7	-7.3 (5.46)		3.11%	-7.3[-18,3.4]
Richter 2002 Form 12	0	8	-19.4 (4.04)		4%	-19.4[-27.32,-11.48]
Shapiro 2002 Form 12	0	6	-20.5 (7.29)		2.24%	-20.5[-34.79,-6.21]
Shapiro 2002 Form 24	0	6	-15.4 (7.92)		2.01%	-15.4[-30.92,0.12]
Subtotal (95% CI)					**52.48%**	**-18.24[-22.15,-14.34]**
Heterogeneity: Tau²=36.3; Chi²=39.22, df=14(P=0); I²=64.3%						
Test for overall effect: Z=9.15(P<0.0001)						
Total (95% CI)					**100%**	**-15.6[-18.29,-12.92]**
Heterogeneity: Tau²=30.63; Chi²=81.01, df=27(P<0.0001); I²=66.67%						
Test for overall effect: Z=11.38(P<0.0001)						
Test for subgroup differences: Chi²=4.39, df=1 (P=0.04), I²=77.21%						



Analysis 1.10. Comparison 1 Beta$_2$-agonists versus placebo (single administration), Outcome 10 Subgroup analysis: maximal percentage fall in FEV$_1$: adults versus children.

Study or subgroup	beta2-agonist N	Control N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
1.10.1 Adults						
Anderson 2001 Salb Disk	0	14	-26 (4.76)		2%	-25.98[-35.31,-16.65]
Anderson 2001 Salb MDI	0	13	-30.9 (4.99)		1.94%	-30.89[-40.67,-21.11]
Egglestone 1981 Terb 250	0	17	-22 (3.77)		2.27%	-22[-29.39,-14.61]
Hawksworth 2002 Salb HFA	0	12	-18.3 (2.83)		2.51%	-18.3[-23.85,-12.75]
Hawksworth 2002 Salb MDI	0	12	-18.8 (2.83)		2.51%	-18.8[-24.35,-13.25]
Larsson 1982 Fen	0	8	-13.7 (5.11)		1.91%	-13.7[-23.72,-3.68]
McAlpine 1990 Form 12	0	11	-25 (4.71)		2.02%	-25[-34.23,-15.77]
McFadden 1986 Salb (I)	0	15	-9.7 (3.73)		2.28%	-9.7[-17.01,-2.39]
McFadden 1986 Salb (II)	0	20	-15.2 (3.23)		2.41%	-15.2[-21.53,-8.87]
Newnham 1993 Salb 200	0	6	-23.3 (7.91)		1.29%	-23.3[-38.8,-7.8]
Newnham 1993 Salm 50	0	5	-19.2 (10.41)		0.92%	-19.2[-39.6,1.2]
Patel 1986 Salb 200	0	9	-21.9 (4.82)		1.99%	-21.9[-31.35,-12.45]
Patel 1986 Tulob 200	0	5	-18.2 (6.46)		1.59%	-18.2[-30.86,-5.54]
Patel 1986 Tulob 400	0	4	-20.2 (7.23)		1.42%	-20.2[-34.37,-6.03]
Pearlman 2007 Salb 90	0	15	-17.7 (3.15)		2.43%	-17.7[-23.87,-11.53]
Richter 2002 Form 12	0	8	-19.4 (4.04)		2.2%	-19.4[-27.32,-11.48]
Richter 2002 Salm 50	0	8	-17.5 (4.17)		2.16%	-17.5[-25.67,-9.33]
Richter 2002 Terb 500	0	8	-16.6 (4.25)		2.14%	-16.6[-24.93,-8.27]
Wolley 1990 Terb 500	0	12	-17 (3.76)		2.27%	-17[-24.37,-9.63]
Subtotal (95% CI)					**38.26%**	**-18.77[-20.78,-16.76]**
Heterogeneity: Tau^2=2.25; Chi^2=20.33, df=18(P=0.31); I^2=11.46%						
Test for overall effect: Z=18.31(P<0.0001)						
1.10.2 Children						
Blake 1999 Salb 180	0	8	-9.7 (4.32)		2.12%	-9.7[-18.17,-1.23]
Blake 1999 Salm 25	0	8	-6 (4.36)		2.11%	-6.01[-14.56,2.54]
Blake 1999 Salm 50	0	8	-6.7 (4.37)		2.11%	-6.66[-15.23,1.91]
Boner 1994 Form 12	0	15	-12.3 (3.35)		2.38%	-12.3[-18.87,-5.73]
Bronski 1995 Salb MDI	0	22	-7 (4.06)		2.19%	-7[-14.96,0.96]
Bronski 1995 Salb Pwd	0	22	3 (4.17)		2.16%	3[-5.17,11.17]
Bronski 1999 Salm Disk	0	12	-6.5 (4.4)		2.1%	-6.5[-15.12,2.12]
Bronski 1999 Salm Diskhal	0	12	-6.4 (4.21)		2.15%	-6.4[-14.65,1.85]
Carlsen 1995 Salm 25	0	12	-11 (5.45)		1.83%	-11[-21.68,-0.32]
Carlsen 1995 Salm 50	0	12	-12 (5.09)		1.92%	-12[-21.98,-2.02]
Cavagni 1993 Salb Jet	0	4	-27.5 (10.52)		0.91%	-27.55[-48.17,-6.93]
Cavagni 1993 Salb MDI	0	4	-13 (10.2)		0.94%	-13[-32.99,6.99]
Daugbjerg 1996 Form 12	0	16	-24 (3.61)		2.31%	-24[-31.08,-16.92]
DeBenedictis 1996 Salm 25	0	6	-16 (6.61)		1.55%	-16[-28.96,-3.04]
DeBenedictis 1996 Salm 50	0	6	-20 (6.77)		1.52%	-20[-33.27,-6.73]
DeBenedictis 1998 Salb	0	12	-22 (5.14)		1.91%	-22[-32.07,-11.93]
Del Col 1993 Salb Jet	0	7	-8.4 (5.47)		1.82%	-8.38[-19.1,2.34]
Del Col 1993 Salb MDI	0	8	-14.2 (5.32)		1.86%	-14.23[-24.66,-3.8]
Dinh Xuan 1989 Terb	0	10	-37.4 (7.21)		1.43%	-37.44[-51.57,-23.31]
Green 1992 Salm 50	0	13	-23.4 (2.67)		2.55%	-23.4[-28.63,-18.17]
Gronnerod 2000 Form 4.5	0	9	-9.2 (3.53)		2.33%	-9.2[-16.12,-2.28]
Gronnerod 2000 Form 9	0	9	-13 (3.53)		2.33%	-13[-19.92,-6.08]
Gronnerod 2000 Terb 500	0	9	-15.1 (3.83)		2.25%	-15.1[-22.61,-7.59]





ADDITIONAL TABLES

Table 1. Summary of study interventions

Study	Intervention (single dose)	Study type (single-dose test or chronic [duration])	When administered before challenge/exercise (min, h)
Anderson 2001 Salb Disk;	Salbutamol diskus 200 mcg	Single dose	30 min
Anderson 2001 Salb MDI	Salbutamol MDI		
Blake 1999 Salb 180	Albuterol 180 mcg	Single dose	30 min, 5 h 30, 11 h 30
Blake 1999 Salm 25	Salmeterol diskus 25 mcg		
Blake 1999 Salm 50	Salmeterol diskus 50 mcg		
Boner 1994 Salb 200	Salbutamol 200 mcg	Single dose	3 h, 12 h
Boner 1994 Form 12	Formoterol 12 mcg		
Boulet 1989 Salb	Salbutamol 200 mcg	Single dose	30 min
Bronski 1995 Salb MDI	Albuterol MDI 180 mcg	Single dose	15 min
Bronski 1995 Salb Pwd	Albuterol rotacaps 200 mcg		
Bronski 1999 Salm Disk	Salmetrol discus 50 mcg	Single dose	30 min, 5 h 30, 11 h 30
Bronski 1999 Salm Diskhal	Salmeterol diskhaler 50 mcg		

Table 1. Summary of study interventions *(Continued)*

Bronski 2002 Salb	Albuterol 180 mcg	Single dose	15 min, 4 h, 8 h, 12 h
Bronski 2002 Form 12	Formoterol 12 mcg		
Bronski 2002 Form 24	Formoterol 24 mcg		
Carlsen 1995 Salm 25	Salmeterol diskhaler 25 mcg	Single dose	10-12 h
Carlsen 1995 Salm 50	Salmeterol diskhaler 50 mcg		
Cavagni 1993 Salb MDI	Salbutamol MDI 200 mcg	Single dose	10 min
Cavagni 1993 Salb Jet	Salbutamol jet disposable 200 mcg		
Clarke 1990 Fen	Fenoterol 100 mcg	Single dose	10 min
Daugbjerg 1996 Salb	Salbutamol 400 mcg	Single dose	3 h, 12 h
Daugbjerg 1996 Form 12	Formoterol 12 mcg		
Debelic 1988 Reproterol	Reproterol 1 mg	Single dose	15 min
DeBenedictis 1996 Salm 25	Salmeterol 25 mcg	Single dose	1 h, 2 h
DeBenedictis 1996 Salm 50	Salmeterol 50 mcg		
DeBenedictis 1998 Salb	Salbutamol 200 mcg	Single dose	20 min
Del Col 1993 Salb MDI	Salbutamol MDI 200 mcg	Single dose	10 min
Del Col 1993 Salb Jet	Salbutamol jet device 200 mcg		
Dinh Xuan 1989 Terb	Terbutaline 500 mcg	Single dose	15 min
Egglestone 1981 Terb 250	Terbutaline 250 mcg	Single dose	1 h
Ferrari 2000 Form 12	Formoterol 12 mcg	Single dose	15 min, 4 h
Garcia 2001 Form 12	Formoterol 12 mcg twice daily	Long-term (4 weeks)	30 min, 12 h at days 1, 14 and 28
Green 1992 Salm 50	Salmeterol 50 mcg	Single dose	1 h, 5 h, 9 h
Gronnerod 2000 Terb 500	Terbutaline 500 mcg	Single dose	15 min, 4 h, 8 h
Gronnerod 2000 Form 9	Formoterol 9 mcg		
Gronnerod 2000 Form 4.5	Formoterol 4.5 mcg		
Hancox 2002	Salbutamol 800 mcg daily	Long-term (1 week)	8 h
Hawksworth 2002 Salb HFA	Salbutamol 180 HFA	Single dose	30 min
Hawksworth 2002 Salb MDI	Salbutamol 180 mcg MDI		
Henricksen 1983 Terb	Terbutaline 32.5 mcg	Single dose	15 min
Henricksen 1992 Salb	Salbutamol 200 mcg	Single dose	30 min, 3 h, 5 h 30, 8 h
Henriksen 1992 Form 12	Formoterol 12 mcg		

Table 1. Summary of study interventions *(Continued)*

Hills 1976 Salb	Salbutamol 200 mcg	Single dose	20 min
Hills 1976 Salmefamol	Salmefamol 200 mcg		
Inman 1996	Salbutamol 800 mcg daily	Long-term (81 weeks)	24 h
Kemp 1994 Salb	Salbutamol 180 mcg	Single dose	30 min, 5 h 30, 11 h 30
Kemp 1994 Salm 42	Salmeterol 42 mcg		
Konig 1981 Metaprot	Metaproterenol 130 mcg	Single dose	10 min, 1 h
Larsson 1982 Fen	Fenoterol 400 mcg	Single dose	10 min
McAlpine 1990 Salb	Salbutamol 200 mcg	Single dose	2 h, 4 h
McAlpine 1990 Form 12	Formoterol 12 mcg		
McFadden 1986 Salb (I)	Salbutamol 200 mcg	Single dose	15 min
McFadden 1986 Salb (II)	Salbutamol 180 mcg	Single dose	15 min
Morton 1989 Rimet	Rimeterol 400 mcg	Single dose	2 min
Nelson 1998	Salmeterol 84 mcg daily	Long-term (29 days)	30 min, 9 h
Newnham 1993 Salb 200	Salbutamol 200 mcg	Single dose	1 h, 6 h, 12 h
Newnham 1993 Salm 50	Salmeterol 50 mcg		
Patel 1986 Salb 200	Salbutamol 200 mcg	Single dose	20 min
Patel 1986 Tulob 200	Tolobuterol 200 mcg		
Patel 1986 Tulob 400	Tolobuterol 400 mcg		
Patessio 1991 Salb 200	Salbutamol 200 mcg	Single dose	2 h, 8 h
Patessio 1991 Form 24	Formoterol 24 mcg		
Pearlman 2006 Salb 180	Salbutamol 180 mcg	Single dose	15 min, 4 h, 8 h, 12 h
Pearlman 2006 Form 12	Formoterol 12 mcg		
Pearlman 2006 Form 24	Formoterol 24 mcg		
Pearlman 2007 Salb 90	Salbutamol 90 mcg	Single dose	20 min
Philip 2007 Salm 50	Salmeterol 50 mcg	Single dose	2 h, 8 h 30, 24 h
Ramage 1994	Salmeterol 100 mcg daily	Long-term (28 days)	6 h, 12 h
Richter 2002 Terb 500	Terbutaline 500 mcg	Single dose	5 min, 30 min, 1 h
Richter 2002 Form 12	Formoterol 12 mcg		
Richter 2002 Salm 50	Salmeterol 50 mcg		

Table 1. Summary of study interventions *(Continued)*

Shapiro 2002	Salbutamol 180 mcg Formoterol 12 mcg Formoterol 24 mcg	Single dose	15 min, 4 h, 8 h, 12 h
Simons 1997	Salmeterol 50 mcg	Long-term (28 weeks)	1 h, 9 h
Stelmach 2008	Formoterol 9 mcg daily	Long-term (28 weeks)	1 h, 9 h
Storms 2004	Salmeterol 100 mcg daily	Long-term (28 weeks)	1 h, 9 h
Sturani 1983 Fen 400 Sturani 1983 Salb 200	Fenoterol 400 mcg Salbutamol 200 mcg	Single dose	30 min
VanHaitsma 2010 Salb	Salbutamol 180 mcg	Single dose	15 min
Vasquez 1984 Salb 400	Salbutamol 400 mcg	Single dose	15 min
Walker 1986 Bitolterol	Bitolterol 1050 mcg	Single dose	45 min
Wolley 1990 Terb 500	Terbutaline 500 mcg	Single dose	25 min, 2 h, 4 h, 6 h

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
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 & 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

Asthma search

1. exp Asthma/

2. asthma$.mp.

3. (antiasthma$ or anti-asthma$).mp.

4. Respiratory Sounds/

5. wheez$.mp.

6. Bronchial Spasm/

7. bronchospas$.mp.

8. (bronch$ adj3 spasm$).mp.

9. bronchoconstrict$.mp.

10. exp Bronchoconstriction/

11. (bronch$ adj3 constrict$).mp.

12. Bronchial Hyperreactivity/

13. Respiratory Hypersensitivity/

14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.

15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.

16. or/1-15

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.

Appendix 2. Cochrane Airways Group Register search strategy

(physical* OR exercis* OR exert* or train* or bronchoconstrict* or bronchospasm* or EIB or EIA OR athlet*)

AND

(bronchodilat* or ((beta* or B2) and (agonist* or adrenergic*)) or salmeterol or formoterol or salbutamol or albuterol or terbutaline or clenbuterol)

[Limited to records coded as 'asthma']

Appendix 3. Raw data for the maximal percent fall in FEV_1 calculations

Study ID	Beta-agonist arm			Placebo arm			Correlation
	Mean	SD	N	Mean	SD	N	
Anderson 2001 Salb Disk	13.42	13.23	27	39.4	17.58	27	0.46
Anderson 2001 Salb MDI	8.51	13.75	27	39.4	17.58	27	0.46
Blake 1999 Salb 180	3.8	7.5	25	13.5	12.7	24	
Blake 1999 Salm 25	7.99	10.2	26	14.0	11.5	23	
Blake 1999 Salm 50	7.34	10.3	24	14.0	11.5	23	
Boner 1994 Form 12	2.2	8.3	15	14.5	13.4	15	
Bronski 1995 Salb MDI	16.0	11.0	44	23.0	20.0	44	
Bronski 1995 Salb Pwd	26.0	13.0	44	23.0	20.0	44	
Bronski 1999 Salm Disk	5.6	10.2	24	12.1	15.6	24	
Bronski 1999 Salm Diskhal	5.7	6.36	24	12.1	15.6	24	
Bronski 2002 Form 12	17.0	0.0	17	38.3	0.0	18	
Bronski 2002 Form 24	14.6	0.0	17	38.3	0.0	18	
Bronski 2002 Salb	8.6	0.0	17	37.1	0.0	18	
Carlsen 1995 Salm 25	19.0	16.7	23	30.0	16.7	23	
Carlsen 1995 Salm 50	18.0	14.3	23	30.0	16.7	23	
Cavagni 1993 Salb Jet	7.15	4.9	8	34.7	22.3	8	
Cavagni 1993 Salb MDI	15.9	9.3	9	28.9	21.8	9	
Clarke 1990 Fen	-19.9	0.0	20	9.8	0.0	20	

(Continued)

Daugbjerg 1996 Form 12	11.0	0.0	16	35.0	0.0	16	
Debelic 1988 Reproterol	12.6	0.0	16	38.5	0.0	16	
DeBenedictis 1996 Salm 25	19.0	12.0	12	35.0	16.0	12	0.28
DeBenedictis 1996 Salm 50	15.0	13.0	12	35.0	16.0	12	0.33
DeBenedictis 1998 Salb	3.7	4.4	12	25.7	18.9	12	
Del Col 1993 Salb Jet	20.76	2.1	15	29.14	15.1	15	
Del Col 1993 Salb MDI	12.37	5.1	15	26.6	16.1	15	
Dinh Xuan 1989 Terb	-2.24	17.7	10	35.2	22.1	10	
Egglestone 1981 Terb 250	10.0	8.24	17	32.0	16.49	17	
Ferrari 2000 Form 12	5.9	7.2	14	29.3	14.3	14	
Green 1992 Salm 50	3.2	4.8	13	26.6	10.27	13	0.30
Gronnerod 2000 Form 4.5	9.2	8.5	27	18.4	10.1	27	
Gronnerod 2000 Form 9	5.4	8.5	27	18.4	10.1	27	
Gronnerod 2000 Terb 500	3.3	10.2	27	18.4	10.1	27	
Hawksworth 2002 Salb HFA	15.4	9	23	33.7	8.3	24	
Hawksworth 2002 Salb MDI	14.9	9	24	33.7	8.3	24	
Henricksen 1983 Terb	26.0	22.4	14	37.0	14.9	14	
Henricksen 1992 Salb	18.0	17.3	12	44.0	13.8	12	
Henriksen 1992 Form 12	8.0	10.4	12	44.0	13.8	12	
Hills 1976 Salb	-4.6	0.0	19	35.5	0.0	19	
Hills 1976 Salmefamol	-2.6	0.0	19	35.5	0.0	19	

(Continued)

Kemp 1994 Salb	7.0	0.0	54	27.0	0.0	52	
Kemp 1994 Salm 42	13.0	0.0	53	27.0	0.0	52	
Konig 1981 Metaprot	19.0	12.0	24	36.0	15.0	24	
Konig 1984 Fen 0.4	4.3	10.1	12	27.8	14.9	12	
Konig 1984 Fen 0.8	2.5	13.0	12	27.8	14.9	12	
Larsson 1982 Fen	-2.7	0.0	8	11.0	0.0	8	
McAlpine 1990 Form 12	7.7	8.6	11	32.7	16.5	11	
McFadden 1986 Salb (I)	1.1	0.0	15	10.8	0.0	15	
McFadden 1986 Salb (II)	-1.1	0.0	20	14.1	0.0	20	
Morton 1989 Rimet	2.8	5.5	10	24.5	8.4	10	
Newnham 1993 Salb 200	3.8	18.2	11	27.1	15.9	11	
Newnham 1993 Salm 50	12.8	16.9	12	32.0	23.2	11	
Patel 1986 Salb 200	6.0	0.0	9	27.9	0.0	9	
Patel 1986 Tulob 200	9.7	0.0	9	27.9	0.0	9	
Patel 1986 Tulob 400	7.7	0.0	9	27.9	0.0	9	
Patessio 1991 Form 24	10.0	0.0	12	30.5	0.0	12	
Pearlman 2006 Form 12	7.6	0.0	22	13.2	0.0	20	
Pearlman 2006 Form 24	5.9	0.0	23	13.2	0.0	20	
Pearlman 2006 Salb 180	3.5	0.0	22	11.1	0.0	19	
Pearlman 2007 Salb 90	4.8	10.8	15	22.5	10.8	15	0.39
Philip 2007 Salm 50	10.7	8.1	46	21.8	8.1	46	

(Continued)

Richter 2002 Form 12	5.7	5.3	24	25.1	12.2	24
Richter 2002 Salm 50	7.6	7.5	24	25.1	12.2	24
Richter 2002 Terb 500	8.5	8.3	24	25.1	12.2	24
Shapiro 2002 Form 12	12.4	14.6	19	32.9	16.8	17
Shapiro 2002 Form 24	17.5	17.5	17	32.9	16.8	17
Shapiro 2002 Salb 180	10.0	18.6	19	31.1	18.7	17
Sturani 1983 Fen 400	15.8	7.9	12	36.0	6.9	12
Sturani 1983 Salb 200	23.2	8.6	12	36.0	6.9	12
VanHaitsma 2010 Salb	4.0	16.4	10	14.3	11.1	10
Vasquez 1984 Salb 400	-0.3	4.9	13	14.3	9.8	12
Walker 1986 Bitolterol	5.0	11.4	12	23.2	16.2	12
Wolley 1990 Terb 500	17.0	6.9	12	34.0	13.8	12

CONTRIBUTIONS OF AUTHORS

MB updated the protocol and was responsible for drafting the full text of the review. MB, CDM and EC selected the studies to be included in the review and extracted and collected data. EC and MB entered data into the Review Manager software for statistical analysis. HS created the 'Summary of findings' table, acting as expert contact for the assessment of risk of bias and for evaluation of the quality of evidence. GWC, MAC and SD acted as independent review authors for solving disagreements among rating authors. All authors critically reviewed the protocol and were involved in revising the full text of the systematic review.

DECLARATIONS OF INTEREST

Disclosures of interest provided by the review authors did not imply any potential conflict of interest with reference to this review.

SOURCES OF SUPPORT

Internal sources

- National Research Council, Institute of Translational Pharmacology (IFT), Italy.

External sources

- Italian National Drug Agency (AIFA), Italy.
- 21st Century Canada Research Chairs Programme; Government of Canada (Ottawa, Ontario), Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Compared with what was originally planned in the protocol, given the high number of papers retrieved in full and reviewed (N = 211), the review authors agreed to narrow the inclusion criteria, considering eligible only double-blind trials that assessed at least one primary outcome of the review. Lack of data reported selected outcomes and the low rate of heterogeneity prevented or made unnecessary some of the subgroup analyses defined a priori. We prepared a 'Summary of findings' table according to recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenergic beta-2 Receptor Antagonists [*administration & dosage]; Asthma, Exercise-Induced [*drug therapy]; Bronchoconstriction; Bronchodilator Agents [*administration & dosage]; Forced Expiratory Volume [drug effects]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans