Effect of Inhaled Glucocorticoids in Childhood on Adult Height

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ABSTRACT

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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. (Funded by the National Heart, Lung, and Blood Institute and the National Center for Research Resources; CAMP ClinicalTrials.gov number, NCT00000575.)

INHALED GLUCOCORTICOIDS ARE THE REC-ommended therapy for persistent asthma in children.[1] In prepubertal children, however, the use of inhaled glucocorticoids has been shown to reduce growth velocity, resulting in a linear growth reduction of 0.5 to 3.0 cm (approx-imately 1 cm on average) during the first few years of therapy.[2-4] This reduction has been re-ported for low-to-medium doses, but the degree of reduction is dependent on the type of inhaled glucocorticoid and the delivery method.[5-9]

Although growth velocity returns to normal within a few years after the initiation of inhaled glucocorticoid therapy (resulting in a deficit in height that is not progressive), the long-term ef-fect of the initial decrease in growth velocity on attainment of adult height is still unclear.[10-12] Retrospective, cross-sectional studies of the ef-fect of inhaled glucocorticoid therapy in child-hood on the attainment of adult height have had conflicting results.[10,13-15] In one small longitudi-nal study,[11] there was no significant difference between actual adult height and predicted adult height in 142 participants who had received budesonide in variable daily doses (mean, 427 μg) during childhood for a mean of 9.2 years.

At the end of the Childhood Asthma Manage-ment Program (CAMP) clinical trial, we predicted that the children receiving budesonide (Pulmicort Turbuhaler, AstraZeneca) for a mean follow-up of 4.3 years would attain the same adult height as the children receiving nedocromil (Tilade, Rhone-Poulenc Rorer) or placebo.[2] It has been hypothesized that children receiving inhaled glucocorticoids grow for a longer period of time, eventually catching up and having no long-term effects from the decreased growth velocity seen in the first few years of therapy.[16] Thus, the ef-fect of inhaled glucocorticoids on height has often been characterized as growth retardation rather than growth suppression. We later re-ported that the heights of the participants in the budesonide group had not caught up with the heights of participants in the placebo group af-ter an additional 4.8 years of follow-up (total, 9.1 years), until the ages of 12 to 23 years.[12] The purpose of the current study was to continue the height follow-up of the CAMP participants to assess the effects of budesonide and nedocromil on adult height.

METHODS

PARTICIPANTS AND STUDY DESIGN

From December 1993 through September 1995, we randomly assigned 1041 children between the ages of 5 and 13 years with mild-to-moderate asthma to one of three study groups in the dou-ble-blind, placebo-controlled CAMP trial. In this study, we compared the efficacy and safety of 200 μg of budesonide administered by means of a dry-powder inhaler twice daily (400 μg per day), 8 mg of nedocromil administered by means of a metered-dose inhaler twice daily (16 mg per day), and placebo. Albuterol was used for asthma symptoms in all three groups. The design, meth-ods, and results of the trial have been described previously.[2,17] At the end of the trial (mean follow-up, 4.3 years), the children were recruited into an observational cohort, as described previously.[12] During follow-up, the children were treated for asthma by their primary care physicians under advisement from the CAMP physicians on the ba-sis of the guidelines of the National Asthma Edu-cation and Prevention Program.[1] Height and weight were measured every 6 months during the ini-tial 4.5 years of observational follow-up and 1 to 2 times a year during the next 8 years. Adult height was determined at a mean (±SD) age of 24.9±2.7 years. Tanner staging was performed annually until the participants were 18 years of age or at-tained sexual maturity. (For details regarding the trial design and phases of the observational fol-low-up, see Fig. S1 in the Supplementary Appen-dix, available with the full text of this article at NEJM.org.) All study phases were approved by the institutional review board at each study cen-ter. Participants who were 18 years of age or older provided written informed consent; those under the age of 18 years provided assent, with written informed consent provided by their par-ents or guardians.

At each clinic visit, a trained technician used a stadiometer (Harpenden 603, Holtain) to mea-sure height, as described in the protocol (available at NEJM.org), and investigators obtained an in-terim history of participants' health and medica-tion use. During the first 8 years of follow-up, this information was supplemented with infor-mation obtained during telephone contacts that were evenly spaced around the clinic visits.

On the basis of reported recommendations,[18-21] adult height was defined as either the mean of all measurements performed at the age of 18 years or older for women and at the age of 20 years or older for men or, if height was not measured at these ages, the most recently obtained height that was less than 1 cm greater than a height obtained at least 1 year previously.

STATISTICAL ANALYSIS

We used a multiple linear regression model to compare mean height in the budesonide and nedocromil groups with that in the placebo group, with adjustment for eight covariates at trial entry: age, race or ethnic group, sex, clinic, height, duration of asthma (<3 years, ≥3 to <7 years, or ≥7 years), severity of asthma (moderate or mild), and presence or absence of skin-test reactivity. Data for each participant were analyzed in the study group to which the participant had been randomly assigned, regardless of subsequent asthma treatment. The adjusted mean height in each study group was computed from the regression model at the mean values for the covariates.[22] To assess the statistical significance of potential variations in height differences between the budesonide or nedocromil group and the placebo group across subgroups defined by race or ethnic group, age at trial entry, and duration of asthma at entry, we added covariate interaction terms to the regression model. Although these post hoc interaction tests may have a low statistical power for detecting variations in height effects across subgroups, we wanted to examine the qualitative consistency of the budesonide and nedocromil effects across subgroups.

We used chi-square tests for categorical variables and t-tests for continuous variables to assess differences in baseline characteristics between participants for whom data regarding adult height were missing and those for whom such data were available. We used logistic-regression analysis to check for systematic differences between participants with adult-height data and those without such data with respect to study-group distribution in subgroups, as defined by the baseline covariates. Effects of missing data on adult height were further addressed in sensitivity analyses with the use of two alternative methods to impute missing adult height. In the first method, we used a single imputation of adult height on the basis of bone age obtained at

the end of the trial and the equations of Tanner et al.[2,19] In the second method, we used multivariate multiple imputation with 13 imputations from simulations of a Bayesian posterior predictive distribution of the missing data, using an iterative Markov chain Monte Carlo method based on the multivariate normal distribution provided by Stata software.[23] All eight covariates in the model for difference in adult height were used together with serial height measurements obtained 2 to 102 months after trial entry. The missing adult height data were assumed to be missing completely at random. Additional sensitivity analyses were performed with the use of seven alternative definitions of adult height.

We used a linear regression model of height in relation to age, using all available age–height pairs for each participant in each 1-year age span, to determine age-specific growth velocity for each participant during the first 2 years of the trial. We assessed study-group differences in growth-velocity trends for participants between the ages of 5 and 15 years separately for each sex by means of a repeated-measures multiple linear regression model,[24] including an indicator variable for treatment, splines for each year of age, and interaction terms for treatment according to age. This analysis was also adjusted for the covariates used in the models of adult height. The significance of study-group differences in velocity trends was determined on the basis of the P value from an F-test of the simultaneous null effects of the study-group indicator and all age splines according to treatment interaction terms. We performed a secondary analysis of adult height in relation to the mean weight-adjusted dose of daily inhaled glucocorticoids (in micrograms per kilogram of body weight) during the first 2 years of the trial, with adjustment for demographic characteristics, status with respect to exposure to cigarette smoke in utero, and total prednisone dose throughout follow-up until adult height was attained, as well as asthma features, physical development, and vitamin D sufficiency or insufficiency at trial entry. The dose of inhaled glucocorticoids and weight were assumed to be constant over each reporting interval.

A two-sided P value of less than 0.05 was considered to indicate statistical significance, except in interaction analyses, for which a P value of less than 0.01 was considered to indicate significance. Statistical analyses were performed with

Figure 1. Enrollment and Outcomes.
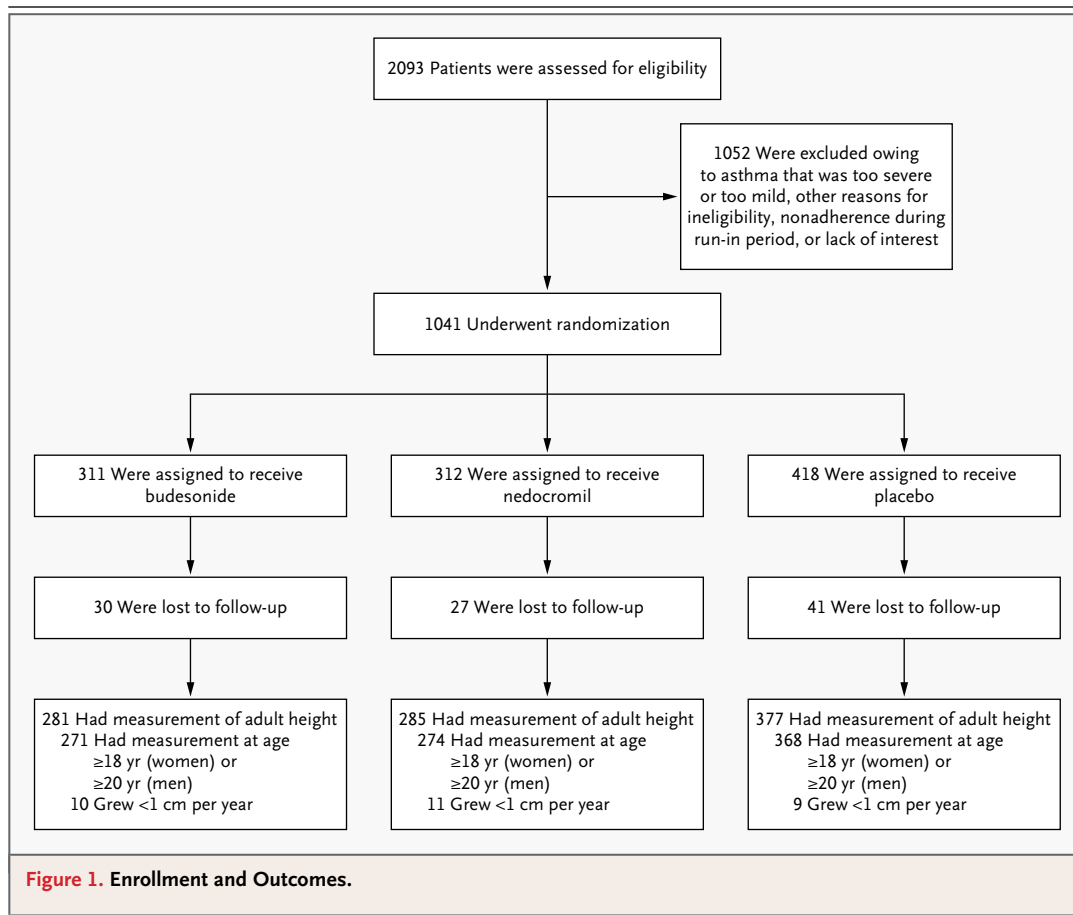
the use of Stata software, version 12 (StataCorp) or SAS software, version 9.2 (SAS Institute).

RESULTS

ADULT HEIGHT

We obtained measurements of adult height for 943 of the original 1041 CAMP participants (90.6%). Of these measurements, 96.8% were obtained from women who were at least 18 years of age or men who were at least 20 years of age; 3.2% of measurements were the most recently obtained heights that were less than 1 cm greater than a height obtained at least 1 year previously (Fig. 1). Adult height was not known for 98 participants (9.4%): 35 female participants with a median age of 12 years (range, 8 to 17) and 63 male participants with a median age of 14 years (range, 7 to 19) at the last height measurement.

The adjusted mean adult height was 1.2 cm lower in the budesonide group than in the placebo group (171.1 cm vs. 172.3 cm, P=0.001);

the mean adult height in the nedocromil group (172.1 cm) was similar to that in the placebo group (P=0.61) (Table 1 and Fig. 2).[25] The deficit in adult height in the budesonide group, as compared with the placebo group, was greater for women (−1.8 cm, P=0.001) than for men (−0.8, P=0.10), but the effect of budesonide on adult height did not vary significantly according to sex (P=0.10 for interaction) (Table 1). Although the deficit was greater for participants who were younger at trial entry than for those who were older and greater for whites than for those of other races or ethnic groups, the effect of budesonide on adult height did not vary significantly according to the age at trial entry (P=0.12 for interaction), race or ethnic group (P=0.50 for interaction), or duration of asthma at trial entry (P=0.35 for interaction) (Table 1, and Table S1 in the Supplementary Appendix). The deficit in the adjusted mean height in the budesonide group, as compared with the placebo group, was 1.3 cm (95% confidence interval [CI], −1.7 to −0.9) after

Table 1. Adjusted Mean Adult Height among 943 Study Participants.*

Variable	Mean Adult Height			Difference in Height			
	Budesonide (N=281)	Nedocromil (N=285)	Placebo (N=377)	Budesonide vs. Placebo (95% CI)	P Value	Nedocromil vs. Placebo (95% CI)	P Value
	cm			*cm*		*cm*	
All participants	171.1	172.1	172.3	−1.2 (−1.9 to −0.5)	0.001	−0.2 (−0.9 to 0.5)	0.61
Sex							
Female	162.8	163.9	164.6	−1.8 (−2.9 to −0.7)	0.001	−0.7 (−1.8 to 0.5)	0.26
Male	176.8	177.6	177.6	−0.8 (−1.8 to 0.2)	0.10	−0.0 (−0.9 to 0.9)	0.98
P value for interaction					0.10		0.49
Age at entry							
5–8 yr	170.7	171.8	172.6	−1.9 (−3.2 to −0.6)	0.004	−0.8 (−2.1 to 0.5)	0.22
9–13 yr	171.4	172.4	171.9	−0.5 (−1.7 to 0.6)	0.37	0.5 (−0.8 to 1.6)	0.48
P value for interaction					0.12		0.15

* Mean values for adult height have been adjusted for age, race or ethnic group, sex, clinic, duration of asthma, asthma severity, presence or absence of skin-test reactivity, and height at trial entry. In the analysis of mean adult height according to sex, 385 participants were female and 558 were male. In the analysis of age at study entry, 489 participants were 5 to 8 years of age and 454 were 9 to 13 years of age.

2 years of treatment and 1.2 cm (95% CI, −2.0 to −0.4) at the end of the CAMP trial and persisted into adulthood without progressing further (−1.2 cm; 95% CI, −1.9 to −0.5) (Fig. 2B).

GROWTH VELOCITY

Overall, age trends with respect to growth velocity in the budesonide and placebo groups differed during the first 2 years of the trial for women (P=0.007) and men (P<0.001) (Fig. S2 in the Supplementary Appendix). For both sexes, the difference in velocity reduction that was seen in the first 2 years of assigned treatment in the budesonide group, as compared with the placebo group, was primarily among prepubertal participants (girls 5 to 10 years of age, P=0.001; girls 11 to 15 years of age, P=0.54; boys 5 to 11 years of age, P<0.001; and boys 12 to 15 years of age, P=0.57).
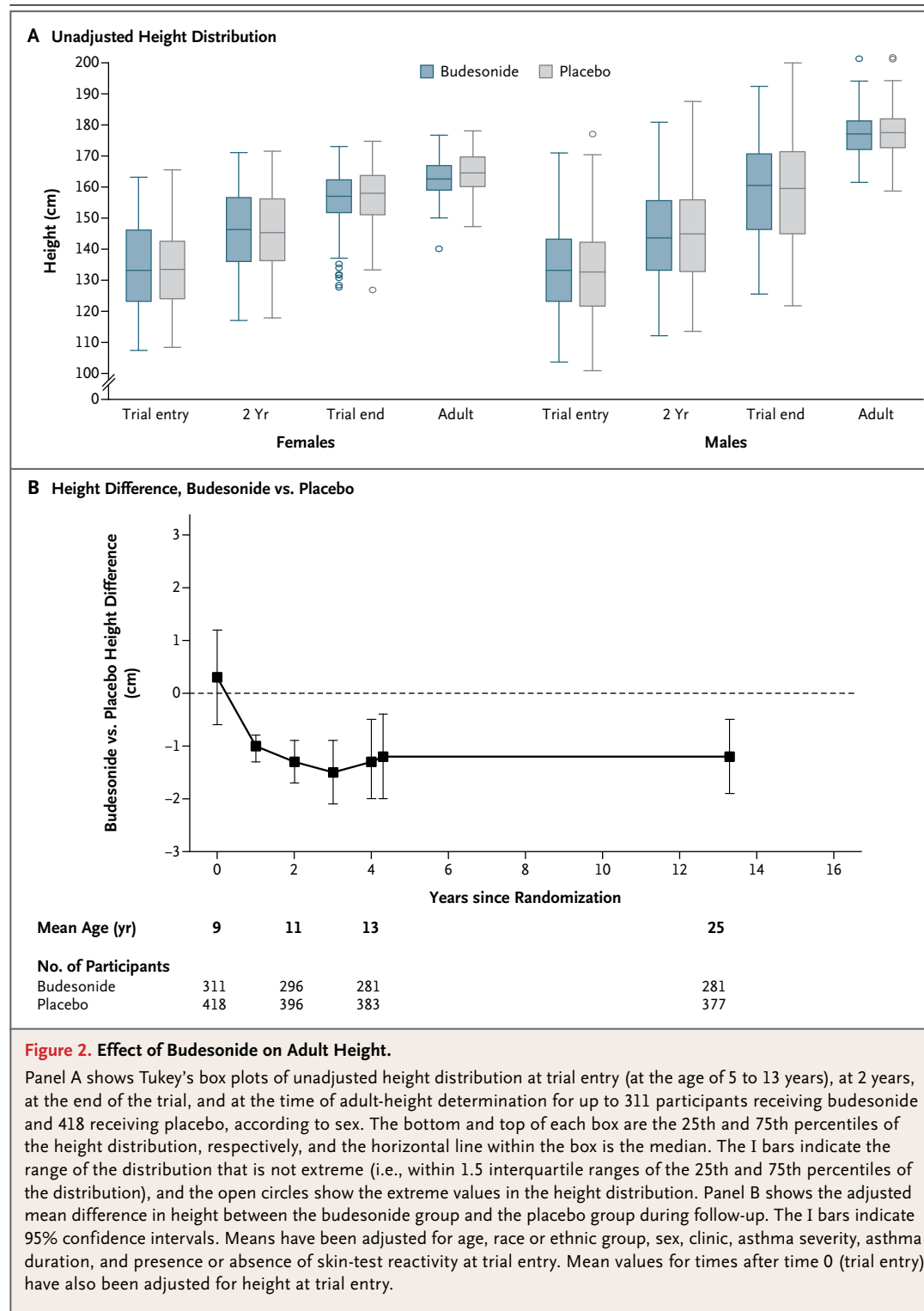
SENSITIVITY ANALYSES

In sensitivity analyses performed to assess the potential effect of missing adult heights, the reduction in adult height in the budesonide group as compared with the placebo group was also calculated with imputation of missing adult heights based on bone age at the end of the trial[19] (−1.1 cm, P=0.004) and multivariate multiple imputation (−1.2 cm, P=0.002). The between-group difference in adjusted mean adult height remained numerically similar to that in the primary analysis and significant for all seven alternative definitions of adult height (Table 2).

At trial entry, data for participants for whom measurements of adult height were not available were similar to data for those with available measurements, except for the variable of the clinic site (P=0.002) (Table S2 in the Supplementary Appendix). There was no interaction between the study group and any of the baseline covariates, suggesting that the study-group comparison among the 943 participants with known adult height may reasonably be generalized to the entire CAMP population.

EFFECTS OF GLUCOCORTICOID DOSE

During the trial period of 4 to 6 years, the mean adjusted total doses of inhaled glucocorticoids were 636.1 mg in the budesonide group and 88.5 mg in the nedocromil group versus 109.4 mg in the placebo group (P<0.001 and P=0.14, respectively). During follow-up after the trial ended, the mean adjusted total doses were 381.0 mg in the budesonide group and 347.9 mg in the nedocromil group versus 355.0 mg in the placebo group (P=0.55 and P=0.87, respectively).

The as-treated secondary analysis of the daily weight-adjusted dose of inhaled glucocorticoids during the first 2 years of the CAMP trial showed that a larger daily dose was associated with a lower adult height (−0.1 cm for each microgram per kilogram, P=0.007). In addition, lower adult height was associated with Hispanic ethnic group (P<0.001) and female sex (P<0.001), as well as a higher Tanner stage (P<0.001), lower height

Figure 2. Effect of Budesonide on Adult Height.

Panel A shows Tukey's box plots of unadjusted height distribution at trial entry (at the age of 5 to 13 years), at 2 years, at the end of the trial, and at the time of adult-height determination for up to 311 participants receiving budesonide and 418 receiving placebo, according to sex. The bottom and top of each box are the 25th and 75th percentiles of the height distribution, respectively, and the horizontal line within the box is the median. The I bars indicate the range of the distribution that is not extreme (i.e., within 1.5 interquartile ranges of the 25th and 75th percentiles of the distribution), and the open circles show the extreme values in the height distribution. Panel B shows the adjusted mean difference in height between the budesonide group and the placebo group during follow-up. The I bars indicate 95% confidence intervals. Means have been adjusted for age, race or ethnic group, sex, clinic, asthma severity, asthma duration, and presence or absence of skin-test reactivity at trial entry. Mean values for times after time 0 (trial entry) have also been adjusted for height at trial entry.

(P<0.001), greater body-mass index (P<0.001), longer duration of asthma (P<0.001), skin-test reactivity (P<0.001), and vitamin D insufficiency (≤30 ng per milliliter, P=0.004) at baseline. The cumulative prednisone dose from trial entry until attainment of adult height did not affect adult height (P=0.76).

Table 2. Adjusted Mean Adult Height, According to the Imputation Strategy Used for Missing Data and Alternative Height Definitions.*

Variable	Total No. of Participants	Mean Adult Height			Difference in Height			
		Budesonide	Nedocromil	Placebo	Budesonide vs. Placebo (95% CI)	P Value	Nedocromil vs. Placebo (95% CI)	P Value
		cm			*cm*		*cm*	
Primary analysis	943	171.1	172.1	172.3	−1.2 (−1.9 to −0.5)	0.001	−0.2 (−0.9 to 0.5)	0.61
Imputation strategy								
Adult height or projected adult height†	991	171.2	172.2	172.3	−1.1 (−1.7 to −0.3)	0.004	−0.1 (−0.8 to 0.6)	0.70
Adult height or multiple-imputation height‡	1041	171.1	172.1	172.3	−1.2 (−1.9 to −0.4)	0.002	−0.2 (−0.9 to 0.5)	0.56
Alternative height definition								
Mean height at age ≥18 yr for women and ≥20 yr for men	913	171.0	172.1	172.3	−1.3 (−2.0 to −0.5)	0.001	−0.2 (−0.9 to 0.6)	0.72
Minimum height at age ≥18 yr for women and ≥20 yr for men	913	170.6	171.7	171.8	−1.2 (−2.0 to −0.5)	0.001	−0.1 (−0.9 to 0.6)	0.72
Maximum height at age ≥18 yr for women and ≥20 yr for men	913	171.4	172.6	172.7	−1.3 (−2.0 to −0.5)	0.001	−0.1 (−0.8 to 0.6)	0.77
Most recent height at age ≥18 yr for women and ≥20 yr for men	913	171.1	172.2	172.3	−1.2 (−2.0 to −0.5)	0.001	−0.1 (−0.9 to 0.6)	0.71
Mean height at age ≥21 yr for women and ≥23 yr for men	780	170.5	171.4	171.6	−1.1 (−1.8 to −0.3)	0.01	−0.2 (−0.9 to 0.6)	0.73
Height at time of growth of <1 cm/yr§	928	171.1	172.1	172.3	−1.2 (−1.9 to −0.5)	0.001	−0.2 (−0.9 to 0.5)	0.59
Mean height at age ≥21 yr for women and ≥23 yr for men or at growth of <1 cm/yr	937	171.1	172.1	172.3	−1.2 (−1.9 to −0.4)	0.002	−0.2 (−0.9 to 0.5)	0.63

* Mean values for adult height have been adjusted for age, race or ethnic group, sex, clinic, duration of asthma, asthma severity, presence or absence of skin-test reactivity, and height at trial entry.
† Projected adult height was calculated from the prediction equations of Tanner et al.,[19] which use height, chronologic age, bone age, and (for girls) age at first menses.
‡ Adult height was imputed for the 98 participants for whom data regarding adult height were missing. The imputation analysis was completed with the use of multivariate normal regression of the available height data for the CAMP group (adult height for 943 participants and up to 21 serial height measurements performed 2 to 102 months after randomization for 1041 participants) on age, race or ethnic group, sex, clinic, duration of asthma, asthma severity, presence or absence of skin-test reactivity, and height at trial entry, stratified according to study group.
§ In this category, adult height was defined as the chronologically later height in the most recent pair of height measurements that were performed at least 1 year apart and differed by less than 1 cm.

DISCUSSION

In an intention-to-treat analysis of the growth-suppressive effect of long-term inhaled glucocorticoid therapy for asthma initiated in children between the ages of 5 and 13 years, we found that the height deficit observed at 1 to 2 years after treatment initiation persisted into adulthood, although the deficit was neither progressive nor cumulative. Our conclusion is based on a randomized comparison of adult height, with height data available for 91% of the CAMP cohort, with the use of recognized definitions of adult height,[18-21] and with consistent findings in sensitivity analyses using imputation strategies for missing data and alternative definitions of adult height (Table 2). We found little evidence that the 98 participants for whom data regarding adult height were missing differed at trial entry from the 943 participants with available data (Table S2 in the Supplementary Appendix).

In contrast, the only other prospective longitudinal cohort study that followed patients into adulthood[11] was an open-label study, and by the time the patients reached adulthood, only 15 of the original controls were available, so the investigators recruited 51 healthy siblings of the patients with asthma to be controls. The investigators in that study based their conclusion of a lack of long-term effect on height on the finding that both controls and participants receiving budesonide attained predicted adult height rather than on a randomized comparison of the adult heights reached by the two groups.

The growth-velocity deficit that we observed in the budesonide group, as compared with the placebo group, during the first 2 years of treatment was primarily among prepubertal children (Fig. S2 in the Supplementary Appendix). Our ability to further disentangle the effects of duration of treatment, age at treatment, and puberty status during treatment on growth velocity was limited because of confounding. Nevertheless, the effect on adult height of budesonide as compared with placebo was clearly demonstrated in the CAMP population.

Two previous 1-year studies of beclomethasone dipropionate also showed a greater reduction in growth in prepubertal children than in pubertal children.[26,27] Like other studies in which prepubertal children received different doses of the same inhaled glucocorticoids that have shown a dose–response effect on growth,[28,29] our study showed a weight-based, dose-dependent effect in the CAMP participants (Table S3 in the Supplementary Appendix).

We found that a longer time since asthma diagnosis at trial entry and atopy (any positive skin test) were independent risk factors for shorter adult height (Table S3 in the Supplementary Appendix). Other investigators have reported an increased incidence of short stature in children with atopy and asthma.[30-32] One of these studies[31] showed that short stature was associated with an early onset of asthma (before the age of 3 years), a finding that is consistent with our data. However, atopy-induced growth retardation has been associated with a delay in bone maturation and thus was thought to be unlikely to affect adult height.[32,33] Our results suggest that when asthma and atopy impair growth, the deficit may persist into adulthood.

We selected a daily dose of 400 μg of budesonide for the CAMP trial to ensure a therapeutic effect in both children with mild asthma and those with moderate asthma.[2] Since then it has been shown that daily administration of 200 μg of budesonide by means of a dry-powder inhaler effectively controls asthma symptoms and reduces exacerbations in children 5 to 11 years of age.[3] Even at this lower dose, there was a reported mean reduction of 1.0 cm in height during the first 2 years of therapy.[3] Although the systemic effects of inhaled glucocorticoids are dose-dependent, they are also dependent on the therapeutic index of the specific inhaled glucocorticoid and the delivery device used.[4-9] Thus, it seems prudent to select inhaled glucocorticoids and devices with higher therapeutic indexes and to use them in the lowest effective doses in children with persistent asthma.[1,9]

In conclusion, the reduction in growth seen in the first few years of administration of inhaled glucocorticoids in prepubertal children persists as lowered adult height. However, in the information about inhaled glucocorticoids and their side effects that is provided to parents, the potential effect on adult height must be balanced against the large and well-established benefit of these drugs in controlling persistent asthma. It is appropriate to use the lowest effective dose for symptom control in order to minimize concern about the effects of inhaled glucocorticoids on adult height.

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