

## EFFECT OF LONG-TERM TREATMENT WITH INHALED BUDESONIDE ON ADULT HEIGHT IN CHILDREN WITH ASTHMA

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## ABSTRACT

**Background** Short-term studies have shown that inhaled corticosteroids may reduce the growth of children with asthma. However, the effect of long-term treatment on adult height is uncertain.

**Methods** We conducted a prospective study in children with asthma to examine the effect of long-term treatment with inhaled budesonide on adult height. We report on 211 children who have attained adult height: 142 budesonide-treated children with asthma, 18 control patients with asthma who have never received inhaled corticosteroids, and 51 healthy siblings of patients in the budesonide group, who also served as controls.

**Results** The children in the budesonide group attained adult height after a mean of 9.2 years of budesonide treatment (range, 3 to 13) at a mean daily dose of 412  $\mu\text{g}$  (range, 110 to 877). The mean cumulative dose of budesonide was 1.35 g (range, 0.41 to 3.99). The mean differences between the measured and target adult heights were +0.3 cm (95 percent confidence interval, -0.6 to +1.2) for the budesonide-treated children, -0.2 cm (95 percent confidence interval, -2.4 to +2.1) for the control children with asthma, and +0.9 cm (95 percent confidence interval, -0.4 to +2.2) for the healthy siblings. The adult height depended significantly ( $P < 0.001$ ) on the child's height before budesonide treatment. Although growth rates were significantly reduced during the first years of budesonide treatment, these changes in growth rate were not significantly associated with adult height.

**Conclusions** Children with asthma who have received long-term treatment with budesonide attain normal adult height. (N Engl J Med 2000;343:1064-9.)

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**B**ECAUSE they are effective, inhaled corticosteroids are widely used to treat children with asthma.<sup>1-3</sup> However, many physicians are concerned about the potential adverse effects of long-term corticosteroid treatment, particularly effects on growth.

In many trials assessing growth during therapy with inhaled corticosteroids, follow-up observations have been conducted for one year or less. Although such studies may provide useful information, their relevance to actual practice is uncertain.<sup>4</sup> Several studies have reported poor correlations between corticosteroid-induced short-term changes in the growth rate of the lower leg and total body growth during the subsequent year.<sup>5-10</sup> Furthermore, the correlation be-

tween consecutive annual measurements of statural height velocity in normal prepubertal children is poor, with only partial correlation between values at one, two, three, and four years.<sup>8</sup> Height velocity computed over periods of three and four years during childhood explains only 34 percent and 38 percent, respectively, of the variation in adult height.<sup>8</sup>

Since 1986, we have been conducting a prospective study of children with persistent asthma to assess total body growth, weight gain, lung function, and hospitalization for asthma exacerbations.<sup>2,11,12</sup> We report here the 10-year growth data for the children who have reached adult height. We also report how growth rate and changes in growth rate relate to adult height.

## METHODS

## Study Design

Children with asthma were recruited for a prospective, long-term study.<sup>2,11,12</sup> We excluded those with other chronic diseases or with a gestational age of less than 32 weeks. All children visited the clinic at six-month intervals for one to two years (the run-in period). During this period, asthma medication was adjusted according to the Danish pediatric-asthma guidelines in use at the time.<sup>13</sup> Three hundred thirty-two children whose asthma was considered to be acceptably controlled without the continuous use of inhaled corticosteroids were then asked to change to treatment with the inhaled corticosteroid budesonide, because several studies had indicated that inhaled corticosteroids should be used more frequently.<sup>14,15</sup> The proposed change in therapy was accepted by the families of 270 children (the budesonide group). The families of 62 children declined to change therapy because of concern about side effects or satisfaction with their current therapy. These children (the controls) continued to take the medication they had used during the run-in period. Control patients were able to change to inhaled budesonide if they chose to at a later time. The study was approved by the ethics committee of Vejle and Fyns counties, and oral informed consent was obtained from all families.

At each six-month visit, we recorded the number of hospital admissions for acute asthma, age, height (mean of three measurements with a Harpenden stadiometer), weight, lung function (as assessed with a bellows spirometer), the dose and frequency of administration of all prescribed drugs, the dose of inhaled budesonide, and the inhalation device used. Changes in medication, if any, were based on a combination of history, lung function, use of a  $\beta_2$ -agonist for rescue therapy, and diary recordings. During the first six years of the study, fixed clinical criteria were used to initiate changes in medication.<sup>2</sup> After this time, the criteria were more flexible.

Throughout the study, the patients were seen by the same two physicians, and all measurements of weight, height (including the heights of siblings and parents), and lung function were performed by the same three nurses. Between scheduled visits, all changes in asthma medication were made under the supervision of the clinic personnel and were recorded. Any asthma medication required to

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control the disease was allowed. Data for children who received prednisolone for more than an average of two weeks per year were excluded from the analysis of adult height. Compliance with asthma medication was checked at each visit by direct questioning and by recording the frequency of renewal of prescriptions.

The data analyzed here were collected from January 1986 through August 1999. The status of the 332 originally enrolled patients at the end of this period is shown in Figure 1. Among those who had reached adult height and for whom information on parental height was available, there remained 142 subjects in the budesonide group and 18 in the control group. The mean age at the diagnosis of asthma was 3.4 years (range, 1 to 10) in the budesonide group and 4.3 years (range, 1 to 9) in the control group. Because data on adult height in children who were not using inhaled corticosteroids were limited because of the small number of children remaining in the control group, the healthy siblings of the children in the budesonide group were recruited for measurement of adult height. There were 149 siblings, of whom 105 had reached adult height. Of these, 38 had received treatment with inhaled corticosteroids and

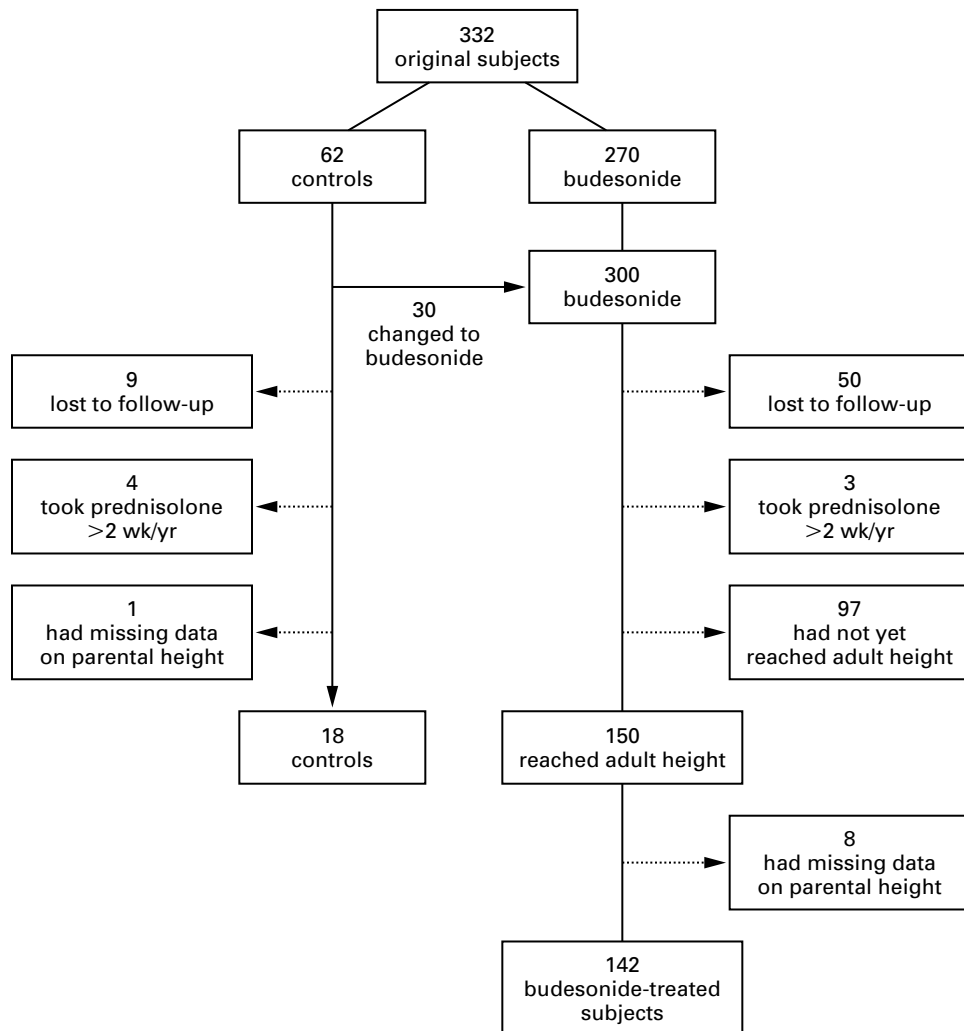
16 refused to participate, leaving 51 healthy siblings for analysis (Table 1).

**Statistical Analysis**

Data were transformed into standard-deviation scores as described by Tanner et al.,<sup>16</sup> according to the following formula: (measured height – mean height for age) ÷ standard deviation of height for age. The measured adult height was the height measured when the height of a child over 15 years of age had increased by less than 0.5 cm for two consecutive years.

The target adult height was calculated as described by Luo et al.,<sup>17,18</sup> with the addition of 0.7 cm to the height for boys and 1.0 cm to the height for girls because of trends over time, as  $45.99 + 0.78x + 0.7$  cm for boys and  $37.85 + 0.75x + 1.0$  cm for girls, where x is the father’s height and the mother’s height summed and divided by 2.

The primary outcome was the measured adult height in relation to the target adult height. The difference between the meas-



**Figure 1.** Status of the 332 Children Included in the Study as of August 1999. Only 20 of the 97 children who were excluded from the analysis because they had not yet reached adult height were 15 years of age or older.

**TABLE 1.** CHARACTERISTICS OF THE STUDY SUBJECTS.

CHARACTERISTIC	BUDESONIDE GROUP AT START OF TREATMENT (N=142)	BUDESONIDE GROUP AT ATTAINMENT OF ADULT HEIGHT (N=142)	CONTROL GROUP AT ATTAINMENT OF ADULT HEIGHT (N=18)	SIBLINGS WHO HAD ATTAINED ADULT HEIGHT (N=51)
Boys/girls — no.	86/56	86/56	11/7	24/27
Age — yr				
Mean	8.7	18.0	18.5	21.4
Range	3–13	16–24	16–22	17–25
Duration of asthma — yr				
Mean	5.3	14.4	14.1	
Range	0.5–12	5–23	3–20	
Prebronchodilator FEV <sub>1</sub> * Mean — % of predicted	69	96	81	
Range — % of predicted	31–101	80–110	62–98	
Value				
≥80% — no. of subjects (%)	64 (45)	140 (99)	11 (61)	
60%–79% — no. of subjects (%)	60 (42)	2 (1)	7 (39)	
30%–59% — no. of subjects (%)	18 (13)	0	0	

\*FEV<sub>1</sub> denotes the forced expiratory volume in one second.

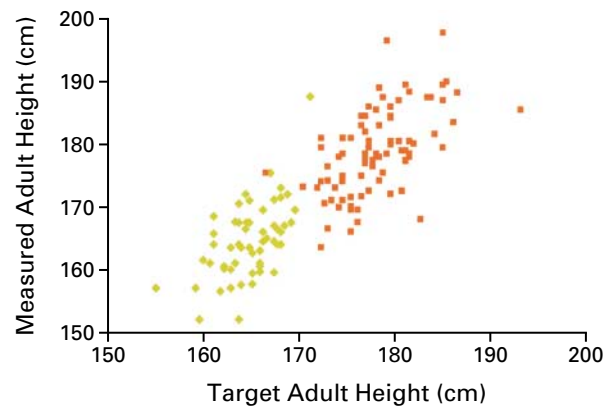
ured and the target height was analyzed by the paired-samples t-test. The assumption of normality was examined by probability plot and accepted.<sup>19</sup>

We assessed the following secondary outcomes: whether the difference between the measured height and the target adult height depended on the mean daily budesonide dose, the total cumulative budesonide dose, the duration of treatment, the duration of asthma at the beginning of treatment or at the time of attainment of adult height, the use or nonuse of intranasal corticosteroids, the growth rate, the standard-deviation score for height or the forced expiratory volume in one second (FEV<sub>1</sub>) before budesonide treatment, and the growth rate and the changes in the growth rate or standard-deviation score for height during the first year of budesonide treatment. The tests were performed by analysis of variance and covariance. All tests were performed for the whole group of children and for girls and boys separately. All reported P values are two-tailed.<sup>19</sup>

### RESULTS

The budesonide-treated children reached their target adult height (Fig. 2) to the same extent as their healthy siblings and the children in the control group (Table 2). There was no reason to suspect that the 20 children who were older than 14 years of age and who had not yet reached their adult height would attain an adult height markedly less than their target adult height. In all groups, more than 95 percent of the children attained an adult height that was within 9 cm above or below their target adult height.

The mean cumulative dose of budesonide at the time of attainment of adult height was 1.35 g (range, 0.41 to 3.99). The mean duration of budesonide treatment at this time was 9.2 years (range, 3 to 13), yielding a mean average daily budesonide dose of 412 μg (range, 110 to 877). Twenty children in the budesonide group who were more than 15 years old had not yet reached their adult height. Their mean cumulative dose of budesonide (1.25 g; range, 0.40 to 3.12) was not significantly different from that of the chil-



**Figure 2.** Measured Adult Height in Relation to Target Adult Height in 142 Children Treated with Inhaled Budesonide for 3 to 13 Years.

Diamonds represent girls, and squares boys.

dren who had attained their adult height (P=0.72). There was no significant correlation between the duration of treatment (P=0.16) or the cumulative dose of budesonide (P=0.14) and the difference between the measured and target adult heights (Fig. 3).

The difference between the measured and target adult heights was not significantly associated with the subject's sex (P=0.30), age at the beginning of budesonide treatment (P=0.13), age at which adult height was attained (P=0.82), or duration of asthma before the start of budesonide treatment (P=0.37).

The standard-deviation score for height and the FEV<sub>1</sub> as a percentage of the predicted value before the start of budesonide treatment were correlated (P=

TABLE 2. MEASURED AND TARGET ADULT HEIGHTS.\*

GROUP	No.	MEASURED ADULT HEIGHT	TARGET ADULT HEIGHT	DIFFERENCE BETWEEN
				MEASURED AND TARGET ADULT HEIGHTS (95% CI)
				centimeters
Budesonide	142	173.2±9.5	172.9±7.5	+0.3 (-0.6 to +1.2)
Girls	56	164.6±6.0	164.8±3.0	-0.2 (-1.6 to +1.0)
Boys	86	178.8±6.8	178.1±4.3	+0.7 (-0.5 to +1.9)
Controls	18	173.9±10.1	174.1±8.2	-0.2 (-2.4 to +2.1)
Siblings	51	172.3±9.5	171.4±8.7	+0.9 (-0.4 to +2.2)
Girls	27	165.8±5.6	165.2±8.7	+0.6 (-1.2 to +2.3)
Boys	24	179.8±7.2	178.5±4.9	+1.3 (-0.7 to +3.3)

\*Patients in the budesonide group had been treated with inhaled budesonide for an average of 9.2 years. Patients in the control group had never been treated with inhaled corticosteroids. The members of the third group were healthy siblings of patients in the budesonide group and had attained adult height. Plus-minus values are means ±SD. CI denotes confidence interval.

0.05), indicating that the severity of asthma influenced growth. Budesonide treatment was associated with a significant change in the growth rate during the first years of treatment, as compared with the run-in period. The mean growth rate was 6.1 cm per year (95 percent confidence interval, 5.7 to 6.5) during the run-in period, 5.1 cm per year (95 percent confidence interval, 4.7 to 5.5;  $P < 0.001$ ) during the first year of treatment, 5.5 cm per year (95 percent confidence interval, 5.1 to 5.9;  $P = 0.02$ ) during the second year, and 5.9 cm per year (95 percent confi-

dence interval, 5.5 to 6.3;  $P = 0.53$ ) during the third year. However, the changes in growth rate during this period were not correlated with the differences between the measured and target adult heights ( $P = 0.44$ ). The initial growth retardation was significantly correlated with age ( $P = 0.04$ ), with a more pronounced reduction in younger children.

The standard-deviation score for height before budesonide treatment and the difference between the measured and target adult heights were correlated ( $P < 0.001$ ), so that children with a low standard-deviation score for height before treatment had a smaller adult height than expected. There was a trend toward an association between the difference between the measured and target adult heights and the duration of asthma at the time adult height was measured ( $P = 0.07$ ).

Forty children in the budesonide group used intranasal corticosteroids for an average of 24 months (range, 6 to 72). The adult height of these children was similar to that of the children who had never used intranasal corticosteroids ( $P = 0.99$ ). Moreover, the difference between the measured and target adult heights was not associated with the cumulative number of months of use of intranasal corticosteroids ( $P = 0.72$ ).

Compliance with budesonide treatment was calculated according to the following formula:  $100 \times (\text{number of doses taken} \div \text{number of doses prescribed})$ . The mean estimated compliance was 68 percent (range, 49 to 90 percent). The difference between the measured and target adult heights was not associated with compliance ( $P = 0.38$ ).

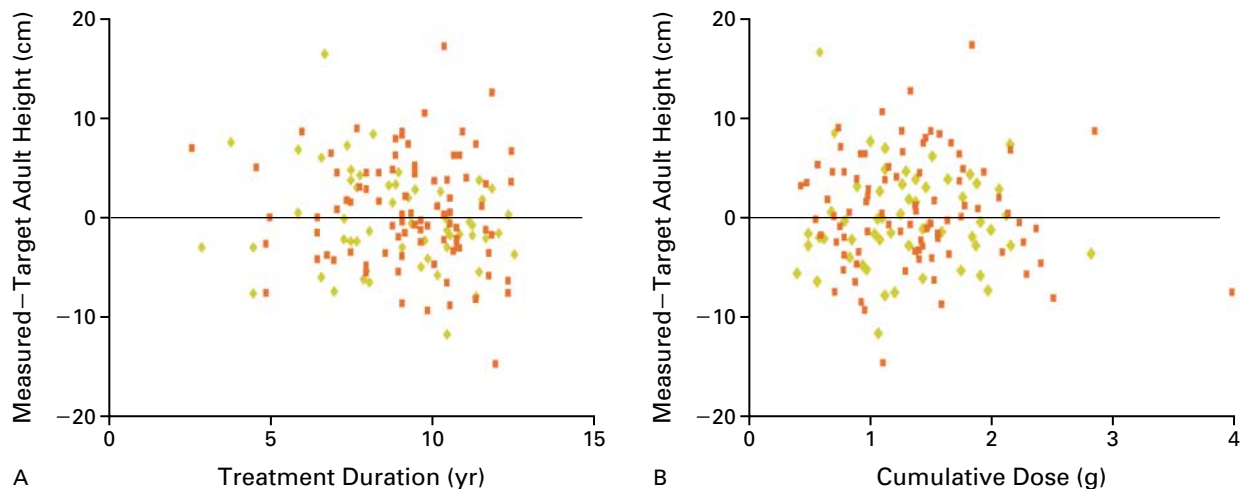


Figure 3. Differences between the Measured Adult Height and the Target Adult Height as a Function of the Duration of Budesonide Treatment (Panel A) and Cumulative Prescribed Budesonide Dose (Panel B). Diamonds represent 56 girls, and squares 86 boys.

## DISCUSSION

We found that children with asthma who had received long-term treatment with inhaled budesonide attained normal adult height. Furthermore, we found no evidence of a dose–response relation between the mean daily dose of budesonide, the cumulative dose of budesonide, or the duration of budesonide treatment and the difference between the measured and target adult heights. Our findings suggest that long-term treatment with inhaled budesonide does not have any clinically important adverse effects on adult height. This corroborates the results of retrospective studies of smaller groups of children treated for shorter periods with inhaled corticosteroids<sup>20,21</sup> and a prospective study of 66 children who were followed for 13 years until they reached adult height.<sup>22</sup>

Normally, 95 percent of the population is expected to attain an adult height within 9 cm above or below their target adult height.<sup>18</sup> This was true for the patients in our study, indicating that great individual sensitivity to the systemic effects of inhaled budesonide was uncommon.

Several studies of growth during a period of one year have reported growth retardation of approximately 1.5 cm per year in children treated with 400  $\mu\text{g}$  of inhaled beclomethasone per day, as compared with those receiving placebo.<sup>23–26</sup> These data have led to the inclusion of warnings about growth retardation in the package inserts for inhaled corticosteroids in the United States. Our results show the effects of continuous treatment for 10 years at the same mean corticosteroid dose as in the 1-year studies. The growth rate during the first year of treatment was on average 1 cm less than that during the run-in period. Thus, our results are consistent with those of shorter studies of beclomethasone. The initial reduction in the annual growth rate did not persist, however, and the adult height was not adversely affected. Furthermore, the initial growth retardation in individual children had no relation to differences between the measured and target adult heights. The reason for the absence of a relation is not clear. Others have also found the growth-retarding effect of inhaled corticosteroids to be more marked during the beginning of treatment.<sup>26–28</sup> Differences in compliance over time did not seem to be the cause.

Another reason for the discrepancy between short-term studies and studies of adult height could be that pubertal children are less sensitive than prepubertal children to the growth-retarding effect of exogenous corticosteroids, as we and others<sup>25</sup> have found. Most growth studies have been performed in children six through nine years of age. Finally, exogenous corticosteroids may retard bone maturation to the same extent that they retard growth.<sup>29–32</sup> This possibility is difficult to assess in children with chronic asthma, regardless of whether they use inhaled corticosteroids. Such children often have retarded bone maturation,

prepubertal growth retardation, and a delayed onset of puberty.<sup>22,33–35</sup>

A weakness of our study is that there were few children remaining in the control group by the time they reached adult height. Therefore, we measured the adult heights of healthy siblings of budesonide-treated children, whose genetic growth potential and living conditions were very similar to those of the subjects in the study group. Although a randomized, double-blind design would have been ideal, this was not possible in our 15-year study. The demographic similarities among the various groups suggest that they were reasonably comparable.

Generally, asthma in our patients was well controlled once treatment with inhaled budesonide was initiated. This made it difficult to assess how the severity of asthma influenced growth. The correlation between the FEV<sub>1</sub> as a percentage of the predicted value and the standard-deviation score for height before budesonide treatment suggests that severe asthma may in itself have a negative effect on growth, as observed in other studies.<sup>36,37</sup> It is less clear whether severe asthma also has an adverse effect on adult height. The strong correlation between the standard-deviation score for height before treatment and the adult height suggests that severe asthma may also adversely affect adult height. This is in agreement with findings in other studies.<sup>20,34,35</sup> However, many patients in the control group who had more severe disease dropped out of our study. Thus, among those who stayed in the study long enough to have their adult height measured, either the disease was milder or the asthma had gone into remission.

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## REFERENCES

1. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids: new developments. *Am J Respir Crit Care Med* 1998;157:S1–S53.
2. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373–81.
3. Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma: report of a workshop held in Eze, France, October 1992. *Am Rev Respir Dis* 1993;148:S1–S126.
4. Allen DB. Limitations of short-term studies in predicting long-term adverse effects of inhaled corticosteroids. *Allergy* 1999;54:Suppl 29:29–34.
5. Marshall W. Evaluation of growth rate in height over periods of less than one year. *Arch Dis Child* 1971;46:414–20.
6. Butler GE, McKie M, Ratcliffe SG. The cyclical nature of prepubertal growth. *Ann Hum Biol* 1990;17:177–98.
7. Voss LD, Wilkin TJ, Bailey BJR, Betts PR. The reliability of height and height velocity in the assessment of growth. *Arch Dis Child* 1991;66:833–7.
8. Karlberg J, Glander L, Albertsson-Wikland K. Distinctions between short- and long-term human growth studies. *Acta Paediatr* 1993;82:631–4.
9. Karlberg J, Low L, Yeung CY. On the dynamics of the growth process. *Acta Paediatr* 1994;83:777–8.
10. Glander L, Karlberg J, Albertsson-Wikland K. Seasonality in lower leg length velocity in prepubertal children. *Acta Paediatr* 1994;83:1249–54.
11. Agertoft L, Pedersen S. Bone mineral density in children with asthma receiving long-term treatment with inhaled budesonide. *Am J Respir Crit Care Med* 1998;157:178–83.
12. Agertoft L, Larsen FE, Pedersen S. Posterior subcapsular cataracts,

- bruises and hoarseness in children with asthma receiving long-term treatment with inhaled budesonide. *Eur Respir J* 1998;12:130-5.
13. Warner JO, Gotz M, Landau LI, et al. Management of asthma: a consensus statement. *Arch Dis Child* 1989;64:1065-79.
  14. Clissold SP, Heel RC. Budesonide: a preliminary review of its pharmacodynamic properties and therapeutic efficacy in asthma and rhinitis. *Drugs* 1984;28:485-518.
  15. Henriksen JM. Effect of inhalation of corticosteroids on exercise induced asthma: randomised double blind crossover study of budesonide in asthmatic children. *BMJ* 1985;291:248-9.
  16. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. *Arch Dis Child* 1966;41:454-71.
  17. Luo ZC, Low LC, Karlberg J. A comparison of target height estimated and final height attained between Swedish and Hong Kong Chinese children. *Acta Paediatr* 1999;88:248-52.
  18. Luo ZC, Albertsson-Wikland K, Karlberg J. Target height as predicted by parental heights in a population-based study. *Pediatr Res* 1998;44:563-71.
  19. Fleiss JL. The design and analysis of clinical experiments. New York: John Wiley, 1986.
  20. Van Bever HP, Desager KN, Lijssens N, Weyler JJ, Du Caju MV. Does treatment of asthmatic children with inhaled corticosteroids affect their adult height? *Pediatr Pulmonol* 1999;27:369-75.
  21. Silverstein MD, Yunginger JW, Reed CE, et al. Attained adult height after childhood asthma: effect of glucocorticoid therapy. *J Allergy Clin Immunol* 1997;99:466-74.
  22. Balfour-Lynn L. Growth and childhood asthma. *Arch Dis Child* 1986;61:1049-55.
  23. Doull IJ, Freezer NJ, Holgate ST. Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med* 1995;151:1715-9.
  24. Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;92:64-77.
  25. Verberne AAPH, Frost C, Roorda RJ, van der Laag H, Kerrebijn KE. One year treatment with salmeterol compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med* 1997;156:688-95.
  26. Simons FER, Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. *N Engl J Med* 1997;337:1659-65.
  27. Saha MT, Laippala P, Lenko HL. Growth of asthmatic children is slower during than before treatment with inhaled glucocorticoids. *Acta Paediatr* 1997;86:138-42.
  28. Doull IJ, Campbell MJ, Holgate ST. Duration of growth suppressive effects of regular inhaled corticosteroids. *Arch Dis Child* 1998;78:172-3.
  29. Aicardi G, Benso L, Vignolo M, et al. Dose-dependent effects of deflazacort and prednisone on growth and skeletal maturation. *Br J Rheumatol* 1993;32:Suppl 2:39-43.
  30. Vignolo M, Milani S, Imbimbo B, et al. Statural growth and skeletal maturation in rheumatic prepubertal children treated with a third generation glucocorticoid (deflazacort) versus prednisone: an interim study. *Clin Exp Rheumatol* 1991;9:Suppl 6:41-5.
  31. Oberger E, Taranger J, Bruning B, Engstrom I, Karlberg J. Long-term treatment with corticosteroids/ACTH in asthmatic children. IV. Skeletal maturation. *Acta Paediatr Scand* 1986;75:744-9.
  32. Morris HG. Growth and skeletal maturation in asthmatic children: effect of corticosteroid treatment. *Pediatr Res* 1975;9:579-83.
  33. Ferguson AC, Murray AB, Tze WJ. Short stature and delayed skeletal maturation in children with allergic disease. *J Allergy Clin Immunol* 1982;69:461-6.
  34. Hauspie R, Susanne C, Alexander F. Maturation delay and temporal growth retardation in asthmatic boys. *J Allergy Clin Immunol* 1977;59:200-6.
  35. Martin AJ, Landau LI, Phelan PD. The effect on growth of childhood asthma. *Acta Paediatr Scand* 1981;70:683-8.
  36. Ninan T, Russell G. Asthma, inhaled corticosteroid treatment, and growth. *Arch Dis Child* 1992;67:703-5.
  37. McCowan C, Neville RG, Thomas GE, et al. Effect of asthma and its treatment on growth: four year follow up of cohort of children from general practices in Tayside, Scotland. *BMJ* 1998;316:668-72.

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