

RISK OF PERSISTENT GROWTH IMPAIRMENT AFTER ALTERNATE-DAY PREDNISONE TREATMENT IN CHILDREN WITH CYSTIC FIBROSIS

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ABSTRACT

Background It is uncertain whether the growth impairment that occurs in children during long-term treatment with glucocorticoids persists after the medication is discontinued and ultimately affects adult height.

Methods We evaluated growth six to seven years after alternate-day treatment with prednisone had been discontinued in 224 children 6 to 14 years of age with cystic fibrosis who had participated in a multicenter trial of this therapy from 1986 through 1991. Of the children, 151 had been randomly assigned to receive prednisone (1 or 2 mg per kilogram of body weight) and 73 to receive placebo. We obtained data on growth up to 1997 from the Cystic Fibrosis Foundation Patient Registry and standardized the data to sex- and age-specific norms from the National Center for Health Statistics. We used z scores to compare growth patterns among treatment groups.

Results In 1997, 68 percent of the patients were 18 years of age or older. The z scores for height declined during prednisone therapy; catch-up growth began two years after treatment with prednisone was discontinued. Among the boys, the z scores for height in those treated with prednisone remained lower than the scores for those who received placebo ($P=0.02$). The mean heights for boys 18 years of age or older were 4 cm less in the prednisone groups than in the placebo group, an equivalent of 13 percentile points ($P=0.03$). Among the girls, differences in height between those who were treated with prednisone and those who received placebo were no longer present two to three years after prednisone therapy was discontinued.

Conclusions Among children with cystic fibrosis who have received alternate-day treatment with prednisone, boys, but not girls, have persistent growth impairment after treatment is discontinued. (N Engl J Med 2000;342:851-9.)

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GLUCOCORTICOIDS are administered to patients with cystic fibrosis for acute indications, such as bronchiolitis,¹ bronchial hyperreactivity,² and allergic bronchopulmonary aspergillosis,³ as well as for long-term treatment of mild-to-moderate obstructive pulmonary disease, to reduce inflammation and improve lung function.⁴⁻⁹ In two randomized clinical trials, patients with cystic fibrosis and mild-to-moderate lung disease who were treated with 1 or 2 mg of prednisone per kilogram of body weight on an alternate-day schedule over a period of two to four years had significantly better pul-

monary function than such patients who were given placebo.^{5,6}

The benefits of long-term treatment with glucocorticoids in terms of pulmonary function in patients with cystic fibrosis^{5,6} must be weighed against the potential adverse effects of the treatment, such as impairment of growth,^{6,10-14} abnormalities in the metabolism of glucose,⁶ adrenal suppression,¹⁴ and the formation of cataracts.^{6,15} Of these adverse effects, growth retardation is the most common and is of particular concern in children. Studies of children with asthma and atopic dermatitis suggest that the long-term administration of glucocorticoids may slow growth.^{10-14,16} The extent of growth suppression varies with the method of administration (e.g., inhaled or oral) and the duration of treatment as well as with the type and dose of glucocorticoid used.^{10,11}

One unanswered question is whether the growth suppression that occurs in children during glucocorticoid treatment persists after the treatment is discontinued and ultimately affects final adult height. In an attempt to answer this question, we evaluated the long-term growth of children with cystic fibrosis who had participated in a multicenter clinical trial of alternate-day treatment with oral prednisone from 1986 through 1991.⁶ We evaluated longitudinal growth both during the treatment period (three to four years) and during an extended period of six to seven years after treatment was discontinued.

METHODS

Study Design and Sources of Data

Our study was an extension of a randomized, double-blind, placebo-controlled, multicenter trial conducted from 1986 through 1991 to assess the efficacy and safety of alternate-day treatment with oral prednisone in children with cystic fibrosis who had mild-to-moderate lung disease.⁶ A total of 285 children (age range, 6 to 14 years) were enrolled at 15 participating cystic fibrosis centers (13 in the United States and 2 in Canada) from April 1986 through December 1987. They were randomly assigned to receive low-dose prednisone (1 mg per kilogram; 95 patients; prednisone tablets provided by Upjohn Pharmaceuticals), high-dose prednisone (2 mg per kilogram; 95 patients), or placebo (95 patients). Prednisone was given on alternate days as a single oral dose taken in the morning, with a maximal daily dose of 60 mg. Written in-

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formed consent was obtained from each child and his or her parent or guardian. The study protocol and the informed-consent form were approved by the institutional review board at each study center. Because of a higher-than-expected number of adverse events, which included impaired growth, abnormalities in glucose metabolism, and the formation of cataracts,⁶ the data safety monitoring committee recommended discontinuation of treatment with high-dose and low-dose prednisone in August 1990 and August 1991, respectively. Accordingly, the trial was terminated in August 1991.

For the current study, we identified children who participated in the prednisone trial and obtained data on their growth from the date of their last follow-up in the trial up to December 1997 from the U.S. Cystic Fibrosis Foundation Patient Registry in Bethesda, Maryland. Of the 285 children enrolled, 42 (15 percent) were Canadian; data on these patients therefore were not reported to the U.S. registry. Of the remaining 243 children, 13 could not be correctly identified from the registry. For another six children, data on growth past the date of their last follow-up in the trial were not available from the registry. These 19 children were evenly distributed with respect to treatment group (placebo group, 8 children; low-dose group, 6 children; and high-dose group, 5 children), sex (9 male children and 10 female children), and center. In terms of base-line characteristics, no significant differences were found between these 19 children and the 224 children included in the current study.

We also retrieved from the registry data on several clinical variables that may influence growth. These included the forced expiratory volume in one second, forced vital capacity, presence or absence of colonization with *Pseudomonas aeruginosa*, presence or absence of meconium ileus at birth, genotype of cystic fibrosis, and use or nonuse of pancreatic-enzyme supplementation.

Growth Measurement and Evaluation

During the prednisone trial, growth was measured every three months with techniques standardized among centers, whereas data from the Cystic Fibrosis Foundation Patient Registry on growth after the discontinuation of treatment were from routine clinical measurements performed at varying time intervals. Despite these differences in the collection of data, we found no significant differences between data from the trial and data from the registry in terms of height and weight.

We standardized height and weight to sex- and age-specific percentiles and z scores on the basis of data on growth in a reference population from the National Center for Health Statistics, using the Epi Info program.¹⁷⁻²⁰ We performed longitudinal comparisons of growth patterns among treatment groups with the use of z scores because of the wide age range of the children at enrollment. A z score of zero corresponds to the 50th percentile, and a z score of -1.0 indicates 1 SD below the mean, which corresponds to approximately the 15th percentile of the reference population.

Statistical Analysis

Statistical software programs (SAS, version 6.12, SAS Institute, Cary, N.C.; and S-Plus, StatSci, MathSoft, Seattle) were used for data processing and analyses. All statistical analyses were performed separately for boys and girls because of the well-documented differences according to sex in the mortality of patients with cystic fibrosis.^{21,22}

We used a Student's t-test or one-way analysis of variance for continuous outcomes and a chi-square test for categorical outcomes to assess differences among groups for variables with a single observation per patient. To assess differences among groups for variables with longitudinal data (multiple observations per patient), we used a repeated-measures analysis with generalized estimating equations and a working assumption of independence among observations.²²⁻²⁴ The identity link was used for continuous outcomes, and the logit link combined with the binomial variance function was used for dichotomous outcomes. All repeated-measures analyses were performed with the use of the Genmod procedure in SAS. Because base-line z scores for height and weight were great-

er in the placebo group than in the prednisone groups, the base-line z score was included as a covariate in all repeated-measures analyses. Additional covariates were age at base line and number of years of follow-up. We compared survival among the groups using the Lifetest procedure in SAS. Statistical significance was set at an α of 0.05 for all analyses.

RESULTS

Characteristics of the Patients

Table 1 summarizes the demographic and disease-related characteristics of the study children. The children started alternate-day treatment with prednisone at a mean age of 9.5 years (range, 6 to 14). Treatment with prednisone was discontinued at mean ages of 12.9 and 13.8 years for the high-dose and low-dose groups, respectively, and growth was followed for another six or seven years after treatment with prednisone was discontinued. At the time of final follow-up, 152 patients (68 percent) were older than 18 years of age.

The low-dose group had a lower rate of death than the other groups ($P=0.05$). No significant differences among the three groups were found in the occurrence of meconium ileus at birth, genotype distribution, the use of pancreatic enzymes, or the prevalence of *P. aeruginosa* colonization. As reported previously,⁶ at the time that prednisone therapy was discontinued, forced expiratory volume in one second and forced vital capacity were significantly higher in the low-dose group than in the other groups. However, these differences were no longer present six or seven years after prednisone therapy was discontinued, because the decline in forced expiratory volume in one second during this period was three times as great in the low-dose group (13.5 percent decline) as the placebo group (4.5 percent decline).

Absolute Height and Weight at 18 Years of Age and Older

The boys who received prednisone were shorter and weighed less than the boys who received placebo (Fig. 1). The mean height after 18 years of age was significantly lower (by 13 percentile points) in the boys who received low-dose prednisone (170.7 ± 7.6 cm, equivalent to the 29th percentile for age; 34 patients) or high-dose prednisone (170.5 ± 6.6 cm, equivalent to the 26th percentile; 31 patients) than in the boys who received placebo (174.6 ± 6.8 cm, equivalent to the 41st percentile; 21 patients) ($P=0.03$). For a given age, the 99th percentile represents the tallest children and the 1st percentile the shortest. A similar trend was observed for weight after 18 years of age; the mean weights were 59.1 ± 9.3 kg in the low-dose group (22nd percentile), 57.0 ± 7.9 kg in the high-dose group (18th percentile), and 63.7 ± 9.4 kg in the placebo group (33rd percentile) ($P=0.01$).

The girls who had received prednisone reached heights and weights that were similar to those of the girls who had received placebo (Fig. 1). Mean heights

TABLE 1. CHARACTERISTICS OF THE 224 CHILDREN WITH CYSTIC FIBROSIS ACCORDING TO ASSIGNED TREATMENT.*

CHARACTERISTIC	PLACEBO (N=73)	1 mg OF PREDNISONE/kg (N=75)	2 mg OF PREDNISONE/kg (N=76)	P VALUE†
Demographic				
Sex — no. (%)				0.21
Male	35 (48)	46 (61)	45 (59)	
Female	38 (52)	29 (39)	31 (41)	
Age — yr				
At start of assigned therapy	9.5±2.8	9.5±2.6	9.4±2.5	0.98
At end of 3 or 4 yr of assigned therapy	13.8±3.3	13.8±2.8	12.9±2.4	0.08
6 or 7 yr after discontinuation of assigned therapy	19.3±3.6	19.9±2.7	19.5±3.2	0.53
Deaths — no. (%)				
At end of 3 or 4 yr of assigned therapy	0	0	0	
At end of 10-yr follow-up	11 (15)	3 (4)	11 (14)	0.05
Diagnostic				
Meconium ileus at birth — no. (%)	17 (23)	7 (9)	13 (17)	0.07
Genotyped for cystic fibrosis — no. (%)	42 (58)	52 (69)	49 (64)	0.32
ΔF508 status — no. (%)				0.15
Homozygous	21 (50)	31 (60)	27 (55)	
Heterozygous	16 (38)	18 (35)	22 (45)	
Neither	5 (12)	3 (6)	0	
Pancreatic-enzyme therapy — no. (%)	71 (97)	70 (93)	73 (96)	0.49
Pulmonary				
<i>Pseudomonas aeruginosa</i> colonization — no. (%)				
At end of 3 or 4 yr of assigned therapy	49 (67)	46 (61)	51 (67)	0.55
6 or 7 yr after discontinuation of assigned therapy	64 (88)	62 (83)	66 (87)	0.37
Forced expiratory volume — % of predicted				
At end of 3 or 4 yr of assigned therapy‡	75.5±19.6	84.8±24.0	75.7±26.0	0.04
6 or 7 yr after discontinuation of prednisone therapy§	71.0±24.3	71.3±27.4	65.9±24.1	0.51
Forced vital capacity — % of predicted				
At end of 3 or 4 yr of assigned therapy‡	86.9±17.2	94.8±20.0	86.7±22.0	0.03
6 or 7 yr after discontinuation of assigned therapy§	83.7±22.2	85.6±25.0	80.7±22.9	0.58

*Plus-minus values are means ±SD. The trial of high-dose prednisone was terminated after three years (in 1990), and the trial of low-dose prednisone was terminated after four years (in 1991). Therefore, up to 1997, the low-dose and high-dose groups had six and seven years, respectively, of follow-up after the discontinuation of prednisone therapy.

†We determined P values by one-way analysis of variance for continuous outcomes, by chi-square test for proportions, and by survival analysis using the log-rank test for the number of deaths.

‡Data were available for 61 children in the placebo group, 67 children in the low-dose group, and 53 children in the high-dose group.

§Data were available for 40 children in the placebo group, 51 children in the low-dose group, and 48 children in the high-dose group.

after 18 years of age were 159.3±4.9 cm in the low-dose group (28th percentile, 20 patients), 159.8±6.7 cm in the high-dose group (33rd percentile, 23 patients), and 160.3±6.9 cm in the placebo group (35th percentile, 23 patients) (P=0.87). Mean weights after 18 years of age were 49.6±7.6 kg in the low-dose group (25th percentile), 53.6±10.1 kg in the high-dose group (34th percentile), and 51.9±7.2 kg in the placebo group (29th percentile) (P=0.31).

Growth throughout the 10-Year Study Period

In both boys and girls, z scores for height declined while the children received prednisone but began to increase about two years after treatment was discontinued (Fig. 2). In boys, the continuous decline in z scores for height during prednisone therapy resulted from the fact that the height velocity in the prednisone groups was approximately 1 cm lower per year than that in the placebo group. There was a sig-

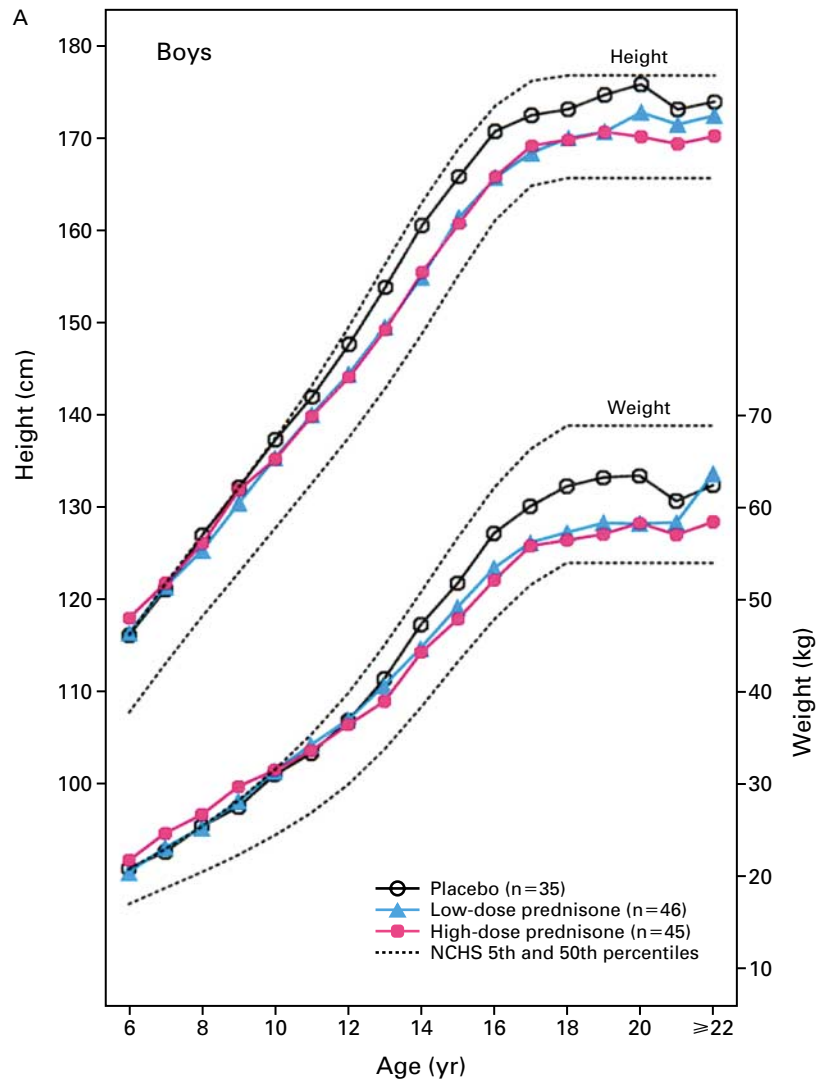


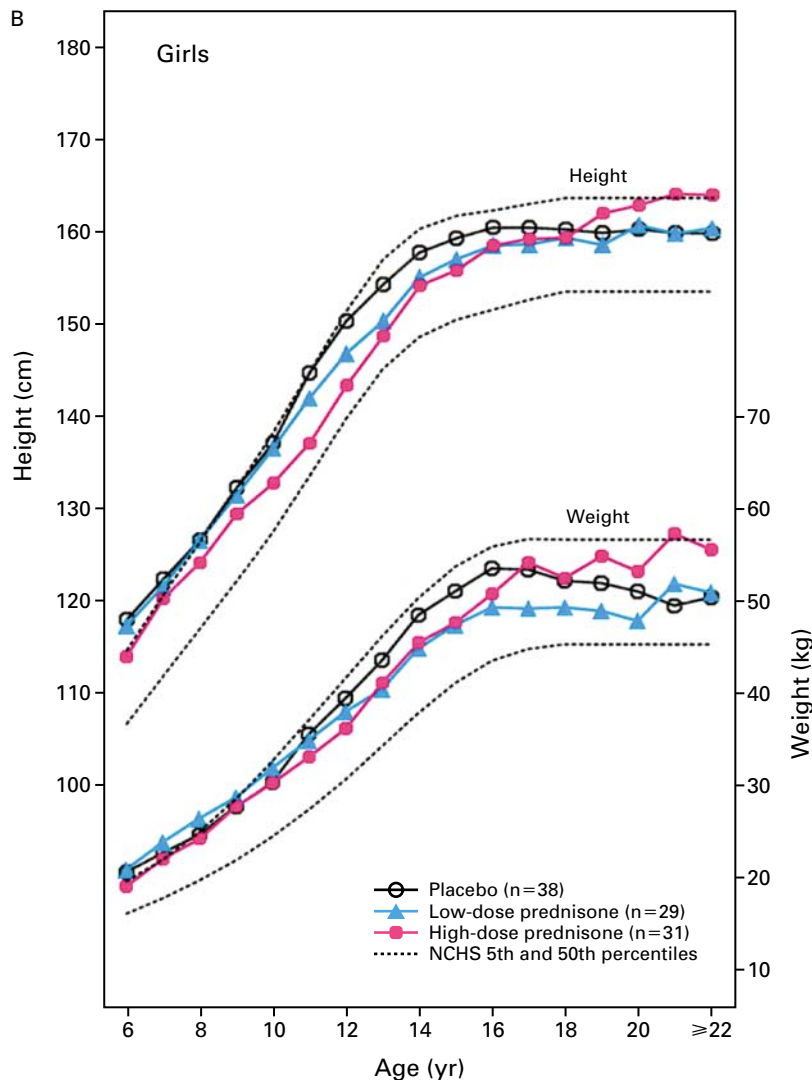
Figure 1. Relation of Height and Weight to Age in Boys (Panel A) and Girls (Panel B, Facing Page) with Cystic Fibrosis Who Received Placebo, Low-Dose Prednisone, or High-Dose Prednisone.

The low dose of prednisone was 1 mg per kilogram, and the high dose 2 mg per kilogram, each given on alternate days. Patients began prednisone therapy at a mean age of 9.5 years (range, 6 to 14) for a period of three or four years. Growth was followed from the beginning of prednisone therapy until six or seven years after therapy was discontinued. After 18 years of age, mean height and weight were significantly lower in boys treated with prednisone than in boys who received placebo ($P=0.03$ for height, and $P=0.01$ for weight). In girls, no significant differences among the groups were found in regard to height and weight after 18 years of age. NCHS denotes National Center for Health Statistics.

nificant difference according to sex in terms of catch-up growth. In boys, the z scores for height remained significantly lower in the two prednisone groups than in the placebo group after 10 years of follow-up ($P=0.03$). In addition, we found that the younger the boy was at the start of prednisone therapy, the worse his z score for height was after prednisone therapy was discontinued. More specifically, boys who started taking prednisone at 6 to 8 years of age had declines of

z scores for height from base line that lasted for 10 years; boys who started taking prednisone at 8 to 12 years of age had catch-up gains in z scores for height beginning about 2 years after prednisone therapy was discontinued; and boys who started taking prednisone at 12 to 14 years of age maintained their baseline z scores for height.

The z scores for height in girls treated with prednisone returned to base-line values and were no longer



significantly lower than those of girls who received placebo beginning at seven years of follow-up ($P=0.26$) (Fig. 2). In addition, girls who started taking prednisone at younger ages did not have greater declines in z scores for height than girls who started at older ages.

Changes in Weight throughout the 10-Year Study Period

The z scores for weight in the children treated with prednisone increased significantly during prednisone therapy but declined to base-line values within one to two years after prednisone therapy was discontinued (Fig. 3). After 10 years of follow-up, z scores for weight in boys treated with high-dose prednisone were significantly lower than those in boys who received placebo ($P=0.04$). In girls, no significant differences among the three groups were found with regard to z scores for weight for the period after prednisone therapy was discontinued ($P=0.84$).

Growth after Adjustment for Pulmonary Status

Because prednisone therapy affects pulmonary function, which has been correlated with growth in patients with cystic fibrosis,^{25,26} we compared growth among the three groups while controlling for three indexes of pulmonary status: forced expiratory volume in one second (percentage of the predicted value), forced vital capacity (percentage of the predicted value), and the presence or absence of *P. aeruginosa* colonization. The negative association between the use of prednisone and the z score for height in boys after prednisone therapy was discontinued remained strong ($P<0.001$) after adjustment for the three variables. A change in P value from 0.003 to 0.006 was noted for the significance of prednisone therapy in predicting z scores for weight. None of the three indexes of pulmonary function correlated significantly with z scores for height ($P>0.12$). However, forced vital

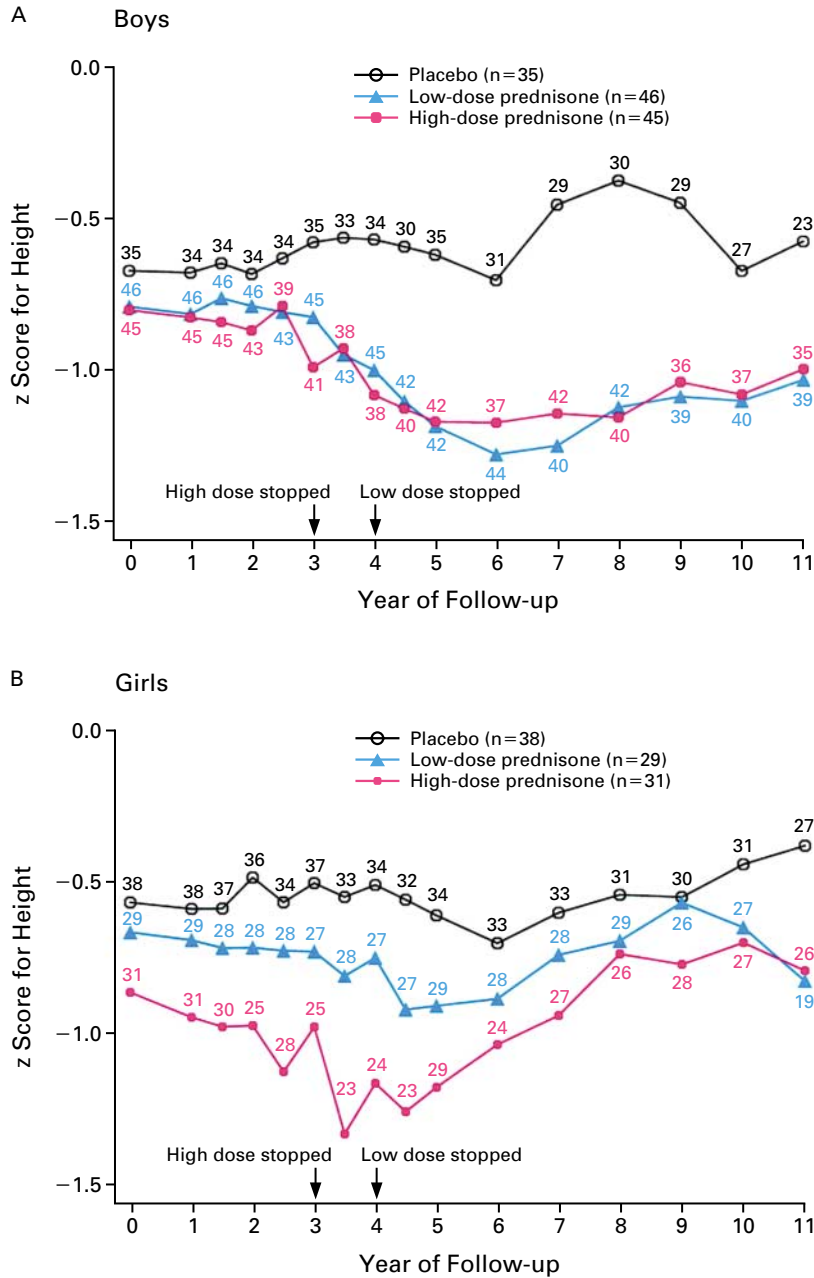


Figure 2. Relation of z Scores for Height to Years of Follow-up in Boys (Panel A) and Girls (Panel B) with Cystic Fibrosis Who Received Placebo, Low-Dose Prednisone, or High-Dose Prednisone.

The low dose of prednisone was 1 mg per kilogram, and the high dose 2 mg per kilogram. The number of subjects at each point of follow-up is indicated. Among the boys, z scores for height remained significantly lower after 10 years in those who received prednisone than in those who received placebo ($P=0.03$). Among the girls, no significant differences in z scores for height were found among treatment groups after six years ($P=0.26$). A z score of zero corresponds to the 50th percentile of the reference population. A z score of -1.0 indicates 1 SD below the mean, which corresponds approximately to the 15th percentile.

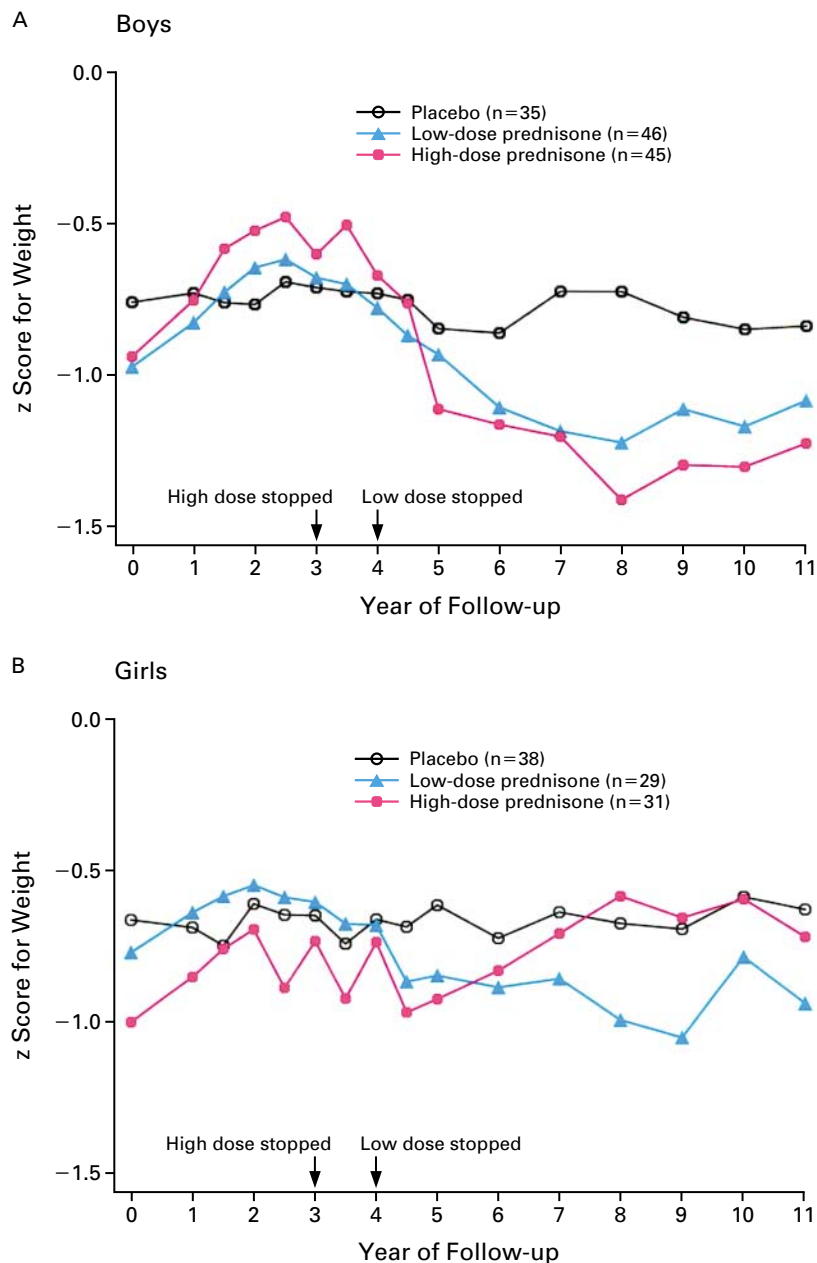


Figure 3. Relation of z Scores for Weight to Years of Follow-up in Boys (Panel A) and Girls (Panel B) with Cystic Fibrosis Who Received Placebo, Low-Dose Prednisone, or High-Dose Prednisone. The low dose of prednisone was 1 mg per kilogram, and the high dose 2 mg per kilogram. In both boys and girls, z scores for weight increased in response to prednisone therapy but declined to base-line values or below one to two years after prednisone therapy was discontinued. Among the boys, z scores for weight after 10 years of follow-up were significantly lower in those treated with high-dose prednisone than in those who received placebo (P=0.04). Among the girls, no significant differences among treatment groups in z scores for weight were found after prednisone therapy was discontinued (P=0.84). The numbers of subjects and an explanation of z scores are presented in Figure 2.

capacity (percentage of the predicted value) correlated positively with z scores for weight ($P=0.003$).

DISCUSSION

The suppression of growth in children as a result of glucocorticoid treatment is well documented.¹⁰⁻¹³ However, few studies have evaluated long-term growth and ultimate height after the discontinuation of treatment with glucocorticoids. Although anecdotal reports have suggested that catch-up growth may be complete, resulting in normal adult height, several controlled studies have indicated that growth deficits are not fully compensated.^{13,27,28} In a meta-analysis, long-term treatment with pharmacologic doses of prednisone was highly correlated with a significant reduction in final height.¹³ In our study, the height deficit that resulted from prednisone therapy in boys with cystic fibrosis persisted after the treatment was discontinued. The deficit was significant not only in comparison with height standards for normal children,¹⁸ but also in comparison, at the time of the last growth measurement, with the heights of children with cystic fibrosis who received placebo; the children in the placebo group, in turn, did not differ significantly from the children who received prednisone in terms of several disease-related characteristics (including genotype, use or nonuse of pancreatic enzymes, pulmonary function, and presence or absence of *P. aeruginosa* colonization). Therefore, these findings provide evidence that in boys, the shorter height attained after 18 years of age was due, at least in part, to the long-term use of prednisone and was not merely a consequence of the underlying disease. Girls who received prednisone reached heights and weights that were similar to those of girls who received placebo.

The differences between the sexes in the degree of growth suppression in response to glucocorticoid therapy in our study patients have also been noted in children with other disorders. Among children with asthma who were treated with inhaled glucocorticoids, reductions in growth rate were greater in boys than in girls.²⁹⁻³¹ This difference may be due to a normally more pronounced deceleration of growth rate in boys before puberty (which occurs later in boys than in girls), which renders them more susceptible to additional slowing of growth. In contrast, girls who are similar in age to those we studied appear to be less susceptible to growth suppression by glucocorticoids. This may be due to the higher secretion of growth hormone in girls during both prepubertal and pubertal years as well as to the earlier onset of the growth acceleration that coincides with puberty.³²

Furthermore, our finding of an association of earlier age at the onset of prednisone therapy with lower final height in boys with cystic fibrosis suggests that susceptibility to a reduction in adult height is associated with prepubertal exposure to glucocorticoids. One possible explanation is that puberty is further de-

layed by long-term treatment with prednisone, which results in a more prolonged decline in expected height. Once boys enter puberty, their growth is more resilient^{33,34} and thus less likely to be impaired by treatment with prednisone, allowing for some recovery in height.

The relation between age and the degree of growth suppression by prednisone may be confounded by other factors. For example, boys who began prednisone therapy at 6 to 8 years of age were 16 to 19 years old at their final follow-up, and it is not known whether their skeletal maturation had been completed. Therefore, further catch-up growth may occur, particularly in view of the multiple delaying effects of cystic fibrosis^{26,35} and long-term prednisone therapy on both puberty and bone maturation. It is also possible that boys who began prednisone therapy in adolescence (at 12 to 14 years of age) were less adherent than other patients to the treatment, a difference that would have reduced the effect of prednisone on growth suppression. An additional potential confounder is undocumented use of prednisone after the trial was terminated, which could have diminished catch-up growth. However, it is also possible that patients in the placebo group may have taken prednisone.

In summary, we found that the growth impairment caused by prolonged alternate-day treatment with prednisone in prepubertal boys with cystic fibrosis persisted after such treatment was discontinued and significantly reduced the height attained after 18 years of age. Both boys and girls gained a substantial amount of weight during prednisone therapy but rapidly lost weight after the treatment was discontinued. Because of these findings, along with the finding that the benefits of prednisone therapy in terms of pulmonary function were no longer present several months or years after prednisone therapy was discontinued, we conclude that prolonged prednisone therapy should not be used in children with cystic fibrosis. Although we did not study children with other chronic diseases, such children sometimes receive prolonged glucocorticoid therapy. Our data suggest that careful adjustment of treatment regimens to achieve the lowest effective dose and the shortest duration of therapy is important to minimizing the risk of permanent growth impairment, particularly in boys.

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