**Effect of Inhaled Corticosteroids on Bone Growth in Children With Asthma**

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**Scenario:** It is known that systemic steroids can slow bone growth. Your 8 year old asthma patient’s mother is concerned that perhaps the daily inhaled steroids (given via a metered dose inhaler or MDI) could have the same effect. What can you tell her?

**Clinical Question:**

Does daily use of inhaled corticosteroids affect bone growth? Good

**→ PICO Question**:

Does daily use of inhaled corticosteroids slow bone growth in children with mild-to-moderate persistent asthma? Good

**P-** Children with mild-to-moderate persistent asthma

**I-** Daily inhaled corticosteroid

**C-**

**O-** Slowed bone growth

**PICO Search Terms**

|  |  |  |  |
| --- | --- | --- | --- |
| **P** | **I** | **C** | **O** |
| Children with mild-to-moderate persistent asthma | Inhaled corticosteroids |  | Slowed bone growth |
| Prepubertal children  with asthma | Inhaled Fluticasone |  | Linear growth |
| School-age children with asthma | Inhaled Budesonide |  | Effect on bone growth |
|  | Inhaled mometasone furoate |  | Reduced final height |
|  | Inhaled nedocromil sodium |  |  |

**Search Strategy**:

Outline the terms used, databases or other tools used, how many articles returned, and how you selected the final articles to base your CAT on:

**Search Terms: “**Children asthma inhaled corticosteroids bone growth”

**Database and Articles Returned:**

Pubmed - 120 articles (Best Match), 118 articles (Most Recent)

Cochrane - 1 Cochrane review, 22 trials

Trip Database - 633 articles by quality filter

**Filters:**

* Human trials
* Best match
* Free
* Full articles
* English
* Children

**Selection Methods (what criteria determined which articles to include in CAT):**

* Appropriateness to research question, ie. inhaled corticosteroids only
* Age of study subjects, ie. prepubescent
* Study did not include other studies included in this CAT
* Studies focusing on mild-moderate persistent asthma

**Articles Chosen** for Inclusion (please copy and paste the abstract with link):

Article #1:

[Inhaled corticosteroids in children with persistent asthma: effects on growth.](https://www.ncbi.nlm.nih.gov/pubmed/25030198)

Zhang L, Prietsch SO, Ducharme FM.

Cochrane Database Syst Rev. 2014 Jul 17;(7):CD009471. doi: 10.1002/14651858.CD009471.pub2. Review.

PMID: 25030198

[Similar articles](https://www.ncbi.nlm.nih.gov/pubmed?linkname=pubmed_pubmed&from_uid=25030198)

### **Background**

Treatment guidelines for asthma recommend inhaled corticosteroids (ICS) as first‐line therapy for children with persistent asthma. Although ICS treatment is generally considered safe in children, the potential systemic adverse effects related to regular use of these drugs have been and continue to be a matter of concern, especially the effects on linear growth.

### **Objectives**

To assess the impact of ICS on the linear growth of children with persistent asthma and to explore potential effect modifiers such as characteristics of available treatments (molecule, dose, length of exposure, inhalation device) and of treated children (age, disease severity, compliance with treatment).

### **Search methods**

We searched the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived from systematic searches of bibliographic databases including CENTRAL, MEDLINE, EMBASE, CINAHL, AMED and PsycINFO; we hand searched respiratory journals and meeting abstracts. We also conducted a search of ClinicalTrials.gov and manufacturers' clinical trial databases to look for potential relevant unpublished studies. The literature search was conducted in January 2014.

### **Selection criteria**

Parallel‐group randomised controlled trials comparing daily use of ICS, delivered by any type of inhalation device for at least three months, versus placebo or non‐steroidal drugs in children up to 18 years of age with persistent asthma.

### **Data collection and analysis**

Two review authors independently performed study selection, data extraction and assessment of risk of bias in included studies. We conducted meta‐analyses using the Cochrane statistical package RevMan 5.2 and Stata version 11.0. We used the random‐effects model for meta‐analyses. We used mean differences (MDs) and 95% CIs as the metrics for treatment effects. A negative value for MD indicates that ICS have suppressive effects on linear growth compared with controls. We performed a priori planned subgroup analyses to explore potential effect modifiers, such as ICS molecule, daily dose, inhalation device and age of the treated child.

### **Main results**

We included 25 trials involving 8471 (5128 ICS‐treated and 3343 control) children with mild to moderate persistent asthma. Six molecules (beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone propionate and mometasone furoate) given at low or medium daily doses were used during a period of three months to four to six years. Most trials were blinded and over half of the trials had dropout rates of over 20%.

Compared with placebo or non‐steroidal drugs, ICS produced a statistically significant reduction in linear growth velocity (14 trials with 5717 participants, MD ‐0.48 cm/y, 95% CI ‐0.65 to ‐0.30, moderate quality evidence) and in the change from baseline in height (15 trials with 3275 participants; MD ‐0.61 cm/y, 95% CI ‐0.83 to ‐0.38, moderate quality evidence) during a one‐year treatment period.

Subgroup analysis showed a statistically significant group difference between six molecules in the mean reduction of linear growth velocity during one‐year treatment (Chi² = 26.1, degrees of freedom (df) = 5, P value < 0.0001). The group difference persisted even when analysis was restricted to the trials using doses equivalent to 200 μg/d hydrofluoroalkane (HFA)‐beclomethasone. Subgroup analyses did not show a statistically significant impact of daily dose (low vs medium), inhalation device or participant age on the magnitude of ICS‐induced suppression of linear growth velocity during a one‐year treatment period. However, head‐to‐head comparisons are needed to assess the effects of different drug molecules, dose, inhalation device or patient age. No statistically significant difference in linear growth velocity was found between participants treated with ICS and controls during the second year of treatment (five trials with 3174 participants; MD ‐0.19 cm/y, 95% CI ‐0.48 to 0.11, P value 0.22). Of two trials that reported linear growth velocity in the third year of treatment, one trial involving 667 participants showed similar growth velocity between the budesonide and placebo groups (5.34 cm/y vs 5.34 cm/y), and another trial involving 1974 participants showed lower growth velocity in the budesonide group compared with the placebo group (MD ‐0.33 cm/y, 95% CI ‐0.52 to ‐0.14, P value 0.0005). Among four trials reporting data on linear growth after treatment cessation, three did not describe statistically significant catch‐up growth in the ICS group two to four months after treatment cessation. One trial showed accelerated linear growth velocity in the fluticasone group at 12 months after treatment cessation, but there remained a statistically significant difference of 0.7 cm in height between the fluticasone and placebo groups at the end of the three‐year trial.

One trial with follow‐up into adulthood showed that participants of prepubertal age treated with budesonide 400 μg/d for a mean duration of 4.3 years had a mean reduction of 1.20 cm (95% CI ‐1.90 to ‐0.50) in adult height compared with those treated with placebo.

### **Authors' conclusions**

Regular use of ICS at low or medium daily doses is associated with a mean reduction of 0.48 cm/y in linear growth velocity and a 0.61‐cm change from baseline in height during a one‐year treatment period in children with mild to moderate persistent asthma. The effect size of ICS on linear growth velocity appears to be associated more strongly with the ICS molecule than with the device or dose (low to medium dose range). ICS‐induced growth suppression seems to be maximal during the first year of therapy and less pronounced in subsequent years of treatment. However, additional studies are needed to better characterise the molecule dependency of growth suppression, particularly with newer molecules (mometasone, ciclesonide), to specify the respective role of molecule, daily dose, inhalation device and patient age on the effect size of ICS, and to define the growth suppression effect of ICS treatment over a period of several years in children with persistent asthma.

Article #2:

[**Linear** **growth** and **bone** **maturation** are **unaffected** by **1** **year** of **therapy** with inhaled flunisolide hydrofluoroalkane in prepubescent children with mild persistent asthma: a randomized, double-blind, placebo-controlled trial.](https://www.ncbi.nlm.nih.gov/pubmed/21962092)

Bensch GW, Greos LS, Gawchik S, Kpamegan E, Newman KB.

Ann Allergy Asthma Immunol. 2011 Oct;107(4):323-9. doi: 10.1016/j.anai.2011.07.017. Epub 2011 Sep 3.

PMID: 21962092

Abstract

BACKGROUND:

Inhaled corticosteroids (ICS) are the preferred long-term therapy for subjects with persistent asthma. However, concerns remain about potential effects of long-term ICS use on growth in children.

OBJECTIVE:

To determine the effect of 1 year of inhalation therapy with flunisolide hydrofluoroalkane (HFA) on growth velocity and bone maturation in children with mild persistent asthma.

METHODS:

In this double-blind, placebo-controlled study, 218 prepubescent (Tanner Stage 1) children with mild persistent asthma ranging in age from 4 to 10 years were evaluated. After a 2-week run-in period, subjects were randomized (1:1) to 2 puff

s flunisolide HFA twice daily (85 μg/puff) or placebo for 52 weeks. Height was assessed by stadiometry at each visit. Growth velocity (cm/52 weeks) was estimated by the slope of the linear regression of height over time. An independent assessor scored hand and wrist radiographs for bone development pretreatment and at week 52. Analysis of covariance was used for all efficacy endpoints.

RESULTS:

The 2 treatment groups were similar at baseline for sex, race, age, weight, and height. At the end of double-blind treatment, mean growth velocity was 6.01 ± 1.84 cm/52 weeks for flunisolide HFA (n = 106) and 6.19 ± 1.30 cm/52 weeks for placebo (n = 112) (P = .425). Mean advancement in bone age during the 1-year study was similar for the 2 groups: 0.93 ± 0.46 years for flunisolide HFA (n = 70) and 1.01 ± 0.41 years for placebo (n = 75) (P = .128).

CONCLUSIONS:

In this study, flunisolide HFA did not suppress growth or bone maturation at the highest approved dose for children with persistent asthma.

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PMID: 21962092 DOI: 10.1016/j.anai.2011.07.017

Article #3:

[**Long-term effects of budesonide or nedocromil in children with asthma**](https://www.ncbi.nlm.nih.gov/pubmed?term=11027739)**.**[Childhood Asthma Management Program Research Group](https://www.ncbi.nlm.nih.gov/pubmed/?term=Childhood%20Asthma%20Management%20Program%20Research%20Group%5BCorporate%20Author%5D), [Szefler S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Szefler%20S%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Weiss S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Weiss%20S%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Tonascia J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Tonascia%20J%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Adkinson NF](https://www.ncbi.nlm.nih.gov/pubmed/?term=Adkinson%20NF%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Bender B](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bender%20B%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Cherniack R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cherniack%20R%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Donithan M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Donithan%20M%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Kelly HW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kelly%20HW%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Reisman J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Reisman%20J%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Shapiro GG](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shapiro%20GG%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Sternberg AL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sternberg%20AL%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Strunk R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Strunk%20R%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Taggart V](https://www.ncbi.nlm.nih.gov/pubmed/?term=Taggart%20V%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Van Natta M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Van%20Natta%20M%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Wise R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wise%20R%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Wu M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wu%20M%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Zeiger R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zeiger%20R%5BAuthor%5D&cauthor=true&cauthor_uid=11027739).

[N Engl J Med.](https://www.ncbi.nlm.nih.gov/pubmed?term=11027739) 2000 Oct 12;343(15):1054-63.

PMID: 11027739

[Link to full article](https://www.nejm.org/doi/10.1056/NEJM200010123431501?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov)

*Abstract:*

BACKGROUND

Anti-inflammatory therapies, such as inhaled corticosteroids or nedocromil, are recommended for children with asthma, although there is limited information on their long-term use.

METHODS

We randomly assigned 1041 children from 5 through 12 years of age with mild-to-moderate asthma to receive 200 μg of budesonide (311 children), 8 mg of nedocromil (312 children), or placebo (418 children) twice daily. We treated the participants for four to six years. All children used albuterol for asthma symptoms.

RESULTS

There was no significant difference between either treatment and placebo in the primary outcome, the degree of change in the forced expiratory volume in one second (FEV1, expressed as a percentage of the predicted value) after the administration of a bronchodilator. As compared with the children assigned to placebo, the children assigned to receive budesonide had a significantly smaller decline in the ratio of FEV1 to forced vital capacity (FVC, expressed as a percentage) before the administration of a bronchodilator (decline in FEV1:FVC, 0.2 percent vs. 1.8 percent). The children given budesonide also had lower airway responsiveness to methacholine, fewer hospitalizations (2.5 vs. 4.4 per 100 person-years), fewer urgent visits to a caregiver (12 vs. 22 per 100 person-years), greater reduction in the need for albuterol for symptoms, fewer courses of prednisone, and a smaller percentage of days on which additional asthma medications were needed. As compared with placebo, nedocromil significantly reduced urgent care visits (16 vs. 22 per 100 person-years) and courses of prednisone. The mean increase in height in the budesonide group was 1.1 cm less than in the placebo group (22.7 vs. 23.8 cm, P=0.005); this difference was evident mostly within the first year. The height increase was similar in the nedocromil and placebo groups.

CONCLUSIONS

In children with mild-to-moderate asthma, neither budesonide nor nedocromil is better than placebo in terms of lung function, but inhaled budesonide improves airway responsiveness and provides better control of asthma than placebo or nedocromil. The side effects of budesonide are limited to a small, transient reduction in growth velocity.

PMID: 11027739 DOI: [10.1056/NEJM200010123431501](https://doi.org/10.1056/NEJM200010123431501)

Article #4:

[**Effect of inhaled glucocorticoids in childhood on adult height.**](https://www.ncbi.nlm.nih.gov/pubmed/22938716)[Kelly HW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kelly%20HW%5BAuthor%5D&cauthor=true&cauthor_uid=22938716)1, [Sternberg AL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sternberg%20AL%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Lescher R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lescher%20R%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Fuhlbrigge AL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Fuhlbrigge%20AL%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Williams P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Williams%20P%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Zeiger RS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zeiger%20RS%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Raissy HH](https://www.ncbi.nlm.nih.gov/pubmed/?term=Raissy%20HH%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Van Natta ML](https://www.ncbi.nlm.nih.gov/pubmed/?term=Van%20Natta%20ML%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Tonascia J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Tonascia%20J%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Strunk RC](https://www.ncbi.nlm.nih.gov/pubmed/?term=Strunk%20RC%5BAuthor%5D&cauthor=true&cauthor_uid=22938716); [CAMP Research Group](https://www.ncbi.nlm.nih.gov/pubmed/?term=CAMP%20Research%20Group%5BCorporate%20Author%5D).

N Engl J Med. 2012 Sep 6;367(10):904-12. doi: 10.1056/NEJMoa1203229. Epub 2012 Sep 3.

PMID: 22938716

**Abstract**

**BACKGROUND—**The use of inhaled glucocorticoids for persistent asthma causes a temporary reduction in growth velocity in prepubertal children. The resulting decrease in attained height 1 to 4 years after the initiation of inhaled glucocorticoids is thought not to decrease attained adult height.

**METHODS—**We measured adult height in 943 of 1041 participants (90.6%) in the Childhood Asthma Management Program; adult height was determined at a mean (±SD) age of 24.9±2.7 years. Starting at the age of 5 to 13 years, the participants had been randomly assigned to receive 400 μg of budesonide, 16 mg of nedocromil, or placebo daily for 4 to 6 years. We calculated differences in adult height for each active treatment group, as compared with placebo, using multiple linear regression with adjustment for demographic characteristics, asthma features, and height at trial entry.

**RESULTS—**Mean adult height was 1.2 cm lower (95% confidence interval [CI], −1.9 to −0.5) in the budesonide group than in the placebo group (P = 0.001) and was 0.2 cm lower (95% CI, −0.9 to 0.5) in the nedocromil group than in the placebo group (P = 0.61). A larger daily dose of inhaled glucocorticoid in the first 2 years was associated with a lower adult height (−0.1 cm for each microgram per kilogram of body weight) (P = 0.007). The reduction in adult height in the budesonide group as compared with the placebo group was similar to that seen after 2 years of treatment (−1.3 cm; 95% CI, −1.7 to −0.9). During the first 2 years, decreased growth velocity in the budesonide group occurred primarily in prepubertal participants.

**CONCLUSIONS—**The initial decrease in attained height associated with the use of inhaled glucocorticoids in prepubertal children persisted as a reduction in adult height, although the decrease was not progressive or cumulative.

Article #5:

[Influence of inhaled corticosteroids on pubertal growth and final height in asthmatic children.](https://www.ncbi.nlm.nih.gov/pubmed/26919136)

De Leonibus C, Attanasi M, Roze Z, Martin B, Marcovecchio ML, Di Pillo S, Chiarelli F, Mohn A.

Pediatr Allergy Immunol. 2016 Aug;27(5):499-506. doi: 10.1111/pai.12558. Epub 2016 May 6.

BACKGROUND:

Controversial data exist on the possibility that inhaled corticosteroids (ICs) affect growth in children with mild-to-moderate asthma. We assessed whether ICs affect growth and final height (FH) in asthmatic children compared to controls.

#### METHODS:

A retrospective study was conducted on 113 asthmatic children compared with 66 control children. Asthmatic children presented with mild-to-moderate asthma and had exclusive ICs. Anthropometric data of four specific time-points were collected for both groups (pre-puberty, onset and late puberty, and FH) and converted to standard deviation scores (SDS). Growth trajectories were assessed as follows: (i) in puberty, using peak height velocity (PHV) and pubertal height gain SDS (PHG-SDS); (ii) until FH achievement, using FH-SDS and FH gain SDS (FHG-SDS). Repeated measurement analysis was performed across longitudinal study visits. A general linear model (GLM) was performed in asthmatic group evaluating the effect of corticosteroid type, treatment duration, and cumulative dose on FH corrected for multiple variables.

#### RESULTS:

At pre-puberty, height and weight SDS were similar between the groups (p > 0.05). Height SDS progressively declined over the study period in asthmatic patients from pre-puberty to FH (p-trend < 0.05), whereas it did not change over time in controls (p-trend > 0.05), in both boys and girls. Asthmatic children had exclusive ICs [budesonide (n = 36) vs. fluticasone (n = 43) vs. mometasone (n = 34)] for a mean period of 6.25 ± 1.20 years and a mean cumulative dose of 560.07 ± 76.02 mg. They showed decreased PHG-SDS and lower PHV compared to controls (all p < 0.05). FH-SDS and FHG-SDS were significantly reduced in asthmatic group compared to controls. FH in asthmatic patients was 2.5 ± 2.89 cm lower in boys and 2.0 ± 2.03 cm lower in girls than controls. The GLM showed that FH achievement was dependent on the type of ICs, duration of the treatment, and cumulative dose (p < 0.05).

#### CONCLUSIONS:

ICs affect pubertal growth determining reduced final height in asthmatic children compared to controls, in a dose- and duration-dependent manner.

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#### KEYWORDS: asthma; children; growth; inhaled corticosteroid therapy; puberty

### Comment in Pediatr Allergy Immunol. 2016 Aug;27(5):445.

PMID: 26919136

Link: https://onlinelibrary.wiley.com/doi/full/10.1111/pai.12558

**Summary of the Evidence**:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Author (Date) | Level of Evidence | Sample/Setting  (# of subjects/ studies, cohort definition etc. ) | Outcome(s) studied | Key Findings | Limitations and Biases |
| Zhang L, Prietsch SO, Ducharme FM. | Systematic Review | **25 trials/articles** were analyzed involving **8471** children with mild to moderate persistent asthma, of whom 5128 were treated with ICS and 3343 with placebo or non‐steroidal drugs. | Assessed the impact of ICS on linear growth of children with persistent asthma and explored potential effect modifiers such as molecules, dose, length of exposure, inhalation device and the treated children's age, disease severity, and compliance with treatment. | Children taking ICS compared with a placebo or NSAID produced a statistically significant reduction in linear growth velocity (14 trials with 5717 participants, MD -0.48 cm/y, 95% CI -0.65 to -0.30, moderate quality evidence) and a change from baseline in height (15 trials with 3275 participants; MD -0.61 cm/y, 95% CI -0.83 to -0.38, moderate quality evidence) during a one-year treatment period. No statistically significant difference in linear growth velocity was found between participants treated with ICS and controls during the second year of treatment (five trials with 3174 participants; MD -0.19 cm/y, 95% CI -0.48 to 0.11, P value 0.22). | The authors may have overlooked certain articles/trials, if growth data was not described in the title or abstract when they were screening for studies. No trials included children with severe persistent asthma. Additionally most studies (15) were only of 1-yr duration. Half of the studies had a 20% drop out rate, and over half of the studies were funded by pharmaceutical companies. Lastly the authors also performed a risk of bias on certain domains for each study and a sensitivity analyses showed that these potential biases did not significantly affect the results of this review. |
| [Kelly HW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kelly%20HW%5BAuthor%5D&cauthor=true&cauthor_uid=22938716)1, [Sternberg AL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sternberg%20AL%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Lescher R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lescher%20R%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Fuhlbrigge AL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Fuhlbrigge%20AL%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Williams P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Williams%20P%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Zeiger RS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zeiger%20RS%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Raissy HH](https://www.ncbi.nlm.nih.gov/pubmed/?term=Raissy%20HH%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Van Natta ML](https://www.ncbi.nlm.nih.gov/pubmed/?term=Van%20Natta%20ML%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Tonascia J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Tonascia%20J%5BAuthor%5D&cauthor=true&cauthor_uid=22938716), [Strunk RC](https://www.ncbi.nlm.nih.gov/pubmed/?term=Strunk%20RC%5BAuthor%5D&cauthor=true&cauthor_uid=22938716); [CAMP Research Group](https://www.ncbi.nlm.nih.gov/pubmed/?term=CAMP%20Research%20Group%5BCorporate%20Author%5D) | Randomized Double- blind trial | 1041 children between 5 and 13 year old with mild to moderate asthma were randomly assigned to either the placebo, budesonide or nedocromil group. During a follow up of 12.5 years, participants’ weight and height were measured. | Assess the effect of daily use of nedocromil and budesonide on children growth. Of all the original participants, the adults height, growth velocity in children and glucocorticoid dependent dose on growth deficit were measured | The adjusted mean adult height was 1.2 cm lower in the budesonide group as compared with the placebo (171.1 cm vs 172.3cm, P= 0.001)  · Deficit in adult height was higher in the budesonide group for women (-1.8cm, P=0.001) than for men in the placebo group (-0.8cm, P=0.10)  · Growth velocity between the budesonide and placebo group varied during the first two years of trial for women and men, P=0.007 and P=<0.001 respectively. Noticeable difference occurred in prepubertal participants (girls and boy 5 to 11 years of age)  · Large daily dose of glucocorticoids during the first 2 years of trial was related with a lower adult height (-0.1 cm per kilogram, P= 0.007). | Confounding variables limited researchers’ ability to further analyze the effects of treatment duration, age at treatment and puberty status on growth velocity.  Limited availability of original controls in the longitudinal cohort study. Healthy sibling used instead of controls so less reliable.  I chose this article because it is a randomized controlled trial with a reasonable sample size of 1041 participants in the age group 5-13. Although this study was initiated in 1993, It followed its participants until adulthood. This study measured height, growth velocity and effect of glucocorticoid dose on children’s height which correlates with our clinical question. |
| [Childhood Asthma Management Program Research Group](https://www.ncbi.nlm.nih.gov/pubmed/?term=Childhood%20Asthma%20Management%20Program%20Research%20Group%5BCorporate%20Author%5D), [Szefler S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Szefler%20S%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Weiss S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Weiss%20S%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Tonascia J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Tonascia%20J%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Adkinson NF](https://www.ncbi.nlm.nih.gov/pubmed/?term=Adkinson%20NF%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Bender B](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bender%20B%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Cherniack R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cherniack%20R%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Donithan M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Donithan%20M%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Kelly HW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kelly%20HW%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Reisman J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Reisman%20J%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Shapiro GG](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shapiro%20GG%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Sternberg AL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sternberg%20AL%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Strunk R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Strunk%20R%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Taggart V](https://www.ncbi.nlm.nih.gov/pubmed/?term=Taggart%20V%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Van Natta M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Van%20Natta%20M%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Wise R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wise%20R%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Wu M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wu%20M%5BAuthor%5D&cauthor=true&cauthor_uid=11027739), [Zeiger R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zeiger%20R%5BAuthor%5D&cauthor=true&cauthor_uid=11027739). | Randomized Control Trial | Randomly assigned 1041 children (ages 5-12) w/  mild-to-moderate asthma to receive 200 μg of budesonide (311 children), 8 mg of nedocromil (312 children), or placebo (418 children) 2qd. Participants treated for 4-6 years. All used albuterol for asthma symptoms. | Evaluated whether continuous, long-term treatment, w/ either an inhaled corticosteroid (budesonide) or an inhaled non corticosteroid drug (nedocromil), safely improves in lung growth as compared for symptomatic treatment only (with albuterol and prednisone as needed).The primary outcome was lung growth, measured in FEV1 after the administration of a bronchodilator. Secondary outcomes included the degree of airway responsiveness, morbidity, physical growth, and psychological development. | Neither budesonide nor nedocromil is better than placebo in terms of lung function, but inhaled budesonide improves airway responsiveness and provides better control of asthma than placebo or nedocromil. The side effects of budesonide are limited to a small, transient reduction in growth velocity.  Any stats such as p value? | Small sample size for randomized trial, larger differences may have been found with a larger trial group. Patients still allowed to use other medication for asthma of any kind, including other systemic steroids and beta-blocking agents. These were not provided by the same company that provided the inhaled drugs for the trial One death from asthma occurred in the nedocromil group; the child had been receiving supplemental treatment, including inhaled corticosteroids, for several months before her Death. One child in the placebo group required intubation for an exacerbation of asthma. No limitations from Pharmaceutical companies or research companies as they did not fund the trial. Supported by contracts with the National Heart, Lung, and Blood Institute and by General Clinical Research Center grants from the National Center for Research Resources |
| Bensch, G.W., Greos, L. S., Gawchik, S., Kpamegan, E., & Newman, K. B. (2011) | Randomized, Double-blind, Placebo-controlled  trial | 218 prepubescent children with mild persistent asthma ranging in age from 4 to 10 years were evaluated. After a 2-week, subjects were randomized to 2 puffs flunisolide HFA twice daily or placebo for 52 weeks. Height, growth velocity, bone development are assessed. | Evaluate the potential effects of long-term ICS use on growth in children. To determine the effect of 1 year of inhalation therapy with flunisolide hydrofluoroalkane (HFA) on growth velocity, bone maturation, and the safety of the flunisolide HFA in children with mild persistent asthma. | Linear growth: 1) Mean growth velocity with flunisolide HFA (5.85 ± 1,70 cm) was similar to placebo (6.12 ± 1.15 cm); 2) Mean change in height with flunisolide HFA was similar to placebo (P = .333).  Bone maturation: The mean change in bone age was similar for subjects who received flunisolide HFA (6.70 ± 1.85 yrs) and placebo (6.72 ± 1.99 yrs).  Safety: Flunisolide HFA was well tolerated. | Methodological Limitations: 1) Sample size: not large enough to find significant relationships; 2) Lack of available and/or reliable data: due to small sample size; 3) Instruments used to collect the data: Measurement error of the stadiometer.  Limitations of the Researcher: Two researchers are employed by the supporting laboratory may have biases toward data and results that only support their hypotheses |
| De Leonibus C, Attanasi M, Roze Z, Martin B, Marcovecchio ML, Di Pillo S, Chiarelli F, Mohn A. | Retrospective cohort | **Cohort:** 113 prepubertal children (aged 5-7) with persistent mild-to-moderate asthma with or rhinitis who:  - Received a daily inhaled corticosteroid treatment (budesonide, mometasone furoate, or fluticasone propionate) for at least 8 months/year  - Were not using systemic corticosteroids for more than 2 weeks/year or nasal corticoids to treat rhinitis  - Were not going into complete remission for asthma  **Control:** 66 children of the same age group without any:  - chronic diseases  - physical disabilities  - abnormalities in pubertal development  - malnutrition or born with low birth weight (<2500 gr) | Height and weight were measured from both groups at four visits:   * Visit 1: baseline prepubertal visit * Visit 2: onset of puberty * Visit 3: late puberty * Visit 4: achievement of final height (FH)   Data was then converted to standard deviation scores (SDS). In puberty, growth was assessed as peak height velocity (PHV), age at peak height velocity (APHV), and pubertal height gain SDS (PHG-SDS), and until FH achievement, growth was assessed using FH-SDS and FH gain SDS. Parental-adjusted height (PAH)-SDS was also assessed to determine the patient’s genetic potential. A general linear model (GLM) was created in the asthmatic group to evaluate the effect of the IC type, treatment duration, and cumulative dose on final height. | FH-SDS: significantly lower in asthmatic children compared to controls in both boys and girls. In cm, FH in asthmatic patients was 2.5± 2.89 cm lower in boys and 2.0± 2.03 cm lower in girls compared to controls.  PHG-SDS: significantly decreased in asthmatic patients compared to controls. Boys: -0.21 vs. 0.03 SDS (p=0.036). Girls: -0.35 vs. 0.02 SDS (p=0.012).  PHV: lower in asthmatic patients compared to controls. Boys: 6.54 vs. 8.18 cm/year (p=0.006). Girls: 5.36 vs. 7.10 cm/year (p=0.015).  APHV: similar to control in both boys and girls.  PAH-SDS: significantly reduced in asthmatic children compared with controls, meaning asthmatic children did not reach their genetic potential.  GLM: showed that IC type, duration, and cumulative dose had a significant effect on FH. Patients on Fluticasone (mean (SD): 164.04 cm) had significantly lower FH compared to children using budesonide (169.41) or mometasone (172.82). Longer duration of treatment and greater cumulative dose were also significantly associated with reduced FH. | -Small sample size  - Retrospective design with potential for selection bias  - Lack of information on bone age and pubertal biochemical markers such as DHEAS, estrogen and testosterone, GH, and IGF-1 levels.  -Clinical based and not population based study design  - Study performed in Italy- questionably applicable to US  - Asthma itself may have detrimental growth effects on its own  → multiple limitations, but article chosen because:   1. Recent (2016) 2. This is the first known study to compare pubertal ages 3. The study was longer than previous studies 4. The study assessed PAH as an additional measurement which further supports the findings 5. Directly answers the search question |

**Conclusion(s)**:

After appraising each of the articles, we found that the strongest and most persuasive articles drew these conclusions: *[Zhang et. al, 2014, Kelly et. al, 2013, Loke et. al, 2016]*

* The studies suggests that children treated daily with ICS may grow approximately 0.5 cm/yr less than those not treated with these medications during the first year of treatment. However the magnitude of ICS‐related growth reduction may depend on the type of drug, dose, and duration.
* Growth reduction seems to be maximal during the first year of therapy and less pronounced in subsequent years of treatment.
* Evidence provided by the Zhang et. al review allows us to conclude that daily use of ICS can cause a small reduction in height in children up to 18 years of age with persistent asthma; this effect seems minor compared with the known benefit of these medications for asthma control.

**Clinical Bottom Line**:

→ The findings support the need to use the lowest effective dose of ICS in children with mild-to-moderate persistent asthma to limit growth reduction as much as possible. The benefit of asthma control outweighs the slight decrease in height in asthmatic children who require ICS. Asthmatic children on ICS should be monitored and seen for routine follow up visits to ensure proper administration and dose of the ICS, and should have the dose lowered whenever possible. Modifiable environmental triggers, such as allergens and smoke, should be considered and properly addressed to avoid asthmatic exacerbations. Alternatives to ICS should be considered for other respiratory issues, along with proper prescription and administration, as ICS should not be used for viral wheeze or infrequent intermittent asthma.

100 - Good job! Very thorough and specific!