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Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth (Review)

Pruteanu AI, Chauhan BF, Zhang L, Prietsch SOM, Ducharme FM

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[Intervention Review]

Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth

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ABSTRACT

Background

Inhaled corticosteroids (ICS) are the first-line treatment for children with persistent asthma. Their potential for growth suppression remains a matter of concern for parents and physicians.

Objectives

To assess whether increasing the dose of ICS is associated with slower linear growth, weight gain and skeletal maturation in children with asthma.

Search methods

We searched the Cochrane Airways Group Specialised Register of trials (CAGR) and the ClinicalTrials.gov website up to March 2014.

Selection criteria

Studies were eligible if they were parallel-group randomised trials evaluating the impact of different doses of the same ICS using the same device in both groups for a minimum of three months in children one to 17 years of age with persistent asthma.

Data collection and analysis

Two review authors ascertained methodological quality independently using the Cochrane Risk of bias tool. The primary outcome was linear growth velocity. Secondary outcomes included change over time in growth velocity, height, weight, body mass index and skeletal maturation.

Main results

Among 22 eligible trials**,** 17 pairs of groups comparisons were derived from 10 trials (3394 children with mild to moderate asthma), measured growth and contributed data to the meta-analysis. Trials used ICS (beclomethasone, budesonide, ciclesonide, fluticasone or mometasone) as monotherapy or as combination therapy with a long-acting beta$_2$-agonist and generally compared low (50 to 100 µg) versus low to medium (200 µg) doses of hydrofluoroalkane (HFA)-beclomethasone equivalent over 12 to 52 weeks. In the four comparisons reporting linear growth over 12 months, a significant group difference was observed, clearly indicating lower growth velocity in the higher ICS dose group of 5.74 cm/y compared with 5.94 cm/y on lower-dose ICS (N = 728 school-aged children; mean difference (MD)0.20 cm/

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y, 95% confidence interval (CI) 0.02 to 0.39; high-quality evidence): No statistically significant heterogeneity was noted between trials contributing data. The ICS molecules (ciclesonide, fluticasone, mometasone) used in these four comparisons did not significantly influence the magnitude of effect (X^2 = 2.19 (2 df), P value 0.33). Subgroup analyses on age, baseline severity of airway obstruction, ICS dose and concomitant use of non-steroidal antiasthmatic drugs were not performed because of similarity across trials or inadequate reporting. A statistically significant group difference was noted in unadjusted change in height from zero to three months (nine comparisons; N = 944 children; MD 0.15, 95% CI -0.28 to -0.02; moderate-quality evidence) in favour of a higher ICS dose. No statistically significant group differences in change in height were observed at other time points, nor were such differences in weight, body mass index and skeletal maturation reported with low quality of evidence due to imprecision.

Authors' conclusions

In prepubescent school-aged children with mild to moderate persistent asthma, a small but statistically significant group difference in growth velocity was observed between low doses of ICS and low to medium doses of HFA-beclomethasone equivalent, favouring the use of low-dose ICS. No apparent difference in the magnitude of effect was associated with three molecules reporting one-year growth velocity, namely, mometasone, ciclesonide and fluticasone. In view of prevailing parents' and physicians' concerns about the growth suppressive effect of ICS, lack of or incomplete reporting of growth velocity in more than 86% (19/22) of eligible paediatric trials, including those using beclomethasone and budesonide, is a matter of concern. All future paediatric trials comparing different doses of ICS with or without placebo should systematically document growth. Findings support use of the minimal effective ICS dose in children with asthma.

PLAIN LANGUAGE SUMMARY

Does altering the dose of inhaled corticosteroids make a difference in growth among children with asthma?

Background

Asthma guidelines recommend inhaled corticosteroids (ICS) as the first choice of treatment for children with persistent asthma that is not well controlled when only a reliever inhaler is used to treat symptoms. Steroids work by reducing inflammation in the lungs and are known to control underlying symptoms of asthma. However, parents and physicians remain concerned about the potential negative effect of ICS on growth.

Review question

Does altering the dose of inhaled corticosteroids make a difference in the growth of children with asthma?

What evidence did we find?

We studied whether a difference could be seen in the growth of children with persistent asthma who were using different doses of the same ICS molecule and the same delivery device. We found 22 eligible trials, but only 10 of them measured growth or other measures of interest. Overall, 3394 children included in the review combined 17 group comparisons (i.e. 17 pairs of groups of children with mild to moderate asthma using a particular dose and type of steroid in 10 trials). Trials used different ICS molecules (beclomethasone, budesonide, ciclesonide, fluticasone or mometasone) either on their own or in combination with a long-acting $beta_2$-agonist (a drug used to open up the airways) and generally compared low doses of corticosteroids (50 to 100 µg) with low to medium (200 µg) doses of corticosteroids (converted in µg HFA-beclomethasone equivalent) over 12 to 52 weeks.

Results

We found a small but statistically significant group difference in growth over 12 months between these different doses clearly favouring the lower dose of ICS. The type of corticosteroid among newer molecules (ciclesonide, fluticasone, mometasone) did not seem to influence the impact on growth over one year. Differences in corticosteroid doses did not seem to affect the change in height, the gain in weight, the gain in body mass index and the maturation of bones.

Quality of the evidence

This review is based on a small number of trials that reported data and were conducted on children with mild to moderate asthma. Only 10 of 22 studies measured the few outcomes of interest for this review, and only four comparisons reported growth over 12 months. Our confidence in the quality of evidence is high for this outcome, however it is low to moderate for several other outcomes, depending on the number of trials reporting these outcomes. Moreover, a few outcomes were reported only by a single trial; as these findings have not been confirmed by other trials, we downgraded the evidence for these outcomes to low quality. An insufficient number of trials have compared the effect of a larger difference in dose, for example, between a high dose and a low dose of ICS and of other popular molecules such as budesonide and beclomethasone over a year or longer of treatment.

Conclusions

We report an ICS dose–dependent reduction in growth velocity in prepubescent school-aged children with mild to moderate persistent asthma. The choice of ICS molecule (mometasone, ciclesonide or fluticasone) was not found to affect the level of growth velocity response

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over a year. The effect of corticosteroids on growth was not consistently reported: among 22 eligible trials, only four comparisons reported the effects of corticosteroids on growth over one year. In view of parents' and clinicians' concerns, lack of or incomplete reporting of growth is a matter of concern given the importance of the topic. We recommend that growth be systematically reported in all trials involving children taking ICS for three months or longer. Until further data comparing low versus high ICS dose and trials of longer duration are available, we recommend that the minimal effective ICS dose be used in all children with asthma.

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Summary of findings for the main comparison. Inhaled corticosteroids dose-response effect

Inhaled corticosteroids dose-response effect

Patient or population: children with persistent asthma
Settings: outpatients
Intervention: lower-dose inhaled corticosteroids

Control: higher-dose ICS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control group (higher-dose ICS)	Intervention group (lower-dose ICS)				
Growth velocity over 12 months (cm/y) (higher is better)	Mean growth velocity was 5.74 cm/y (range, 5.6 to 5.88)	Corresponding growth velocity on lower-dose ICS was 0.2 cm/y higher: mean 5.94 cm/y (95% CI 5.76 to 6.13)	**MD 0.20** (0.02 to 0.39)	728 (4 studies)	⊕⊕⊕⊕ high	Skoner 2011 data analysed using LRS model were used
Change in height over 3 months (cm) (higher is better)	Unadjusted mean change in height over 3 months was 1.34 cm (range, 0.9 to 1.8 cm)	Corresponding unadjusted change in height on lower-dose ICS was 0.15 cm lower: mean 1.19 cm (95% CI 1.06 to 1.32)	**MD -0.15** (-0.28 to -0.02)	944 (9 studies)	⊕⊕⊖⊖ moderate[1]	Data analysis was unadjusted for confounders
Change in height over 12 months (cm) (higher is better)	Unadjusted mean change in height over a year was 4.56 cm (range, 3.6 to 5.73 cm)	Corresponding unadjusted change in height on lower-dose ICS was 0.25 cm higher; mean 4.81 cm (95% CI 4.52 to 5.1)	**MD 0.25** (-0.04 to 0.54)	548 (4 studies)	⊕⊕⊖⊖ moderate[1]	Data analysis was unadjusted for confounders
Change in SD scores over 12 months (height) (low change is better)	Unadjusted mean change in SD score was -0.18 (range, -0.01 to -0.27)	Corresponding mean unadjusted change on lower-dose ICS was 0.08 less; mean -0.10 (95% CI -0.21 to 0.02)	**MD 0.08** (-0.03 to 0.20)	328 (3 studies)	⊕⊕⊖⊖ moderate[1]	Data analysis was unadjusted for confounders
Change in weight over 12 months (kg) (higher is better)	Mean change in weight was 3.4 kg	Corresponding mean change in weight on lower-dose ICS was 0.3 kg lower: mean 3.1 (95% CI 2.58 to 3.62)	**MD** -0.30 (-0.82 to 0.22)	408 (1 study)	⊕⊕⊖⊖ low[2]	Based on only 1 trial

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Change in BMI over 12 months (kg/m^2) (higher is better)	Mean change in BMI was 0.7 kg/m^2	Corresponding mean change in BMI on lower-dose ICS was 0.2 kg/m^2 less: mean 0.5 (95% CI 0.21 to 0.79)	**MD** -0.20 (-0.49 to 0.09)	408 (1 study)	⊕⊕⊖⊖ low[2]	Based on only 1 trial
Change in skeletal maturation over 12 months (years) (higher is better)	Mean change in skeletal maturation was 0.95 years	Corresponding mean change in skeletal maturation on lower-dose ICS was 0.18 years more; mean 1.13 (95% CI 0.97 to 1.29)	**MD** 0.18 (0.02 to 0.34)	181 (1 study)	⊕⊕⊖⊖ low[2]	Based on only 1 trial

*The basis for the **assumed risk** was the weighted mean control group risk across studies. 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.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Data analysis was unadjusted for confounders.
[2]Based on only 1 trial.

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BACKGROUND

This protocol is the first of a series of three review protocols exploring the safety profile of inhaled corticosteroids (ICS) in terms of growth in children with persistent asthma. The present review explored the dose-response effect of ICS on growth. The second review compares the long-term effects of ICS on growth (Zhang 2011), and the third examines the effects of different drugs and delivery devices on growth. For more comprehensive background data and additional references, see Zhang 2011.

Description of the condition

Asthma is defined as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment (GINA 2014). In developed countries, the prevalence of childhood asthma has markedly increased over the past few decades (ISAAC 1998; Masoli 2004; Asher 2010); however, this increase has recently reached a plateau in some of these countries (Lai 2009; Asher 2010). In contrast, asthma prevalence is sharply increasing in developing countries (Africa, Central and South America, Asia and the Pacific region), probably as a result of rapid and ongoing urbanisation and westernisation (Braman 2006; Asher 2010). The global burden of childhood asthma is continuing to rise.

Description of the intervention

ICS are widely considered the first-line treatment for persistent asthma, both in adults and in children (NHLBI 2007; BTS 2012; GINA 2014; Chauhan 2012; Lougheed 2012). Studies have demonstrated the clinical benefits of ICS in controlling asthma symptoms, reducing exacerbations and hospitalisations, decreasing airway hyperresponsiveness and airway inflammation, improving pulmonary function, improving quality of life and reducing asthma-related deaths (Juniper 1990; Van Essen-Zandvliet 1992; Olivieri 1997; Van Rensen 1999; Suissa 2000; Covar 2003; Adams 2011a; Adams 2011b; Adams 2011c). Seven ICS are currently available for clinical use worldwide: beclomethasone dipropionate, budesonide, fluticasone propionate, mometasone fumarate, ciclesonide, flunisolide and triamcinolone acetate. Each inhaled corticosteroid has different pharmacokinetic and pharmacodynamic properties and biologic characteristics; however, all ICS can achieve similar therapeutic benefits when given at equipotent doses (Sobande 2008; BTS 2012; GINA 2014; Lougheed 2012).

The optimal doses of ICS for persistent childhood asthma remain unclear. The most recent asthma guidelines recommend initiating ICS at low or medium daily doses for children with mild to moderate persistent asthma; however, patients with more severe asthma and those with poor response to low to moderate doses of ICS may require higher doses (≥ 400 µg/d of hydrofluoroalkane (HFA)-beclomethasone or equivalent) to achieve satisfactory control of asthma (NHLBI 2007; BTS 2012; GINA 2014; Lougheed 2012).

Although ICS are generally considered safe treatment for children with asthma, the potential systemic adverse effects related to long-term use of these drugs have been, and continue to be, a matter of concern, especially the effects on growth (Pedersen 2001; Allen 2002). In 1998, based on a report of the panel of experts, the US Food and Drug Administration (FDA) required labels on all ICS warning of a potential reduction in growth in children (FDA 1998). Since that time, the relationship between ICS and growth impairment in children with asthma has been extensively debated in the literature and more so with the advent of new molecules with allegedly safer profiles (Witzmann 2000; Brand 2001; Creese 2001; Wolthers 2001; Carlsen 2002; Price 2002a; Sizonenko 2002; Salvatoni 2003; Allen 2006).

How the intervention might work

ICS are the most potent anti-inflammatory drugs available for long-term treatment of persistent asthma. Possible molecular mechanisms for the anti-inflammatory effects of ICS and for corticosteroid-induced growth impairment have been reviewed previously (Barnes 2003; Zhang 2011).

Why it is important to do this review

One Cochrane systematic review (Sharek 2000a) produced solid evidence supporting growth suppression estimated at 1.5 cm per year over seven to 12 months for 400 µg/d inhaled chlorofluorocarbon (CFC)-propelled beclomethasone (equivalent to 200 µg/d of HFA-propelled beclomethasone) in children with asthma. This review lately has been converted to a journal article (Sharek 2000b). However, it remains unclear whether corticosteroid-induced growth retardation is dose dependent. We therefore decided to conduct this systematic review to evaluate the relationship between dose of ICS and risk of growth impairment in children with persistent asthma.

OBJECTIVES

To assess whether increasing the dose of ICS is associated with slower linear growth, weight gain and skeletal maturation in children with asthma.

METHODS

Criteria for considering studies for this review

Types of studies

Parallel-group randomised controlled trials.

Types of participants

Children one to 17 years of age with the diagnosis of persistent asthma.

Types of interventions

Each treatment group should be given the same ICS at two or more different doses via the same delivery system for at least three months. ICS may be administered as monotherapy or in combination with other non-steroidal asthma drugs (e.g. long-acting beta-agonists (LABAs), leukotriene receptor antagonists (LTRAs)). In all included trials, the intervention group depicted is the lower-dose ICS and the control (comparison) group is the higher-dose ICS.

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Types of outcome measures

Primary outcomes

Linear growth velocity (cm/y), obtained by measuring height at a number of time points during the study and performing linear regression of height over time (Price 2002a).

Secondary outcomes

- Change in growth velocity standard deviation (SD), defined as the difference between an individual's growth velocity and predicted growth velocity divided by the predicted growth velocity SD for individuals of the same age and sex (and ethnicity if available) (Pedersen 2001).
- Change in absolute height (cm) over time.
- Change in weight (kg or z-score) over time.
- Change in body mass index (added post hoc).
- Change in skeletal maturation (added post hoc).

We did not intend to include lower leg length measured by knemometry as the outcome because this measurement correlates poorly with statural height and tends to overestimate potential effects of ICS on growth (Efthimiou 1998; Allen 1999).

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register of Trials (CAGR), which were derived through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and through handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). All records in the CAGR coded as 'asthma' were searched using the following terms.

(((steroid* or corticosteroid* or glucocorticoid*) and inhal*) or budesonide or Pulmicort or fluticasone or Flixotide or Flovent or ciclesonide or Alvesco or triamcinolone or Kenalog or beclomethasone or beclometasone or Becotide or Becloforte or Becodisk or QVAR or Flunisolide or AeroBid or mometasone or Asmanex or Symbicort or Advair or Inuvair) AND (grow* or height* or SDS) AND (child* or paediat* or pediat* or adolesc* or teen* or prepubertal* or pre-pubertal* or puberty or pubertal* or infan* or toddler* or bab* or young*) AND (dose* or dosage* or delivery* or administ* or response* or high* or low*)

We also conducted a search of the ClinicalTrials.gov website. All databases were searched from their inception until March 2014 with no restriction on language of publication.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We also searched manufacturers' clinical trial databases for potentially relevant unpublished studies, if needed.

Data collection and analysis

Selection of studies

Two review authors (AP and LZ or SP) independently assessed the titles and abstracts of all potential studies for inclusion identified by the search strategy. Full-text articles were retrieved when they appeared to meet the inclusion criteria or when data in the title and abstract were insufficient to permit a clear decision regarding their inclusion. We resolved disagreements through discussion, or, if required, we consulted the third review author.

Data extraction and management

Two review authors (AP and BC) independently extracted data from the included trials using specially designed and pilot-tested data extraction forms. For trials with multiple reports, we extracted data from each report separately and combined information across multiple data collection forms afterwards. We resolved disagreements by discussion and entered the extracted data into RevMan version 5.1 (Review Manager 5).

We extracted the following data.

- Study characteristics: year of publication, name of the first author, setting and source of funding/sponsorship.
- Methods: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting and other sources of bias.
- Participants: sample size, demographics, inclusion and exclusion criteria.
- Intervention: type of ICS, dosage, frequency of administration, inhalation device, treatment duration and adherence to treatment, if available.
- Comparator: the same corticosteroid given at different dosage regimens (the same details as for intervention).
- Co-interventions: type, dosage regimen and duration.
- Results: mean value of the outcome measures in each group, SD or other metrics for uncertainty (standard errors (SEs), confidence intervals (CIs), P values for differences in means) of outcome measurements in each group, number of participants who underwent randomisation, number of participants on whom outcomes were measured in each group.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Disagreements were resolved by discussion or by involving the third review author. We assessed the risk of bias according to the following domains.

- Allocation sequence generation.
- Concealment of allocation.
- Blinding of participants and investigators.
- Incomplete outcome data.
- Selective outcome reporting.
- Other risk of bias.

We noted other sources of bias. We graded each potential source of bias as low, high or unclear risk. Studies were deemed to be of high methodological quality if information on randomisation generation, blinding and incomplete outcome data was available, indicating a low risk of bias.

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Measures of treatment effect

Measurements of growth were continuous outcomes, so we used mean difference (MD) and 95% CI as the metrics for treatment effects, as appropriate.

Unit of analysis issues

We considered each individual comparison as the unit of analysis. We used analysed participants as sample size rather than the number of participants randomly assigned in the included studies. We had planned three pair-wise comparisons of ICS doses in HFA-beclomethasone or equivalent: low (≤ 200 µg) versus medium (201 to 400 µg) versus high dose (> 400 µg) and low (≤ 200 µg) versus high (> 400 µg) dose (Lougheed 2012). The ICS dose equivalence used for this review was based on Canadian Asthma Guidelines (Lougheed 2012), which are based on a combination of the dose equivalency mentioned in GINA 2014 and reported safety and efficacy data: 1 µg fluticasone = 1 µg mometasone = 1 µg ciclesonide = 1 µg of hydrofluoroalkane HFA-beclomethasone = 2 µg budesonide = 2 µg CFC-BDP = 4 µg flunisolide = 4 µg triamcinolone acetate.

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. In cases of substantial heterogeneity (I^2 > 50%), we explored potential sources of heterogeneity by performing prespecified subgroup analysis and sensitivity analysis. We also conducted these analyses to explore the possibility of an effect modifier even if no significant heterogeneity was observed.

Assessment of reporting biases

We planned to contact study authors to ask them to provide missing outcome data if we suspected reporting bias. When this was not possible, and when the missing data were thought to introduce serious bias, we planned to explore the impact of excluding such studies on the overall assessment of results by performing a sensitivity analysis**.**

Data synthesis

We performed the meta-analyses using the Cochrane statistical package RevMan 5 (Review Manager 5). We used the fixed-effect model unless statistical heterogeneity was found, in which case we used the random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses for the primary outcome, measured at various points in time.

- Participant age: preschoolers (two to five years), prepubertal children (> five to 12 years), adolescents (> 12 to 18 years).
- Asthma severity: mild versus moderate versus severe.
- ICS molecule: beclomethasone, budesonide, fluticasone, mometasone, ciclesonide, flunisolide, triamcinolone.
- Concomitant use of non-steroidal antiasthmatic drugs: ICS alone, ICS combined with non-steroidal drugs, such as LABAs and LTRAs.
- Dose difference of ICS in HFA-beclomethasone or equivalent (added as post hoc analysis).

Sensitivity analysis

Sensitivity analysis was used to assess the potential impact of particular decisions or missing information on the findings of the review (Higgins 2008). We planned to carry out the following sensitivity analyses with regards to primary outcome by excluding from the analysis trials with the following.

- High risk of bias owing to missing data or unbinding, or both.
- Rate of adherence to ICS lower than 75% or lack of available data regarding adherence to treatment.
- Pharmaceutical industry sponsorship.

RESULTS

Description of studies

Results of the search

The literature search conducted until March 2014 identified a total of 406 citations and abstracts (Figure 1). Of these, 71 potential full texts were reviewed thoroughly for inclusion criteria. Twenty-two trials, including 34 comparisons (Characteristics of included studies), were eligible for inclusion. Of these, 12 trials (17 comparisons) contributed no usable data to this review; four trials (five comparisons) either presented data in a different format than was specified in the protocol or reported incomplete data (Jonasson 2000; Chen 2001; Teper 2004; Gelfand 2006; Gelfand 2006 b); seven trials (11 comparisons) did not measure children's growth as an outcome (Jonasson 1998; Giorgi 1998; Peden 1998; Peden 1998 b; Baker 1999; Baker 1999 b; Kemp 1999; Kemp 1999 b; Doniec 2004; Kerwin 2008; Kerwin 2008 b) and one trial was published as an abstract (Lemanske 2004). Consequently, 10 trials (17 comparisons) published as full text contributed at least one outcome to the meta-analysis.

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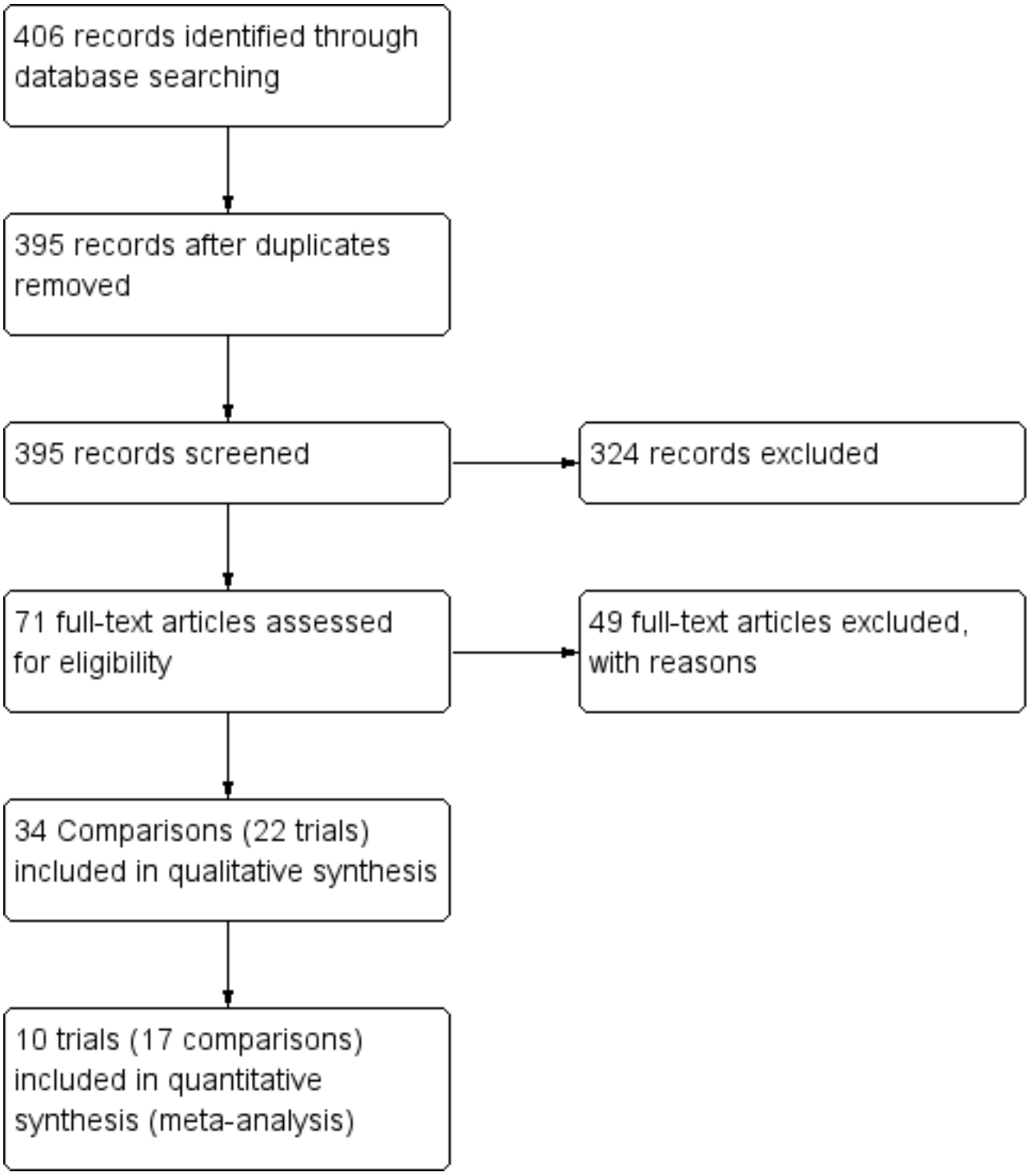
Figure 1. Flow diagram of screening of trials.



Included studies

Ten trials, reporting 17 comparisons (Allen 1998; Shapiro 1998; Shapiro 1998 b; Shapiro 1998 c; Shapiro 1998 d; Verberne 1998; Verberne 1998 b; Wasserman 2006; Sorkness 2007; Skoner 2008; Pedersen 2010; Pedersen 2010 b; Vaessen-Verberne 2010; Brand 2011; Brand 2011 b; Skoner 2011; Skoner 2011 b) and enrolling 3394 children with confirmed persistent asthma, contributed data to the review. The following information pertains only to the 17 comparisons (from 10 included trials) contributing data to this review (Characteristics of included studies). The FDA has produced a guideline on evaluation of the effects of orally inhaled and intranasal corticosteroids, specific to placebo-controlled trials in children (US FDA 2007); although some criteria were not relevant for dose-response studies, we ascertained the compliance status to these guidelines of trials that contributed data to the meta-analysis (Table 1; Table 2; Table 3).

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Design

All trials used a parallel-group design.

Participants

Three comparisons involved children two to five years of age (Wasserman 2006; Brand 2011; Brand 2011 b), six comparisons involved prepubertal children, five to 12 years of age (Allen 1998; Skoner 2008; Pedersen 2010; Pedersen 2010 b; Skoner 2011; Skoner 2011 b), and eight comparisons involved prepubertal and pubertal children (Shapiro 1998; Shapiro 1998 b; Shapiro 1998 c; Shapiro 1998 d; Verberne 1998; Verberne 1998 b; Sorkness 2007; Vaessen-Verberne 2010). Most trials described a gender ratio hovering around 65% male participants. With regards to asthma severity, one comparison (Skoner 2008) focused on asthmatic individuals with mild airway obstruction, two comparisons (Verberne 1998; Verberne 1998 b) focused on asthmatic individuals with mild to moderate airway obstruction, four comparisons (Shapiro 1998; Shapiro 1998 b; Shapiro 1998 c; Shapiro 1998 d) focused on asthmatic individuals with moderate to severe airway obstruction and the remaining six comparisons (Allen 1998; Wasserman 2006; Pedersen 2010; Pedersen 2010 b; Skoner 2011; Skoner 2011 b) failed to report the severity of baseline airway obstruction. Two comparisons (Brand 2011; Brand 2011 b) pertained to preschool children with recurrent wheezing and a positive asthma predictive index or a positive screening test for atopy. Asthma triggers were seldom reported.

Intervention duration

The duration of intervention varied from 12 weeks (seven comparisons; Shapiro 1998; Shapiro 1998 b; Shapiro 1998 c; Shapiro 1998 d; Wasserman 2006; Pedersen 2010; Pedersen 2010 b) to 24 weeks (two comparisons; Brand 2011; Brand 2011 b) to 26 weeks (one comparison; Vaessen-Verberne 2010) to 52 weeks (seven comparisons; Allen 1998; Verberne 1998; Verberne 1998 b; Sorkness 2007; Skoner 2008; Skoner 2011; Skoner 2011 b).

Intervention drugs

The ICS molecule used was beclomethasone dipropionate (BDP) (two comparisons; Verberne 1998; Verberne 1998 b), budesonide (BUD) (four comparisons; Shapiro 1998; Shapiro 1998 b; Shapiro 1998 c; Shapiro 1998 d), ciclesonide (CIC) (five comparisons; Skoner 2008; Pedersen 2010; Pedersen 2010 b; Brand 2011; Brand 2011 b), fluticasone propionate (FP) (four comparisons; Allen 1998; Wasserman 2006; Sorkness 2007; Vaessen-Verberne 2010) or mometasone fumarate (MF) (two comparisons; Skoner 2011; Skoner 2011 b). The difference in the dose of ICS between two comparison groups (reported in HFA-beclomethasone equivalent) varied by ≤ 150 µg in most trials. Most compared 100 µg (low dose) versus 200 µg (the cutoff limit between low and medium doses of ICS); in only four comparisons (Shapiro 1998 b; Shapiro 1998 d; Verberne 1998; Vaessen-Verberne 2010) was the difference in the dose of ICS between groups ≥ 400 µg. Different devices were used, including aerochamber, diskhaler, dry powder inhaler, metered-dose inhaler with or without spacer, nebuliser and turbohaler (further details are available in the Characteristics of included studies table). Yet all trials used the same inhalation device in within-trial group comparisons. Adherence rate to ICS was reported by three of 10 trials; when reported, adherence was at or above 80%. All trials but one (Sorkness 2007) were funded by the pharmaceutical industry.

Co-intervention

Three comparisons (Verberne 1998; Pedersen 2010; Pedersen 2010 b) enrolled only participants receiving ICS as monotherapy. Eleven comparisons (Allen 1998; Shapiro 1998; Shapiro 1998 b; Shapiro 1998 c; Shapiro 1998 d; Wasserman 2006; Skoner 2008; Brand 2011; Brand 2011 b; Skoner 2011; Skoner 2011 b) reported accepting participants who were using co-interventions with additional antiasthmatic drugs such as LABAs, antileukotrienes or theophylline. Three comparisons (Verberne 1998 b; Sorkness 2007; Vaessen-Verberne 2010) specifically compared ICS alone versus ICS + LABA, without other co-interventions.

Outcomes

The primary outcome was linear growth velocity (zero to 12 months), which was documented in four comparisons involving prepubescent children (Allen 1998; Skoner 2008; Skoner 2011; Skoner 2011 b); in all cases, linear growth was analysed in three or more height measurements by regression analysis, with adjustment for co-variates in all but one trial (Allen 1998). Secondary outcomes included change in height, growth velocity, weight, body mass index and skeletal maturation.

Excluded studies

Of 406 citations searched, 384 (94%) were excluded for the following exclusive reasons (Figure 1): (1) duplicate references (N = 11), (2) not a randomised controlled trial (N = 76), (3) not a parallel-group study (N = 84), (4) participants aged < one year or ≥ 18 years (N = 33), (5) participants not asthmatic (or participants with asthma selected for another co-morbidity, e.g. hypertension, diabetes) (N = 16), (6) participants with episodic asthma (N = 2), (7) acute and emergency care settings (N = 13), (8) no daily ICS stable dose in all participants in one of the comparison groups (N = 86), (9) not testing an additional ICS dose using the same molecule in all participants of the other comparison group (N = 50), (10) co-interventions with oral corticosteroids (N = 3), and (11) treatment administered for less than 12 weeks (N = 10). Reasons for exclusion are provided in the Characteristics of excluded studiestable.

Risk of bias in included studies

Details on risk of bias for each included trial are presented in the Characteristics of included studies tables. A graphical summary of risk of bias judgements is presented in Figure 2. Although all trials were randomised, only 14 comparisons (41%) reported the method of randomisation.

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

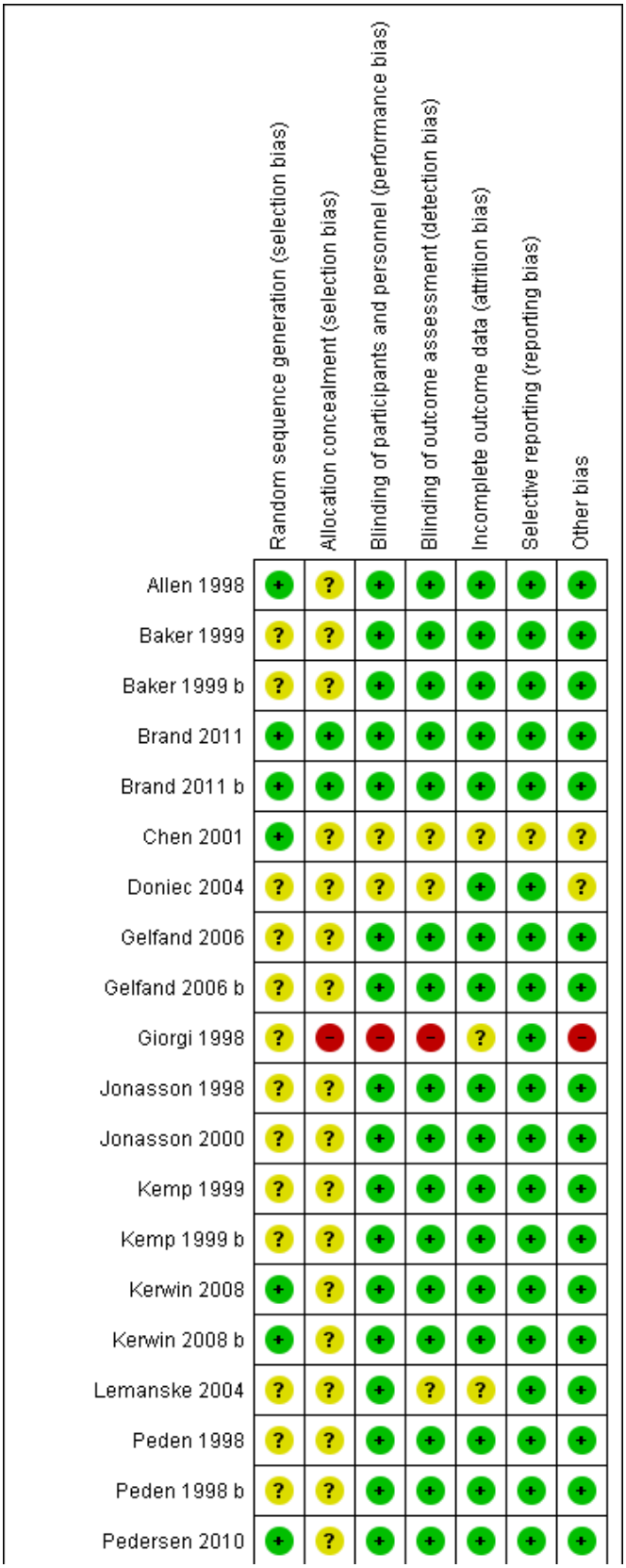

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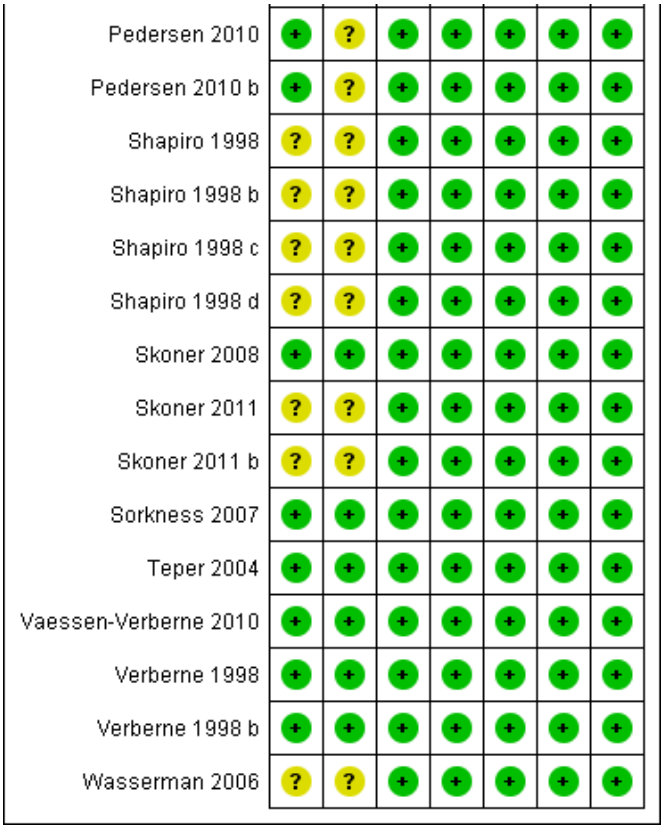
Figure 2. (Continued)



Allocation

26 comparisons did not mention the method of concealment of treatment, and eight comparisons (23.5%) reported use of an appropriate concealment technique.

Blinding

31 comparisons (90%) reported double-blinding with convincing details, two comparisons (Chen 2001; Doniec 2004) did not report sufficient information to allow the review authors to ascertain blinding and one comparison (Giorgi 1998) used an open-label study design.

Incomplete outcome data

31 comparisons (91%) reported all data with balanced numbers in both groups, and data from three comparisons (Giorgi 1998; Chen 2001; Lemanske 2004) were unclear. All trials reported numbers of and reasons for withdrawals in both comparison groups. The proportion of overall withdrawals was variable between studies (10% to 30%), with a balance in withdrawal rates noted between groups given different ICS doses.

Selective reporting

33 comparisons (97%) reported all outcomes mentioned in the methods section, with no apparent bias, and one comparison (Chen 2001) was unclear.

Other potential sources of bias

In 31 comparisons, we encountered no other significant sources of bias, two comparisons (Chen 2001; Doniec 2004) were unclear and one comparison (Giorgi 1998) was an open-label study for which the primary outcome was not specified clearly.

Except for three trials, all eligible trials contributing data were of high methodological quality. Two of four comparisons contributing to the primary outcome (Allen 1998; Skoner 2008) were of high methodological quality.

Effects of interventions

See: **Summary of findings for the main comparison** Inhaled corticosteroids dose-response effect

Primary outcomes

Linear growth velocity (cm/y)

A statistically significant group difference in linear growth (cm/y) over 12 months was noted between intervention (lower ICS dose) and control (higher ICS dose) groups (four comparisons; N = 728 children; MD 0.20 cm/y, 95% CI 0.02 to 0.39; Figure 3); no heterogeneity was apparent. The different molecules used (mometasone, ciclesonide and fluticasone) did not seem to influence the magnitude of effect: χ^2 = 2.19; df = 2; P value 0.33; Analysis 1.2; Figure 4). Data from Skoner 2011 weighed 10% in the primary outcome analysis. In Skoner 2011, growth velocity was analysed using two different statistical models: a longitudinal random slope (LRS) model and an individual regression (IR) model; results from both of these methods were reported. The IR model

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resulted in poor estimates of growth rate with lower precision, as admitted by the study authors, and led to a different confidence interval around the pooled results. In contrast, the LRS model provided more robust growth rates. Consequently, we chose the data derived using the best (LRS) model, which led to a significant group difference in the primary outcome, recognising that use of the IR model would have led to a group difference approaching, but not reaching, statistical significance.

Figure 3. Forest plot of comparison: 1 Inhaled corticosteroids dose-response effect, outcome: 1.1 Growth velocity (cm/y) by stadiometry from 0-12 months.

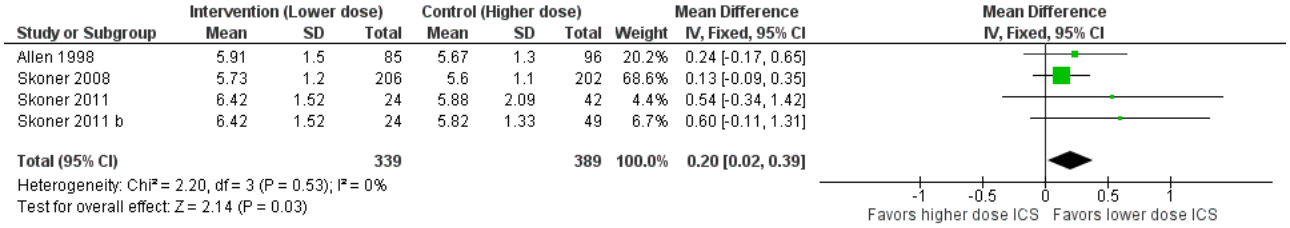
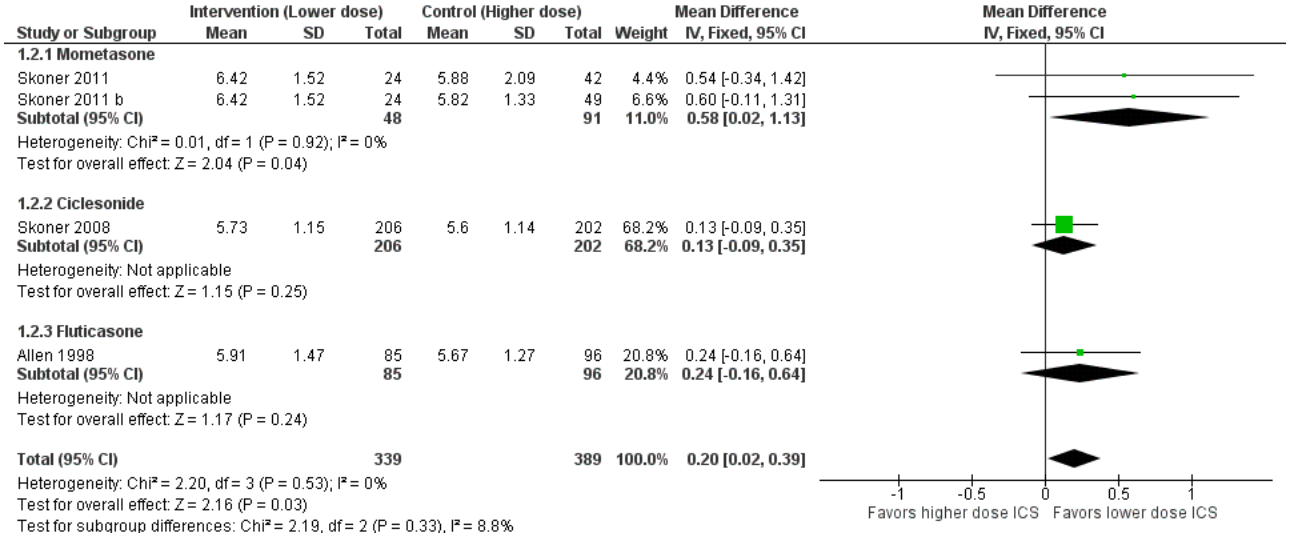


Figure 4. Forest plot of comparison: 1 Inhaled corticosteroids dose-response effect, outcome: 1.2 Subgroup analysis on the ICS molecules: growth velocity by stadiometry from 0-12 months.



We could not perform subgroup analysis on age, severity and ICS dose, as all trials contributing data to the primary outcome had similar characteristics in that they enrolled prepubertal children with mild or unknown severity of airway obstruction, used similarly low ICS doses and did not report or failed to specify the use of co-interventions. Of note, in all four comparisons contributing data, the ICS dose difference between the two groups was less than or equal to 150 µg of HFA-beclomethasone.

As all trials contributing data to the primary outcome were published in full text with high methodological quality and were sponsored by the pharmaceutical industry, we could not perform sensitivity analyses to assess bias due to publication status, poor methodology or funding status. As the adherence rate for ICS was seldom or incompletely reported, sensitivity analysis was not performed on this criterion.

No statistically significant group differences in linear growth (standardised in cm/y) were seen over the first three months (six comparisons; N = 1114 children; MD -0.12, 95% CI -0.51 to 0.27; Analysis 1.3) and no heterogeneity was apparent. Only two comparisons from the same trial provided data on growth velocity from zero to six months (Analysis 1.4) and from three to six months (Analysis 1.5); in both cases, a statistically significant group difference was not reported.

Secondary outcomes

Change in growth velocity (cm/y)

Only one trial reported change in growth velocity from zero to 12 months with no statistically significant group difference (one comparison; N = 181 children; MD 0.06 cm/y, 95% CI -0.43 to 0.55; Analysis 1.6).

Change in height (cm)

This outcome reflects the net change between final and initial height, without linear regression or adjustment for important co-variates such as age, sex, puberty and baseline height. A statistically significant group difference was noted in the change in height from zero to three months in favour of the higher ICS dose (nine comparisons; N = 944 children; MD -0.15 cm, 95% CI -0.28 to -0.02; Analysis 1.7); children were described as having mild to moderate

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to severe asthma, and the ICS used were cicleconide, budesonide and fluticasone. However, the group difference was not statistically significant over longer or subsequent periods, that is, from zero to six months (three comparisons; N = 211 children; MD -0.03, 95% CI -0.33 to 0.27) (Analysis 1.8), from three to six months (two comparisons; N = 58 children; MD -0.01, 95% CI 0.74 to 0.71) (Analysis 1.9) and from zero to 12 months (four comparisons; N = 548 children; MD 0.25, 95% CI -0.04 to 0.54; Analysis 1.10).

Change in standard deviation score (SDS) (height)

No statistically significant group difference in change in SDS (height) from zero to 12 months was reported (three comparisons; N = 328 children; MD 0.08, 95% CI -0.03 to 0.20; Analysis 1.11).

Change in weight (kg)

No significant group difference in change in weight was seen from zero to three months (Analysis 1.12), from zero to six months (Analysis 1.13) and from zero to 12 months (Analysis 1.14).

Change in body mass index (BMI) (kg/m^2)

No significant group difference in change in BMI was noted from zero to six months (Analysis 1.15) or from zero to 12 months (Analysis 1.16).

Change in skeletal maturation

Only one trial reported change in skeletal maturation, with a statistically significant group difference from zero to 12 months in favour of a lower ICS dose (one comparison; N = 181 children; MD 0.18, 95% CI 0.02 to 0.34; Analysis 1.17).

DISCUSSION

This meta-analysis aggregated data from 10 paediatric trials, providing 17 comparisons, as several studies tested more than two different doses of ICS or provided additional data subgrouped by age. In the four trials reporting the main outcome, a statistically significant group difference was seen in linear growth velocity measured by stadiometry over 12 months in prepubertal school-aged children treated with low doses (i.e. 50 to 100 µg) versus low to medium doses (i.e. 200 µg of fluticasone, mometasone and ciclesonide). Of note, the statistically significant group difference was observed despite the small ICS dose difference between compared groups, varying between 100 and 150 µg/d (although most vary by 100 µg/d) of HFA-propelled beclomethasone or equivalent in the four studies pooled. Of interest, a change in height between zero and three months showed a significant decrease of 0.15 cm in the opposite direction, that is, in disfavour of a lower ICS dose, underlying the impact of neglecting important co-variates influencing growth (e.g. sex). This also raised the possibility of a beneficial effect of rapidly achieving asthma control (although this was not measured) and the impact of the timing of measurement of effect size, as this unadjusted group difference was not observed over subsequent and longer time periods. No statistically significant change from baseline in linear growth velocity, weight and body mass index was noted over zero to 12 months of ICS therapy in children. Our findings suggest a clear, yet small, dose-dependent effect on growth when ICS are used at 200 µg/d or less—the cutoff for low to medium doses of ICS in children.

The main outcome, growth velocity, that is, the pattern of growth measured repeatedly over time and adjusted for relevant co-variates (in all individual trials but one (Allen 1998)), was measured in prepubertal school-aged children (< 12 years) treated with fluticasone propionate, ciclesonide and mometasone for 52 weeks. Of the 10 trials contributing data, only three trials (four comparisons) contributed data to the primary outcome (i.e. growth velocity (cm/y)) from zero to 12 months; all performed repeated height measurements using a stadiometer, were funded by pharmaceutical companies and were of high methodological quality. Trials used either a dry powder inhaler or a metered-dose inhaler with spacer to deliver these three molecules with lower systemic bioavailability than budesonide and beclomethasone. Because of trial homogeneity, it was not possible to explore a possible modifier effect of age, severity of airway obstruction, asthma control, use of co-interventions and ICS dose difference on growth velocity. Indeed, trials contributing data to this outcome predominantly compared low ICS doses versus low to medium doses, with a dose difference of 100 to 150 µg/d of HFA-beclomethasone equivalent (GINA 2014); higher doses of ICS theoretically offer greater potential for growth suppression (NHLBI Expert Panel Report 2012).

No effect of the choice of molecules within those tested was apparent. Indeed, several placebo-controlled trials and Cochrane reviews have documented molecule dependency of growth suppression of ICS. Zhang and colleagues (Zhang 2011) are evaluating the growth-suppressive effect of several ICS molecules compared with placebo, reporting minimal and less effect of fluticasone, mometasone and ciclesonide compared with budesonide and beclomethasone. Trials aggregated in this latter review had independently documented a growth-suppressive effect at equivalent ICS doses of between 1.1 and 1.2 cm/y (CAMP Research Group 2000; CAMP Research Group 2012) with budesonide, 0.7 cm/y with mometasone (Skonner 2011), a non-significant group difference of 0.43 cm/y with fluticasone (Sharek 2000b) and none with ciclesonide (Skoner 2008) in prepubertal school-aged children, suggesting molecule dependence of the impact of ICS on growth. This finding is consistent with that of a previous Cochrane systematic review (Sharek 2000a), which had produced solid evidence supporting the growth suppression of 400 µg of inhaled CFC-propelled beclomethasone (equivalent to 200 HFA-BDP) estimated at 1.54 cm/y over seven to 12 months in children with mild to moderate asthma. Current findings provide a clear indication that the use of ICS molecules believed to have no or little suppressive effect does have a minor, yet statistically significant, effect on growth when used at the lowest cutoff of the medium dosage compared with a lower dose.

In this review, the observed group difference of 0.2 cm in growth velocity over the first year of treatment (with an upper confidence interval limit of 0.4 cm/y), associated with an ICS dose higher by 100 to 150 µg, represents less than half the observed effect with similar doses compared with placebo (CAMP Research Group 2000; Sharek 2000a; Sharek 2000b; Skonner 2011; CAMP Research Group 2012). It is consistent with a very small dose-response effect and arguably is impossible to detect on a standard growth curve. One must recognise that the small observed group difference with the use of most recent molecules (fluticasone, mometasone and ciclesonide) might be much higher with a higher ICS dose and/or with older molecules (budesonide and beclomethasone), which have well-documented growth-suppressing effects.

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The two included trials (Shapiro 1998 b; Verberne 1998) that compared low doses versus higher doses of ICS (800 HFA-BDP equivalent) contributed between 3% and 30% of the weight in only a few outcomes (1.7, 1.8, 1.10, 1.11 and 1.12), such that we cannot adequately explore the possibility of a differential effect on growth of a high versus low ICS dose. Although poorly controlled asthma may delay growth in children (NHLBI Expert Panel Report 2012), evidence to support this statement is weak. Yet we cannot rule out the possibility of a growth-suppressive effect of poorly controlled asthma in children receiving a lower ICS dose, which could counterbalance the growth suppression associated with a higher ICS dose. If disease-associated growth suppression was indeed possible, even in children with mild to moderate asthma, the design of this review is adequate, as we are interested in the net growth-suppressive effect of ICS therapy in children with asthma. In the absence of a placebo-controlled group, we cannot rule out the unlikely hypothesis that most growth retardation may occur at a very low dose of ICS therapy, which could explain the clinically small group difference between different ICS doses. The systemic availability of ICS is directly related to cortisol suppression and growth suppression, especially in children. The particle size of the drug molecule and use of different devices influence systemic availabilities (Martin 2002; Agertoft 2003; Agertoft 2003a). The third of this series of Cochrane reviews will examine the effects of different devices on the growth of asthmatic children.

As trials contributing data lasted a maximum of one year, the long-term impact of different ICS doses on growth velocity beyond one year could not be explored. Our observations complement those of several placebo-controlled studies, suggesting that the growth-suppressive effect of ICS is non-cumulative (Simons 1997) and may be associated with partial catch-up (Guilbert 2006a), as a growth deficit may be sustained until adulthood (CAMP Research Group 2012).

Of interest, the significant group difference in the 'unadjusted' change in height between zero and three months suggests a favourable effect of ICS on growth in the first three months of use, perhaps via improved asthma control. Of note, 54% of the weight of this analysis is derived from a single trial testing various doses of ciclesonide (with a molecule with no demonstrated suppressive effect on growth) in children with partially or poorly controlled asthma (Pedersen 2010; Pedersen 2010 b). However, this hypothesis is weakened by the absence of any statistically significant effect observed between three and six months and between zero and six months, suggesting a transient beneficial effect on growth, insufficient power or a type 1 error, that is, falsely identifying a significant effect when one does not exist. Of importance, the absence of adjustment for important confounders decreases the quality of the evidence derived from this outcome.

No statistically significant group difference was observed in other aggregated parameters, namely, change from baseline in weight, change in SD scores (height) and body mass index. A significant group difference in skeletal maturation of a quarter of a year was observed, in disfavour of a higher dose (200 µg/d), with an ICS group difference of 100 µg/d of HFA-propelled beclomethasone or equivalent (Allen 1998). Given that children with asthma may have delayed puberty (boys more than girls) (NHLBI Expert Panel Report 2012), whether the delayed maturation is due to poorer asthma control or is associated with greater use of ICS, or both, remains to be determined. Nevertheless, the observation on skeletal maturation, derived from a single study, requires replication.

Summary of main results

Three industry-funded trials with high methodological quality (resulting in four dose comparisons) contributed data to the main outcome, that is, growth velocity; they measured 728 school-aged children with mild to moderate asthma and used one of three molecules (fluticasone, ciclesonide or mometasone) to compare groups with a dose difference ≤ 150 µg over 52 weeks. A significant group difference in linear growth was observed over 12 months, indicating lower growth velocity in the higher ICS dose group (mean difference 0.20 cm/y, 95% CI 0.02 to 0.39); no heterogeneity was apparent. Within aggregated trials, the different ICS molecules did not significantly influence the magnitude of effect (P value 0.33), but no trial contributing data to the main outcome used budesonide or beclomethasone.

Overall completeness and applicability of evidence

This review summarises the best evidence available until March 2014 as derived from 10 trials (resulting in 17 comparisons) aggregating 3394 children with mild to moderate persistent asthma. Most trials were of high methodological quality. The systematic search, which identified eligible trials from published and unpublished reports (406 citations) and used selection and data extraction by two independent review authors, minimised the risk of inclusion bias. The outstanding collaboration of study authors and pharmaceutical groups from six trials (resulting in eight comparisons) allowed us to obtain additional unpublished data and to confirm methodological quality, both of which strengthened the meta-analysis. Because of the paucity of trials reporting these data, four of 15 secondary outcomes could not be aggregated. The long-term impact of low versus high ICS dose on growth velocity, weight, skeletal maturation and body mass index in children using the same and older ICS molecules beyond one year of follow-up remains to be addressed. Sensitivity analysis could not be performed, as all trials were at low risk of bias, the adherence rate of ICS was seldom reported and all included trials contributing data to the main outcome were funded by the pharmaceutical industry and published as full text. In real life, most physicians would adjust downward or upward the dose of ICS needed to maintain control; we acknowledge that the artificially fixed dose for one to four years would overestimate growth suppression when compared with the recommended practice of decreasing to the minimal effective dose, yet this is a basic requirement of FDA guidelines for assessment of the effects of ICS on growth. Our study results support the Global Initiative for Asthma (GINA) guideline recommendations and serve as a reminder that physicians should strive to adjust to the minimal effective ICS dose, irrespective of the ICS molecule selected.

Quality of the evidence

The quality of evidence of growth velocity was high, but for outcomes reflecting change in height from baseline between treatment groups, the quality of evidence was downgraded to moderate owing to possible prognostic imbalance from the use of unadjusted data in the analysis. We downgraded the quality of evidence to low for BMI, weight and skeletal maturation due to imprecision (See Summary of findings for the main comparison).

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Potential biases in the review process

Some bias may or may not have affected the magnitude of effect. All trials contributing data to the main outcome used a stadiometer to measure growth; this enhances the internal validity of the findings. As each trial compared different doses using the same device, we could not explore the possibility that the magnitude of effect may be associated with the choice of inhalation device; however a linked Cochrane review is addressing this point (Zhang 2011).

Agreements and disagreements with other studies or reviews

To our knowledge, no prior systematic review has evaluated the relationship between dose of ICS and risk of growth impairment in children with persistent asthma.

AUTHORS' CONCLUSIONS

Implications for practice

In prepubescent school-aged children with mild to moderate persistent asthma, a very small but statistically significant difference in linear growth over 12 months was observed between groups using ICS, with a dose difference ≤ 150 µg HFA-beclomethasone equivalent over 52 weeks. A group difference of 0.2 cm was observed, favouring higher growth velocity with the lower ICS dose of fluticasone, mometasone or ciclesonide. As ICS doses most often were in the low range or at the limit of low and medium doses (200 µg), data were insufficient to allow exploration of a potential dose-response relationship between ICS for a difference greater than 150 µg. We are unable to comment on the possible effects on growth of different ICS molecules, although fluticasone, mometasone and ciclesonide at doses of 200 µg/d or less did not appear to explain any variation in the size of effect across the studies. In view of prevailing parents' and physicians' concerns about the growth-suppressive effect of ICS, lack or inadequate reporting of growth measurements in more than 86% (19/22) of eligible paediatric trials is a matter of concern and should call for systematic reporting of growth in all ICS paediatric trials. Until more data on low versus moderate and higher ICS doses are available, we recommend that ICS should be used at the lowest effective dose with the safest ICS molecules, and that children's growth should be systematically monitored during any ICS treatment.

Implications for research

Long-term (longer than one year) trials of high methodological quality with adequate documentation of linear growth velocity in children with asthma treated with ICS are needed to provide a fair comparison of the safety of different ICS dose options. Future trials should aim for the following design characteristics.

- Pragmatic effectiveness trials.
- Double-blinding, adequate randomisation and complete reporting of withdrawals and dropouts with intention-to-treat analysis.
- Parallel-group design.
- Complete reporting of continuous (denominators, mean change and mean standard deviation of change) and dichotomous (denominators and rate) data.
- Minimal intervention period of 12 to 24 weeks to assess medium-term effects and, over several years, to assess the long-term impact of different ICS doses.
- Measuring and reporting, at minimum, of linear growth velocity at different time points during the study.
- Measuring and reporting of the change in standard deviation score (SDS) in growth velocity, in absolute gain in height, in weight z-score, in BMI and in skeletal maturation between the beginning and the end of treatment.
- Adequate reporting of the adherence rate and concomitant use of non-steroidal antiasthmatic drugs.
- Additional studies evaluating the impact on growth of LABA (long-acting beta-agonist) as a concomitant drug in children with ICS.

Given the paucity of paediatric trials reporting growth, growth measurements should be a requirement for all ICS drug trials whether funded by pharmaceutical companies or national granting agencies.

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CHARACTERISTICS OF STUDIES

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

Allen 1998

Methods	DESIGN: prospective, randomised, double-blind, parallel-group trial; in 19 clinical centres
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 219 ANALYSED PARTICIPANTS: N = 219 INTERVENTION: ICS (fluticasone propionate 100 µg/d): 85 CONTROL: ICS (fluticasone propionate 200 µg/d): 96 WITHDRAWALS: reported AGE: mean (years) (range): INTERVENTION: ICS (fluticasone propionate 100 µg/d): 8.1 ± 0.2 (4.5-11.9) CONTROL: ICS (fluticasone propionate 200 µg/d): 7.9 ± 0.2 (4.0-11.6) GENDER: N (male %): INTERVENTION: ICS (fluticasone propionate 100 µg/d): 62 (73) CONTROL: ICS (fluticasone propionate 200 µg/d): 72 (75) ASTHMA SEVERITY: persistent asthma for at least 3 months ASTHMA DURATION: not reported MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: Participants taking ICS or other antiasthma medications (e.g. β_2-agonists, theophylline, cromolyn) were allowed to continue taking these medications as needed during the run-in period ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • Children aged 4 to 11 years with persistent asthma of all severity diagnosed ≥ 3 months as defined in the American Thoracic Society criteria • Normal growth rates as defined by height measurements between the 5th and 95th centiles and growth velocity between the 10th and 97th centiles • Prepubescent as defined by a sexual maturity rating of 1 in any Tanner classification • On maintenance dose of ICS and required to maintain a fixed dosage regimen for at least 3 months before screening • Previous systemic corticosteroid use limited to a total of 60 days within the 2 years before study entry EXCLUSION CRITERIA • Patients who have received systemic, intranasal or ophthalmic corticosteroids within the month before study entry, or who had cataracts, glaucoma or any other significant concurrent disease or condition
Interventions	PROTOCOL DURATION

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Allen 1998 *(Continued)*

- Run-in = 2 weeks
- Intervention = 52 weeks

DEVICE: Diskhaler (Glaxo Wellcome, Eureaux, France)

DOSE OF ICS

- INTERVENTION: fluticasone propionate 100 µg/d
- CONTROL: fluticasone propionate 200 µg/d

CRITERIA FOR WITHDRAWAL FROM STUDY: reported

Outcomes	ANALYSIS: Comparisons between treatment groups for nonparametric variables were based on the Cochran-Mantel-Haenszel test, controlling for investigators; comparisons for parametric variables were based on an analysis of variance F test, controlling for investigator. Traditional safety analyses were based on data from the intent-to-treat population, comprising all participants exposed to the study drug, whereas growth analyses were based on the same population minus participants who achieved pubescence during the study OUTCOMES: reported at 52 weeks GROWTH: Outcomes were measured at the beginning and at the end of the run-in period; after the first, second and fourth weeks of the treatment period; and then every 4 weeks throughout the 52-week treatment period • Mean height increases from baseline to 52 weeks • Mean growth velocity at the end of treatment • Mean change from baseline in skeletal age: bone age of the left hand and wrist was performed at baseline and at 24 and 52 weeks GROWTH MEASUREMENT TECHNIQUE: All height measurements were taken using identical wall-mounted Harpenden stadiometers (manufactured by Holtain, Crymmych, Wales) PULMONARY FUNCTION TESTS: not reported FUNCTIONAL STATUS: not reported BIOMARKERS: not reported ADVERSE EVENTS: reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (1998) FUNDING: sponsored by a grant from Glaxo Wellcome Inc. CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer random number generator: “At the end of the run-in period, eligible patients were stratified according to ICS use at study entry and randomly allocated to receive fluticasone propionate 50 µg or 100 µg, or matching placebo, twice daily via a Diskhaler”
Allocation concealment (selection bias)	Unclear risk	Insufficient information

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Allen 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Baker 1999

Methods	DESIGN: randomised, double-blind, placebo-controlled, parallel-group study; multi-centre
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 193 INTERVENTION: ICS (budesonide 250 µg/d): 94 CONTROL: ICS (budesonide 500 µg/d): 99 WITHDRAWALS: reported AGE: mean (months) (range): INTERVENTION: ICS (budesonide 250 µg/d): 54.6 (8-107) CONTROL: ICS (budesonide 500 µg/d): 54.3 (7-105) GENDER: N (male %): INTERVENTION: ICS (budesonide 250 µg/d): 59 (63) CONTROL: ICS (budesonide 500 µg/d): 62 (63) ASTHMA SEVERITY: moderate persistent asthma ASTHMA DURATION: mean disease duration months (range): INTERVENTION: ICS (budesonide 250 µg/d): 34.2 (2-92) CONTROL: ICS (budesonide 500 µg/d): 32.4 (4-96) MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: not reported ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • Patients aged 6 months to 8 years with diagnosis of asthma

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Baker 1999 *(Continued)*

- Use of at least 1 asthma medication daily with periodic using of a rescue medication as needed for at least 3 months before visit 1
- On same ICS at stable dose for at least 2 months before visit 1
- Demonstrated $FEV_1 \geq 50\%$ of predicted value and 15% reversibility after a standard dose of ICS

EXCLUSION CRITERIA

- Severe and/ or unstable asthma
- Long-term use of systemic steroids within 12 weeks of visit 1
- Intermittent use of systemic steroids within 30 days

Interventions	PROTOCOL DURATION • Run-in = 2 to 3 weeks • Intervention = 12 weeks DEVICE: medication or placebo given by the Pari LC-Jet Plus nebuliser connected to a Pari Master compressor (Pari Respiratory Equipment, Inc, Richmond, VA) with use of a mouthpiece or face mask DOSE OF ICS • INTERVENTION: budesonide 250 µg/d • CONTROL: budesonide 500 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: Done in "all patients treated" (intention-to-treat). Analysis of variance techniques and Fisher's exact test used OUTCOMES: GROWTH MEASUREMENT TECHNIQUE: not reported PULMONARY FUNCTION TESTS • Mean change in FEV_1 throughout weeks 0 to 12 • Mean change in morning and evening PEFR throughout weeks 0 to 12 FUNCTIONAL STATUS • Change from baseline in daytime and nighttime symptoms BIOMARKERS • Serum cortisol after ACTH stimulation test ADVERSE EVENTS: reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (1999) FUNDING: supported in part by Astra USA CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement

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Baker 1999 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Baker 1999 b

Methods	DESIGN: randomised, double-blind, placebo-controlled, parallel-group study; multi-centre
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 192 INTERVENTION: ICS (budesonide 250 µg/d): 94 CONTROL: ICS (budesonide 1000 µg/d): 98 WITHDRAWALS: reported AGE: mean (months) (range): INTERVENTION: ICS (budesonide 250 µg/d): 54.6 (8-107) CONTROL: ICS (budesonide 1000 µg/d): 53.0 (9-107) GENDER: N (male %): INTERVENTION: ICS (budesonide 250 µg/d): 59 (63) CONTROL: ICS (budesonide 1000 µg/d): 68 (69) ASTHMA SEVERITY: moderate persistent asthma ASTHMA DURATION: mean disease duration months (range): INTERVENTION: ICS (budesonide 250 µg/d): 34.2 (2-92) CONTROL: ICS (budesonide 1000 µg/d): 33.3 (4-88) MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported

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Baker 1999 b *(Continued)*

	DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: not reported ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • As above EXCLUSION CRITERIA • As above
Interventions	PROTOCOL DURATION • Run-in = 2 to 3 weeks • Intervention = 12 weeks DEVICE: medication or placebo given by the Pari LC-Jet Plus nebuliser connected to a Pari Master compressor (Pari Respiratory Equipment, Inc, Richmond, VA) with use of a mouthpiece or face mask DOSE OF ICS • INTERVENTION: budesonide 250 µg/d • CONTROL: budesonide 1000 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	As above
Notes	As above

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

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Brand 2011

Methods	DESIGN: randomised, double-blind, placebo-controlled, parallel-group study; in 77 centres
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 370 ANALYSED PARTICIPANTS: N = 369 INTERVENTION: ICS (ciclesonide 40 µg/d): 248 CONTROL: ICS (ciclesonide 80 µg/d): 246 WITHDRAWALS: reported AGE: mean (years) (range): INTERVENTION: ICS (ciclesonide 40 µg/d): 4.0 (2.0-6.0) CONTROL: ICS (ciclesonide 80 µg/d):4.0 (2.0-6.0) GENDER: N (male %): INTERVENTION: ICS (ciclesonide 40 µg/d): 164 (66.1) CONTROL: ICS (ciclesonide 80 µg/d): 160 (65.3) ASTHMA SEVERITY: ASTHMA DURATION: median disease duration months (range): INTERVENTION: ICS (ciclesonide 40 µg/d): 21.6 (3.8-81.1) CONTROL: ICS (ciclesonide 80 µg/d): 22.5 (5.9-79.8) MEAN (± SD) β_2-AGONIST USE (puffs/d): reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: ICS pretreatment n (%): INTERVENTION: ICS (ciclesonide 40 µg/d): 143 (57.7) CONTROL: ICS (ciclesonide 80 µg/d):138 (56.3) MEAN BASELINE ICS DAILY DOSE mg (SD): beclomethasone dipropionate equivalent INTERVENTION: ICS (ciclesonide 40 µg/d): 353.0 (141.6) CONTROL: ICS (ciclesonide 80 µg/d): 339.7 (143.0) ATOPY (% of participants): reported; N (%) of participants with history of allergies ASIAN: INTERVENTION: ICS (ciclesonide) at specific dose (40 µg/d): 16 (36.4) CONTROL: ICS (ciclesonide 80 µg/d): 21 (47.7) NON-ASIAN: INTERVENTION: ICS (ciclesonide 40 µg/d): 106 (52.0) CONTROL: ICS (ciclesonide 80 µg/d): 107 (53.2)

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Brand 2011 *(Continued)*

	ELIGIBILITY CRITERIA • Children aged 2 to 6 years with documented clinical history of asthma (defined as 3 or more episodes of wheezing, or troublesome recurrent symptoms and/or episodes of wheezing, as reported by parents) for 6 months, plus a positive stringent asthma predictive index or a positive screening test for atopy EXCLUSION CRITERIA • Previous use of systemic steroids • Respiratory tract infection in the month before the study • History of exclusive episodic viral wheezing • Concomitant severe diseases • Diseases impairing lung function or precluding ICS use • > 2 hospitalisations for wheezing in the past year • History of life-threatening wheeze or mechanical ventilation • Premature birth • Abnormal height
Interventions	PROTOCOL DURATION • Run-in = 2 to 4 weeks • Intervention = 24 weeks DEVICE: study medication dispensed via a hydrofluoroalkane metered-dose inhaler, one puff daily in the evening, administered with a spacer (AeroChamber Plus) DOSE OF ICS • INTERVENTION: ciclesonide 40 µg/d • CONTROL: ciclesonide 80 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: Efficacy analyses were planned a priori to be conducted in the intent-to-treat population. The Tarone trend test examined the probability of a participant's experiencing severe wheeze exacerbation before study end in those using ciclesonide 160 mg versus placebo, and in the other ciclesonide groups versus placebo. Subsequently, the proportion of participants experiencing severe wheeze exacerbation was compared between pooled ciclesonide groups and the placebo group using Fisher's exact test. Diary data were analysed using non-parametric methods, and lung function and stadiometry data using analysis of co-variance OUTCOMES: GROWTH MEASUREMENT TECHNIQUE: Participant height was measured by stadiometry at the start of the treatment period, after 12 weeks' treatment and at study end PULMONARY FUNCTION TESTS • Change in lung function at study end compared with baseline in children aged 4 to 6 years able to provide reliable and reproducible spirometry measurements following published recommendations for this age group: FEV_1, PEFR and $FEF_{25\%-75\%}$ FUNCTIONAL STATUS • (Time to) severe wheeze exacerbation, defined as worsening of asthma/wheeze symptoms requiring treatment with systemic steroids as judged by the treating physician • Percentage of wheeze-controlled days (days without wheeze and without use of rescue medication) • Daily symptom score

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Brand 2011 *(Continued)*

	• Use of rescue medication BIOMARKERS • Serum and urinary cortisol levels were measured at baseline, after 12 weeks' treatment (urine levels only) and at study end ADVERSE EVENTS: reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (2011) FUNDING: supported by Nycomed Pharmaceuticals, Konstanz, Germany CONFIRMATION OF METHODOLOGY: received Data received from study author and Takeda Global Research & Development Centre (Europe), Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer random number generator: "using a computer-generated randomisation list following age-stratified block randomisation (2-3 yrs and 4 -6 yrs)"
Allocation concealment (selection bias)	Low risk	Central allocation (including telephone, web-based and pharmacy-controlled randomisation): "Allocation of treatment was performed by an independent telephone centre, and was blinded to study investigators enrolling the patients"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way
Other bias	Low risk	Study apparently free of other sources of bias

Brand 2011 b

Methods	DESIGN: randomised, double-blind, placebo-controlled, parallel-group study; in 77 centres
Participants	SYMPTOMATIC PARTICIPANTS

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Brand 2011 b *(Continued)*

RANDOMLY ASSIGNED: N = 377

ANALYSED PARTICIPANTS: N = 377

INTERVENTION: ICS (ciclesonide 40 µg/d): 248

CONTROL: ICS (ciclesonide 160 µg/d): 253

WITHDRAWALS: reported

AGE: mean (years) (range):

INTERVENTION: ICS (ciclesonide 40 µg/d): 4.0 (2.0-6.0)

CONTROL: ICS (ciclesonide 160 µg/d): 4.0 (2.0-6.0)

GENDER: N (male %):

INTERVENTION: ICS (ciclesonide 40 µg/d): 164 (66.1)

CONTROL: ICS (ciclesonide 160 µg/d): 137 (54.1)

ASTHMA SEVERITY:

ASTHMA DURATION: median disease duration months (range):

INTERVENTION: ICS (ciclesonide 40 µg/d): 21.6 (3.8-81.1)

CONTROL: ICS (ciclesonide 160 µg/d): 23.5 (5.9-77.1)

MEAN (± SD) β_2-AGONIST USE (puffs/d): reported

DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN:

ICS PRETREATMENT n (%):

INTERVENTION: ICS (ciclesonide 40 µg/d): 143 (57.7)

CONTROL: ICS (ciclesonide 160 µg/d): 135 (53.4)

MEAN BASELINE ICS DAILY DOSE mg (SD): beclomethasone dipropionate equivalent

INTERVENTION: ICS (ciclesonide 40 µg/d): 353.0 (141.6)

CONTROL: ICS (ciclesonide 160 µg/d): 335.8 (142.2)

ATOPY (% of participants): reported; N (%) of participants with history of allergies

ASIAN:

INTERVENTION: ICS (ciclesonide 40 µg/d): 16 (36.4)

CONTROL: ICS (ciclesonide 160 µg/d): 21 (46.7)

NON-ASIAN

INTERVENTION: ICS (ciclesonide 40 µg/d): 106 (52.0)

CONTROL: ICS (ciclesonide 160 µg/d): 122 (58.7)

ELIGIBILITY CRITERIA

- As above

EXCLUSION CRITERIA

- As above

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Brand 2011 b *(Continued)*

Interventions	PROTOCOL DURATION • Run-in = 2 to 4 weeks • Intervention = 24 weeks DEVICE: study medication dispensed via a hydrofluoroalkane metered-dose inhaler, one puff daily in the evening, administered with a spacer (AeroChamber Plus) DOSE OF ICS • INTERVENTION: ciclesonide 40 µg/d • CONTROL: ciclesonide 160 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	As above
Notes	As above

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer random number generator
Allocation concealment (selection bias)	Low risk	Central allocation (including telephone, web-based and pharmacy-controlled randomisation)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Chen 2001

Methods	Randomised, single-blind, placebo-controlled, parallel-group study; 1 centre
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 20

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Chen 2001 *(Continued)*

INTERVENTION: ICS: (beclomethasone dipropionate 200 µg/d): 10

CONTROL: ICS (beclomethasone dipropionate 400 µg/d): 10

WITHDRAWALS: no withdrawals

AGE: mean (years) (range):

INTERVENTION: ICS (beclomethasone dipropionate 200 µg/d): average 7 years

CONTROL: ICS (beclomethasone dipropionate 400 µg/d): average 9 years

GENDER: N (male %): not reported

ASTHMA SEVERITY: mild asthma

ASTHMA DURATION: not reported

MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported

DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: not reported

ATOPY (% of participants): not reported

ELIGIBILITY CRITERIA

- Children with mild asthma, diagnosed according to the Chinese Medical Society Respiratory Diseases Branch Asthma Group
- Not using any corticosteroid in past 6 months before inclusion in the study

EXCLUSION CRITERIA

- Not reported

Interventions	PROTOCOL DURATION • Run-in = 12 weeks • Intervention = 52 weeks DEVICE: not reported (in translation of the study) DOSE OF ICS • INTERVENTION: beclomethasone dipropionate 200 µg/d • CONTROL: beclomethasone dipropionate 400 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: not reported (in translation of the study) OUTCOMES GROWTH MEASUREMENT TECHNIQUE: not reported (in translation of the study) PULMONARY FUNCTION TESTS • Bronchial inhalation of histamine provocation test FUNCTIONAL STATUS • Children's height BIOMARKERS

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Chen 2001 *(Continued)*

	• HPAA function • BMD, osteocalcin, serum calcium concentration, serum phosphorus concentration, blood alkaline phosphatase ADVERSE EVENTS: not reported WITHDRAWALS: no withdrawals
Notes	PUBLICATION: full paper (2001) FUNDING: not reported CONFIRMATION OF METHODOLOGY: not received Study author could not be contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a random number table: “The patients were allocated by random number table and stratified by moderate and severe grades”
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding or incomplete blinding; single-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding or incomplete blinding; single-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for missing outcome data unlikely to be related to true outcomes
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Doniec 2004

Methods	DESIGN: randomised, parallel-group clinical study
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 22 INTERVENTION: ICS (budesonide 200 µg/d): 9 CONTROL: ICS (budesonide 800 µg/d): 11 WITHDRAWALS: reported AGE: mean (years) (range):

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Doniec 2004 *(Continued)*

	INTERVENTION: ICS (budesonide 200 µg/d): 11.8 ± 2.0 CONTROL: ICS (budesonide 800 µg/d): 13.2 ± 2.3 GENDER: N (male %): INTERVENTION: ICS (budesonide 200 µg/d): 6 (66.6) CONTROL: ICS (budesonide 800 µg/d): 6 (54.5) ASTHMA SEVERITY: mild asthma ASTHMA DURATION: median (months) (range): not reported MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: none (steroid naive) ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • Mild asthma diagnosed according to GINA protocol • Steroid naive • Treated with disodium cromoglycate EXCLUSION CRITERIA: not reported
Interventions	PROTOCOL DURATION • Run-in = not reported • Intervention = 12 weeks DEVICE: dry powder inhaler (Pulmicort Turbuhaler) DOSE OF ICS • INTERVENTION: budesonide 200 µg/d • CONTROL: budesonide 800 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: Student's t test OUTCOMES GROWTH MEASUREMENT TECHNIQUE: not reported PULMONARY FUNCTION TESTS: at start of study and at 12 weeks • FEV_1; FVC FUNCTIONAL STATUS: not reported BIOMARKERS: at start of study and at 12 weeks • Plasma levels of native and cryptic met-enkephalin ADVERSE EVENTS: not reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (2004)

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Doniec 2004 *(Continued)*

	FUNDING: not reported CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Gelfand 2006

Methods	DESIGN: randomised, double-blind, multi-centre, placebo-controlled, parallel-group clinical study. This comprises 2 identical trials
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 511 INTERVENTION: ICS (ciclesonide 40 µg/d): 252 CONTROL: ICS (ciclesonide 80 µg/d): 259 WITHDRAWALS: reported AGE: mean (years) (range): INTERVENTION: ICS (ciclesonide 40 µg/d): 8.14 ± 0.14 (4-11) CONTROL: ICS (ciclesonide 80 µg/d): 8.20 ± 0.13 (4-11) GENDER: N (male %): INTERVENTION: ICS (ciclesonide 40 µg/d): 160 (63.5) CONTROL: ICS (ciclesonide 80 µg/d): 169 (65.3)

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Gelfand 2006 *(Continued)*

	ASTHMA SEVERITY: persistent asthma with all severity ASTHMA DURATION: mean (months) (range): INTERVENTION: ICS (ciclesonide 40 µg/d): 4.32 ± 0.18 (0.26-11.26) CONTROL: ICS (ciclesonide 80 µg/d): 4.35 ± 0.17 (0.25-11.10) MEAN (± SD) β_2-AGONIST USE (puffs/d): INTERVENTION: ICS (ciclesonide 40 µg/d): 1.60 CONTROL: ICS (ciclesonide 80 µg/d): 1.64 DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: placebo ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • Children aged 4 to 11 years with persistent asthma of all severity diagnosed ≥ 6 months as defined in National Institute of Health Guidelines • Patients on controller medications • Had FEV_1 predicted value ≥ 40% and ≤ 100% at the screening visit after β_2-agonists were withheld for ≥ 6 hours EXCLUSION CRITERIA • Patients with a history of life-threatening asthma or 2 or more hospitalisations for asthma exacerbations 1 year or less before the study, receiving treatment with injectable or oral corticosteroids within 30 days before screening or with a urine cortisol level < 10 µg/dL at screening
Interventions	PROTOCOL DURATION • Run-in = 5 to 21 days • Intervention = 12 weeks DEVICE: HFA-metered dose inhaler DOSE OF ICS • INTERVENTION: ciclesonide 40 µg/d • CONTROL: ciclesonide 80 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: intention-to-treat analysis. All participants receiving 1 or more doses of study medication with 1 or more post-baseline measurements of FEV_1 and height were included in the analysis. Missing values for withdrawals were handled by the last value extended principle OUTCOMES: reported at 12 weeks. Outcomes were measured every 1, 2, 4, 8 and 12 weeks GROWTH MEASUREMENT TECHNIQUE: not reported PULMONARY FUNCTION TESTS • Change in FEV_1 percentage predicted between baseline and week 12 • Change in FEV_1 percentage predicted at all visits • Absolute change in FEV_1 • Change in AM PEFR and PM PEFR from baseline

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Gelfand 2006 *(Continued)*

	FUNCTIONAL STATUS • 24-Hour asthma symptom score • Albuterol use • Nighttime awakenings • Percentage of asthma symptom-free days • Quality of life assessments BIOMARKERS • Blood samples for cortisol measurements • Cosyntropin stimulation test ADVERSE EVENTS: reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (2006) FUNDING: funded by Aventis Pharmaceuticals CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified: ”We report the results of a prespecified integrated analysis of the efficacy and safety data from 2 identical, double-blinded, randomised, placebo-controlled studies of ciclesonide (at doses of 40, 80, and 160 µg) administered once daily to children with persistent asthma”
Other bias	Low risk	Study apparently free of other sources of bias

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Gelfand 2006 b

Methods	DESIGN: randomised, double-blind, multi-centre, placebo-controlled, parallel-group clinical study. This comprises 2 identical trials
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 505 INTERVENTION: ICS (ciclesonide 40 µg/d): 252 CONTROL: ICS (ciclesonide 160 µg/d): 253 WITHDRAWALS: reported AGE: mean (years) (range): INTERVENTION: ICS (ciclesonide 40 µg/d): 8.14 ± 0.14 (4-11) CONTROL: ICS (ciclesonide 160 µg/d): 8.33 ± 0.12 (4-11) GENDER: N (male %): INTERVENTION: ICS (ciclesonide 40 µg/d): 160 (63.5) CONTROL: ICS (ciclesonide 160 µg/d): 154 (60.9) ASTHMA SEVERITY: persistent asthma with all severity ASTHMA DURATION: mean (months) (range): INTERVENTION: ICS (ciclesonide 40 µg/d): 4.32 ± 0.18 (0.26-11.26) CONTROL: ICS (ciclesonide 160 µg/d): 4.38 ± 0.17 (0.53-12.06) MEAN (± SD) β_2-AGONIST USE (puffs/d): INTERVENTION: ICS (ciclesonide 40 µg/d): 1.60 CONTROL: ICS (ciclesonide 160 µg/d): 1.72 DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: placebo ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • As above EXCLUSION CRITERIA • As above
Interventions	PROTOCOL DURATION • Run-in = 5 to 21 days • Intervention = 12 weeks DEVICE: HFA-metered-dose inhaler DOSE OF ICS • INTERVENTION: ciclesonide 40 µg/d • CONTROL: ciclesonide 160 µg/d

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Gelfand 2006 b *(Continued)*

	CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	As above
Notes	As above

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Giorgi 1998

Methods	DESIGN: randomised, open-label, multi-centre, parallel-group clinical study
Participants	CHILDREN WITH MILD ASTHMA RANDOMLY ASSIGNED: N = 29 INTERVENTION: ICS (flunisolide 600 µg/d): 15 CONTROL: ICS (flunisolide 1200 µg/d): 14 WITHDRAWALS: reported AGE: mean (years) (range): INTERVENTION: ICS (flunisolide 600 µg/d) 8.6 (6-11) CONTROL: ICS (flunisolide 1200 µg/d) 8.5 (7-10) GENDER: N (male %): INTERVENTION: ICS (flunisolide 600 µg/d) 11 (73%) CONTROL: ICS (flunisolide 1200 µg/d) 9 (64%)

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Giorgi 1998 *(Continued)*

	ASTHMA SEVERITY: mild asthma ASTHMA DURATION: mean (months) (range): INTERVENTION: ICS (flunisolide 600 µg/d) 4.8 (3-7) CONTROL: ICS (flunisolide 1200 µg/d) 4.9 (3-7) MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: placebo ATOPY N (% of participants): reported INTERVENTION: ICS (flunisolide 600 µg/d) 9 (60%) CONTROL: ICS (flunisolide 1200 µg/d) 10 (71%) ELIGIBILITY CRITERIA • Prepubertal children with mild asthma who used inhaled beta stimulants regularly were eligible for participation in the study EXCLUSION CRITERIA • Patients with any other pulmonary disease, serious concomitant disease or a history of bone fractures were excluded from participation
Interventions	PROTOCOL DURATION • Run-in = 2 weeks. • Intervention = 12 weeks DEVICE: jet nebulisers (Soffio Nuovo, Markos, Monza, Italy) DOSE OF ICS • INTERVENTION: flunisolide 600 µg/d • CONTROL: flunisolide 1200 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: no intention-to-treat analysis OUTCOMES: reported at 12 weeks. Outcomes were measured at 2, 3 and 4 months GROWTH MEARSUREMENT TECHNIQUE: not reported PULMONARY FUNCTION TESTS: not measured FUNCTIONAL STATUS: not measured BIOMARKERS • OC • BALP • PICP • ICTP ADVERSE EVENTS: not reported WITHDRAWALS: reported

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Giorgi 1998 *(Continued)*

Notes	PUBLICATION: full paper (1998) FUNDING: funded by Valeas Pharmaceuticals CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This trial was randomised but the technique of randomisation was not described
Allocation concealment (selection bias)	High risk	No allocation concealment used in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	No measures reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals per group not reported
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	This was an open-label study and the primary outcome was not specified clearly

Jonasson 1998

Methods	DESIGN: a randomised, double-blind, placebo-controlled trial
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 83 INTERVENTION: ICS (budesonide 100 µg/d o.d.): 41 CONTROL: ICS (budesonide 200 µg/d o.d.): 42 WITHDRAWALS: reported AGE: mean (years) (range): INTERVENTION: ICS (budesonide 100 µg/d o.d.): 10.0 CONTROL: ICS (budesonide 200 µg/d o.d.): 9.8 GENDER: N (male %): INTERVENTION: ICS (budesonide 100 µg/d o.d.): 23 (54.7)

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Jonasson 1998 *(Continued)*

CONTROL: ICS (budesonide 200 µg/d o.d.): 31(75.6)

ASTHMA SEVERITY: mild asthma

ASTHMA DURATION: not reported

MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported

DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: none within 2 months

ATOPY: N (% of participants):

INTERVENTION: ICS (budesonide 100 µg/d o.d.): 25 (59.5)

CONTROL: ICS (budesonide 200 µg/d o.d.): 31 (75.6)

ELIGIBILITY CRITERIA

- Diagnosis of asthma, based on definition in the International Consensus report and in the Nordic Consensus report
- Patients had three previous obstructive episodes or one previous obstructive episode with atopy; at least one of these episodes had to have occurred within the year before the first visit

EXCLUSION CRITERIA

- Patients used ICS within 2 months, or cromoglycate and/or nedocromil within 4 weeks, of entry
- Patient had a lower respiratory tract infection or exacerbation of asthma requiring an emergency department visit and/or hospitalisations in the 4 weeks before entry

Interventions	PROTOCOL DURATION • Run-in = 2 weeks • Intervention = 12 weeks DEVICE: Turbuhaler inhalers DOSE OF ICS • INTERVENTION: budesonide 100 µg/d o.d. • CONTROL: budesonide 200 µg/d o.d. CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: intention to-treat; analysis of variance (ANOVA). Missing values were handled by applying the last value extended principle. For diary variables, this was accomplished by extending the period means OUTCOMES GROWTH MEASUREMENT TECHNIQUE: not reported PULMONARY FUNCTION TESTS • Mean maximum fall in FEV_1 (% fall from pre-exercise value) after the exercise test measured at baseline and after 12 weeks of treatment • Mean percentage increase in PD_{20} (µmol) from baseline to end of treatment • Change in PEFR (% pred) (lung function measured every 4 weeks); the difference FEV_1, $FEF_{25\%}$, $FEF_{50\%}$ and $FEF_{75\%}$ at all visits throughout the study period FUNCTIONAL STATUS

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Jonasson 1998 *(Continued)*

	• Mean values for asthma symptoms BIOMARKERS: not done ADVERSE EVENTS: reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (1998) FUNDING: not provided CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation: "patients were randomised into four parallel groups in balanced blocks"
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study appears to be free of other sources of bias

Jonasson 2000

Methods	DESIGN: double-blind, placebo-controlled, single-centre extension trial
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 60 INTERVENTION: ICS (budesonide 100 µg/d o.d.): 28 CONTROL: ICS (budesonide 200 µg/d o.d.): 32 WITHDRAWALS: reported AGE: mean (years) (range):

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Jonasson 2000 *(Continued)*

INTERVENTION: ICS (budesonide 100 µg/d o.d.): 9.5

CONTROL: ICS (budesonide 200 µg/d o.d.): 10.0

GENDER: male N (%):

INTERVENTION: ICS (budesonide 100 µg/d o.d.): 23 (82.1)

CONTROL: ICS (budesonide 200 µg/d o.d.): 17 (53.1)

ASTHMA SEVERITY: mild asthma

ASTHMA DURATION: not reported

MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported

DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: All participants in the present study were already randomly assigned to 4 parallel groups in balanced blocks 3 months before inclusion in the present study (see study above, Jonasson 1998)

ATOPY: N (% of participants):

INTERVENTION: ICS (budesonide 100 µg/d o.d.): 20 (71.4)

CONTROL: ICS (budesonide 200 µg/d o.d.): 21(65.6)

ELIGIBILITY CRITERIA

- Must have participated in and completed the initial 12-week trial (see study above, Jonasson 1998)

EXCLUSION CRITERIA

- See study above, Jonasson 1998

Interventions	PROTOCOL DURATION • Run-in = preceded by a 12-week trial • Intervention = 96 weeks DEVICE: Turbuhaler inhalers DOSE OF ICS • INTERVENTION: budesonide 100 µg/d • CONTROL: budesonide 200 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY:
Outcomes	ANALYSIS: Statistical analysis was carried out on the intention-to-treat principle. Missing values for withdrawals were handled by the last value extended principle. Analysis was done by analysis of covariance (ANCOVA) and ANOVA models. An additive model was used when diary variables, lung-function variables and the maximum fall in FEV_1 after the exercise test were analysed; a multiplicative model was used when plethysmography variables and PD_{20} were analysed OUTCOMES GROWTH MEASUREMENT TECHNIQUE: Growth velocity was determined from measurements of participant height at every visit throughout the study period by a wall-fixed stadiometer (Seca, Hamburg, Germany). Three trained persons carried out all height measurements during the study. The child was measured standing upright without shoes with the heels touching the wall to which the stadiometer was fixed. The movable part of the measuring device was placed lightly on the child's head before the child's height was read from a centimetre scale. At baseline, the participant's height was measured by 2 persons, and the mean value was registered

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Jonasson 2000 *(Continued)*

PULMONARY FUNCTION TESTS

- Change from baseline in maximum fall in FEV_1 after exercise test
- Changes in airway responsiveness (PD_{20})
- Difference FEV_1, $FEF_{25\%}$, $FEF_{50\%}$ and $FEF_{75\%}$ at all visits throughout the study period

FUNCTIONAL STATUS

- Asthma symptom scores

BIOMARKERS

- Blood sample for complete blood count and eosinophil count
- Skin prick tests

ADVERSE EVENTS: reported

WITHDRAWALS: reported

Notes	PUBLICATION: full paper (2000) FUNDING: not provided CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation: *"All patients in the present study were already randomised into four parallel groups in* *balanced blocks 3 months before inclusion in the present study"*
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

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Kemp 1999

Methods	DESIGN: multi-centre, randomised, double-blind, placebo-controlled, parallel-group study
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 174 INTERVENTION: ICS (budesonide 250 µg/d): 91 CONTROL: ICS (budesonide 500 µg/d): 83 WITHDRAWALS: reported AGE: mean (range) (months) INTERVENTION: ICS (budesonide 250 µg/d): 55.2 ± 25.5 (7-107) CONTROL: ICS (budesonide 500 µg/d): 52.4 ± 27.9 (10-107) GENDER: male N (%) INTERVENTION: ICS (budesonide 250 µg/d): 63 (69.2) CONTROL: ICS (budesonide 500 µg/d): 58 (69.9) ASTHMA SEVERITY: mild persistent asthma ASTHMA DURATION: mean (range) in months INTERVENTION: ICS (budesonide 250 µg/d): 35.4 ± 22.4 (5-97) CONTROL: ICS (budesonide 500 µg/d): 36.7 ± 25.1 (5-107) MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: not reported. Participants discontinued their chronic asthma medication at the end of the study ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • Age of 6 months to 8 years • Clinically diagnosed with asthma • Exacerbations of cough or wheezing in the 6 months before the study • Daily use of at least 1 chronic asthma medication • Periodic use of a bronchodilator for at least 3 months before enrolment • FEV_1 ≥ 50% of predicted normal and reversibility of 15% after albuterol (if possible to perform spirometric) EXCLUSION CRITERIA • Severe or unstable asthma • Symptoms limited to seasonal allergen exposure • Oral GCSs used intermittently within 30 days or prolonged treatment within 12 weeks of enrolment • Hospitalised for treatment of air obstruction within 30 days of enrolment • Upper or lower respiratory tract infection within 14 days of enrolment • Any other concomitant lung disease
Interventions	PROTOCOL DURATION • Run-in = 2 weeks

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Kemp 1999 *(Continued)*

	• Intervention = 12 weeks DEVICE: Pari LC-Jet Plus nebuliser (with mouthpiece or face mask) DOSE OF ICS • INTERVENTION: budesonide 250 µg/d • CONTROL: budesonide 500 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: not reported
Outcomes	ANALYSIS: intention-to-treat analysis; ANOVA; Fisher's exact test OUTCOMES: at enrolment, at randomisation, after 2, 4, 8 and 12 weeks of treatment GROWTH MEASUREMENT TECHNIQUE: not reported PULMONARY FUNCTION TESTS • Change in FEV_1 percentage predicted between baseline and week 12 • Absolute change in FEV_1 • Change in AM PEFR and PM PEFR from baseline FUNCTIONAL STATUS • Nighttime and daytime asthma symptom scores • Change from baseline in number of days that breakthrough medication was used BIOMARKERS: baseline and at end of study (12 weeks) • Blood samples for cortisol measurements and cosyntropin stimulation test ADVERSE EVENTS: reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (1996) FUNDING: funded by AstraZeneca CONFIRMATION OF METHODOLOGY: not received

Risk of bias

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

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Kemp 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Kemp 1999 b

Methods	DESIGN: multi-centre, randomised, double-blind, placebo-controlled, parallel-group study
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 174 INTERVENTION: ICS (budesonide 250 µg/d): 91 CONTROL: ICS (budesonide 1000 µg/d): 93 WITHDRAWALS: reported AGE: mean (range) (months) INTERVENTION: ICS (budesonide 250 µg/d): 55.2 ± 25.5 (7-107) CONTROL: ICS (budesonide 1000 µg/d): 56.0 ± 27.2 (6-107) GENDER: male N (%) INTERVENTION: ICS (budesonide 250 µg/d): 63 (69.2) CONTROL: ICS (budesonide 1000 µg/d): 56 (60.2) ASTHMA SEVERITY: mild persistent asthma ASTHMA DURATION: mean (range) in months INTERVENTION: ICS (budesonide 250 µg/d): 35.4 ± 22.4 (5-97) CONTROL: ICS (budesonide 1000 µg/d): 36.1 ± 24.4 (5-107) MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: not reported. Participants discontinued their chronic asthma medication at the end of the study ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • As above EXCLUSION CRITERIA • As above
Interventions	PROTOCOL DURATION

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Kemp 1999 b *(Continued)*

	• Run-in = 2 weeks • Intervention = 12 weeks DEVICE: Pari LC-Jet Plus nebuliser (with mouthpiece or face mask) DOSE OF ICS • INTERVENTION: budesonide 250 µg/d • CONTROL: budesonide 1000 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: not reported
Outcomes	As above
Notes	As above

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Kerwin 2008

Methods	DESIGN: randomised, parallel-group, double-blind, placebo-controlled trial; in multiple centres
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 206 INTERVENTION: ICS (budesonide 200 µg/d): 104 CONTROL: ICS (budesonide 800 µg/d): 102 WITHDRAWALS: reported

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Kerwin 2008 *(Continued)*

AGE: mean (SD) years:

INTERVENTION: ICS (budesonide 200 µg/d): 11.7 (2.8)

CONTROL: ICS (budesonide 800 µg/d): 11.5 (2.9)

GENDER: male N (%)

INTERVENTION: ICS (budesonide 200 µg/d): 59 (56.7)

CONTROL: ICS (budesonide 800 µg/d): 64 (62.7)

ASTHMA SEVERITY: mild asthma

ASTHMA DURATION: mean (SD) years

INTERVENTION: ICS (budesonide 200 µg/d): 6.7 (3.7)

CONTROL: ICS (budesonide 800 µg/d): 6.8 (3.9)

MEAN (± SD) β_2-AGONIST USE (puffs/d):

INTERVENTION: ICS (budesonide 200 µg/d): 0.5 (0.8)

CONTROL: ICS (budesonide 800 µg/d): 0.3 (0.7)

DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: Participants continued their usual ICS therapies (if any) and added a once-daily placebo treatment

ATOPY (% of participants): not reported

ELIGIBILITY CRITERIA

- Patients aged 6 to 17 years who had been diagnosed with asthma for ≥ 3 months
- Patients who had not previously been treated with an ICS or had been treated with a low-dose of ICS (maintained at a constant dose level) for no longer than 30 days before visit 1
- Patients who had a pre-bronchodilator FEV_1 of 75% to 90% (patients aged 6–11 years) or 60% to 90% (patients aged 12–17 years) of predicted
- Patients who met reversibility criteria (≥ 12%)
- Patients with a pre-bronchodilator FEV_1 between 91% and 95% of predicted normal were eligible if the ratio of FEV_1 to forced vital capacity (FEV_1/FVC) was < 0.80

EXCLUSION CRITERIA

- Severe asthma as judged by the investigator
- Life-threatening asthma (including any prior asthma intubation, respiratory arrest or seizures as a result of exacerbation of asthma)
- ≥ 2 asthma-related hospitalisations in the past year
- Use of systemic corticosteroids within 4 weeks of entry
- Use of other controller therapies (e.g. leukotriene modifiers [LTMs], long-acting β_2-adrenergic agonists [LABAs]) within 2 weeks of entry
- Recent clinically relevant respiratory disease as judged by the investigator (e.g. chronic obstructive pulmonary disease)
- Acute asthma exacerbation, or other significant disease
- Use of an experimental drug or device within 30 days of entry
- Smoking
- Hypersensitivity to study products

Interventions	PROTOCOL DURATION

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Kerwin 2008 *(Continued)*

- Run-in = 11 to 17 days
- Intervention = 12 weeks

DEVICE: dry powder inhaler

DOSE OF ICS

- INTERVENTION: budesonide 200 µg/d
- CONTROL: budesonide 800 µg/d

CRITERIA FOR WITHDRAWAL FROM STUDY: reported

Outcomes	ANALYSIS: Efficacy was assessed on an intent to-treat (ITT) basis; between-group differences in changes from baseline in the primary variable were also evaluated in the per-protocol population. Primary and secondary spirometry data and diary data were fit with an analysis of co-variance (ANCOVA) model; results of urine cortisol analysis were summarised with descriptive statistics OUTCOMES GROWTH MEASUREMENT TECHNIQUE: not reported PULMONARY FUNCTION TESTS: measured at randomisation; week 2, 4, 8 and 12 • Mean change from baseline in percentage of predicted normal FEV_1 to the average during the 12-week treatment period for each active treatment versus placebo FUNCTIONAL STATUS • Morning and evening PEFR • Daytime and nighttime asthma symptom scores • Inhalations of albuterol per day BIOMARKERS • Blood sample for pharmacokinetics • Urine collected over 24 hours for cortisol assessment ADVERSE EVENTS: reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (2008) FUNDING: funded by AstraZeneca LP CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer random number generator: "Using a computer-generated allocation schedule stratified by pharmacokinetic participation, patients were randomised in balanced blocks to receive 12 weeks of one of the following five treatments"
Allocation concealment (selection bias)	Unclear risk	Insufficient information

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Kerwin 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Kerwin 2008 b

Methods	DESIGN: randomised, parallel-group, double-blind, placebo-controlled trial; in multiple centres
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 204 INTERVENTION: ICS (budesonide 180 µg/d): 108 CONTROL: ICS (budesonide 360 µg/d): 96 WITHDRAWALS: reported AGE: mean (SD) years: INTERVENTION: ICS (budesonide 180 µg/d): 11.7 (2.9) CONTROL: ICS (budesonide 360 µg/d): 11.5 (2.9) GENDER: male N (%) INTERVENTION: CS (budesonide 180 µg/d): 76 (70.4) CONTROL: ICS (budesonide 360 µg/d): 67 (69.8) ASTHMA SEVERITY: mild asthma ASTHMA DURATION: mean (SD) years INTERVENTION: ICS (budesonide 180 µg/d): 7.1 (4.2) CONTROL: ICS (budesonide 360 µg/d): 7.2 (4.1) MEAN (± SD) β_2-AGONIST USE (puffs/d): INTERVENTION: ICS (budesonide 180 µg/d): 0.4 (0.9) CONTROL: ICS (budesonide 360 µg/d): 0.5 (1.0) DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: Participants continued their usual ICS therapies (if any) and added a once-daily placebo treatment

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Kerwin 2008 b *(Continued)*

	ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • As above EXCLUSION CRITERIA • As above
Interventions	PROTOCOL DURATION • Run-in = 11 to 17 days • Intervention = 12 weeks DEVICE: dry powder inhaler DOSE OF ICS • INTERVENTION: budesonide 180 µg/d • CONTROL: budesonide 360 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	As above
Notes	As above

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer random number generator
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

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Lemanske 2004

Methods	DESIGN: randomised, double-blind clinical trial
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: 205 WITHDRAWALS: not reported AGE: median (years) (range): 4 to 9 years GENDER: N (male %): not reported ASTHMA SEVERITY ASTHMA DURATION: median (months) (range): not reported MEAN (± SD) β_2-AGONIST USE (puffs/d): median (months) (range): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: not reported ATOPY (% of participants): not reported ELIGIBILITY CRITERIA: not reported EXCLUSION CRITERIA: not reported
Interventions	PROTOCOL DURATION • Run-in = not reported • Intervention = 48 weeks DEVICE: metered-dose inhaler DOSE OF ICS • INTERVENTION: mometasone furoate 100 µg/d • CONTROL: mometasone furoate 200 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY:
Outcomes	ANALYSIS: Efficacy was assessed on an intent to-treat (ITT) basis; between-group differences in changes from baseline in the primary variable were also evaluated in the per-protocol population. Primary and secondary spirometry data and diary data were fit with an analysis of co-variance (ANCOVA) model; results of urine cortisol analysis were summarised with descriptive statistics OUTCOMES GROWTH MEASUREMENT TECHNIQUE: stadiometric height measured and growth velocities calculated PULMONARY FUNCTION TESTS • PEFR FUNCTIONAL STATUS • Growth velocity • Bone age • Bone metabolism • Ophthalmic examination • Asthma control BIOMARKERS

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Lemanske 2004 *(Continued)*

	• Plasma and urine cortisol ADVERSE EVENTS: reported WITHDRAWALS: not reported
Notes	PUBLICATION: abstract; full paper not found FUNDING: not reported CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was randomised but the randomisation technique was not mentioned
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Incomplete reporting of details for judgement
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes described
Other bias	Low risk	No apparent risk of bias noted

Peden 1998

Methods	DESIGN: randomised, double-blind, double-dummy, placebo-controlled, parallel-group study; multi-centre
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 177 INTERVENTION: ICS (fluticasone 100 µg/d): 90 CONTROL: ICS (fluticasone 200 µg/d): 87 WITHDRAWALS: reported AGE: median (years) (range): 4 to 11 years INTERVENTION: ICS (fluticasone 100 µg/d): not reported

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Peden 1998 *(Continued)*

	CONTROL: ICS (fluticasone 200 µg/d): not reported GENDER: N (male %): INTERVENTION: ICS (fluticasone 100 µg/d): 53 (59) CONTROL: ICS (fluticasone 200 µg/d): 60 (68) ASTHMA SEVERITY: mild to moderate persistent asthma ASTHMA DURATION: not reported MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: not reported ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • Patients aged 4 to 11 years with diagnosis of chronic asthma • Symptoms requiring maintenance treatment over the 3 months immediately before the study • Baseline PEFR ≤ 85%; FEV_1 of 50% to 85%; reversibility of FEV_1 ≥ 15% documented within 6 months before study EXCLUSION CRITERIA • Life-threatening asthma or other severe concurrent disease • Exposure to or chicken-pox within 3 weeks before the study • Lower respiratory tract infection within the previous 2 weeks • Use of oral or parenteral corticosteroids within 1 month before study, use of methotrexate or gold salts, any over-the counter medication that might affect asthma course or medication • Participation in any previous clinical trial with the Diskus or Diskhaler device
Interventions	PROTOCOL DURATION • Run-in = 2 weeks • Intervention = 12 weeks DEVICE: Diskus or Diskhaler DOSE OF ICS • INTERVENTION: fluticasone 100 µg/d • CONTROL: fluticasone 200 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: done by intention-to treat analysis. Investigators used analysis of variance F test; nonparametric van Elteren test; and Kaplan-Meier estimates of survival OUTCOMES: weekly for first 4 weeks and every other week for remaining 8 weeks GROWTH MEASUREMENT TECHNIQUE: not reported PULMONARY FUNCTION TESTS • Mean change from baseline in FEV_1, morning PEFR FUNCTIONAL STATUS • Mean change in asthma symptom scores, albuterol use, nighttime awakenings/nights

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Peden 1998 *(Continued)*

	BIOMARKERS: at screening and at 12 weeks • Mean morning plasma cortisol concentration • Mean total urinary free-cortisol excretion ADVERSE EVENTS: reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (1998) FUNDING: funded by Glaxo Wellcome CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation Randomly assigned by strata (baseline therapy of ICS or cromolyn or β_2-agonist)
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Peden 1998 b

Methods	DESIGN: randomised, double-blind, double-dummy, placebo-controlled, parallel-group study; multi-centre
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 174 INTERVENTION: ICS (fluticasone 100 µg/d): 91 CONTROL: ICS (fluticasone 200 µg/d): 83 WITHDRAWALS: reported

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Peden 1998 b *(Continued)*

	AGE: median (years) (range): 4 to 11 years INTERVENTION: ICS (fluticasone 100 µg/d): not reported CONTROL: ICS (fluticasone 200 µg/d): not reported GENDER: N (male %): INTERVENTION: ICS (fluticasone 100 µg/d): 50 (55) CONTROL: ICS (fluticasone 200 µg/d): 50 (60) ASTHMA SEVERITY: mild to moderate persistent asthma ASTHMA DURATION: median (months) (range): not reported MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: not reported ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • As above EXCLUSION CRITERIA • As above
Interventions	PROTOCOL DURATION • Run-in = 2 weeks • Intervention = 12 weeks DEVICE: Diskus or Diskhaler DOSE OF ICS • INTERVENTION: fluticasone 100 µg/d • CONTROL: fluticasone 200 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	As above
Notes	As above

Risk of bias

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

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Peden 1998 b *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Pedersen 2010

Methods	DESIGN: randomised, double-blind, placebo-controlled, parallel-group clinical study
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 465 ANALYSED PARTICIPANTS: N = 465 INTERVENTION: ICS (ciclesonide 40 µg/d): 305 CONTROL: ICS (ciclesonide 80 µg/d): 312 WITHDRAWALS: reported AGE: median (years) (range): INTERVENTION: ICS (ciclesonide 40 µg/d): 8.0 (6-11) CONTROL: ICS (ciclesonide 80 µg/d): 8.0 (6-11) GENDER: N (male %): INTERVENTION: ICS (ciclesonide 40 µg/d): 210 (68.9%) CONTROL: ICS (ciclesonide 80 µg/d): 191 (61.2%) ASTHMA SEVERITY: persistent asthma but severity not reported ASTHMA DURATION: median (months) (range): INTERVENTION: ICS (ciclesonide 40 µg/d): 41.4 (6-127) CONTROL: ICS (ciclesonide 80 µg/d): 41.9 (5-128) MEAN (± SD) β_2-AGONIST USE (puffs/d): median (months) (range) INTERVENTION: ICS (ciclesonide 40 µg/d): 1.43 (0.00-7.86) CONTROL: ICS (ciclesonide 80 µg/d): 1.43 (0.00-7.14) DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: placebo ATOPY (% of participants): not reported ELIGIBILITY CRITERIA

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Pedersen 2010 *(Continued)*

- Male and female outpatients aged 6 to 11 years with a history of persistent bronchial asthma for ≥ 6 months
- Ability to perform reproducible lung function tests and use an acceptable MDI inhalation technique
- In the 30 days before study entry, participants could be treated with rescue medication only; a constant dose of fluticasone propionate 200 mg/d or equivalent; or other controller medications
- Randomisation criteria at the end of the run-in period included mean PEFR value (over last week) of 40% to 90% of predicted value, as well as FEV_1 reversibility of 12% predicted after inhalation of 200 to 400 mg salbutamol
- In addition, participants had to present asthma symptoms on at least 6 of the last 10 days of the baseline period, or had to have used at least 8 puffs of rescue medication within the last 10 days of the baseline period

EXCLUSION CRITERIA

- History of near fatal asthma; respiratory tract infection or asthma exacerbation within the last 30 days; 2 or more in-patient hospitalisations for asthma in the previous year; use of systemic glucocorticosteroids within 30 days before study entry or for > 60 days in the previous 2 years

Interventions	PROTOCOL DURATION • Run-in = 2 to 4 weeks • Intervention = 12 weeks DEVICE: metered-dose inhaler with or without spacer DOSE OF ICS • INTERVENTION: ciclesonide 40 µg/d • CONTROL: ciclesonide 80 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: intent-to-treat analysis OUTCOMES: reported at 12 weeks; change in height reported as least squares mean growth rate GROWTH MEASUREMENT TECHNIQUE: At investigational sites where a stadiometer was available, height was also measured at the start and the end of the treatment period, as stadiometry is widely acknowledged as the most reliable means of measuring height and is recommended by the Food and Drug Administration (FDA) for studies assessing growth PULMONARY FUNCTION TESTS: mean change in FEV_1 and PEFR reported FUNCTIONAL STATUS • Percentage of days with asthma control • Change in asthma symptom score • Change in use of rescue medications • Change in PAQLQ overall score BIOMARKERS • Change in urinary cortisol ADVERSE EVENTS: reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (2010)

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Pedersen 2010 *(Continued)*

	FUNDING: funded by Nycomed CONFIRMATION OF METHODOLOGY: not received Data received from Takeda Global Research & Development Centre (Europe) Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer random number generator: "Patients were then randomised into one of four treatment groups in a 2:2:2:1 ratio (ciclesonide 40 mg: ciclesonide 80 mg: ciclesonide 160 mg: placebo) by means of a computer generated randomisation scheme"
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Pedersen 2010 b

Methods	Same as above
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = ANALYSED PARTICIPANTS: N = 462 INTERVENTION: ICS (ciclesonide 40 µg/d): 305 CONTROL: ICS (ciclesonide 160 µg/d): 310 WITHDRAWALS: reported AGE: median (years) (range): INTERVENTION: ICS (ciclesonide 40 µg/d): 8.0 (6-11) CONTROL: ICS (ciclesonide 160 µg/d): 9.0 (6-11) GENDER: N (male %):

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Pedersen 2010 b *(Continued)*

	INTERVENTION: ICS (ciclesonide 40 µg/d): 210 (68.9%) CONTROL: ICS (ciclesonide 160 µg/d): 218 (70.3%) ASTHMA SEVERITY: persistent asthma but severity not reported ASTHMA DURATION: median (months) (range): INTERVENTION: ICS (ciclesonide 40 µg/d): 41.4 (6-127) CONTROL: ICS (ciclesonide 160 µg/d): 41.7 (6-129) MEAN (± SD) β_2-AGONIST USE (puffs/d): median (months) (range) INTERVENTION: ICS (ciclesonide 40 µg/d): 1.43 (0.00-7.86) CONTROL: ICS (ciclesonide 160 µg/d): 1.57 (0.00-7.71) DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: placebo ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • Same as above EXCLUSION CRITERIA • Same as above
Interventions	PROTOCOL DURATION • Run-in = 2 to 4 weeks • Intervention = 12 weeks DEVICE: metered-dose inhaler with or without spacer DOSE OF ICS • INTERVENTION: ciclesonide 40 µg/d • CONTROL: ciclesonide 160 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	Same as above
Notes	Same as above

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer random number generator
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Low risk	Blinding of participants and key study personnel ensured

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Pedersen 2010 b *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Shapiro 1998

Methods	DESIGN: randomised, double-blind, placebo-controlled, parallel-group, multi-centre study
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 202 ANALYSED: N = 74 INTERVENTION: ICS (budesonide 100 µg/d): 102 CONTROL: ICS (budesonide 200 µg/d): 100 WITHDRAWALS: reported AGE: mean (range) years INTERVENTION: ICS (budesonide 100 µg/d): 11.8 (6-18) CONTROL: ICS (budesonide 200 µg/d): 12.1 (6-18) GENDER: male N (%) INTERVENTION: ICS (budesonide 100 µg/d): 76 (74.5) CONTROL: ICS (budesonide 200 µg/d): 76 (76) ASTHMA SEVERITY: moderate to severe persistent asthma ASTHMA DURATION: duration of ICS-dependent asthma: mean (range) years INTERVENTION: ICS (budesonide 100 µg/d): 2.8 (0.5-11) CONTROL: ICS (budesonide 200 µg/d): 2.5 (0.5-13) MEAN (± SD) β_2-AGONIST USE (puffs/d): INTERVENTION: ICS (budesonide 100 µg/d): 2.8 CONTROL: ICS (budesonide 200 µg/day): 3.1 DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: Participants discontinued their previous ICS at randomisation ATOPY (% of participants): not reported

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Shapiro 1998 *(Continued)*

	ELIGIBILITY CRITERIA • Aged 6 to 18 years • Reversible airway obstruction at the screening visit, defined by a 15% increase in forced expiratory volume in 1 second after inhalation of 180 or 360 mg of the $beta_2$-agonist • FEV_1 of 50% or greater, and 85% or less of predicted value • Ability to use a peak flow meter • Use of a minimum of 2 asthma medications every day during the previous 6 months, 1 of which must have been an ICS • Female patients of childbearing potential must have had a negative result on a serum pregnancy test EXCLUSION CRITERIA • History of carcinoma, diabetes, significant chest infection or any other major disorder
Interventions	PROTOCOL DURATION • Run-in = 2 weeks • Intervention = 12 weeks DEVICE: dry powder inhaler DOSE OF ICS • INTERVENTION: budesonide 100 µg/d • CONTROL: budesonide 200 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: done by analysis of variance. Poportion of patients who discontinued enrolment in the study was compared between treatment groups by using the Cochran-Mantel-Haenszel statistic OUTCOMES GROWTH MEASUREMENT TECHNIQUE: not reported PULMONARY FUNCTION TESTS • Mean change from baseline FEV_1 (percentage of predicted value) throughout the treatment period (from baseline to week 12) • Mean change from baseline in morning PEFR by treatment week and as average value throughout 12-week treatment period (weeks 0 to 12) FUNCTIONAL STATUS • Daytime and nighttime asthma symptom scores BIOMARKERS: before randomisation and after 12 weeks of treatment • Blood samples for cortisol measurements • Cosyntropin stimulation test ADVERSE EVENTS: reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (1998) FUNDING: supported by a grant from Astra, USA

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Shapiro 1998 *(Continued)*

	CONFIRMATION OF METHODOLOGY: data received from Symbicort and Established Respiratory Brands, AstraZeneca R&D, Mölndal, Sweden

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Shapiro 1998 b

Methods	DESIGN: randomised, double-blind, placebo-controlled, parallel-group, multi-centre study
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 201 ANALYSED: N = 75 INTERVENTION: ICS (budesonide 100 µg/d): 102 CONTROL: ICS (budesonide 400 µg/d): 99 WITHDRAWALS: reported AGE: mean (range) years INTERVENTION: ICS (budesonide 100 µg/d): 11.8 (6-18) CONTROL: ICS (budesonide 400 µg/d): 11.8 (6-18) GENDER: male N (%) INTERVENTION: ICS (budesonide 100 µg/d): 76 (74.5) CONTROL: ICS (budesonide 400 µg/d): 85 (85.8)

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Shapiro 1998 b *(Continued)*

	ASTHMA SEVERITY: moderate to severe persistent asthma ASTHMA DURATION: duration of ICS-dependent asthma: mean (range) years INTERVENTION: ICS (budesonide 100 µg/d): 2.8 (0.5-11) CONTROL: ICS (budesonide 400 µg/d): 2.4 (0.5-13) MEAN (± SD) β_2-AGONIST USE (puffs/d): INTERVENTION: ICS (budesonide 100 µg/d): 2.8 CONTROL: ICS (budesonide 400 µg/d): 3.2 DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: Participants discontinued their previous ICS at randomisation ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • As above EXCLUSION CRITERIA • As above
Interventions	PROTOCOL DURATION • Run-in = 2 weeks • Intervention = 12 weeks DEVICE: dry powder inhaler DOSE OF ICS • INTERVENTION: budesonide 100 µg/d • CONTROL: budesonide 400 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	As above
Notes	As above

Risk of bias

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

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Shapiro 1998 b *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Shapiro 1998 c

Methods	Same as Shapiro 1998	
Participants	Same as Shapiro 1998 ANALYSED: N = 55	
Interventions	Same as Shapiro 1998	
Outcomes	Same as Shapiro 1998	
Notes	Same as Shapiro 1998	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

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Shapiro 1998 d

Methods	Same as Shapiro 1998b
Participants	Same as Shapiro 1998b ANALYSED: N = 52
Interventions	Same as Shapiro 1998b
Outcomes	Same as Shapiro 1998b
Notes	Same as Shapiro 1998b

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Skoner 2008

Methods	DESIGN: randomised, double-blind, multi-centre, placebo-controlled, parallel-group study
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 440 ANALYSED: N = 408 INTERVENTION: ICS (ciclesonide 40 µg/d): 221 CONTROL: ICS (ciclesonide 160 µg/d): 219 WITHDRAWALS: reported

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Skoner 2008 *(Continued)*

AGE: mean (range) years

INTERVENTION: ICS (ciclesonide 40 µg/d): 7.1 (5.5-9.1)

CONTROL: ICS (ciclesonide 160 µg/d): 7.2 (5.5-9.0)

GENDER: male N (%)

INTERVENTION: ICS (ciclesonide 40 µg/d): 150 (67.9)

CONTROL: ICS (ciclesonide 160 µg/d): 147 (67.1)

ASTHMA SEVERITY: mild persistent asthma

ASTHMA DURATION: at screening (6 months before randomisation) mean (SD) years

INTERVENTION: ICS (ciclesonide 40 µg/d): 3.79 (1.95)

CONTROL: ICS (ciclesonide 160 µg/d): 3.96 (1.98)

MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported

DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: placebo.

ATOPY (% of participants): not reported

ELIGIBILITY CRITERIA

- Diagnosis of mild, persistent asthma for 3 months before screening
- Forced expiratory volume in 1 second (FEV_1) of 80% predicted (after 4-hour albuterol withhold)
- Effective use of metered-dose inhaler (MDI) devices
- Tanner stage 1
- Normal height (5th–95th percentiles inclusive) at screening
- Growth velocity at the third or higher percentile during the 6-month run-in period
- Use of noncorticosteroid asthma medication on an as-needed or daily basis or low ICS dosages

EXCLUSION CRITERIA

- Inability or refusal to use study devices
- Any ICS within 30 days before screening, at a dosage exceeding fluticasone propionate 100 g/d or equivalent
- Previous daily or alternate-day oral corticosteroid treatment for a total of 60 days within 2 years before visit 3 or within 30 days before screening
- Receipt of 2 14-day courses of intranasal corticosteroids (which had to be separated by 3 months) or ICS treatment for 14 days during the run-in period

Interventions	PROTOCOL DURATION • Run-in = 24 weeks • Intervention = 48 weeks DEVICE: metered-dose inhaler without a spacer DOSE OF ICS • INTERVENTION: ciclesonide 40 µg/d • CONTROL: ciclesonide 160 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported

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Skoner 2008 *(Continued)*

Outcomes	ANALYSIS: Using an analysis of co-variance (ANCOVA) model, all growth analyses were conducted by using the modified intention-to-treat (mITT) population, which included all randomly assigned participants who completed 4 months of study treatment and who had stadiometry measurements at baseline and >= 4 months OUTCOMES GROWTH MEASUREMENT TECHNIQUE: All investigators were provided with detailed written and visual instructions, took part in onsite training and attended workshops before study initiation to standardise stadiometer measurements. In addition, most investigators had previous experience with Harpenden stadiometers. Study centres were supplied with identical Harpenden stadiometers, which were calibrated within 4 hours of each measurement, and height was measured at all visits using standard techniques. Measurements were taken by a trained technician, and an effort was made to use the same technician at each visit. A median of 4 acceptable serial measurements was used in the analysis PULMONARY FUNCTION TESTS • Mean (SE) changes in FEV_1 (L) from baseline to study end FUNCTIONAL STATUS • Linear growth velocity during double-blind treatment period (before randomisation every 3 months, after randomisation every month and 4 months and every 2 months and completion of double-blind treatment and 2 months after the end of study) • Mean change in stadiometer height (cm) from baseline (using mean range of the 4 stadiometer height measurements recorded at each visit) BIOMARKERS • Urine samples (24 hours or 10 hours overnight) for cortisol measurements before randomisation and after completion of double-blind treatment • Wrist radiographs for assessment of bone age before randomisation and after completion of double-blind treatment ADVERSE EVENTS: reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (2008) FUNDING: Financial support for this study was provided by Sanofi-aventis US and Altana Pharma US, Inc, a Nycomed company CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer random number generator: ”The randomisation schedule was generated by the Biostatistics Department of Quintiles, Inc (Kansas City, MO) and was stratified according to age-gender classification”
Allocation concealment (selection bias)	Low risk	Central allocation (including telephone, web-based and pharmacy-controlled randomisation): “Randomization was conducted at a central location (Q-Tone, Durham, NC) and was determined by an interactive voice response system, based on information entered by personnel at each investigative center”

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Skoner 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Skoner 2011

Methods	DESIGN: a phase III, multi-centre, randomised, placebo-controlled, parallel-group, double-blind, long-term safety study
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 92 ANALYSED: N = 66 INTERVENTION: ICS (mometasone furoate 100 µg/d): 48 CONTROL: ICS (mometasone furoate 100 µg twice daily): 44 WITHDRAWALS: reported AGE: mean (range) years INTERVENTION: ICS (mometasone furoate 100 µg/d): 6.4 (4-9) CONTROL: ICS (mometasone furoate 100 µg twice daily): 6.3 (4-9) GENDER: male N (%) INTERVENTION: ICS (mometasone furoate 100 µg/d): 34 (70.8) CONTROL: ICS (mometasone furoate 100 µg twice daily): 28 (63.6) ASTHMA SEVERITY: persistent asthma; severity not reported ASTHMA DURATION: mean (range) years INTERVENTION: ICS (mometasone furoate 100 µg/d): 3.8 (0.67-8.0) CONTROL: ICS (mometasone furoate 100 µg twice daily): 4.0 (0.83-9.0) MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: washout period of 3 months ATOPY (% of participants): not reported

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Skoner 2011 *(Continued)*

	ELIGIBILITY CRITERIA • Children aged 4–9 years with a history of asthma ≥ 6 months • Forced expiratory volume in 1 second (FEV_1) of at least 75% of predicted normal at both the screening visit and the baseline visit, when all restricted medications had been withheld • Increase in absolute FEV_1 of at least 12% after reversibility testing at the screening visit or historically within the past 12 months • Children 4 to 5 years old who could not demonstrate reversibility were qualified for enrolment if the investigator determined that the patient met National Heart, Lung and Blood Institute criteria for diagnosis of asthma at this age • Normal height (5th–95th percentile on standard growth charts) upon measurement with a stadiometer; at least one stadiometer measurement taken between 3 and 24 months before screening • Skeletal age within 2 years of chronological age (as determined by left hand-wrist radiograph) • Morning (8 am ± 1 h) plasma cortisol levels ≥ 5 µg/dL • No greater than stage 1 in the Tanner Classification of Sex Maturity, as measured by preadolescent penis and testes in boys, and preadolescent pubic hair and breasts in girls; female premenarchal EXCLUSION CRITERIA • Increase or decrease in FEV_1 ≥ 20% between screening and baseline visits • ≥ 12 puffs per day of albuterol on any 2 consecutive days between screening and baseline visits • Inpatient hospitalisation for asthma control within the previous 3 months • Ventilator support for respiratory failure secondary to asthma within the previous 5 years • Hospital admission for the management of airway obstruction on 2 or more occasions over the past 6 months • Asthma requiring daily use of nebulised SABA or any use of long-acting β_2-agonists • Asthma requiring long-term use of inhaled or systemic corticosteroids • Inability to use a DPI device or a peak flow meter • History or evidence of abnormal growth • Presence of any disease or condition with the potential to substantially affect growth or that required concomitant corticosteroid therapy • Evidence of gross malnutrition • History of any disease that could have interfered with study evaluations • Individuals experiencing an upper or lower respiratory tract infection within 2 weeks of screening and baseline visits
Interventions	PROTOCOL DURATION • Run-in = 1 to 2 weeks • Intervention = 52 weeks DEVICE: dry powder inhaler DOSE OF ICS • INTERVENTION: mometasone furoate 100 µg/d • CONTROL: mometasone furoate 100 µg twice daily CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: Analyses were done using a longitudinal random slope (LRS) model, an individual regression (IR) model and an analysis of variance (ANOVA) by extracting sources of variation due to treatment, age and gender OUTCOMES

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Skoner 2011 *(Continued)*

	GROWTH MEASUREMENT TECHNIQUE: Growth velocity was determined from heights measured by a Harpenden stadiometer during the 52-week treatment period PULMONARY FUNCTION TESTS: This study was not designed to evaluate efficacy measures PULMONARY FUNCTION TESTS • Forced vital capacity, FEV_1 and $FEF_{25\%-75\%}$ at each study visit FUNCTIONAL STATUS • Occurrences of clinical asthma exacerbations: deterioration of asthma that resulted in hospitalisation, asthma symptoms requiring the addition of medication (other than SABA therapy), exacerbations requiring oral corticosteroid bursts or exacerbations requiring a significant increase in medication dosages • Growth velocity, determined from heights measured by a Harpenden stadiometer during the 52-week treatment period • Growth velocity during the 3-month follow-up period BIOMARKERS • Plasma and urine cortisol values at screening, week 26 and the final treatment visit (week 52) ADVERSE EVENTS: reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (2011) FUNDING: supported by Merck & Co, Inc CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation; randomly assigned in a 1:1:1 ratio to different comparison groups
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

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Skoner 2011 b

Methods	DESIGN: a phase III, multi-centre, randomised, placebo-controlled, parallel-group, double-blind, long-term safety study
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 98 ANALYSED: N = 73 INTERVENTION: ICS (mometasone furoate 100 µg/d): 48 CONTROL: ICS (mometasone furoate 200 µg/d qd): 50 WITHDRAWALS: reported AGE: mean (range) years INTERVENTION: ICS (mometasone furoate 100 µg/d): 6.4 (4-9) CONTROL: ICS (mometasone furoate 200 µg/d qd): 6.6 (4-9) GENDER: male N (%) INTERVENTION: ICS (mometasone furoate 100 µg/d): 34 (70.8) CONTROL: ICS (mometasone furoate 200 µg/d qd): 33 (66) ASTHMA SEVERITY: persistent asthma; severity not reported ASTHMA DURATION: mean (range) years INTERVENTION: ICS (mometasone furoate 100 µg/d): 3.8 (0.67-8.0) CONTROL: ICS (mometasone furoate 200 µg/d qd): 3.6 (0.42-8.0) MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: washout period of 3 months ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • As above EXCLUSION CRITERIA • As above
Interventions	PROTOCOL DURATION • Run-in = 1 to 2 weeks • Intervention = 52 weeks DEVICE: dry powder inhaler DOSE OF ICS • INTERVENTION: mometasone furoate 100 µg/d qd • CONTROL: mometasone furoate 200 µg/d qd

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Skoner 2011 b *(Continued)*

	CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	As above
Notes	As above

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation; randomly assigned in a 1:1:1 ratio to different comparison groups
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Sorkness 2007

Methods	DESIGN: randomised, double-blind, multi-centre, parallel-group study
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 190 ANALYSED: N = 190 INTERVENTION: ICS (fluticasone/salmeterol 100/50 µg/d): 96 CONTROL: ICS (fluticasone 200 µg/d): 94 WITHDRAWALS: reported AGE: mean (SD) years INTERVENTION: ICS (fluticasone/salmeterol 100/50 µg/d): 9.8(2.2) CONTROL: ICS (fluticasone 200 µg/d): 10.3 (2.1) GENDER: male N (%) INTERVENTION: ICS (fluticasone/salmeterol(100/50 µg/d): 96

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Sorkness 2007 *(Continued)*

CONTROL: ICS (fluticasone 200 µg/d): 94

ASTHMA SEVERITY: mild to moderate persistent asthma

ASTHMA DURATION: mean (range) years

INTERVENTION: ICS (fluticasone/salmeterol 100/50 µg/d): 96

CONTROL: ICS (fluticasone 200 µg/d): 94

MEAN (± SD) β_2-AGONIST USE (puffs/d):

DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN:

ATOPY (% of participants): 78%

ELIGIBILITY CRITERIA

- Physician-diagnosed asthma, age 6 to younger than 14 years
- Ability to perform reproducible spirometry
- FEV_1 (measured more than 4 hours since the most recent use of a bronchodilator) 80% predicted normal at screening and 70% predicted normal at randomisation
- Methacholine FEV_1 PC_{20} 12.5 mg/mL.
- All children had mild to moderate persistent asthma, as defined by diary-reported symptoms or beta-agonist use (not including pre-exercise) or peak flows < 80% calculated from the mean of morning and evening peak flows obtained during the final week of the run-in period, on average at least 3 times per week

EXCLUSION CRITERIA

- Other lung diseases; respiratory tract infection, asthma exacerbation or systemic corticosteroid use within 4 weeks
- 2 or more asthma hospitalisations in the past year
- History of a life-threatening asthma exacerbation
- 4 courses of systemic corticosteroids in the past year
- Cigarette smoking within the past year
- Pregnancy or lactation
- Failure to practice abstinence or to use a medically acceptable birth control method
- History of adverse reactions to the PACT medications

Interventions	PROTOCOL DURATION • Run-in = 2 to 4 weeks • Intervention = 48 weeks (1 year) DEVICE: Diskus (GlaxoSmithKline, Research Triangle Park, NC) DOSE OF ICS • INTERVENTION: fluticasone 100 + salmeterol 50 µg/d • CONTROL: fluticasone 200 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY:
Outcomes	ANALYSIS: Primary analysis of asthma control days consisted of the 3 pair-wise comparisons by ANOVA with post hoc pair-wise comparisons of group means OUTCOMES GROWTH MEASUREMENT TECHNIQUE: Height was measured using the calibrated stadiometer

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Sorkness 2007 *(Continued)*

PULMONARY FUNCTION TESTS

- Percentage predicted FEV_1
- FEV_1/FVC
- Pre-BD AM PEFR, % predicted
- Pre-BD PM PEFR, % predicted
- Methacholine FEV_1
- PC_{20}
- Maximum bronchodilator response

FUNCTIONAL STATUS

- Percentage of asthma control days
- Growth
- Failureto respond to treatment
- ACQ
- Monthly asthma control days
- Monthly episode-free days

BIOMARKERS

- eNO

ADVERSE EVENTS: reported

WITHDRAWALS: reported

Notes	PUBLICATION: full paper (2007) FUNDING: grants from National Heart, Lung and Blood Institute, USA CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A stratified randomisation scheme was applied on the basis of bronchodilator response (< 12% or 12% change in FEV_1), race (white or non-white) and methacholine FEV_1 PC_{20} (< 2 or 2 mg/mL)
Allocation concealment (selection bias)	Low risk	Matching placebo was provided by sponsor
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Well-balanced withdrawal in comparison groups. No missing outcome data. Primary and secondary outcomes specified

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Sorkness 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	Protocol available. All analyses performed under the intent-to-treat paradigm
Other bias	Low risk	Study apparently free of other sources of bias

Teper 2004

Methods	DESIGN: randomised, double-blind, placebo-controlled clinical study.
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 20 INTERVENTION: ICS (fluticasone 100 µg/d): 10 CONTROL: ICS (fluticasone 250 µg/d): 10 WITHDRAWALS: reported AGE: months ± SD: INTERVENTION: ICS at specific dose: 13.1 ± 5.2 CONTROL: ICS (fluticasone 250 µg/d): 14.2 ± 5.7 GENDER: N (male %): INTERVENTION: ICS (fluticasone 100 µg/d): 6 (60%) CONTROL: ICS (fluticasone 250 µg/d): 7 (70%) ASTHMA SEVERITY: recurrent wheezing ASTHMA DURATION (mean years ± SD): not reported MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: not reported ATOPY (% of participants): not reported ELIGIBILITY CRITERIA • Age younger than 2 years • Asthma symptoms (defined as 3 or more episodes of wheeze, with clinical improvement after bronchodilators, as assessed by physician) • Family history of asthma or any other clinical finding indicating atopy EXCLUSION CRITERIA • Children with history of severe respiratory infection, cystic fibrosis, aspirative pathology, pulmonary or airways anomalies, bronchopulmonary dysplasia and congenital heart disease, or who previously received ICS or sodium cromoglycate
Interventions	PROTOCOL DURATION • Run-in = not reported • Intervention = 24 weeks

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Teper 2004 *(Continued)*

	DEVICE: metered-dose inhaler with aerochamber DOSE OF ICS • INTERVENTION: fluticasone 100 µg/d • CONTROL: fluticasone 250 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: not reported OUTCOMES: reported at 24 weeks; change in height reported as standard deviation score GROWTH MEASUREMENT TECHNIQUE: Participant's recumbent length was determined by means of a calibrated stadiometer. Three consecutive measurements were taken to obtain the mean value. Height was expressed as standard deviation score (SDS) for chronological age, according to Tanner and Whitehouse PULMONARY FUNCTION TESTS: not reported FUNCTIONAL STATUS • Number of wheezing episodes • Number of days on albuterol BIOMARKERS • Serum insulin-like growth factor binding protein 3 • Serum cortisol • Serum osteocalcin • Serum bone alkaline phosphates fraction ADVERSE EVENTS: not reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (2005) FUNDING: not reported CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer random number generator: ”Each child was then provided with a numbered,blinded metered-dose aerosol inhaler containing FP (50 or 125 µg per actuation) or placebo, depending on their study group”
Allocation concealment (selection bias)	Low risk	Sequentially numbered drug containers of identical appearance
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured

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Teper 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Vaessen-Verberne 2010

Methods	DESIGN: randomised, multi-centre, parallel-group, double-blind study
Participants	SYMPTOMATIC ON CONVENTIONAL DOSES OF INHALED CORTICOSTEROIDS RANDOMLY ASSIGNED: N = 158 ANALYSED: N = 151 INTERVENTION: ICS (fluticasone 200 µg/d): 78 CONTROL: ICS (fluticasone 400 µg/d): 80 WITHDRAWALS: reported AGE: years ± SD: INTERVENTION: ICS (fluticasone 200 µg/d): 9.4 ± 1.8 CONTROL: ICS (fluticasone 400 µg/d): 9.3 ± 1.9 GENDER: N (male %): INTERVENTION: ICS (fluticasone 200 µg/d): 42 (54%) CONTROL: ICS (fluticasone 400 µg/d): 49 (61%) ASTHMA SEVERITY: not reported ASTHMA DURATION (mean years ± SD): reported INTERVENTION: ICS (fluticasone 200 µg/d): 5.7 ± 3.1 CONTROL: ICS (fluticasone 400 µg/d): 5.5 ± 3.0 MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: not reported ATOPY: N (% of participants): reported INTERVENTION: ICS (fluticasone 200 µg/d): 60 (77%) CONTROL: ICS (fluticasone 400 µg/d): 58 (73%) ELIGIBILITY CRITERIA • Male or female subjects aged 6 to 16 years (inclusive) • Subjects with a documented history of asthma for at least 6 months • Subjects with a documented history of BHR within 12 months before inclusion or BHR on visit 1 and/or visit 2/2A (PD_{20} methacholine < 150 µg or an equivalence for histamine)

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Vaessen-Verberne 2010 *(Continued)*

- Subjects who had received BDP, budesonide up to 100 to 200 µg bd or fluticasone propionate at a dose of up to 125 µg bd for at least 4 weeks before the start of the run-in period
- Subjects who had a normal length SD score between –2 SD and +2 SD as inclusion criteria for entry into the treatment period (end of run-in period)
- Subjects who had recorded a cumulative symptom score (daytime plus nighttime) totaling > 14 the last 14 days of the run-in period
- Compliance for use of FP during run-in period of at least 50%
- Recorded data on > 70% of daily entries into their DRC throughout run-in period

EXCLUSION CRITERIA

- Children with history of severe respiratory infection, cystic fibrosis, aspirative pathology, pulmonary or airways anomalies, bronchopulmonary dysplasia and congenital heart disease, or who previously received ICS or sodium cromoglycate

Interventions	PROTOCOL DURATION • Run-in = 4 weeks • Intervention = 26 weeks DEVICE: Diskus DOSE OF ICS • INTERVENTION: fluticasone 100 µg with salmeterol 50 µg twice day • CONTROL: fluticasone 200 µg twice daily CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: intention-to-treat analysis OUTCOMES: Many outcomes were reported at 26 weeks; participants were evaluated at 1, 6, 16 and 26 weeks GROWTH MEASUREMENT TECHNIQUE: Height was recorded using a stadiometer at the start of the run-in period, and at the start and at the end of the treatment period PULMONARY FUNCTION TESTS • FEV_1 • FVC • FEV_1/FVC • MEF_{50} • PEFR • PD_{20} methacholine FUNCTIONAL STATUS • Percentage of symptom-free days BIOMARKERS • Exhaled nitric oxide ADVERSE EVENTS • Statural growth • Exacerbations • Adverse events

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Vaessen-Verberne 2010 *(Continued)*

	WITHDRAWALS: reported
Notes	PUBLICATION: full paper (2010) FUNDING: funded by GlaxoSmithKline CONFIRMATION OF METHODOLOGY: received Data received from the study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer random number generator
Allocation concealment (selection bias)	Low risk	Central allocation (including telephone, web-based and pharmacy-controlled randomisation)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way
Other bias	Low risk	Study apparently free of other sources of bias

Verberne 1998

Methods	Double-blind, randomised, parallel-group trial; multi-centre
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 87 ANALYSED: N = 87 INTERVENTION: ICS (beclomethasone 400 µg/d): 57 CONTROL: ICS (beclomethasone 800 µg/d): 30 WITHDRAWALS: reported AGE: mean (range) years INTERVENTION: ICS (beclomethasone 400 µg/d): 11.1 (6-16)

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Verberne 1998 *(Continued)*

CONTROL: ICS (beclomethasone 800 µg/d): 11.4 (6-16)

GENDER: male N (%)

INTERVENTION: ICS (beclomethasone 400 µg/d): 36 (63)

CONTROL: ICS (beclomethasone 800 µg/d): 36 (60)

ASTHMA SEVERITY: mild to moderate asthma

ASTHMA DURATION: mean (range) years

INTERVENTION: ICS (beclomethasone 400 µg/d): 8.5 years

CONTROL: ICS (beclomethasone 800 µg/d): 9.0 years

MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported

DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: 200-800 µg/d at least 3 months before the start of the study

ATOPY (% of participants): 89%

ELIGIBILITY CRITERIA

- FEV_1 between 55% and 90% of predicted value
- Increase of at least 10% in FEV_1 after inhalation of 0.8 mg salbutamol
- Airway hyperresponsiveness to methacholine greater than 2 standard deviations
- Ability to produce reproducible lung function tests
- History of stable asthma for at least 1 month without exacerbations or respiratory tract infections
- Use of ICS between 200 and 800 µg for at least 3 months before the start of the study

EXCLUSION CRITERIA: not reported

WITHDRAWAL CRITERIA:

- Participant needed 3 or more prednisolone courses within 3 months
- It was not ethical to continue blinded treatment according to the investigator
- Participant or parents wanted to stop

Interventions	PROTOCOL DURATION • Run-in = 6 weeks • Intervention = 54 weeks DEVICE: All drugs were administered as Rotadisks in combination with a Diskhaler (Glaxo Wellcome, Greenford, UK) DOSE OF ICS • INTERVENTION: beclomethasone 400 µg/d • CONTROL: beclomethasone 800 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: analyses of co-variance OUTCOMES GROWTH MEASUREMENT TECHNIQUE: Height was measured using a stadiometer in centimetres, corrected to 1 decimal place

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Verberne 1998 *(Continued)*

	PULMONARY FUNCTION TESTS • FEV_1 and PEFR (change from baseline during treatment) • Airway responsiveness (change from baseline during treatment) FUNCTIONAL STATUS • Daytime and nighttime symptoms • Periods of exacerbations BIOMARKERS: not done ADVERSE EVENTS: reported WITHDRAWALS: reported
Notes	PUBLICATION: full paper (1998) FUNDING: Glaxo Wellcome BV CONFIRMATION OF METHODOLOGY: not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer random number generator: "Randomization was stratified by sex, age, center, baseline FEV_1 and prior dose of ICS, using a computerized minimization method"
Allocation concealment (selection bias)	Low risk	Central allocation (including telephone, web-based and pharmacy-controlled randomisation): "independent randomisation center"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Verberne 1998 b

Methods	Double-blind, randomised, parallel-group trial; multi-centre
Participants	SYMPTOMATIC PARTICIPANTS

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Verberne 1998 b *(Continued)*

	RANDOMLY ASSIGNED: N = 90 ANALYSED: N = 90 INTERVENTION: ICS (beclomethasone + salmeterol 400 µg/d): 60 CONTROL: ICS (beclomethasone 800 µg/d): 30 WITHDRAWALS: reported AGE: mean (range) years INTERVENTION: ICS (beclomethasone 400 µg/d): 10.8 (6-16) CONTROL: ICS (beclomethasone 800 µg/d): 11.4 (6-16) GENDER: male N (%) INTERVENTION: ICS (beclomethasone 400 µg/d): 40 (60) CONTROL: ICS (beclomethasone 800 µg/d): 36 (60) ASTHMA SEVERITY: mild to moderate asthma ASTHMA DURATION: mean (range) years INTERVENTION: ICS (beclomethasone 400 µg/d): 7.8 years CONTROL: ICS (beclomethasone 800 µg/d): 9.0 years MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: 200-800 µg/d at least 3 months before the start of the study ATOPY (% of participants): 89% ELIGIBILITY CRITERIA • As above EXCLUSION CRITERIA: not reported WITHDRAWAL CRITERIA • As above
Interventions	PROTOCOL DURATION • Run-in = 6 weeks • Intervention = 54 weeks DEVICE: All drugs were administered as Rotadisks in combination with a Diskhaler (Glaxo Wellcome, Greenford, UK) DOSE OF ICS • INTERVENTION: beclomethasone 400 µg + salmeterol 100 µg/d • CONTROL: beclomethasone 800 µg/d CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	As above

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Verberne 1998 b *(Continued)*

Notes	As above

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer random number generator: "Randomization was stratified by sex, age, center, baseline FEV_1 and prior dose of ICS, using a computerized minimization method"
Allocation concealment (selection bias)	Low risk	Central allocation (including telephone, web-based and pharmacy-controlled randomisation): "independent randomisation center"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

Wasserman 2006

Methods	DESIGN: randomised, double-blind, placebo-controlled, parallel-group study; multi-centre
Participants	SYMPTOMATIC PARTICIPANTS RANDOMLY ASSIGNED: N = 219 ANALYSED: N = 218 INTERVENTION: ICS (fluticasone 88 µg/d): 111 CONTROL: ICS (fluticasone 176 µg/d): 108 WITHDRAWALS: reported AGE: mean (months) (range): INTERVENTION: ICS (fluticasone 88 µg/d): 35.6 (24-47) CONTROL: ICS (fluticasone 176 µg/d): 35.5 (24-47) GENDER: N male (%): INTERVENTION: ICS (fluticasone 88 µg/d): 70 (63)

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Wasserman 2006 *(Continued)*

CONTROL: ICS (fluticasone 176 µg/d): 63 (58.3)

ASTHMA SEVERITY: not reported

ASTHMA DURATION: mean (months) (range):

INTERVENTION: ICS (fluticasone 88 µg/d): 25.0 (6-46)

CONTROL: ICS (fluticasone 176 µg/d): 24.4 (4-46)

MEAN (± SD) β_2-AGONIST USE (puffs/d): not reported; LS mean (SE) change to end point was reported

DOSE OF ICS AT STUDY ENTRY AND AT RUN-IN: not reported

ATOPY (% of participants): not reported

ELIGIBILITY CRITERIA

- Children aged 24 to 47 months who had experienced at least 2 exacerbations in the year before screening
- Regular maintenance therapy for asthma during the 6 weeks before screening and/or short-acting agonist therapy at least twice weekly during the 3 weeks before screening

EXCLUSION CRITERIA

- History of life-threatening asthma
- Upper or lower respiratory tract infection
- Use of systemic or moderate to high doses of ICS within 8 weeks
- Treatment with more than 2 courses of systemic corticosteroids during the previous 6 months
- Use of investigational drug within 30 days of screening

Interventions	PROTOCOL DURATION • Run-in = 2 to 4 weeks • Intervention = 12 weeks DEVICE: metered-dose inhaler. Treatments were administered via a valve holding (Aerochamber Plus [Trudell Medical International, London, Ontario] or OptiChamber [Respironics, Murrysville, PA], each used by approximately half of the children) with an attached face mask DOSE OF ICS • INTERVENTION: fluticasone propionate 88 µg/d = 44 µg bid • CONTROL: fluticasone propionate 176 µg/d = 88 µg bid CRITERIA FOR WITHDRAWAL FROM STUDY: reported
Outcomes	ANALYSIS: Safety analyses were based on data from the intent-to-treat population; analysis of co-variance was used OUTCOMES GROWTH MEASUREMENT TECHNIQUE: Growth (standing height) was measured in triplicate and at approximately the same time of day using a calibrated stadiometer at screening and at weeks 1, 2, 4, 8 and 12 PULMONARY FUNCTION TESTS: morning PEFR measurements (in children capable of performing this manoeuvre) FUNCTIONAL STATUS • Growth (standing height) at screening and at weeks 1,2, 4, 8 and 12

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Wasserman 2006 *(Continued)*

- 24 hour asthma symptom scores
- Time to treatment failure
- % of symptom-free 24 hour days

BIOMARKERS

- Urine cortisol values at screening and at week 12

ADVERSE EVENTS: reported

WITHDRAWALS: reported

Notes	PUBLICATION: full paper (2006) FUNDING: grant from GlaxoSmithKline Inc CONFIRMATION OF METHODOLOGY: received Data received from GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation; randomly assigned in 1:1:1 ratio; stratified by age (< 36 months; > 36 months)
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol not available but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study apparently free of other sources of bias

ACQ = asthma control questionnaire; ACTH = adrenocorticotrophic hormone; ANCOVA = analysis of co-variance; ANOVA = analysis of variance; BALP = bone alkaline phosphate; BD = bronchodilator; BMD = body mass index; eNO = exhaled nitric oxide; $FEF_{25\%–75\%}$ = forced expiratory flow between 25% and 75% of FVC; FEV_1 = forced expired volume in 1 second; FVC = forced vital capacity; GCS = glucocorticosteroids; HPAA = hypothalamic-pituitary-adrenal axis; ICS = inhaled corticosteroids; ICTP = type I collagen telopeptide; ITT = intent-to-treat; MEF_{50} = maximal expiratory flow at 50%; mITT = modified intent-to-treat; OC = serum osteocalcin; o.d. = once daily; PACT = Pediatric Asthma Controller Trial; PAQLQ = Paediatric Asthma Quality of Life Questionnaire; PD_{20} = dose of methacholine causing a 20% fall in forced expiratory volume in 1 sec (FEV1) from baseline; PEFR = peak expiratory flow rate; PICP = procollagen type I carboxyterminal propeptide; SD = standard deviation; SE = standard error.

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

Study	Reason for exclusion
Agertoft 2004	Not a parallel-group study
Antoniu 2003	No daily ICS in 1 of the intervention groups (control group)
Apold 1975	Not a randomised controlled trial
Asrilant 1975	Not a randomised controlled trial
Bateman 2008	Participants aged ≥ 18 years
Baxter-Jones 1998	Other group did not evaluate an additional ICS dose using the same molecule
Berger 2005	Enrolled participants were children younger than 1 year of age
Bernstein 1999	Other group did not evaluate an additional ICS dose using the same molecule
Birkebaek 1995	Not a parallel-group study
Breborowicz 2005	Not a randomised controlled trial
Brook 1998	Not a randomised controlled trial
Brown 1973	Not a randomised controlled trial
Chuchalin 2008	Participants aged ≥ 18 years
Dickson 1973	Not a randomised controlled trial
Ferguson 2002	Other group did not evaluate an additional ICS dose using the same molecule
Godfrey 1973	Not a randomised controlled trial
Godfrey 1974	Not a randomised controlled trial
Guarnaccia 1996	Not a randomised controlled trial
Guo 2002	Not a parallel-group study
Gwynn 1977	Not a randomised controlled trial
Hansel 2006	Participants aged ≥ 18 years
Kaiser 2008	Other group did not evaluate an additional ICS dose using the same molecule
Karpel 2007	Co-intervention was not equivalent between comparison groups and/or was not stable throughout the observation period
Kemp 2004	Participants aged ≥ 18 years
Lang 2013	No daily ICS in 1 of the intervention groups
Laursen 1986	Participants aged ≥ 18 years

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Study	Reason for exclusion
Lipworth 1996	Not a parallel-group study
Lovera 1975	Not a randomised controlled trial
McAllen 1974	Not a parallel-group study
Neffen 2006	Duplicate study
Nelson 2000	Co-intervention not equivalent between comparison groups and/or not stable throughout the observation period
Niu 1998	Treatment administered for < 12 weeks
Otsuki 2009	No daily ICS in 1 of the intervention groups (control group)
Pearlman 2005	Not a randomised controlled trial
Pedeersen 2003	Not a parallel-group study
Pedersen 2002	Other group did not evaluate an additional ICS dose using the same molecule
Peroni 2005	Co-intervention not equivalent between comparison groups and/or not stable throughout the observation period
Phipatanakul 2003	No daily ICS in 1 of the intervention groups (control group)
Pines 1973	Not a randomised controlled trial
Skoner 2000	No daily ICS in 1 of the intervention groups (control group)
Skoner 2006	Duplication of already published paper
Skoner 2010	Treatment administered for < 12 weeks
Szefler 2008	No daily ICS in 1 of the intervention groups (control group)
Thompson 1998	Treatment administered for < 12 weeks
Turpeinen 2008	No daily ICS in 1 of the intervention groups (control group)
Visser 2001	No daily ICS in 1 of the intervention groups (control group)
Visser 2001a	Duplication of already published paper
Visser 2004	No daily ICS in 1 of the intervention groups (control group)
Wasserman 1996	Participants aged ≥ 18 years
Wasserman 1996 b	Participants aged ≥ 18 years
Waugh 2002	Not a randomised controlled trial
Williams 2010	No daily ICS in 1 of the intervention groups (control group)
Wolthers 1995	Not a parallel-group study

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Study	Reason for exclusion
Xu 2005	No daily ICS in 1 of the intervention groups (control group)

DATA AND ANALYSES

Comparison 1. Inhaled corticosteroids dose-response effect

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Growth velocity (cm/y) by stadiometry from 0-12 months	4	728	Mean Difference (IV, Fixed, 95% CI)	0.20 [0.02, 0.39]
2 Subgroup analysis on the ICS molecules: growth velocity by stadiometry from 0-12 months	4	728	Mean Difference (IV, Fixed, 95% CI)	0.20 [0.02, 0.39]
2.1 Mometasone	2	139	Mean Difference (IV, Fixed, 95% CI)	0.58 [0.02, 1.13]
2.2 Ciclesonide	1	408	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.09, 0.35]
2.3 Fluticasone	1	181	Mean Difference (IV, Fixed, 95% CI)	0.24 [-0.16, 0.64]
3 Growth velocity (cm/y) by stadiometry from 0-3 months	6	1114	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.51, 0.27]
4 Growth velocity (cm/y) by stadiometry from 0-6 months	2	60	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-2.40, 1.75]
5 Growth velocity (cm/y) by stadiometry from 3-6 months	2	58	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-3.35, 3.10]
6 Change in growth velocity (cm/y) by stadiometry from 0-12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Change in height (cm) by stadiometry from 0-3 months	9	944	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.28, -0.02]
8 Change in height (cm) by stadiometry from 0-6 months	3	211	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.27, 0.33]
9 Change in height (cm) by stadiometry from 3-6 months	2	58	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.74, 0.71]
10 Change in height (cm) by stadiometry from 0-12 months	4	548	Mean Difference (IV, Fixed, 95% CI)	0.25 [-0.04, 0.54]
11 Change in SD scores (height) from 0-12 months	3	328	Mean Difference (IV, Random, 95% CI)	0.08 [-0.03, 0.20]

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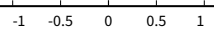
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Change in weight (kg) from 0-3 months	5	449	Mean Difference (IV, Random, 95% CI)	0.27 [-0.13, 0.66]
13 Change in weight (kg) from 0-6 months	2	346	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.24, 0.24]
14 Change in weight (kg) from 0-12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15 Change in BMI (kg/m^2) from 0-6 months	2	278	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.22, 0.33]
16 Change in BMI (kg/m^2) from 0-12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17 Change in skeletal maturation (years) from 0-12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 1 Growth velocity (cm/y) by stadiometry from 0-12 months.

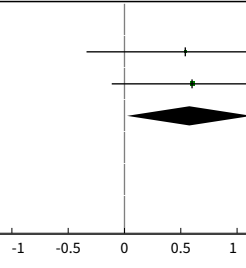
Study or subgroup	Intervention (Lower dose) N	Mean(SD)	Control (Higher dose) N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Allen 1998	85	5.9 (1.5)	96	5.7 (1.3)		20.21%	0.24[-0.17,0.65]
Skoner 2008	206	5.7 (1.2)	202	5.6 (1.1)		68.62%	0.13[-0.09,0.35]
Skoner 2011	24	6.4 (1.5)	42	5.9 (2.1)		4.45%	0.54[-0.34,1.42]
Skoner 2011 b	24	6.4 (1.5)	49	5.8 (1.3)		6.73%	0.6[-0.11,1.31]
Total ***	**339**		**389**			**100%**	**0.2[0.02,0.39]**
Heterogeneity: Tau^2=0; Chi^2=2.2, df=3(P=0.53); I^2=0%							
Test for overall effect: Z=2.14(P=0.03)							



Favors higher dose ICS — Favors lower dose ICS

Analysis 1.2. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 2 Subgroup analysis on the ICS molecules: growth velocity by stadiometry from 0-12 months.

Study or subgroup	Intervention (Lower dose) N	Mean(SD)	Control (Higher dose) N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.2.1 Mometasone							
Skoner 2011	24	6.4 (1.5)	42	5.9 (2.1)		4.38%	0.54[-0.34,1.42]
Skoner 2011 b	24	6.4 (1.5)	49	5.8 (1.3)		6.63%	0.6[-0.11,1.31]
Subtotal ***	**48**		**91**			**11%**	**0.58[0.02,1.13]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%							
Test for overall effect: Z=2.04(P=0.04)							



Favors higher dose ICS — Favors lower dose ICS

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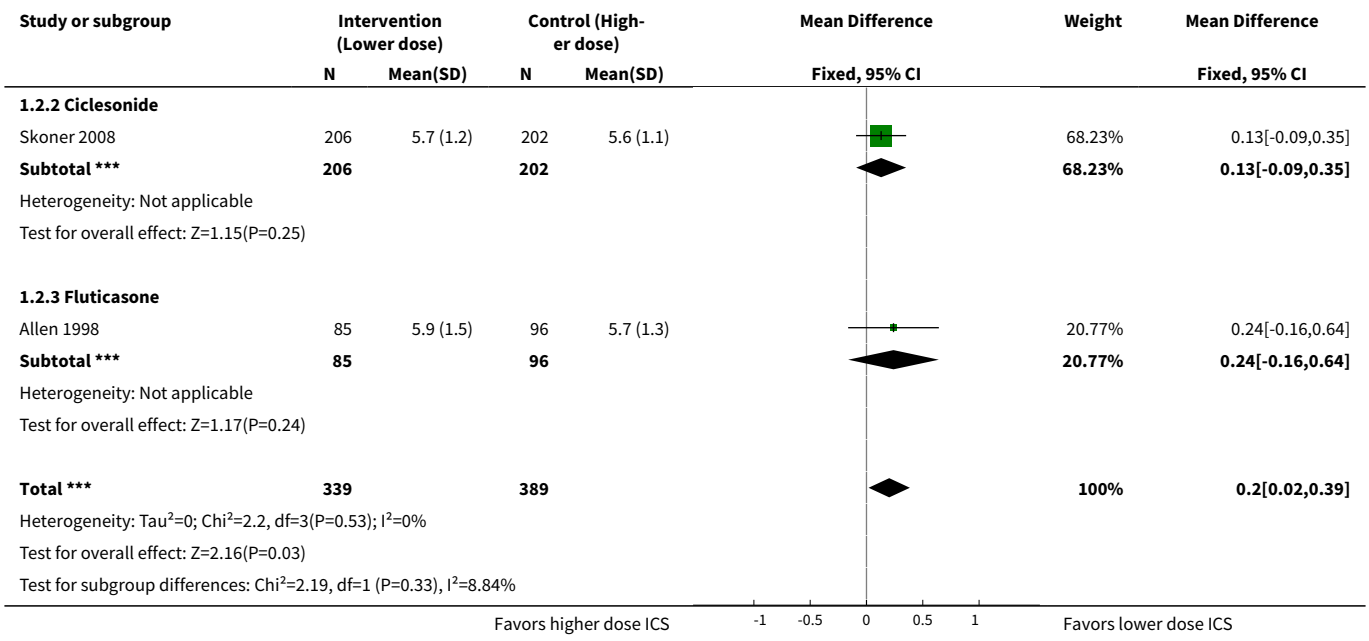
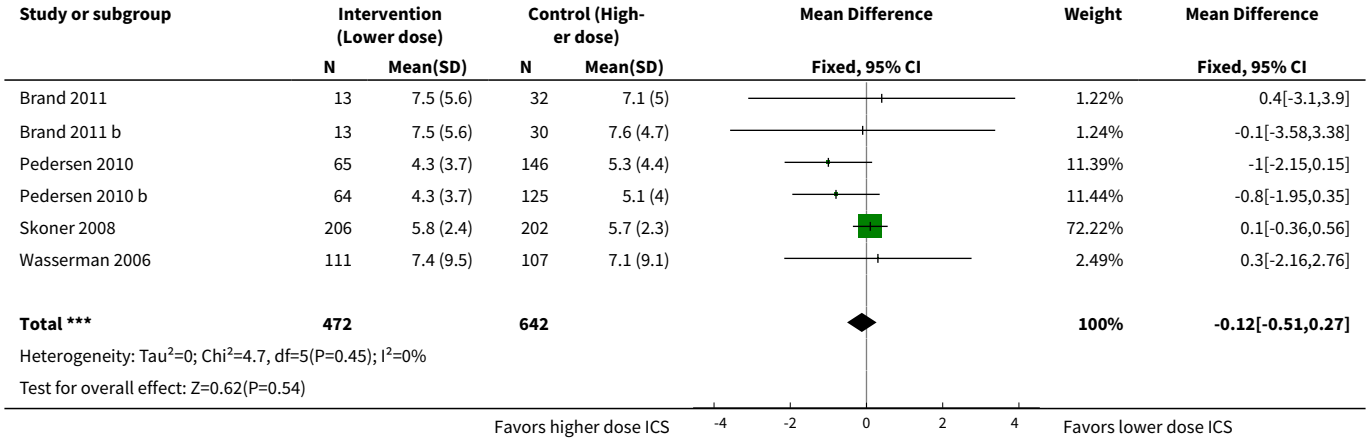
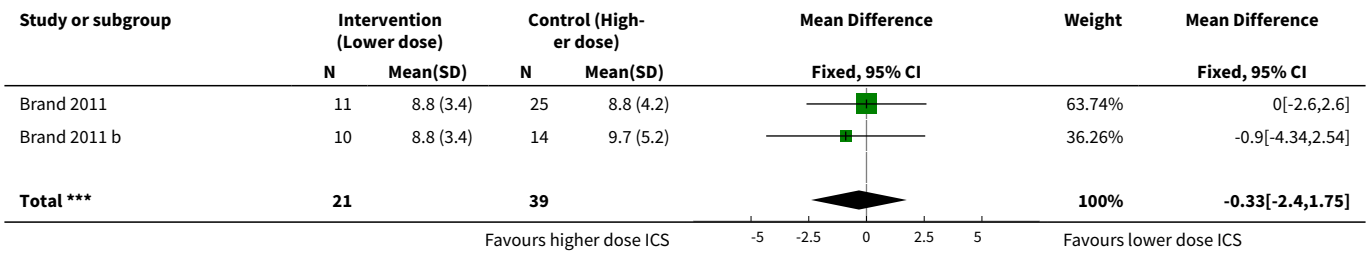


Analysis 1.3. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 3 Growth velocity (cm/y) by stadiometry from 0-3 months.



Analysis 1.4. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 4 Growth velocity (cm/y) by stadiometry from 0-6 months.



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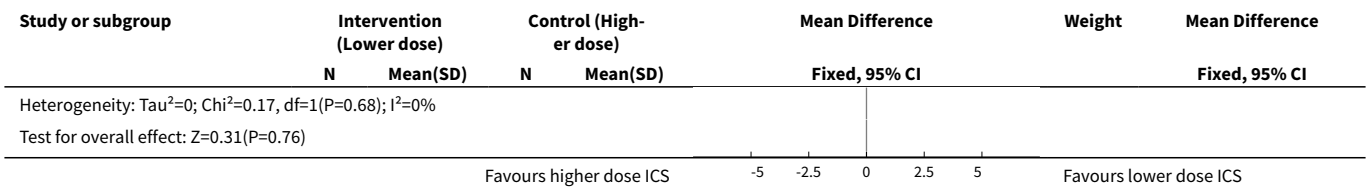
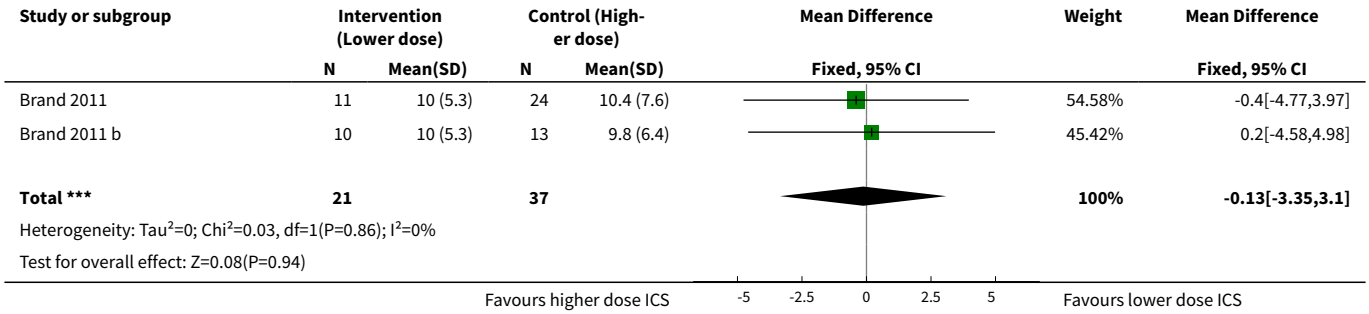
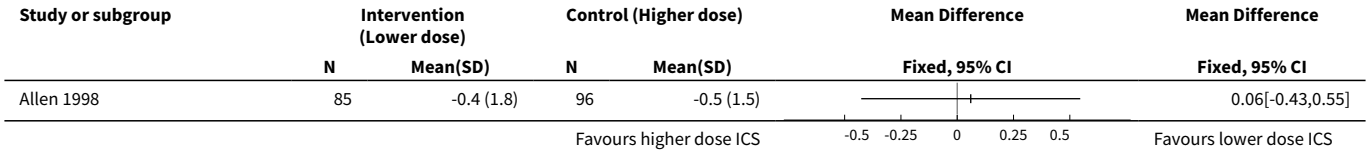


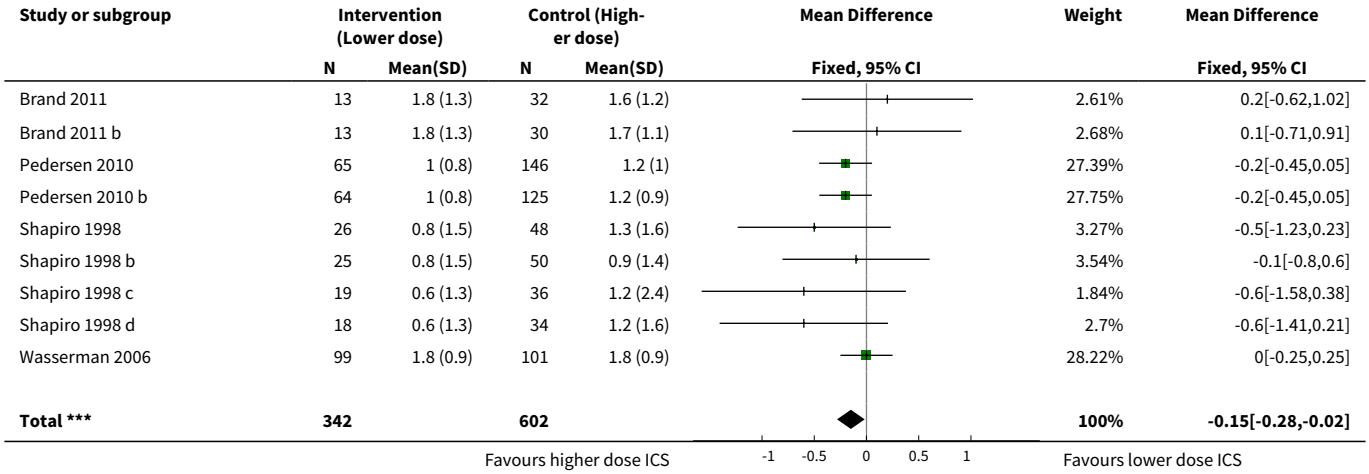
Analysis 1.5. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 5 Growth velocity (cm/y) by stadiometry from 3-6 months.



Analysis 1.6. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 6 Change in growth velocity (cm/y) by stadiometry from 0-12 months.



Analysis 1.7. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 7 Change in height (cm) by stadiometry from 0-3 months.



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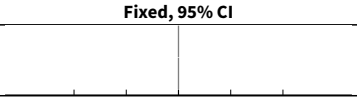
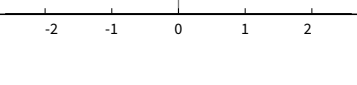
Study or subgroup	Intervention (Lower dose) N	Mean(SD)	Control (Higher dose) N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=5.66, df=8(P=0.68); I²=0%							
Test for overall effect: Z=2.21(P=0.03)							



Favours higher dose ICS — Favours lower dose ICS

Analysis 1.8. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 8 Change in height (cm) by stadiometry from 0-6 months.

Study or subgroup	Intervention (Lower dose) N	Mean(SD)	Control (Higher dose) N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Brand 2011	11	4.1 (1.5)	25	4.1 (1.9)		6.81%	0[-1.16,1.16]
Brand 2011 b	10	4.1 (1.5)	14	4.5 (2.4)		3.73%	-0.4[-1.96,1.16]
Vaessen-Verberne 2010	72	3 (1)	79	2.9 (1)		89.46%	0.05[-0.27,0.37]
Total ***	**93**		**118**			**100%**	**0.03[-0.27,0.33]**
Heterogeneity: Tau²=0; Chi²=0.31, df=2(P=0.86); I²=0%							
Test for overall effect: Z=0.19(P=0.85)							



Favours higher dose ICS — Favours lower dose ICS

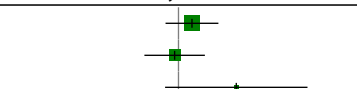
Analysis 1.9. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 9 Change in height (cm) by stadiometry from 3-6 months.

Study or subgroup	Intervention (Lower dose) N	Mean(SD)	Control (Higher dose) N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Brand 2011	11	2.3 (1.2)	24	2.4 (1.6)		57.17%	-0.1[-1.06,0.86]
Brand 2011 b	10	2.3 (1.2)	13	2.2 (1.5)		42.83%	0.1[-1,1.2]
Total ***	**21**		**37**			**100%**	**-0.01[-0.74,0.71]**
Heterogeneity: Tau²=0; Chi²=0.07, df=1(P=0.79); I²=0%							
Test for overall effect: Z=0.04(P=0.97)							

Favours higher dose ICS — Favours lower dose ICS

Analysis 1.10. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 10 Change in height (cm) by stadiometry from 0-12 months.

Study or subgroup	Intervention (Lower dose) N	Mean(SD)	Control (Higher dose) N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Allen 1998	85	5.9 (1.5)	96	5.7 (1.3)		48.67%	0.21[-0.2,0.62]
Sorkness 2007	94	5.3 (1.5)	96	5.3 (1.8)		37.18%	-0.06[-0.53,0.41]
Verberne 1998	57	4.5 (2.7)	30	3.6 (2.4)		6.71%	0.9[-0.21,2.01]
Verberne 1998 b	60	5.1 (2.4)	30	3.6 (2.4)		7.45%	1.5[0.45,2.55]



Favours higher dose ICS — Favours lower dose ICS

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Study or subgroup	Intervention (Lower dose) N	Mean(SD)	Control (Higher dose) N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Total ***	**296**		**252**			**100%**	**0.25[-0.04,0.54]**
Heterogeneity: Tau²=0; Chi²=8.45, df=3(P=0.04); I²=64.49%							
Test for overall effect: Z=1.72(P=0.09)							

Favours higher dose ICS -2 -1 0 1 2 Favours lower dose ICS

Analysis 1.11. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 11 Change in SD scores (height) from 0-12 months.

Study or subgroup	Intervention (Lower dose) N	Mean(SD)	Control (Higher dose) N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Vaessen-Verberne 2010	72	-0 (0.2)	79	-0 (0.1)		38.09%	-0.01[-0.06,0.04]
Verberne 1998	57	-0.2 (0.3)	30	-0.3 (0.2)		30.85%	0.11[0,0.22]
Verberne 1998 b	60	-0.1 (0.3)	30	-0.3 (0.2)		31.06%	0.17[0.07,0.27]
Total ***	**189**		**139**			**100%**	**0.08[-0.03,0.2]**
Heterogeneity: Tau²=0.01; Chi²=11.31, df=2(P=0); I²=82.31%							
Test for overall effect: Z=1.38(P=0.17)							

Favours higher dose ICS -0.2 -0.1 0 0.1 0.2 Favours lower dose ICS

Analysis 1.12. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 12 Change in weight (kg) from 0-3 months.

Study or subgroup	Intervention (Lower dose) N	Mean(SD)	Control (Higher dose) N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Shapiro 1998	25	1.1 (1.6)	48	0.9 (1.9)		18.52%	0.2[-0.63,1.03]
Shapiro 1998 b	25	1.1 (1.6)	50	0.7 (1.5)		21.47%	0.4[-0.35,1.15]
Shapiro 1998 c	18	1.8 (1.8)	36	1.1 (1.6)		13.87%	0.7[-0.28,1.68]
Shapiro 1998 d	18	1.8 (1.8)	34	0.9 (1.8)		12.81%	0.9[-0.13,1.93]
Wasserman 2006	94	0.4 (2.2)	101	0.6 (1.7)		33.33%	-0.2[-0.75,0.35]
Total ***	**180**		**269**			**100%**	**0.27[-0.13,0.66]**
Heterogeneity: Tau²=0.04; Chi²=5.02, df=4(P=0.29); I²=20.31%							
Test for overall effect: Z=1.33(P=0.18)							

Favours higher dose ICS -2 -1 0 1 2 Favours lower dose ICS

Analysis 1.13. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 13 Change in weight (kg) from 0-6 months.

Study or subgroup	Intervention (Lower dose) N	Mean(SD)	Control (Higher dose) N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Brand 2011	57	1.1 (1)	121	1.1 (1.2)		49.14%	0[-0.34,0.34]

Favours higher dose ICS -0.5 -0.25 0 0.25 0.5 Favours lower dose ICS

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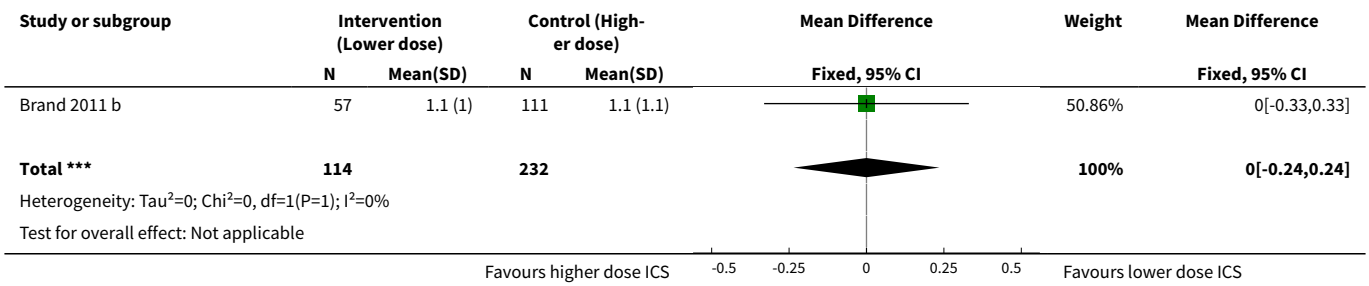
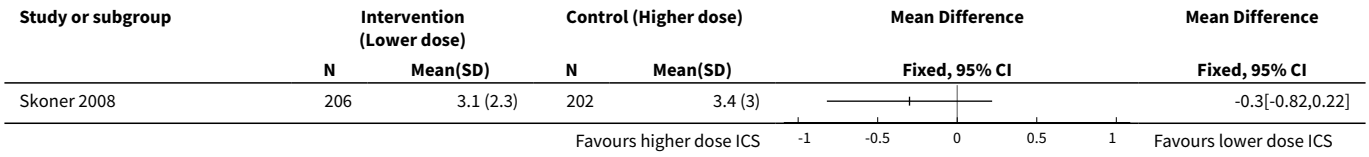
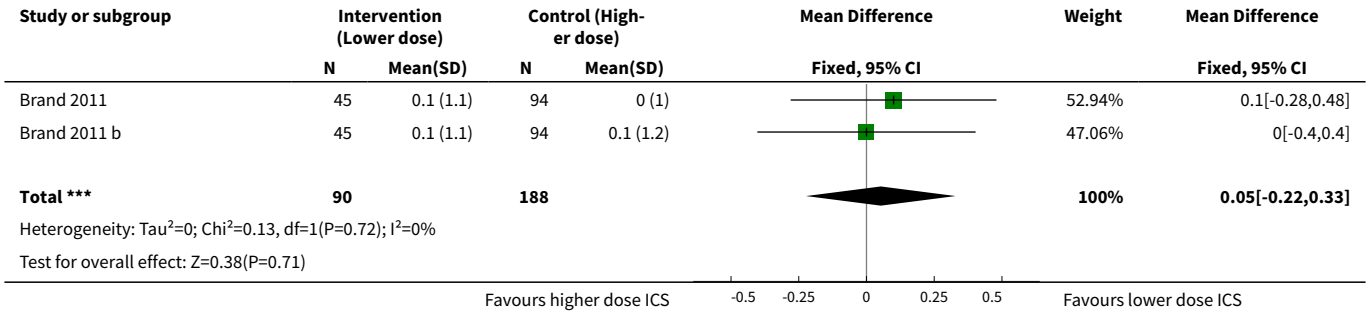


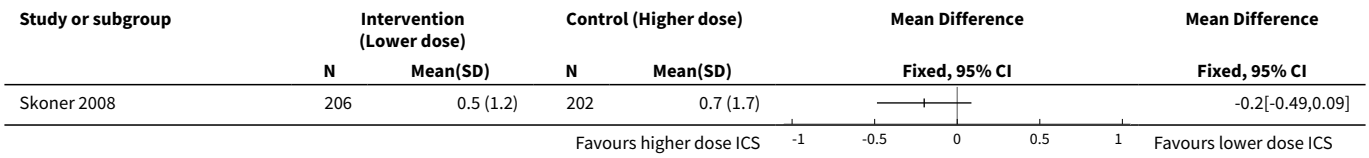
Analysis 1.14. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 14 Change in weight (kg) from 0-12 months.



Analysis 1.15. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 15 Change in BMI (kg/m²) from 0-6 months.



Analysis 1.16. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 16 Change in BMI (kg/m²) from 0-12 months.



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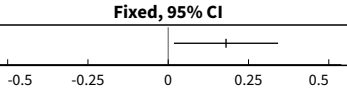
Analysis 1.17. Comparison 1 Inhaled corticosteroids dose-response effect, Outcome 17 Change in skeletal maturation (years) from 0-12 months.

Study or subgroup	Intervention (Lower dose)		Control (Higher dose)		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Allen 1998	85	1.1 (0.6)	96	1 (0.5)		0.18[0.02,0.34]



Favours higher dose ICS

Favours lower dose ICS

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ADDITIONAL TABLES

Table 1. FDA study design

Study	Run-in period ≥ 16 weeks	Tx period ≥ 48 weeks	Follow-up period (to access catch-up period)	Follow-up period ≥ 8 weeks	Recommended age (male: 3-10.5 years; female: 3-9.5 years, prepuberty (Tanner 1))	Mild asthma severity	No use of spacers	Placebo or active control group with no growth-suppressing effect
Allen 1998	No (2 weeks)	Yes (52 weeks)	No	No	Yes	Yes	Yes	Yes
Brand 2011	No (2-4 weeks)	No (24 weeks)	No	No	Partially (2-6 years)	Yes	No	Yes (placebo or montelukast if control was insufficient)
Pedersen 2010	No (2-4 weeks)	No (12 weeks)	No	No	Yes (6-11 years)	No	No*	Yes
Shapiro 1998	No (2 weeks)	No (12 weeks)	No	No	No (6-18 years)	No	Yes	Yes
Skoner 2008	Yes (6 months)	Yes (52 weeks)	Yes	Yes (8 weeks)	Yes (5-8 years)	Yes	Yes	Yes
Skoner 2011	No (1-2 weeks)	Yes (52 weeks)	Yes	Yes (12 weeks)	Yes	Yes	No	Yes
Sorkness 2007	No (2-4 weeks)	Yes (48 weeks)	No	No	No (6-14 years)	No (mild to moderate)	No	Yes (montelukast)
Vaessen-Verberne 2010	No (6 weeks)	No (26 weeks)	No	No	No (6-16 years)	No (moderate)	Yes	No
Verbern 1998	No (6 weeks)	Yes (54 weeks)	Yes+	No	No (6-16 years)	No	Yes	Yes (salmeterol)
Wasserman 2006	No (2-4 weeks)	No (12 weeks)	No	No	Partially (24-47 months)	NR	No	Yes

FDA = US Food and Drug Administration; NR = not reported.
All studies were randomised, placebo-controlled, double-blind, parallel-group trials.

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Table 2. FDA statistical methods

	Intention-to-treat analysis	Exclusion of pubescent children in analysis	Low and balanced withdrawals or missing data or patient dropouts	Data presented as linear regression model but not change in height	Baseline height, age, sex used as confounders in analysis model	Catch-up growth analysed with a linear regression model	No nasal steroid during the study
Allen 1998	Yes	Yes	Yes	Yes	No	NA	Yes
Brand 2011	Yes	NA	Yes	Yes	Yes	NA	NR
Pedersen 2010	Yes	NR	No (dropout in placebo: 24% vs active treatment: 16%-18%)	No	No	NA	NR
Shapiro 1998	NR	NR	No	NR	NR	NA	NR
Skoner 2008	Yes	NR	Yes	Yes	Yes	Yes	Yes
Skoner 2011	NR	NR	No	Yes	Yes	Yes	NR
Sorkness 2007	Yes	No	Yes	No	No	NA	NR
Vaessen-Verberne 2010	Yes	No	Yes	Yes	Yes	NA	NR
Verbern 1998	NR	NO	Yes	Yes	Yes	No	NR
Wasserman 2006	Yes	NA	Yes	Yes	Yes	NA	Yes

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Table 3. FDA possible sources of bias

	Use of stadiometer	Height evaluation by same trained blinded examiner	Height evaluation at the same time of the visit day	Repeated (≥ 3) measurements during the study period	Record of compliance
Allen 1998	Yes	NR	NR	Yes	Yes
Brand 2011	Yes	NR	NR	Yes	Yes
Pedersen 2010	Yes	NR	NR	No	No
Shapiro 1998	NR	NR	NR	No	Yes
Skoner 2008	Yes	Yes	Yes	Yes	Yes
Skoner 2011	Yes	Yes	Yes	Yes	Yes
Sorkness 2007	Yes	NR	NR	No	Yes
Vaessen-Verberne 2010	Yes	NR	NR	No	Yes
Verbern 1998	Yes	NR	NR	Yes	Yes
Wasserman 2006	Yes	NR	Yes	Yes	NR

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	weekly
EMBASE (Ovid)	weekly
CENTRAL (*The Cochrane Library*)	monthly
PsycINFO (Ovid)	monthly
CINAHL (EBSCO)	monthly
AMED (EBSCO)	monthly

Handsearches: core respiratory conference abstracts

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

MEDLINE search strategy used to identify trials for the CAGR

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.

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4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

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

WHAT'S NEW

Date	Event	Description
17 January 2016	Amended	During the translation process some text has been edited in the PLS and Abstract for clarity.

CONTRIBUTIONS OF AUTHORS

Aniela Ignea Pruteanu reviewed the literature search conducted until March2014, identified and reviewed all citations for relevance, reviewed all included trials for methodology and data extraction, verified all references, described the studies and performed data entry, analysed and interpreted results of the meta-analysis, wrote the first draft of the manuscript and approved the final version.

Bhupendrasinh Chauhan reviewed all included trials for methodology and data extraction, verified the description of studies and data entry, contributed to analysis and interpretation of data, revised all drafts of the manuscript, prepared responses to editorial comments and approved the final version.

Linjie Zhang wrote the review protocol, reviewed the literature search conducted until March2014, identified and reviewed half of the citations for relevance and approved the final version of the review.

Sílvio OM Prietsch provided input to drafting of the protocol, reviewed the literature search conducted until March 2014 and identified and reviewed half of the citations for relevance.

Prof Francine Ducharme revised and approved the protocol, requested the literature search, identified and contacted corresponding authors and/or pharmaceutical companies to solicit their collaboration in this review and in identifying other possibly relevant trials, corresponded with authors or pharmaceutical companies to verify methodology and data extraction, verified all references, described studies and performed data entry, analysed and interpreted results and approved the final version of the meta-analysis.

DECLARATIONS OF INTEREST

Aniela Ignea Pruteanu, Bhupendrasinh Chauhan, Linjie Zhang and Sílvio OM Prietsch: none known.

Prof. Francine Ducharme has received travel support, research funds and fees for speaking from Glaxo SmithKline, Novartis, Nycomed and/or Merck Frosst Inc.

SOURCES OF SUPPORT

Internal sources

- None, Other.

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review is different from the protocol in the following ways.

- Limited lower age to one year instead of 'up to 18 years.'
- Defined which other interventions were accepted: other non-steroidal asthma drugs (e.g. long-acting beta-agonists or leukotriene receptor antagonists).
- Added post hoc secondary outcomes (change in body mass index; change in skeletal maturation).
- Removed subgroup analyses as they were included as different outcomes: time points of outcome measurements.
- Added post hoc analysis: ICS dose difference (in µg of HFA-beclomethasone or equivalent) between groups.
- Added two outcomes: change in body mass index and change in skeletal maturation.
- Following recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008), the fixed effect model was used for the data analysis if the heterogeneity of pooled trials is less than 50%; otherwise the random effects model was used, despite the use of random effect models was proposed for all data analysis in the protocol.
- Several included trials contributed more than one comparison and one group compared with two or more groups. So the individual comparison was used as the unit of analysis in place of individual trial.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenal Cortex Hormones [*administration & dosage] [adverse effects]; Androstadienes [administration & dosage] [adverse effects]; Anti-Asthmatic Agents [*administration & dosage] [adverse effects]; Asthma [*drug therapy]; Beclomethasone [administration & dosage] [adverse effects]; Budesonide [administration & dosage] [adverse effects]; Dose-Response Relationship, Drug; Fluticasone; Growth [*drug effects]; Growth Disorders [*chemically induced]; Mometasone Furoate; Pregnadienediols [administration & dosage] [adverse effects]; Pregnenediones [administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans

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