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Long-Term Budesonide or Nedocromil Treatment, Once Discontinued, Does Not Alter the Course of Mild to Moderate Asthma in Children and Adolescents

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Abstract

Objectives—To determine whether long-term, continuous use of inhaled anti-inflammatory medications affects asthma outcomes in children with mild-moderate asthma after use is discontinued.

Study design—Of 1,041 participants in the Childhood Asthma Management Program randomized clinical trial, 941 (90%) were followed to determine whether 4.3 years of twice daily budesonide or nedocromil (each compared with placebo) affected subsequent asthma outcomes during a 4.8 year post-trial period in which treatment was managed by the participant's physician.

Results—The groups treated continuously during the trial with either budesonide or nedocromil did not differ from placebo in lung function, control of asthma, or psychological status at the end of 4.8 years of post-trial follow-up; however, the decreased mean height in the budesonide group relative to the placebo group at the end of the trial (1.1 cm, $P=0.005$) remained statistically significant (0.9 cm, $P=0.01$) after an additional 4.8 years and was more pronounced in girls (1.7 cm; $P=0.001$) than boys (0.3 cm; $P=0.49$). Participants used inhaled corticosteroids during 30% of the post-trial period in all groups.

Conclusions—Clinically meaningful improvements in control of asthma and improvements in airway responsiveness achieved during continuous treatment with inhaled corticosteroids do not persist after continuous treatment is discontinued.

Asthma is a disease of chronic airway inflammation characterized by reversible airway obstruction and increased airway responsiveness^{1, 2}. Inhaled anti-inflammatory therapy improves control of asthma symptoms and pulmonary function^{1, 3, 4}. Inhaled corticosteroids (ICS) have been shown to be the most effective form of anti-inflammatory therapy, with benefits for periods of more than one year seen in controlled clinical trials^{5, 6}. The Childhood Asthma Management Program (CAMP) was a randomized clinical trial comparing 3 treatments for mild to moderate asthma^{5, 7}. CAMP demonstrated that budesonide, 200 mcg *bid*, led to

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significantly lower airway responsiveness to methacholine, fewer hospitalizations, fewer urgent care visits, greater reduction in need for albuterol for symptoms, fewer courses of prednisone, and a smaller percentage of days on which additional asthma medications were needed, compared with placebo over a 4.3-year interval ⁵. CAMP also found that nedocromil, 8 mg *bid*, significantly reduced urgent care visits and courses of prednisone compared with placebo, but did not affect airway responsiveness, symptoms, or hospitalizations ⁵. Budesonide increased forced expiratory volume in one second (FEV₁) post bronchodilator in the first year of the trial, but neither budesonide nor nedocromil had an impact on this measure of lung function at end of the trial ⁵. Side effects of budesonide were limited to a small reduction in height, with no detrimental impact of either treatment documented on bone density, fracture rate, or psychological measures ⁵.

Although asthma control improved in the patients treated with anti-inflammatory medications during the 4.3 years of the CAMP trial, the long-term benefits and safety of these medications, particularly ICS, remained to be determined. Therefore, patients enrolled in CAMP were re-enrolled in an observational post-trial follow-up study to determine whether the 4.3 years of regular anti-inflammatory treatment once discontinued influenced asthma control, pulmonary function as measured by pre and post bronchodilator spirometry, airway lability, physical growth, bone density, and psychological status.

Methods

Children age 5 to 12 years, with mild to moderate asthma, defined by the presence of symptoms or by the use of an inhaled bronchodilator at least twice weekly or the use of daily medication for asthma, enrolled in the CAMP trial between December 1993 and September 1995 ⁷. At the time of enrollment in the trial, the children's airway responsiveness to methacholine, as indicated by the concentration of the drug that caused a 20 percent decrease in the FEV₁, was 12.5 mg/mL or less ⁷.

Follow up after study medication discontinuation

At the end of the CAMP trial, study medication (budesonide Turbuhaler® 200 mcg *bid* or nedocromil 8 mg *bid* versus matching placebos) was discontinued, and participants were followed by the CAMP investigators during a washout period over 8 calendar months (March 1999 through October 1999). Although the goal was to treat all patients with albuterol alone during the washout period, patients who were using open label asthma medications in addition to the study medication continued on those medications and patients whose asthma was judged too severe to tolerate albuterol alone were prescribed open label asthma medication according to National Asthma Education and Prevention Program (NAEPP) guidelines. Each participant was seen twice during the washout period, once for a methacholine challenge and once for pre and post bronchodilator spirometry. Initiation of medication for asthma, prednisone use, urgent care use and hospitalizations were reported by participants or parents to clinic staff during the washout period. At the end of the washout period, participants were invited to enroll in a 4.5-year post-trial follow-up study, during which care was advised based on NAEPP guidelines ^{1, 8} in communications to the primary care physicians. Each participant's parent or guardian signed a written informed consent approved by the local institutional review board, with re-consent of the participants themselves at age 18 years.

During the post-trial follow-up study initiated in November 1999, participants were seen twice yearly in a CAMP clinic and were interviewed by telephone twice yearly (between clinic visits).

One clinic visit each year included pre and post bronchodilator spirometry; this visit was timed to occur at the participant's randomization anniversary. The second annual visit included pre bronchodilator spirometry and a methacholine challenge (a challenge was not performed within

28 days of an upper respiratory tract infection or the use of prednisone for exacerbation of asthma) and was timed to occur about six months from the participant's randomization anniversary. At each visit, the study coordinator queried the participant (or parents, depending on the participant's age) about health history since the previous contact, reviewed medicines used for asthma in the past seven days, and queried the number of courses of oral corticosteroids used since the last contact. Height (measured with a Harpenden stadiometer) and weight were measured at each visit. Sexual maturation was assessed by Tanner staging annually until the age of 18 years, or until Tanner stage 5 in all parameters was measured on 2 consecutive examinations.

The telephone interviews used the same interim health history and medication use questionnaire used at the twice yearly clinic visits, for a total of 4 interviews per year. Medication use in the past 7 days was assumed to represent use in the 3 months since the last contact.

Bone density (total bone mineral density of the spine from L1 to L4, BMD, g/cm²) was measured 7 and 9 years after randomization it by DEXA using a Hologic or Lunar scanner with either a fan or pencil beam. The Lunar measures were standardized to the Hologic measures by the equation: Hologic BMD = 0.885 × Lunar BMD¹⁰. As patients grow taller, the pencil and fan beam values deviate from one another, requiring further correction¹⁰. Pencil beam values for participants 1.4 m or greater in height were standardized to fan beam values by the equation: fan beam BMD = pencil beam BMD + 0.0549¹¹. These corrections were sufficient to pool Hologic and Lunar values, except in the case of Lunar values from the Denver clinic; no amount of adjustment allowed pooling those values with the others.

The Child Behavior Checklist¹² was completed annually by a parent for participants less than 18 years. The Pediatric Asthma Quality of Life questionnaire¹³ was completed annually by participants.

Information obtained during each visit, including spirometry, symptoms, and medication requirements, was used to recommend treatment in accordance with the NAEPP Guidelines^{1, 8} in a letter to the participant's primary care provider after each clinic visit.

Statistical analysis

The outcome measures and statistical methods parallel the measures and methods used in the primary results paper 5, but with outcome measures defined during the 4.8 years of post-trial follow-up after discontinuation of continuous use of study medication according to the trial protocol. Each participant was included in the treatment group assigned at randomization, regardless of the course of subsequent treatment for asthma (intention-to-treat analysis). The mean differences between the budesonide or nedocromil group and the placebo group in age, duration of follow-up, and percentage of time on asthma treatments during the post-trial period were assessed using t-tests. Rates of morbidity outcomes (prednisone courses, urgent care visits due to asthma, hospitalizations due to asthma, and fractures) during the post-trial period were calculated as the number of outcome events occurring during the post-trial period divided by the number of person-years of post-trial follow-up. Relative risks (RR) of each morbid outcome, comparing the budesonide or nedocromil group to the placebo group, were calculated using multivariable Poisson regression with an offset for the person-years of follow-up¹⁴. Differences in means of continuous outcomes, comparing the budesonide or nedocromil group to the placebo group, measured at the end of the post-trial period (pre and post bronchodilator lung function measures, airway lability measures, physical growth measures, psychological measures, and quality of life measures) were determined from multivariable linear regression models for each continuous outcome. The multivariable Poisson and linear regression models included two binary variables to indicate the budesonide or nedocromil treatment groups and

the following eight covariates: the value of the outcome measure at randomization (continuous outcomes only), the child's age at randomization, race or ethnic group (African American, Hispanic, or other; two indicator variables), sex, clinic (seven indicator variables), duration of asthma at randomization (at least 7 years, less than 3 years, or other; two indicator variables), severity of asthma at randomization (moderate vs. mild), and skin test reactivity at randomization (any reactivity vs. none). Adjusted means for each continuous post-trial outcome measure in each treatment group were derived from the regression model using mean values for all covariates except treatment group indicators 15. The statistical significance of differential treatment effects on height in males and females, comparing the budesonide or nedocromil group to the placebo group, was assessed by adding a sex by treatment group interaction term to the multivariable regression model for post-trial mean height. Adjusted mean values for each measure of morbidity, lung function after the use of a bronchodilator, and bronchodilator reversibility during 9 years of follow-up after randomization to the budesonide, nedocromil or placebo groups were derived from the regression model using mean values for all covariates except treatment group indicators and replacing the treatment group indicators with indicator variables for each treatment by follow-up assessment time combination.

The P-values presented for all analyses are two-sided and have not been adjusted for multiple comparisons. The multivariable Poisson regression analyses were performed using Stata Statistical Software (Release 9; StataCorp LP, College Station, TX); all other analyses were performed with SAS software (Version 6.12; SAS Institute, Inc., Cary, N.C.).

Results

Study population and completion of follow-up

Ninety percent of the original CAMP cohort (941 of 1041) enrolled in the post-trial follow-up study. The enrollees were similar to the non-enrollees except with respect to clinic; percentage of participants at a clinic enrolling ranged from 78% to 99% ($P<0.001$; Table_[H2] I; available at www.jpeds.com). Despite 10% non enrollment across the original cohort, the participants in the budesonide, nedocromil, and placebo groups who enrolled in the follow-up study were similar with respect to characteristics at CAMP randomization (Table II; available at www.jpeds.com). At the end of the post-trial follow-up period, age and duration of follow-up were similar in the three groups (Table III; available at www.jpeds.com). The percent of scheduled visits completed during the post-trial follow-up period was greater than 96% in each of the three groups. Mean duration of follow-up in the post-trial period was 4.8 ± 0.5 years.

Treatment for asthma during the post-trial follow-up period

Treatment for asthma reported by the participants in the post-trial follow-up period was similar in the budesonide, nedocromil, and placebo groups (Table III). The mean percentage of time on ICS was approximately 30% in each group. The mean percentage of time not using any medication for asthma was 42%-45% in the three groups.

Asthma morbidity

During the post-trial follow-up period, the budesonide group had 29% fewer prednisone courses ($P=0.05$) and 36% fewer urgent care visits ($P=0.05$) compared with the placebo group (Table III and Figure); however, 15 and 32 participants, respectively, would need to be treated with budesonide regularly for 4.3 years to prevent one prednisone course per year and one urgent care visit per year after discontinuation of treatment.

Prednisone courses and urgent care visits in the nedocromil group were not significantly different than in the placebo group (Table III and Figure). Twenty-six and 59 participants would

need to be treated with nedocromil regularly for 4.3 years to prevent one prednisone course per year or one urgent care visit per year after discontinuation.

Spirometry

There were no differences between either the budesonide or nedocromil group and the placebo group in FEV₁ % of predicted or forced vital capacity (FVC) % of predicted both before and after bronchodilator at end of post-trial follow-up (Table III and Figure). FEV₁/FVC was significantly higher in the nedocromil group before (P=0.02), but not after (P=0.06) bronchodilator, compared with the placebo group.

Airway lability

There were no differences between either the budesonide or nedocromil group and placebo in bronchodilator reversibility at the end of post-trial follow-up (Table III). Methacholine responsiveness in the budesonide group returned to placebo level by the end of washout⁵ and remained similar to placebo at the end of the post-trial follow-up (Table III). There was no difference between nedocromil and placebo in methacholine responsiveness.

Possible side effects of medications

The statistically significant decreased height in the budesonide group relative to the placebo group observed at the end of the trial (1.1 cm, P=0.005) persisted with a decrease of 0.9 cm (P=0.01) at end of post-trial follow-up. The decrease in height was observed for girls (1.7 cm, P=0.001), but not for boys (0.3 cm, P=0.49; interaction P=0.03). Twenty-five percent of girls and 54% of boys had not yet achieved adult height by the end of the post-trial follow-up. There were no differences during post-trial follow-up between either the budesonide or nedocromil group and placebo in rate of occurrence of fractures, development of sexual maturation, or any of the psychological or asthma-specific quality of life measures examined (Table III).

Discussion

Compared with placebo, regular use of budesonide, and to a limited extent nedocromil, improved clinical measures of asthma control during the 4.3-year CAMP treatment period⁵. However, after the study medications were discontinued and treatment was managed by the participants' primary care physicians, asthma morbidity, including prednisone courses and urgent care use, and asthma medication use were not appreciably affected by earlier long-term treatment with either medication. The reductions after study medication discontinuation of 29% for prednisone courses and 36% for urgent care visits in the budesonide group relative to the placebo group must be considered in the context of the very low levels of these events in all groups during the post-trial follow-up period (Figure). Furthermore, although the reductions in prednisone use and urgent care visits reached the 0.05 level of statistical significance, these reductions are probably not clinically relevant because 15 and 32 patients would have had to be treated with budesonide for 4.3 years to prevent 1 prednisone course or 1 urgent care visit per year, respectively, during the post-trial follow-up. In contrast, only 2 and 10 patients needed to be treated with budesonide to prevent 1 prednisone course per year or urgent care visit per year, respectively, during treatment in the CAMP clinical trial⁵. Perception of symptoms and activity restrictions were similar across all three groups during the post-trial follow-up (Table III).

Characterizing the treatment regimen subsequent to the CAMP trial as a discontinuation of regular treatment is supported by the reduction in ICS use in the budesonide group during the post-trial compared with the trial (31.3% of time during the post-trial versus 96.8% of time during the trial), the similar proportion of post-trial follow-up time on ICS in all three groups, the low rate of use of nedocromil across all three groups (less than 1% of time in all groups,

and the similar proportion of follow-up time not using asthma medication across all three groups (Table III).

During treatment in the CAMP trial, regular use of budesonide improved significantly pre-bronchodilator, but not post-bronchodilator, FEV₁ and FEV₁/FVC, compared with placebo; these effects were not seen in the nedocromil group during the CAMP trial⁵. At the end of the post-trial follow-up, participants treated earlier with budesonide or nedocromil did not have improvement in any parameter of lung function, except a small but significant 1.4% higher pre bronchodilator FEV₁/FVC percent at the end of follow-up achieved in the nedocromil group compared with placebo. Given that there was no effect of nedocromil on either pre- or post-bronchodilator FEV₁/FVC during active treatment, the effect of nedocromil on pre-bronchodilator FEV₁/FVC seen at the end of the post-trial follow-up is likely spurious.

The reductions in prednisone courses and urgent care visit rates that occurred as the participants were followed from mean age 8.9 years to mean age 18.1 years (Figure) are a particularly notable finding of the study. These reductions are consistent with the known improvement in clinical course that occurs as children become adolescents¹⁶. The reductions could have also been related in part to a reluctance of the treating physicians to prescribe prednisone during acute exacerbations compared with the protocol-mandated use of prednisone for exacerbations during the trial. The reductions are unlikely to be due to an incomplete collection of data, as there were four contacts each year (two clinic visits and two telephone visits) with careful questioning about prednisone use and urgent care at each contact.

The inability of long-term treatment with either an ICS or mast cell stabilizer to modify the course of asthma after their discontinuation was observed against the background of the overall decrease in asthma morbidity. Results of regular treatment with anti-inflammatory medication, especially ICS, were most noticeably different from placebo early during the course of the trial when symptoms and morbidity were most apparent. In the second year of regular treatment, the effects on spirometry began to wane, and by the end of the trial, levels returned toward those seen in the placebo group (Figure). Outcomes of bronchodilator reversibility, annual prednisone course rate, and annual urgent care visit rate in the ICS-treated group were returning toward placebo levels by the end of the trial, but were still different at that point (Figure). Return toward placebo levels during the trial is unlikely to be due to reductions or discontinuation of use of ICS, as the difference in methacholine responsiveness between the ICS and placebo groups persisted throughout the trial, with rapid return of responsiveness in ICS-treated participants to placebo levels within 0.3 years after discontinuation⁵.

The data obtained during the CAMP trial support the current guidelines recommending regular treatment with ICS for patients with at least mild persistent asthma⁴. At the end of the first year of treatment, symptoms, exacerbations, airway responsiveness, and FEV₁ were all improved⁵. At the end of 4-6 years of treatment, symptoms, exacerbations, and airway responsiveness were still improved, but FEV₁ had returned to levels seen in placebo-treated participants⁵. These results are similar to other studies of long-term ICS treatment in young children with recurrent wheeze¹⁷, school age children with moderate asthma¹⁸, and school age children and adults with recent onset asthma^{6,19}.

The follow-up of the CAMP participants after discontinuation of regular anti-inflammatory medication indicates that continued benefit of these medications likely requires continued use. This is similar to studies of young children with recurrent wheeze treated with ICS for 2 years¹⁷ and school age children with asthma treated with ICS for 28-36 months²⁰, where discontinuation of ICS was associated with a return to placebo levels for episode days and exacerbations requiring oral steroids¹⁷ and increases in symptoms, additional bronchodilator

use, and airway responsiveness²⁰ within several months, suggesting no long-term effect of treatment.

Questions remain about the long-term safety of inhaled anti-inflammatory agents, especially ICS. Results obtained during the 4.3 years of regular treatment with budesonide revealed a small decrease in height of 1.1 cm compared with placebo. At the last visit of the post-trial follow-up (mean time since randomization of 9.1 years) the reduction in growth in the budesonide group relative to placebo was less, but still observed at 0.9 cm ($P=0.01$). This decrease in height was observed only in girls. It should be noted, however, that 25% of girls and 54% of boys still had not achieved final adult height at the end of the post-trial period. These findings are in contrast to those of Tinkelman et al²¹, who observed more pronounced growth suppression in boys than girls treated with beclomethasone, but treatment was only for one year. There were no effects of nedocromil treatment on growth. There were no differences between either budesonide or nedocromil compared with placebo in bone density, fracture rate, and psychological status, or asthma specific quality of life at the end of the post-trial period.

Ninety percent of the participants in the CAMP trial enrolled in the post-trial follow-up study. Despite differential enrollment among clinics, the participants in the follow-up study were similar at CAMP trial baseline to those who did not enroll. Therefore the results of the follow-up study are not biased by incomplete enrollment.

Budesonide, 200 mcg *bid*, and considerably less so nedocromil, 8 mg *bid*, improved multiple dimensions of asthma control compared with placebo in children with mild to moderate asthma during the CAMP trial. However, neither treatment had a clinically meaningful modifying effect on the course of asthma (clinical course, pulmonary function, or airway lability) during follow-up after regular use was discontinued and the participants were cared for by their primary care physician with recommendations based on NAEPP Guidelines. Inhaled corticosteroids at doses used in the CAMP trial are generally safe and effective medications to control asthma for the long-term, but do have a small and significant effect on growth, and do not have a durable effect on the course of asthma once continuous treatment stops. Selection of patients who would experience long-term benefit from regular use of anti-inflammatory medications is an ongoing clinical challenge that will likely require determination of individual asthma/allergy phenotypes and/or genotypes along with factors such as age, ongoing symptoms, and recent morbidity.

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List of abbreviations

CAMP	Childhood Asthma Management Program
ICS	Inhaled corticosteroid
FEV ₁	Forced expiratory volume in one second
NAEPP	National Asthma Education and Prevention Program
FVC	Forced Vital Capacity

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Figure.

Mean values for measures of morbidity, lung function after the use of a bronchodilator, and bronchodilator reversibility during 9 years of follow-up after randomization to the budesonide, nedocromil, and placebo groups: A, Annual prednisone course rate; B, Annual urgent care visit rate; C, Post bronchodilator FEV₁ % of predicted; D, Post bronchodilator FVC % of predicted; E, Post bronchodilator FEV₁/FVC; F, Bronchodilator reversibility. All data to the left of the vertical line on each graph were obtained during the trial when participants were treated regularly with budesonide 200 mcg *bid*, nedocromil 4 mg *bid*, or placebo. All data to the right of the vertical line on each graph were obtained during the post-trial follow-up period after regular treatment with study medications was discontinued.

Table 1

Comparison of non enrollees to enrollees in the post-trial follow-up study, as of entry into the CAMP trial

	N	Non-enrollees (N=99)*	Enrollees (N=941)	P†
Total	1040*	9.5%	90.5%	
Treatment group in CAMP trial				
Budesonide	311	27.3%	30.2%	0.55
Nedocromil	311	34.3%	29.4%	
Placebo budesonide	208	22.2%	19.8%	
Placebo nedocromil	210	16.2%	20.6%	
Clinic				
Albuquerque	121	16.2%	11.2%	<0.001
Baltimore	128	3.0%	13.3%	
Boston	124	9.1%	12.2%	
Denver	143	32.3%	11.8%	
San Diego	122	12.1%	11.7%	
Seattle	144	14.1%	13.8%	
St Louis	133	2.0%	13.9%	
Toronto	125	11.1%	12.1%	
Age at randomization (yrs)				
5-6	233	20.2%	22.6%	0.16
7-9	456	37.4%	44.5%	
10-13	351	42.4%	32.8%	
Race or ethnic group				
White or other	804	79.8%	77.1%	0.09
Black	138	7.1%	13.9%	
Hispanic	98	13.1%	9.0%	
Sex				
Female	419	45.5%	39.7%	0.28
Male	621	54.5%	60.3%	
Severity of asthma				
Mild	498	48.5%	47.8%	0.90
Moderate	542	51.5%	52.2%	
FEV ₁ % of predicted‡				
Pre bronchodilator	--	98.8 ± 18.0	97.2 ± 17.2	0.38
Post bronchodilator	--	108.3 ± 16.1	106.8 ± 16.3	
FVC % of predicted‡				
Pre bronchodilator	--	106.5 ± 15.2	104.2 ± 14.4	0.14
Post bronchodilator	--	110.1 ± 15.0	106.6 ± 13.8	
FEV ₁ /FVC (%)				
Pre bronchodilator	--	80.2 ± 8.6	79.7 ± 8.3	0.53
Post bronchodilator	--	85.1 ± 6.7	85.5 ± 6.5	

	N	Non-enrollees (N=99)*	Enrollees (N=941)	P†
Duration of since doctor diagnosis of asthma				
Less than 3 years	264	29.3%	25.1%	0.04
At least 3 but less than 7 years	519	38.4%	51.4%	
At least 7 years	251	32.3%	23.4%	
Enrollment cohort				
Dec 1993 - Jun 1994	235	32.3%	21.6%	0.09
Jul - Dec 1994	373	30.3%	36.5%	
Jan - Jun 1995	368	33.3%	35.6%	
Jul - Sep 1995	64	4.0%	6.4%	

Plus - minus values are means $\pm$ SD. Not all percentages add to 100 because of rounding. FEV₁ = forced expiratory volume in one second. FVC = forced vital capacity.

* Excludes participant who died during CAMP trial.

† P value for homogeneity among groups.

‡ Predicted values were obtained from Hankinson et al, 1999.

Table 2

Characteristics of participants in the post-trial follow-up study as of entry into the CAMP trial (N=941), by treatment group in the CAMP trial

	Treatment group in CAMP trial:		
	Bud (N=284)	Ned (N=277)	Plbo (N=380)
Age at randomization – yrs	9.0 ± 2.0	8.8 ± 2.1	8.9 ± 2.2
Race or ethnic group – no. (%)			
Non Hispanic white	186 (65.5)	197 (71.1)	266 (70.0)
Non Hispanic black	44 (15.5)	33 (11.9)	54 (14.2)
Hispanic	29 (10.2)	24 (8.7)	32 (8.4)
Other	25 (8.8)	23 (8.3)	28 (7.4)
Sex – no. (%)			
Female	115 (40.5)	95 (34.3)	164 (43.2)
Male	169 (59.5)	182 (65.7)	216 (56.8)
Age at onset of asthma symptoms – yrs	3.1 ± 2.3	3.1 ± 2.4	3.0 ± 2.5
Time since doctor diagnosis of asthma – yrs	5.2 ± 2.5	5.0 ± 2.6	5.0 ± 2.7
Treatments in 6 mos before enrollment – no. of patients (%)			
Cromolyn or nedocromil	125 (44.0)	135 (48.7)	154 (40.5)
Inhaled corticosteroid	116 (41.4)	103 (37.3)	139 (36.8)
Oral corticosteroid	98 (34.9)	88 (31.9)	149 (39.3)
Severity of asthma – no. (%)			
Mild	134 (47.2)	134 (48.4)	182 (47.9)
Moderate	150 (52.8)	143 (51.6)	198 (52.1)
Hospitalizations for asthma in year before enrollment – no./100 person-years	7.0	5.1	6.8
Recordings on daily diary card			
Episode-free days* – no./mo	9.5 ± 7.5	9.4 ± 7.6	9.3 ± 7.2
Use of albuterol for symptoms – puffs/wk	10.6 ± 9.9	10.6 ± 9.8	10.2 ± 9.7
Night awakenings – no./mo	0.9 ± 1.7	1.0 ± 1.8	0.8 ± 1.5
Days with symptoms interfering with daily activity – no./mo	2.4 ± 4.5	2.2 ± 3.3	1.9 ± 2.9
Pre bronchodilator lung function			
FEV ₁ % of predicted [†]	96.6 ± 16.8	97.2 ± 17.4	97.7 ± 17.4
FVC % of predicted [†]	104.1 ± 14.1	104.1 ± 14.2	104.3 ± 14.8
FEV ₁ /FVC (%)	79.4 ± 8.3	79.4 ± 7.9	80.1 ± 8.7
Post bronchodilator lung function			
FEV ₁ % of predicted [†]	106.3 ± 16.2	106.6 ± 16.3	107.3 ± 16.4
FVC % of predicted [†]	106.6 ± 14.0	106.3 ± 13.4	106.8 ± 14.0
FEV ₁ /FVC (%)	85.4 ± 6.5	85.3 ± 6.3	85.8 ± 6.7
Airway lability			
Bronchodilator reversibility – % [§]	11.0 ± 10.1	10.4 ± 9.9	10.7 ± 10.0
FEV ₁ PC ₂₀ methacholine – mg/ml [¶]	1.08 ± 3.22	1.12 ± 3.31	1.06 ± 3.13
Physical growth			

	Treatment group in CAMP trial:		
	Bud (N=284)	Ned (N=277)	Plbo (N=380)
Females			
Height (cm)	134.8 ± 13.6	132.4 ± 13.8	133.5 ± 13.3
Tanner breast stage			
1 – no. (%)	80 (69.6)	71 (74.7)	114 (69.5)
2 or higher – no. (%)	35 (30.4)	24 (25.3)	50 (30.5)
N	115	95	164
Bone density (g/cm ²)**	0.68 ± 0.12	0.66 ± 0.13	0.65 ± 0.10
N	98	84	141
Males			
Height (cm)	134.0 ± 13.0	133.1 ± 14.0	133.1 ± 14.5
Tanner genital stage			
1 – no. (%)	122 (73.1)	131 (72.8)	165 (76.7)
2 or higher – no. (%)	45 (26.6)	49 (26.9)	50 (23.1)
N	169	182	216
Bone density (g/cm ²)**	0.65 ± 0.10	0.63 ± 0.09	0.64 ± 0.09
N	151	162	192
Overall			
Height (cm)	134.3 ± 13.2	132.8 ± 13.9	133.3 ± 14.0
Bone density (g/cm ²)**	0.66 ± 0.11	0.64 ± 0.10	0.64 ± 0.09
N	249	246	333
Child Behavior Checklist ^{//} questionnaire			
Total problem T-score	50.9 ± 10.6	51.2 ± 10.0	51.7 ± 9.7
Externalizing T-score	49.5 ± 9.8	50.0 ± 9.2	50.4 ± 9.3
Internalizing T-score	52.5 ± 10.2	52.6 ± 10.2	53.0 ± 10.0

Bud = budesonide, Ned = nedocromil, Plbo = Placebo.

Plus - minus values are means ± SD. FEV₁ denotes the forced expiratory volume in one second and FEV₁PC₂₀ denotes the concentration of methacholine that caused a 20 percent decrease in FEV₁.

Note: P value for homogeneity among groups > 0.05 for each characteristic in the table.

* An episode-free day is defined as a day with no night awakenings, albuterol, prednisone, school absence, or physician contact due to asthma; morning and evening peak flow ≥ 80% of personal best; and no episode of wheezing, coughing, chest tightness, or shortness of breath.

[†] Predicted values were obtained from Hankinson et al, 1999.

[§] ((Post bronchodilator value – Pre bronchodilator value)/pre bronchodilator value) × 100.

[¶] Values are geometric means ± SD.

** Bone density means do not include patients enrolled at Denver due to incompatibilities with scanner values from other CAMP sites.

^{//} The Child Behavior Checklist is a 118 item questionnaire completed by the parent about the child age 17 or less. The total problem score (range 1-100) produces a composite index of behavior problems, the externalizing T-score (range 1-100) measures fearful, shy, anxious, and inhibited behavior, and the internalizing T-score (range 1-100) measures aggressive, antisocial, and under-controlled behavior.

Age, follow-up, asthma treatment, morbidity, lung function, airway lability, physical growth, psychological measures, and quality of life measures of participants in the post-trial follow-up study, by treatment group in the CAMP trial

Table III

	Treatment group in CAMP trial			P	
	Bud (N=284)	Ned (N=277)	Plbo (N=380)	Bud vs Plbo	Ned vs Plbo
<i>Age and follow-up</i>					
Age at end of trial	13.4	13.2	13.3	0.60	0.33
Age at end of post-trial (yrs)	18.2	18.0	18.2	0.61	0.54
Duration of post-trial (yrs)	4.8	4.9	4.8	0.89	0.02
% of scheduled visits completed during post-trial	96.3%	98.3%	96.8%	0.54	0.04
<i>Asthma treatment</i>					
% of time on ICS during trial	96.8%	14.1%	18.0%	<0.001	0.09
% of time on ICS post-trial	31.3%	30.9%	30.2%	0.69	0.80
% of time on nedocromil during trial	0.13%	94.5%	0.03%	0.37	<0.001
% of time on nedocromil post-trial	0.04%	0.90%	0.07%	0.75	0.007
% of time on long acting bronchodilator post-trial	12.3%	16.5%	16.5%	0.05	>0.99
% of time on leukotriene modifier post-trial	14.5%	13.3%	13.2%	0.53	0.93
% of time on albuterol only post-trial	20.5%	22.5%	21.7%	0.50	0.67
% of time not reporting any medication for asthma post-trial	45.2%	42.4%	45.4%	0.96	0.31
<i>Morbidity during post-trial</i>					
Prednisone courses for asthma					
Number	247	277	462		
Number/person-year [†]	0.17	0.19	0.23		
RR vs Plbo [†]	0.71	0.83	1.00	0.05	0.28
Urgent care visits due to asthma					
Number	96	109	203		
Number/person-year [†]	0.06	0.07	0.09		
RR vs Plbo [†]	0.64	0.81	1.00	0.05	0.33
Hospitalizations due to asthma					
Number	20	22	19		

	Treatment group in CAMP trial			P	
	Bud (N=284)	Ned (N=277)	Plbo (N=380)	Bud vs Plbo	Ned vs Plbo
Number/person-year [†]	0.008	0.010	0.006		
RR vs Plbo [†]	1.39	1.70	1.00	0.31	0.09
Fractures [§]					
Number	73	97	88		
Number/person-year [†]	0.052	0.066	0.046		
RR vs Plbo [†]	1.12	1.42	1.00	0.56	0.04
<i>Pre bronchodilator lung function at end of post-trial ¶</i>					
FEV ₁ % of predicted [¶]	93.7	93.5	92.7	0.25	0.35
FVC % of predicted [¶]	103.5	102.2	103.2	0.75	0.18
FEV ₁ /FVC (%)	78.3	79.1	77.7	0.28	0.02
<i>Post bronchodilator lung function at end of post-trial ¶</i>					
FEV ₁ % of predicted [¶]	100.1	100.2	99.3	0.31	0.28
FVC % of predicted [¶]	104.0	103.7	104.0	0.93	0.66
FEV ₁ /FVC (%)	83.2	83.5	82.6	0.21	0.06
<i>Airway lability at end of post-trial ¶</i>					
Bronchodilator reversibility (%) ^{***}	7.3	8.0	8.1	0.17	0.86
FEV ₁ PC ₂₀ methacholine (mg/ml) ^{††}	4.43	4.07	4.27	0.74	0.67
<i>Physical growth at end of post-trial ¶</i>					
Females					
Height (cm)	162.4	163.5	164.1	0.001	0.29
Tanner breast stage	4.8	4.8	4.8	0.92	0.39
N 115	95	164			
Bone density (g/cm ²) ^{‡‡}	1.06	1.05	1.05	0.45	0.81
N 98	84	141			
Males					
Height (cm)	175.2	175.9	175.5	0.49	0.39

	Treatment group in CAMP trial			P	
	Bud (N=284)	Ned (N=277)	Plbo (N=380)	Bud vs Plbo	Ned vs Plbo
Tanner genital stage (males)	4.8	4.8	4.8	0.17	0.60
N 169	182	216			
Bone density (g/cm ²) ^{†,‡}	1.02	1.01	1.02	0.75	0.80
N 151	162	192			
Overall					
Height (cm)	170.1	171.1	171.0	0.01	0.94
Interaction, females versus males				0.03	0.23
Bone density (g/cm ²) ^{†,‡}	1.03	1.03	1.03	0.59	0.94
<i>Psychological measures at end of post-trial ¶</i>					
Children=s Behavior Checklist					
Total problem T-score	42.5	43.3	42.6	0.89	0.59
Externalizing T-score	47.2	47.5	47.0	0.87	0.66
Internalizing T-score	47.6	47.6	47.7	0.92	0.93
<i>Quality of life measures at end of post-trial ¶</i>					
Pediatric Asthma Quality of Life Questionnaire					
Activity limitations domain score	6.2	6.3	6.3	0.33	0.70
Symptoms domain score	6.3	6.3	6.4	0.65	0.28
Emotional function domain score	6.7	6.7	6.7	0.72	0.97

The post-trial follow-up period began during March 1999-June 1999 when study medication was discontinued for each participant and ran through April 2004.

Bud = budesonide, Ned = nedocromil, Plbo = Placebo, RR = relative risk.

[†] Rate has been adjusted for age at randomization (continuous), race or ethnic group (African American, Hispanic, or other), gender, clinic, duration of asthma at randomization (less than 3 years, at least 7 years, or other), severity of asthma at randomization (moderate or mild), and skin test reactivity at randomization (any reactivity or none).

[‡] Defined as fractured, broken, or cracked bone.

[¶] Outcome (value at end of post-trial follow-up) has been adjusted for age at randomization (continuous), race/ethnicity (African American, Hispanic, or other; 2 indicator variables), sex, clinic (7 indicator variables), duration of asthma at randomization (less than 3 years, at least 7 years, other; 2 indicator variables), severity of asthma at randomization (moderate vs. mild), skin test reactivity at randomization (any reactivity vs none), and the value of the outcome measure at randomization (continuous). The Pediatric Asthma Quality of Life outcomes are not adjusted for the value of the outcome measure at randomization because the questionnaire was not obtained at randomization.

^{||} Predicted values were obtained from Hankinson et al.

*** [(Post BD value – pre BD values)/pre BD value] × 100.

^{††} Ratio of followup value to baseline value.

^{‡‡} Analyses do not include values for patients randomized at Denver due to incompatibilities with scanner values from other CAMP sites.