

Attained adult height after childhood asthma: Effect of glucocorticoid therapy

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Background: Although oral and inhaled glucocorticoid therapy may impair growth in children with asthma, the effect of glucocorticoid therapy and asthma on attained adult height has not been extensively studied in representative children in the community.

Objectives: The study was designed to compare the attained adult height of children with asthma with the attained adult height of nonasthmatic children and to compare the attained adult height of asthmatic children treated with glucocorticoids with the attained adult height of asthmatic children who did not receive glucocorticoids.

Methods: Residents of Rochester, Minnesota, with onset of asthma from 1964 to 1987 and age- and sex-matched nonasthmatic residents of Rochester were studied. Glucocorticoid exposure was assessed from medical records. The mean of 5 stadiometer measurements of adult height, adjusted for sex and parental height, was analyzed.

Results: One hundred fifty-three patients with asthma (mean age at onset, 6.1 ± 4.8 years) and 153 age- and sex-matched nonasthmatic subjects were studied. Adult height of patients with asthma (mean age at measurement, 25.7 ± 5.2 years) was not significantly different from the adult height of nonasthmatic subjects; the overall difference, adjusted for mid-parental height, was -0.20 cm (95% confidence interval from -0.27 to 1.64). The adult height of asthmatic children treated with glucocorticoids was not significantly different from the adult height of patients with asthma not treated with glucocorticoids; the difference after adjusting for mid-parental height was -0.2 cm (95% confidence interval from -0.1 to 0.6).

Conclusions: We conclude that the attained adult height of patients with asthma is not different from the adult height of age- and sex-matched nonasthmatic subjects and that the attained adult height of asthmatic children treated with glucocorticoids is not significantly different from the adult height of children not treated with glucocorticoids. (*J Allergy Clin Immunol* 1997;99:466-74.)

Key words: Asthma, height, growth, glucocorticoids

Asthma is a common condition with a prevalence in Rochester, Minnesota, of approximately 8%.¹ The incidence of asthma is highest in the early years of life, and asthma may be active throughout a child's growing years. Children with asthma have been reported to have shorter stature and smaller increase in height for age (slower height velocity) than children without asthma.² Although it is well recognized that daily and alternate-day administration of glucocorticoids may impair growth,³⁻⁶ shorter stature for age has been observed in children with asthma who have not been treated with glucocorticoids.⁷⁻¹⁰ Mechanisms other than the effect of glucocorticoid treatment have been postulated to explain the shorter stature of children with asthma including chronic hypoxia, diminished lung function, chronic infection, undernutrition, sleep disturbance, and long-term stress.¹¹⁻¹³

In addition to growth retardation, children with asthma have been reported to have delayed maturation as measured by time of appearance of secondary sexual characteristics and by skeletal age.^{7,14} Some investigators have found that although change in height (i.e., height velocity) is transiently reduced, catch-up growth occurs,⁷ and asthmatic children attain normal adult height.^{10,14,15} Other investigators have not found evidence of catch-up growth.^{16,17} Whether the attained adult height of children with asthma, especially children who have received glucocorticoids, is equal to predicted height and comparable to attained adult height of children without asthma is controversial.

With increasing recognition of the importance of the role of inflammation in asthma and the efficacy of glucocorticoid therapy in reducing inflammation, glucocorticoids are presently prescribed more often and earlier in the treatment of patients with asthma. Inhaled glucocorticoid therapy is often used to avoid the adverse effects of long-term oral glucocorticoid treatment.¹⁸ Beclomethasone and triamcinolone have not been associated with reduced height or growth in previous studies.^{19,20} However, a recent randomized clinical trial of aerosol beclomethasone compared with oral theophylline in treatment of children, ages 6 to 17 years, with mild to moderately severe asthma demonstrated reduced growth in the beclomethasone group compared with the oral theophylline group.²¹ No population-based study, however, has reported the adult height of children treated with glucocorticoids.

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We previously identified a population-based cohort of Rochester, Minnesota, residents with onset of asthma between 1964 and 1983.¹ This cohort, updated through 1987, includes 778 children with definite asthma whose symptoms began during childhood and who have now attained their adult height. An advantage of studying this retrospective cohort is that the subjects will have already experienced the outcome of interest (i.e., attained adult height). For this study we invited all available members of this cohort to participate in a study of asthma and adult height. We evaluated whether patients with onset of asthma during childhood have shorter adult height than nonasthmatic subjects and whether patients with asthma who received glucocorticoids for treatment of their asthma during childhood had shorter adult height than patients with asthma who did not receive glucocorticoids.

METHODS

Study setting

Rochester, Minnesota, is located 90 miles southeast of Minneapolis and is centrally located in Olmsted County. In 1990 the population of Rochester was 70,745 (94% white). With the exception of a higher proportion of residents employed in the health care industry, the characteristics of Rochester are similar to those of the U.S. white population. Population-based epidemiologic research is possible in this setting because essentially all medical care for Rochester residents is provided by the Mayo Clinic and its affiliated hospitals, by the Olmsted Medical Group and its affiliated hospital, and by a small number of other physicians. The medical diagnoses and surgical procedures for all providers are recorded in automated databases, and the original medical records of all providers are available for review through the resources of the National Institutes of Health-funded Rochester Epidemiology Project.

Study design

The first study aim was to compare the adult height of asthmatic children with the adult height of children without asthma. For this aim, a retrospective cohort study design was selected to compare the outcome of adult height of the cohort with asthma with the adult height of an age- and sex-matched cohort of nonasthmatic subjects. The second study aim was to compare the adult height of asthmatic children who received glucocorticoids with the adult height of asthmatic children who did not receive glucocorticoids. For this aim, a retrospective cohort study design was also selected in which the exposure of interest was glucocorticoid therapy and the outcome was attained adult height.

Subjects

We previously identified the cohort of Rochester residents with onset of asthma from 1964 through 1983¹ and have partially updated the cohort through 1987. For this study, Rochester residents with definite asthma, by the predetermined criteria used for the previous study of the epidemiology of asthma,¹ who experienced the onset of their asthma during childhood and who attained adult height (age ≤ 17 years for girls and ≤ 19 years for boys) were eligible and were asked to participate. With the resources of the Rochester Epidemiology Project, an age- and sex-matched subject without asthma who resided in Rochester in the same year as the onset of asthma for

the corresponding asthmatic study subject was identified from the list of Rochester residents who had ever received care at the Mayo Clinic and was invited to volunteer for the study. All subjects gave informed consent to be enrolled in the study. The study was approved by the Mayo Clinic Institutional Review Board.

Data collection

Information for the study was collected from three sources: (1) directly from study subjects by means of a pretested structured questionnaire, (2) from nurse abstractor review of all inpatient and outpatient medical records of Rochester providers of care for study subjects, and (3) from direct measurements of adult height for all study subjects and pulmonary function test results for study subjects. Date of birth and gender of all subjects were available from the medical records. All asthma medications listed anywhere in the medical record from onset of asthma until age of attaining adult height were recorded for all subjects. All data concerning the date, dose, route, frequency, amount prescribed, and number of refills were recorded. The recorded height and the date the height was recorded were abstracted from medical records for at least one visit each year for all years in which there was a clinic visit until the study subject attained adult height or was lost to follow-up. When more than one measurement was available, the first measurement in each year was recorded. All subjects were asked to accurately report their current height and the height of their natural parents and to estimate their parents' height in relation to their own height.

Measurement of adult height

All subjects had a stadiometer measurement of standing height with shoes removed measured by the same study nurse, using a single stadiometer that was calibrated periodically against a known standard. The measurements were repeated five times, and the mean of five recordings was analyzed.

Data analysis

For each study subject, mid-parental height was used to adjust for subject's mother's and father's height.^{22, 23} The formula used was:

Mid-parental height (boys)

$$= (\text{Mother's height} + \text{Father's height} + 13 \text{ cm}) \div 2$$

Mid-parental height (girls)

$$= (\text{Mother's height} + \text{Father's height} - 13 \text{ cm}) \div 2$$

The height of asthmatic subjects was compared with the height of nonasthmatic subjects in two ways, both of which adjusted for survey-reported mid-parental height. The first comparison ignored the matching and assessed the relationship between the mean of the five measurements of adult height and asthma status by means of analysis of covariance. The second comparison used a paired analysis to account for the matching. Here, the difference between a subject's mean measured height and mid-parental height was calculated. This difference from mid-parental height was compared between the asthmatic subjects and the age- and sex-matched nonasthmatic subjects by using a signed-rank test.

Among asthmatic subjects, the relationship between mean measured adult height and glucocorticoid exposure was assessed by using analysis of covariance. Each subject's glucocorticoid exposure was classified as any chart-recorded exposure or

TABLE I. Patient and parental height for asthmatic cohort and age- and sex-matched nonasthmatic cohort

Variable & sex	Asthmatic cohort		Nonasthmatic cohort		p Value*
	n	Mean $\pm$ SD	n	Mean $\pm$ SD	
Mean measured height (cm)					
Female	78	165.9 $\pm$ 6.1	78	165.1 $\pm$ 6.6	0.60
Male	75	179.1 $\pm$ 7.0	75	179.4 $\pm$ 6.1	0.80
Survey-reported father's height (cm)					
Female	73	175.4 $\pm$ 6.0	69	174.0 $\pm$ 7.5	0.24
Male	68	176.7 $\pm$ 6.1	68	177.2 $\pm$ 7.1	0.66
Survey reported mother's height (cm)					
Female	76	161.3 $\pm$ 6.0	72	160.7 $\pm$ 6.3	0.75
Male	70	161.5 $\pm$ 6.4	70	161.9 $\pm$ 5.2	0.65
Mid-parental height (cm)					
Female	73	161.9 $\pm$ 4.8	68	161.1 $\pm$ 5.1	0.47
Male	68	175.6 $\pm$ 5.0	68	176.1 $\pm$ 4.5	0.70

*Rank sum test.

no chart-recorded exposure and separately classified as any chart-recorded oral exposure, only inhaled glucocorticoid exposure recorded in the chart, or no chart-recorded exposure. Additionally, the relationship between mean measured adult height and cumulative glucocorticoid exposure was assessed in an analysis of covariance model. Cumulative childhood exposure to glucocorticoids was calculated by using all recorded exposures before subjects attained adult height (age 17 years for girls and age 19 years for boys). For each episode of glucocorticoid use, exposure was calculated by multiplying the dose in milligrams by the number of doses per day and by the total number of days exposed. A tapering dose was treated as half the initial dose multiplied by the number of days over which the dose was tapered. All of the individual episodes of glucocorticoid exposure were then added together to yield a cumulative exposure to glucocorticoids. In an additional analysis, glucocorticoid potency adjustment was made by adjusting each specific glucocorticoid exposure by the potency of the glucocorticoid relative to the potency of prednisone; all adjusted exposures were then summed to arrive at a cumulative adjusted exposure. Cumulative glucocorticoid exposure and cumulative adjusted glucocorticoid exposure were also separately calculated for subjects with any oral glucocorticoid exposure and for subjects with only inhaled glucocorticoid exposure. The distributions of cumulative glucocorticoid exposure and cumulative adjusted glucocorticoid exposure were highly skewed, and accordingly, the natural logarithms of cumulative glucocorticoid exposure and adjusted glucocorticoid exposure were used in the analysis of covariance models. Analyses were performed by using SAS software (SAS Institute). A *p* value less than 0.05 was considered statistically significant.

RESULTS

At the time the study was initiated, 778 members of the updated asthma cohort had experienced onset of asthma during childhood and had attained adult height (age 17 in girls and age 19 in boys) and were therefore eligible for the study. Fifty-six members of the original cohort were excluded because of unavailable current addresses (37 cases), revised diagnoses (4 cases), deaths (2 cases), or other miscellaneous reasons (13 cases). The remaining 722 Rochester residents with onset of asthma before attaining adult height were invited to participate.

Letters to 99 cohort members were returned from the post office as "unclaimed," indicating that a current address for these patients was not available. Thus 623 members of the original cohort were assumed to have been contacted. Sixty-two (10%) declined to participate, 300 (48%) did not respond, and 261 (42%) completed the study questionnaire. One hundred fifty-three (25%) were available for height measurement, were enrolled in the study, and comprise the asthma cohort.

There were 153 study subjects with asthma, 78 women (51%) and 75 men (49%). The asthmatic subjects' mean age at onset of asthma was 6.1 ± 4.8 years (median, 5.2 years). The asthmatic subjects' mean age at first glucocorticoid exposure was 12.5 ± 3.9 years; the mean interval between onset of asthma and first glucocorticoid exposure was 7.3 ± 4.8 years. The mean age at last glucocorticoid exposure before attaining adulthood was 14.6 ± 3.7 years, and the mean interval between first and last glucocorticoid exposure was 7.3 ± 4.8 years. Age at time of measurement of adult height was 25.7 ± 5.2 years. Table I summarizes the mean of the five stadiometer measurements of adult height, the reported father's height and mother's height, and the calculated mid-parental height for the asthmatic cohort and for the age- and sex-matched comparison cohort of Rochester residents without asthma. The measured height, survey-reported father's height and mother's height, and calculated mid-parental height of the asthmatic cohort were not significantly different from corresponding values for the nonasthmatic cohort as determined by the rank-sum test. Note that the mean measured height was greater than the mean mid-parental height for women and men for both the cohort with asthma and the comparison cohort.

Asthma and adult height

In the unmatched analysis, the height of patients with asthma, after adjusting for sex and mid-parental height, was not significantly different from the height of nonasthmatic subjects (*p* = 0.82). The adult height of the

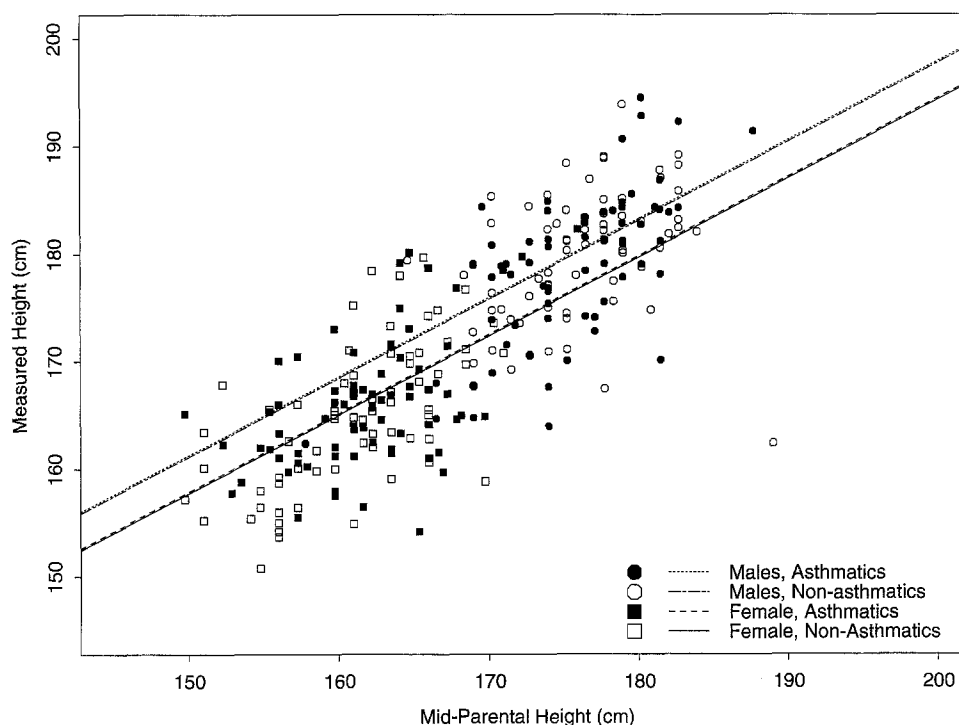


FIG. 1. Adult height of men and women with asthma and age- and sex-matched nonasthmatic subjects by mid-parental height. Lines indicate the following equation: Adult height = 48.2 cm + (0.15 cm) $\times$ Asthma + (3.44 cm) $\times$ Male + (0.73 cm) $\times$ Mid-parental height, where Asthma = 1 if asthmatic, 0 if nonasthmatic; Male = 1 if male, 0 if female.

asthmatic cohort and the age- and sex-matched nonasthmatic cohort by mid-parental height, and the lines indicating predicted adult height, are shown in Fig. 1. After adjustment for sex and mid-parental height, patients with asthma were 0.15 cm (0.06 inches) taller than nonasthmatic subjects. The difference in the measured height between the asthmatic subjects and matched nonasthmatic subjects was only 0.21 ± 9.42 cm ($p = 0.95$). The measured heights of both the cohort with asthma and the nonasthmatic comparison cohort are greater than their expected mid-parental heights (3.7 ± 5.4 cm and 3.6 ± 5.8 cm, respectively; both $p < 0.01$). Finally, the paired comparison of difference in the measured adult height (adjusted for mid-parental height) of the asthmatic subjects compared with the nonasthmatic subjects was only 0.20 ± 8.17 cm; $p = 0.78$). In all comparisons results were consistent for both women and men.

Glucocorticoids and adult height of patients with asthma

Overall, 58 (38%) of the patients with asthma had exposure to glucocorticoids recorded in their medical records. Glucocorticoid exposure was similar for women (28 of 78 or 36%) and men (30 of 75 or 40%). The patients with asthma who received inhaled glucocorticoids had a mean of 3.3 doses (median, 4 doses) prescribed per day. The patients with asthma who received oral or parenteral glucocorticoids had a mean of

2.4 courses (median, 1 course) of oral or parenteral glucocorticoids during their childhood years. The mean of the five measurements of adult height, survey-reported parental height, mid-parental height, and difference between measured height and mid-parental height for women and men by any glucocorticoid exposure or no glucocorticoid exposure is shown in Table II. Among the 58 patients with asthma who were exposed to glucocorticoids, 40 had received oral glucocorticoids (19 women and 21 men), and 18 had received only inhaled glucocorticoids (9 women and 9 men).

The adult height of patients with asthma treated with glucocorticoids was not significantly different from the adult height of patients with asthma who did not receive glucocorticoids. After adjusting for mid-parental height, the adult height of patients with asthma treated with glucocorticoids was approximately 1.2 cm (approximately 0.5 inch) less than the height of patients with asthma not treated with steroids. The 95% confidence interval for glucocorticoid therapy was (-3.1 cm, 0.6 cm). The adult height of patients with asthma by mid-parental height and the lines indicating predicted adult height for those with any glucocorticoid therapy and those with no glucocorticoid therapy are shown in Fig. 2.

In the analysis that classified glucocorticoid exposure as any oral glucocorticoid use, inhaled glucocorticoid use only, or no glucocorticoid use, neither exposure to oral glucocorticoids (ever) nor exposure to inhaled glucocorticoids only was associated with adult height after ad-

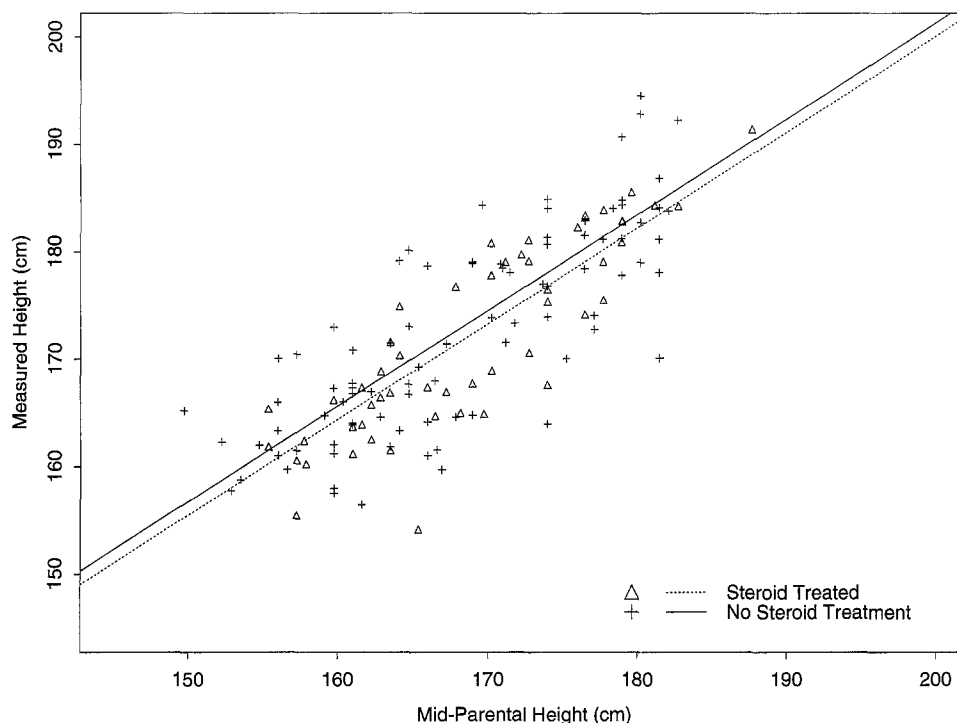


FIG. 2. Adult height of patients with asthma who received any glucocorticoid therapy during childhood or adolescence and patients with asthma who received no glucocorticoid therapy during childhood or adolescence by mid-parental height. Lines indicate the following equation: Adult height = 23.2 cm + (1.26 cm) × Glucocorticoid + (0.89 cm) × Mid-parental height, where Glucocorticoid = 1 if glucocorticoid recorded in medical record, 0 if no glucocorticoid therapy recorded in medical record.

TABLE II. Patient and parental height of patients with asthma by glucocorticoid use and sex

Variable	Glucocorticoid use		No glucocorticoid use		p Value*
	n	Mean ± SD	n	Mean ± SD	
Measured adult height (cm)					
Female	28	166.3 ± 6.4	50	165.6 ± 6.0	0.61†
Male	30	178.1 ± 7.3	45	179.7 ± 6.8	0.33
Calculated mid-parental height (cm)					
Female	27	163.3 ± 4.9	46	161.0 ± 4.6	0.05
Male	25	174.8 ± 6.0	43	176.1 ± 4.4	0.33†
Difference in measured height and mid-parental height (cm)					
Female	27	3.0 ± 4.9	46	4.8 ± 5.8	0.18
Male	25	2.8 ± 4.2	43	3.6 ± 6.0	0.48†

*t test.

†Rank sum test.

justing for mid-parental height. In an analysis that adjusted for mid-parental height, the adult height of patients with asthma who received oral glucocorticoids (ever) was 1.4 cm less than the height of patients with asthma not treated with steroids. The 95% confidence interval of the difference was (−3.5 cm, 0.7 cm). The adult height of patients with asthma who received only inhaled glucocorticoids was 0.9 cm less than the height of patients with asthma not treated with glucocorticoids. The 95% confidence interval of the difference was (−3.8

cm, 2.0 cm). The adult height of patients with asthma by mid-parental height and the lines indicating predicted adult height of those who received oral or parenteral glucocorticoids, inhaled glucocorticoids only, or no glucocorticoid therapy are shown in Fig. 3.

Cumulative glucocorticoid exposure and adult height

Glucocorticoid exposure is summarized for all patients with asthma and for those who received oral

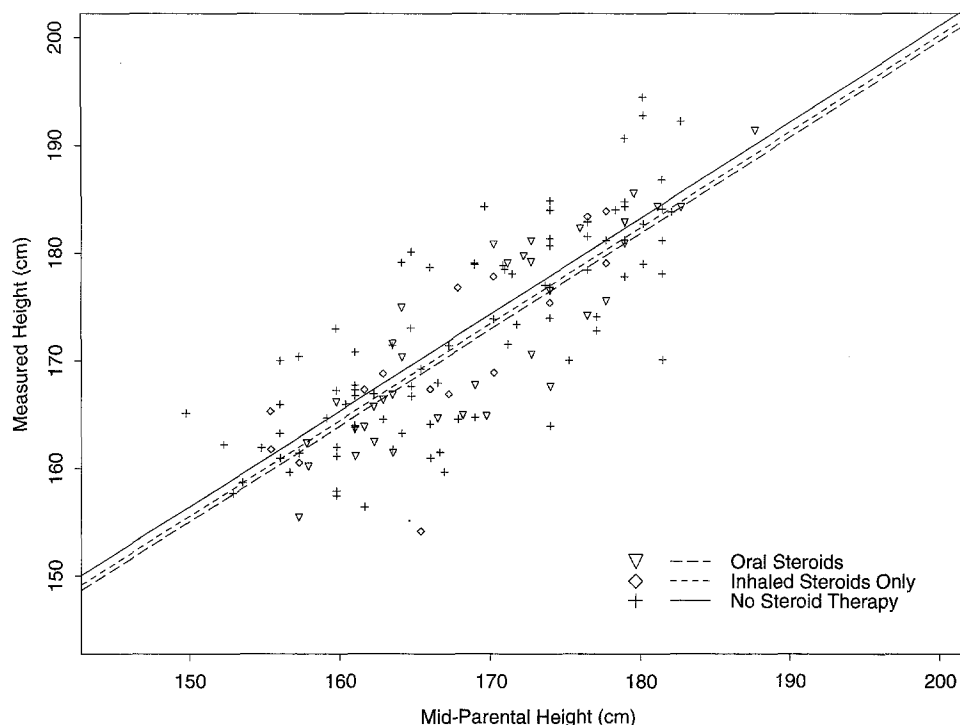


FIG. 3. Adult height of patients with asthma who received oral or parenteral glucocorticoid therapy during childhood or adolescence, patients with asthma who received only inhaled glucocorticoids during childhood or adolescence, and patients with asthma who had no glucocorticoid exposure by mid-parental height. Lines indicated the following equation: Adult height = $23.0 \text{ cm} - (1.40 \text{ cm}) \times \text{Oral} - (0.90 \text{ cm}) \times \text{Inhaled} + (0.89 \text{ cm}) \times \text{Mid-parental height}$, where Oral = 1 if any glucocorticoid exposure, 0 if no exposure to oral glucocorticoids; and Inhaled = 1 if only inhaled glucocorticoid exposure, 0 if no exposure to any inhaled steroids.

TABLE III. Cumulative childhood glucocorticoid exposure and glucocorticoid potency-adjusted exposure after onset of asthma until attaining adult height

	Cumulative glucocorticoid exposure			Adjusted cumulative glucocorticoid exposure		
	<i>n</i>	Median (total mg)	Mean $\pm$ SD (total mg)	<i>n</i>	Median (total mg)	Mean $\pm$ SD (total mg)
All glucocorticoid use						
Women	28	78	667 $\pm$ 1403	28	171	939 $\pm$ 2070
Men	30	293	490 $\pm$ 632	30	364	979 $\pm$ 1628
Oral glucocorticoids (any)						
Women	19	280	960 $\pm$ 1632	19	280	1262 $\pm$ 2445
Men	21	400	632 $\pm$ 699	21	411	1086 $\pm$ 1794
Inhaled glucocorticoids (only)						
Women	9	8	47 $\pm$ 91	9	43	257 $\pm$ 498
Men	9	15	157 $\pm$ 226	9	83	729 $\pm$ 1205

Of the 19 women in the oral glucocorticoid group, 12 also received inhaled glucocorticoids. For these 12 women, the mean $\pm$ SD cumulative inhaled glucocorticoid exposure was 264 ± 523 mg (median, 28 mg); the cumulative inhaled potency-adjusted glucocorticoid exposure was 1015 ± 2304 mg (median, 87 mg). Of the 21 men in the oral glucocorticoid group, 10 also received inhaled glucocorticoids. For these 10 men, the mean $\pm$ SD cumulative inhaled glucocorticoid exposure was 353 ± 578 mg (median, 83 mg); the cumulative inhaled potency-adjusted glucocorticoid exposure was 1281 ± 2217 mg (median, 459 mg).

glucocorticoids (ever) or inhaled glucocorticoids only for men and women in Table III. The distribution of exposures is quite skewed, and therefore median and mean $\pm$ SD are reported. Note that patients with asthma whose treatment included courses of oral glucocorticoids generally had higher cumulative exposure ($p = 0.003$) and

adjusted cumulative exposure ($p = 0.03$) to glucocorticoids than patients with asthma who received only inhaled glucocorticoids. After adjusting for mid-parental height, measured adult height was not statistically significantly associated with cumulative glucocorticoid exposure or with cumulative glucocorticoid exposure ad-

justed for glucocorticoid potency ($p = 0.89$ and 0.79 , respectively). The relationship between measured height, adjusted by mid-parental height, and glucocorticoid exposure is shown in Fig. 4.

Height of asthma cohort and enrolled subjects

This study enrolled patients from a population-based cohort of Rochester residents with onset of asthma before attaining adult height. To assess whether the sample of patients enrolled in the study differs from original cohort members not enrolled, adult height reported in the medical records of enrolled patients was compared with the adult height reported in the medical records of members of the original cohort not enrolled in the study. The medical record height of enrolled women (mean, 165.6 ± 5.9 cm; $n = 72$) and men (mean, 179.0 ± 7.7 cm; $n = 54$) was not significantly different from the medical record height of cohort women (mean, 164.1 ± 6.7 cm; $n = 134$) and men (mean, 178.4 ± 7.5 cm; $n = 160$) not enrolled in the study. To assess whether the sample of patients who completed questionnaires but did not enroll in the study differed from enrolled subjects who completed questionnaires and had a stadiometer measurement of adult height, we compared the self-reported height of enrolled subjects with the self-reported height of those who only responded to the questionnaire. The self-reported height of enrolled women (mean, 163.2 ± 6.6 cm; $n = 78$) and men (mean, 177.1 ± 7.0 cm; $n = 75$) was not significantly different from the self-reported height of women (mean, 162.6 ± 6.2 cm; $n = 50$) and men (mean, 177.5 ± 5.3 cm; $n = 57$) who only responded to the questionnaire.

DISCUSSION

This study used a population-based incidence cohort of patients with asthma as a sampling frame to enroll subjects with onset of asthma before attaining adult height. The adult height of patients with asthma, adjusted for parental height, was not significantly different from the height of nonasthmatic subjects, suggesting that, overall, asthma does not have an important effect on attained adult height. The attained adult height of patients with asthma who received glucocorticoids was not significantly different from the adult height of patients with asthma not treated with glucocorticoids. The actual magnitude of the observed difference, 1.22 cm or approximately 0.48 inch, was small, suggesting no clinically important differences in adult height. Analyses of the attained adult height of patients with asthma who had received any oral or parenteral glucocorticoid treatment and patients with asthma who had received only inhaled glucocorticoid treatment compared with patients with asthma not treated with glucocorticoids also confirmed that differences in height were not statistically significant. The actual magnitudes of any differences were small (1.4 cm or 0.55 inch and 0.90 cm or 0.35 inch, respectively) and are not likely to be clinically important. Finally, additional analyses based on cumulative glucocorticoid exposure and glucocorticoid potency-ad-

justed exposure showed no significant dose-response effect. Our findings are reassuring in that they suggest that, overall, asthma per se and glucocorticoid treatment of asthma do not have a clinically important impact on attained adult height.

Our findings suggest that, overall, patients with asthma treated with glucocorticoids may be 1.2 cm (0.5 inch) shorter than patients with asthma not treated with glucocorticoids. We can use the 95% confidence interval to interpret the range that may include the actual difference. Thus patients with asthma treated with glucocorticoids could be as much as -3.1 cm (1.2 inches) shorter or 0.6 cm (0.2 inches) taller than patients with asthma not treated with steroids. Our best estimate of the difference in attained adult height (1.2 cm or approximately 0.5 inch) is small and in our judgment not clinically important. The lower limit of the 95% confidence interval, 3.1 cm, is less than one half of the standard deviation of adult height. Our study had a 96% power to detect a difference of 2 inches between the two groups but only a 47% power to detect a difference of 1 inch between the two groups.

Our findings are not inconsistent with results of studies that document impaired growth during glucocorticoid exposure. The effect of glucocorticoids on attained adult height may depend on the particular glucocorticoids used, route of delivery dose, duration of use, and whether glucocorticoids were given continuously or intermittently during childhood and adolescence. Our findings indicate that for most patients with asthma, the actual use of glucocorticoids in management of asthma was not associated with a clinically important effect on attained adult height. It is possible that the glucocorticoid exposure of patients with asthma may be too small to produce a substantial effect on attained adult height or that patterns of use in courses of glucocorticoids with intervening periods without glucocorticoid exposure included adequate periods of growth to allow children and adolescents to attain expected adult height.

Glucocorticoid exposure was assessed from review of all the inpatient and ambulatory medical records of all providers of care for the patients with asthma. Access to the patients' original records, which is available through the Rochester Epidemiology Project, assures a high level of ascertainment of glucocorticoid prescriptions. Medical record documentation of glucocorticoid use may underestimate actual use because refills may not be completely recorded in the medical record. Conversely, medical record documentation of glucocorticoid use may overestimate actual use because of noncompliance. Unfortunately, we are not able to directly verify actual medication exposure in this long-term observational study. Nevertheless, we believe that the striking effectiveness of glucocorticoids in treatment of asthma, clinical concerns about adverse effects of high doses or prolonged glucocorticoid use, and general concern about treatment with medication in children result in reasonably accurate documentation of glucocorticoid exposure for the analyses of the relationship of any

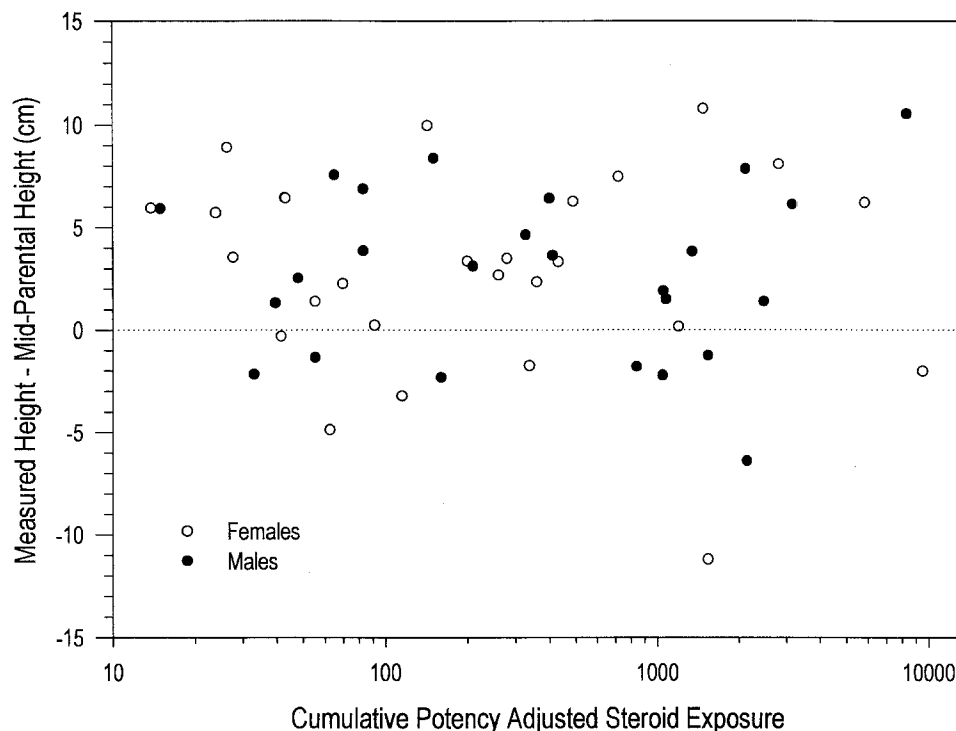


FIG. 4. Difference between measured adult height of patients with asthma and mid-parental height versus logarithm of cumulative potency-adjusted glucocorticoid from onset of asthma to age of adult height (17 years for girls and 19 years for boys).

exposure, type of exposure, or cumulative exposure to attained adult height.

To evaluate potential selection bias in recruitment and enrollment of study subjects, we compared the medical record adult height of the eligible patients from the original cohort and the medical record adult height of enrolled study subjects and found no significant differences. We also compared self-reported adult height of potential subjects who completed the questionnaire with the self-reported height of enrolled study subjects and again found no significant differences. Thus we believe that enrolled study subjects are a representative selection of children treated with glucocorticoids.

Interestingly, both patients with asthma and nonasthmatic subjects exceeded their expected (mid-parental) height; patients with asthma were 3.7 cm (approximately 1.5 inches) taller than expected, and nonasthmatic subjects were 3.6 cm (approximately 1.4 inches) taller than expected. This increase in stature has been observed historically in the United States²⁴ and has been observed recently in the Japanese population.²⁵

We enrolled subjects from a population-based cohort with onset of asthma from 1964 through 1983 who had attained adult height by December 1992. During this period, there were changes in physicians' use of glucocorticoids for treatment of childhood asthma. In the 1960s and 1970s, oral glucocorticoids were used in the lowest possible dosages for only the most severe cases; whereas in the 1980s and 1990s, inhaled glucocorticoids

with less potential for inducing systemic effects were used in children with mild to moderate asthma. Although generally regarded as safe at conventional doses, higher doses of inhaled glucocorticoids may not be risk-free.²⁶ In addition, suppression of growth velocity has been reported in some children receiving recommended pharmacologic doses of these preparations.^{6, 21, 27-29}

Findings from our retrospective study are consistent with those of previously published prospective studies involving fewer children but more homogeneous treatment regimens. In a long-term study involving 66 asthmatic children, 29 required treatment with 400 to 600 $\mu\text{g/day}$ of beclomethasone dipropionate, 33 required treatment with cromolyn sodium, and four required only bronchodilator therapy.⁷ Of the 60 children who were followed up until they attained adult height, all eventually attained normal predicted final adult height, although the report did not list group mean or individual data. A recently reported meta-analysis of the effect of oral and inhaled glucocorticoids on the growth of asthmatic children included 21 studies and 810 patients.³⁰ As expected, significant weak growth impairment was observed for prednisone and other oral glucocorticoids, but a significant moderate tendency was observed for inhaled beclomethasone dipropionate therapy to be associated with attaining normal stature. In particular, there was no statistical evidence for beclomethasone dipropionate to be associated with growth impairment at higher

doses, for longer therapy duration, or among patients with more severe asthma.

Our study was limited by reliance on medical record documentation of oral glucocorticoid exposure, recruitment of only 25% of eligible contacted members of the original cohort, and use of self-reported parental height. Our study had several strengths. The clinically relevant end point of attained adult height was accurately measured. Adult height of patients with asthma was compared with the adult height of age- and sex-matched nonasthmatic subjects. Parental height was used to adjust measured height. Glucocorticoid exposure was analyzed by route of glucocorticoid exposure, cumulative exposure, and potency-adjusted cumulative exposure. Finally, it should be noted that prospective studies of the impact of glucocorticoids on the clinically relevant end point (attained adult height) are unlikely to be forthcoming in the near future because of the many years needed to follow up a cohort until the end point of final adult height is attained. Thus we believe that our retrospective cohort provides a unique opportunity to assess the effect of glucocorticoid exposure on adult height.

Our findings should reassure physicians, parents, and patients that glucocorticoids, as commonly prescribed for treatment of childhood asthma, do not have an important impact on adult height.

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