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Corticosteroid use and bone mineral accretion in children with asthma: effect modification by vitamin D

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Abstract

Background—The adverse effects of corticosteroids on bone mineral accretion (BMA) have been well documented. Vitamin D insufficiency, a prevalent condition in the pediatric population, has also been associated with decreased bone mineral density (BMD).

Objective—To determine whether children with asthma who have lower vitamin D levels are more susceptible to the negative effects of corticosteroids on BMD over time.

Methods—Children aged 5–12 years with mild-to-moderate asthma who participated in the Childhood Asthma Management Program were followed for a mean of 4.3 years. Total doses of inhaled and oral corticosteroids (OCS) were recorded, serum 25-hydroxyvitamin D3 levels were measured at the beginning of the trial and serial DEXA scans of the lumbar spine were performed. Annual BMA rates were defined as: [(BMD at 4 years follow-up − BMD at baseline)/4 years].

Results—BMA was calculated for 780 subjects. In boys, baseline vitamin D levels significantly modified the relationship between OCS and BMA (vitamin D x OCS interaction, p=0.023). Stratification by vitamin D levels showed a decrease in BMA with increased use of OCS in vitamin D insufficient boys only (p<0.001). Compared to vitamin D sufficient boys, vitamin D insufficient boys exposed to more than 2 courses of oral corticosteroids per year had twice the decrease in BMA rate (relative to boys who were OCS-unexposed).

Conclusions—Vitamin D levels significantly modified the effect of oral corticosteroids on bone mineral accretion in boys. Further research is needed to examine whether vitamin D supplementation in children with poorly controlled asthma may confer benefits to bone health.

Keywords

Asthma; vitamin D; bone mineral density; corticosteroids

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Introduction

Osteoporosis and osteopenia are diseases characterized by low bone mass, with osteopenia affecting 34.5 million individuals above the age of 50 years in the United States[1]. The consequential fractures are major causes of morbidity and high healthcare expenditures. Bone mineral mass is a key determinant of fracture risk and while the accretion of bone mass starts in the fetus, the skeletal system continues its development and maturation throughout childhood and adolescence. Since most of the skeletal mass is achieved before the end of the second decade of life[2], factors affecting bone mineral accretion (BMA), defined as the change in bone mineral density (BMD) over time, during this critical period may also affect bone mass and fracture risk later in life.

Vitamin D plays an essential role in bone metabolism. Its active form, 1,25-dihydroxyvitamin D, enhances bone mineralization by increasing intestinal calcium and phosphorus absorption and inducing osteoclast maturation[3]. An estimated 55% of the US population has a serum 25-hydroxyvitamin D level below 30 ng/ml, the usual cutoff for vitamin D insufficiency[4]. In the pediatric population, the association between severe vitamin D deficiency and rickets is well established. In addition, vitamin D insufficiency has been associated with low bone mass and bone mineral density[5].

The adverse effects of corticosteroids on bone health are also well recognized. In adults, corticosteroid use is associated with decreased bone mineral density[6]. In children, this causal relationship is more complex and additional factors need to be taken into account, such as sex, age, height, pubertal status and skeletal maturity[7]. In asthma, a condition affecting about 12.9% of the US population[8], the risk of adverse side effects from corticosteroid usage is of genuine concern, since inhaled corticosteroids (ICSs) are the most commonly prescribed medications for the long term control of asthma and oral corticosteroids are the therapy of choice for inflammatory control of acute asthma exacerbations[9]. We previously reported that oral corticosteroid (OCS) usage in children with asthma was associated with significant decrements in bone mineral accretion rates[10]; these effects were most dramatic in boys with high cumulative oral corticosteroid intake.

Given that both vitamin D insufficiency and corticosteroid usage may each have adverse effects on BMD, we hypothesized that children with lower vitamin D levels may be more susceptible to the negative effects of corticosteroids on BMD over time. To test this hypothesis, we analyzed the joint effects of vitamin D levels and corticosteroid dosing on BMA on subjects participating in the Childhood Asthma Management Program (CAMP).

Methods

Study population

The demographics of the subjects enrolled in CAMP and the study design have been described previously[11]. Briefly, 1,041 children with mild-to-moderate asthma aged 5 to 12 years were randomized to budesonide, nedocromil or placebo. This was a multi-center trial designed to evaluate the long-term effects of these treatments on lung growth. Follow-up visits occurred at two and four months after randomization and every four months thereafter. The children's parents or guardians provided informed consent and the study was approved by the local institutional review board. Subjects were followed for a mean of 4.3 years.

Serum 25-hydroxyvitamin D3

Serum levels of 25-hydroxyvitamin D3 (hereafter referred to as vitamin D) were measured at the beginning of the study for 1,024 patients (98% of enrolled subjects) using a

radioimmunoassay method[12, 13]. We categorized this measurement into insufficient (≤30 ng/mL) and sufficient (>30 ng/mL) based on previous recommendations[14] and consistent with our prior publications in this area[12, 15].

Bone mineral density

BMD measurements (g/cm^2) of the lumbar spine (L1–L4) were performed yearly during the study period and were described previously in detail[10]. Measurements were taken by dual energy x-ray absorptiometry (DEXA) using the Hologic (Waltham, MA) QDR-1500 at 6 centers or the Lunar (Madison, WI) DPX at 2 centers at the beginning of the study. Hologic DEXA machines were further divided by the use of pencil beam or fan beam measurements. In order to compare BMD measurements, Lunar measures were converted to Hologic values using the following equation: Hologic BMD = 0.885 × Lunar BMD[16]. Furthermore, the following adjustment was made to account for deviations between pencil and fan beam measurements: fan-beam BMD = pencil-beam BMD + 0.549 if height ≥ 1.40 m. Subjects from one study center were excluded because of the inability to standardize the initial DEXA values. Due to the lack of adequate BMD references for our population, yearly bone mineral accretion (BMA, g/cm^2/year) over the duration of the trial was chosen to be the primary outcome, consistent with our previous work[10]. BMA is a measure closely related to BMD and represents the average gain of BMD over time, hereby defined as [(BMD at 4 years follow-up − BMD at baseline)/4 years]. A 4-year follow-up was chosen because this approximated the end of the trial and the number of patients with a BMD measure was maximized at that time point. BMD z-scores were calculated using CAMP internal references[10].

Corticosteroid dosages

During the study period, patients were randomized to inhaled budesonide 200μg twice daily, nedocromil 8mg twice daily or placebo twice daily[11]. The use of beclomethasone dipropionate or other ICS was also allowed if the control of asthma was inadequate. For asthma exacerbations, short courses of oral prednisone were prescribed per protocol. Each burst consisted of 2 mg/kg per day up to 60 mg of prednisone for 2 days followed by 1 mg/kg per day up to 30 mg for 2 days. If there was insufficient improvement, an option to continue dosing was available. Dosage, duration and frequency of ICS and oral prednisone bursts were recorded at each follow-up visit.

For analysis purposes, three measures of corticosteroid exposure were examined: exposure to budesonide vs. nedocromil or placebo (intention-to-treat analysis), cumulative ICS and cumulative OCS. The cumulative ICS dose was divided into 3 categories: 0, >0–437, and ≥438 mg. The arbitrary cut point of 438 mg represents 3 years of full dosage of budesonide (400 μg/day) out of the 4 years of the study, consistent with our prior analysis[10]. The cumulative oral corticosteroid (OCS) dose was divided into 4 categories: 0, >0–4, >4–8, ≥9 bursts of 180 mg (60/60/30/30 mg/day as one burst for patients weighing at least 30 kg). We chose these cutoffs because over the follow-up period, this is equivalent to 0, ≤1, and >1 to 2 and >2 courses of OCS per year, a clinically meaningful measure of OCS use that is easy to interpret.

Statistical analysis

A descriptive analysis of baseline characteristics and univariate predictors was performed. When applicable, a chi-square test was used to compare proportions, a t-test to compare means and Wilcoxon rand sum test to compare medians. A Cochran-Armitage trend test was performed to compare Tanner stages between groups. Variables that were significantly associated with the outcome and one of the exposures at a $p<0.10$ were included in the multivariable model. Multiple linear regression models were constructed and the effect of

different steroid exposures on BMA was tested for effect modification by vitamin D levels via incorporation of a formal interaction term and confirmed through stratified analyses. For each steroid exposure, analyses were stratified by gender and vitamin D levels (≤30 ng/mL vs. >30 ng/mL). Using a total sample size of 780, there is an 80% power to detect a difference in BMA of 0.005 g/cm^2/year between the vitamin D insufficient and sufficient groups, at a significance level of 0.05. P values are 2-sided. All analyses were performed using R, version 2.12.1 (www.r-project.org).

Results

Patient demographics

From the 7 eligible study centers, a total of 780 subjects had a baseline vitamin D level and a BMD measurement at baseline and at 4 years follow-up. The subjects lost to follow-up had a lower BMI and higher vitamin D level compared to the study participants, but other demographics did not differ significantly, including the percent of randomization to budesonide (Table E1 in Online Repository). The median vitamin D level was 34.3 ng/mL (IQR 26.9, 45.6) and the median BMA was 0.041 g/cm^2/year (IQR 0.026, 0066). Baseline characteristics of the study population by vitamin D status are presented in Table I. The majority of subjects were at Tanner stage 1 (breast stage for girls and genital stage for boys) at the beginning of the trial. While there is a clear progression through the pubertal stages throughout the trial, there was a predominance of females in later pubertal stages (Tanner 3, 4, and 5) at 4 years follow-up (p=0.0001).

Effect of corticosteroids on BMA

There were 231 (29.6%) subjects randomized to the budesonide treatment arm and an additional 147 subjects from the other 2 treatment arms were exposed to any ICS, with a median cumulative ICS dose of 560 mg (IQR 295, 585). The majority of subjects received ≥438 mg (n=235) of which 92.8% were from the budesonide randomized arm. The majority of the subjects received OCSs during the trial, with a median cumulative OCS dose of 540 mg (IQR 205, 1064). Among those who received ≥5 bursts of OCS (≥1 course per year), the median number of bursts was 8.0. Univariate regression analysis showed that age, sex, height, BMI, Tanner stage, race, and baseline BMD to be significantly associated with BMA and one of the exposures. Therefore, all multivariable regression analyses were adjusted for these variables. Overall, randomization to budesonide (p=0.77) and cumulative ICS use (p=0.09) had no significant effect on BMA, but there was a dose-dependent decrease in BMA among individuals taking OCSs (p=0.008), consistent with our previous results over a longer follow-up period (median 7 years)[10].

Effect of corticosteroids on BMA by vitamin D status

Table II shows the change in annual BMA with different corticosteroid exposures, stratified by vitamin D level and sex. Vitamin D status at baseline did not modify the relationship between CAMP randomization to budesonide and BMA using intention-to-treat analysis (interaction between budesonide and vitamin D level, p=0.53 for boys and p=0.79 for girls). In vitamin D sufficient boys, a significant decrease in BMA was noted with increasing ICS use (p=0.007). However, there was no significant effect modification by vitamin D on the relationship between cumulative ICS and BMA (p=0.48 for boys and p=0.90 for girls). A significant interaction term between vitamin D and OCS use for boys (p=0.02) supports an effect modification by vitamin D on the effect of OCS on BMA. In boys, there was a significant decrease in BMA with increasing use of OCSs in the vitamin D insufficient group only (p <0.001; 95% CI −0.008, −0.002). Specifically, each increase in category of OCS exposure was associated with a significant decrease in BMA (0.005 g/cm^2/year). Of the vitamin D insufficient CAMP boys taking more than two courses of OCS per year and

compared to those taking no OCS, the difference in medians was −0.027 g/cm^2/year for BMA and −0.819 for BMD z-score, compared to −0.014 g/cm^2/year and −0.122 respectively for vitamin D sufficient boys. Figure 1 shows the difference in BMA between OCS-exposed and OCS-unexposed boys, with twice the difference in BMA associated with moderate to high OCS usage noted in the vitamin D insufficient group compared to the vitamin D sufficient group. An OCS dose-dependent decrease in BMD z-score was also observed in vitamin D insufficient boys ($p<0.001$; 95% CI −0.279, −0.077; interaction term $p=0.04$, Table III). In females, there was no significant decrease in BMA with increasing OCS intake and no effect modification by vitamin D. Interestingly, among those not exposed to steroids, BMA was higher in the vitamin D insufficient group (Table II). Compared to their vitamin D sufficient counterparts, these subjects were overall younger, had lower BMI percentiles, were in lower pubertal stages and consisted of more white subjects (Table E2–E4 in Online Repository). After adjustment for covariates, vitamin D insufficiency was not associated with BMA ($p=0.65$, $p=0.38$, $p=0.06$ for non-exposed to budesonide, ICS and OCS, respectively).

Discussion

In this evaluation of the combined effects of vitamin D and corticosteroid use on BMA and BMD in children with asthma, we found a dose-dependent effect of OCS use on BMA in boys that was significantly modified by serum $25(OH)_2D$ levels. Specifically, boys with lower vitamin D levels (≤30 ng/mL) had a doubling of the decrease in BMA following exposure to a moderate to high number of OCS treatment courses for asthma exacerbations (Figure 1). This effect was most notable in subjects taking the equivalent to >2 courses of OCS per year, a relatively common occurrence in clinical practice. A longitudinal observational study in the UK reported that about 12% of children aged 5 to 11 years with diagnosed asthma received one or more courses of OCS per year[17]. This, combined with the high prevalence of vitamin D insufficiency[4], suggests that many children with asthma are particularly vulnerable to decrements in bone density. There was no evidence of an effect of cumulative ICS or budesonide as per randomization on BMA and no evidence of effect modification by vitamin D. This is consistent with previous findings that ICS use has no adverse effects on BMD in children[10, 18–20].

Our study adds to several existing studies that have cited an association of OCS usage to decreased BMD or BMA[10, 21, 22], by noting a specific subgroup, vitamin D insufficiency, as being at greatest risk for this adverse outcome. We observed that among both boys and girls who were not exposed to OCS, BMA and BMD z-score were higher in those who were vitamin D insufficient. However, the association between vitamin D insufficiency and increased BMA was not significant after adjustment for baseline BMD, sex, BMI percentile and Tanner stage, stressing the importance of these risk factors when examining BMA. While the clinical significance of a decreased BMA and changes in BMD z-score as related to future fractures are not well established in children given the lack of prospective longitudinal studies, in adults, a 1 standard deviation decreased in spine BMD is associated with a 2-fold increase in fracture risk[23]. Additionally, Van Staa et al reported a 1.3 times increase in odds of fracture in children aged 4–17 years taking ≥4 courses of OCS over a mean follow-up of 2.7 years[24]. Further research is needed to determine whether OCS bursts combined with vitamin D insufficiency during childhood and adolescence has a cumulative effect on peak bone mass and long-term fracture risks.

There are several potential biologic reasons to support the interaction of corticosteroids with vitamin D on bone health. Corticosteroids reduce bone mineral accretion and contribute to corticosteroid-induced osteoporosis by impairing the function and differentiation of osteoblasts and by increasing osteoclasts activity. Furthermore, they induce apoptosis of

osteoblasts while having an anti-apoptotic effect on osteoclasts, resulting in accelerated bone resorption[25]. At the intestinal level, corticosteroids inhibit vitamin D-dependent intestinal calcium absorption and decreased expression of specific duodenal calcium transporters[6, 26]. Rickets and osteomalacia are well-documented adverse effects of severe vitamin D deficiency. Vitamin D insufficiency has been associated with compensatory increase in parathyroid hormone (PTH) secretion[27], which can lead to bone resorption and reduced bone mineral density[28]. Differentiation and prevention of osteoclast apoptosis is mediated by the binding of receptor activator of NF-κB ligand (RANKL) to its receptor RANK, which can be neutralized by RANKL's inhibitor osteoprotegerin (OPG). Both corticosteroids and vitamin D insufficiency contribute to bone loss by increasing the RANKL/OPG ratio[29].

In this study, the adverse dosage-dependent effect of OCS on BMA and the effect modification by serum vitamin D levels were significant only in boys, despite adjustment for Tanner staging. While there is an established sexual dimorphism in cortical bone density development, the relative importance of sex hormones on trabecular bone density, which is measured by DEXA, is being elucidated. Murine models suggest that androgens are mainly responsible for the development of trabecular bone mass in males[30], in contrast to the important role of estrogens in females[31]. In this cohort, more girls progressed through the later stages of puberty than boys. Thus, it is likely that more girls were exposed to increased estrogen levels than boys were exposed to increased androgen levels. In girls, the associated estrogen surge may have also masked the small negative effect of corticosteroids and low vitamin D levels on bone health. Given the same chronological age, boys have a consistently lower biological age compared to girls[32]. This is reflected by the fact that boys achieve a peak bone mass later than girls. It is recognized that the growing skeleton is particularly susceptible to the adverse effects of corticosteroids[24]. Hence, it is possible that the delayed bone maturation pattern in boys predisposes them to increased adverse effects from corticosteroids and low vitamin D.

In addition to its direct effect on bone, low vitamin D levels may be associated with decreased BMA through increased OCS use in children with asthma. In the CAMP cohort, Brehm et al found that individuals with vitamin D insufficiency and receiving ICS had 1.7 times increased odds of severe asthma exacerbation over the 4 years of the trial, compared to those who were vitamin D sufficient and on ICS. This corroborates with their previous study of 616 Costa Rican children with asthma, where higher vitamin D levels were associated with a reduced odds of hospitalization[15]. Vitamin D insufficiency results in increased exacerbations, which in turn lead to increased OCS use, thus leading to further decrease in BMA. Together with our findings, this suggests that patients with frequent exacerbations may benefit from a vitamin D level assessment as these individuals are at greatest risk for decreased BMA.

Although CAMP included a higher proportion of minority subjects (13.3% black, 9.4% Hispanic and 9.0% others[11]) compared to other pediatric asthma trials, it was a predominantly white, non-disadvantaged cohort, therefore the generalizability of our findings need to be addressed. Children at risk for hypovitaminosis D, including those with a nonwhite ethnicity, who are obese, or in low socioeconomic status, may be even more susceptible to the adverse effects of steroids on bone health. Interestingly, a recent study described a significant decrease in BMD with decreasing vitamin D levels in whites and Mexican-Americans, but not among blacks[33]. Furthermore, in blacks, the inverse association between vitamin D and parathyroid hormone was observed only below the threshold of vitamin D deficiency (20 ng/mL), suggesting that African-Americans may require much lower vitamin D levels to experience the associated side effects. Further studies are

warranted to examine the effects of vitamin D on bone health among individuals of different ethnic backgrounds.

The current study is limited by the fact that only one measure of serum vitamin D was used. Ideally, vitamin D measurements over time may allow for a more confident classification of whether an individual is vitamin D sufficient or insufficient and for the identification of seasonal variability in vitamin D levels. However, our results remained unchanged after adjusting for the season when vitamin D level was drawn (data not shown). In CAMP, a second vitamin D measurement was taken at the end of the study. The present study focused on the ability of vitamin D to modify the effects of corticosteroids on future BMA; therefore only the baseline level was used. Furthermore, using only subjects who had consistent levels at both time points (insufficient or sufficient at both times) significantly restricted our sample size. There was also potential for misclassification of subjects given that the measurements were not necessarily drawn during the same seasons. Nonetheless, using only individuals with consistent levels of vitamin D (n=479), the interaction between the number of course of OCS and vitamin D on BMA remained significant (p=0.042). A large longitudinal, population-based study showed that despite seasonal variations in serum vitamin D, subjects with low serum vitamin D levels are unlikely to have substantial improvement 14 years later[35]. Hofmann et al also found a significant correlation between vitamin D levels at baseline and 1 and 5 years[36]. Taken together, these findings support the use of a single vitamin D level measurement as predictor for future disease. Since bone health was not a primary outcome in CAMP, we did not have data on each subject's physical activity level or dietary changes. Although these variables are associated with BMA, diet is a limited source of vitamin D[37] and overall physical activity is not associated with vitamin D, therefore confounding, if present, is minimal. Physical activity outdoor may be a proxy for sun exposure, but to the extent that this would influence serum vitamin D status will be reflected in the serum levels that we have measured. Our study may have lacked power to detect some association, as CAMP was not designed to assess BMA. Although we found a significant association between ICS exposure and decreasing BMA in vitamin D sufficient boys (p=0.007), the interaction between vitamin D and ICS exposure was not significant (p=0.48). This observed association may be due to an outlier effect, although we may not have adequate power to detect a true effect modification by vitamin D.

Conclusion

Our study demonstrates a dosage-dependent effect of intermittent oral corticosteroid use on bone mineral accretion in boys with asthma, which is significantly modified by baseline serum vitamin D levels. The findings of this study may have important clinical implications. Vitamin D insufficiency and asthma are two prevalent conditions in children. The use of oral corticosteroids is also a common occurrence among children with asthma. This study not only supports an adverse effect on bone mineral accretion associated with increasing use of OCS in boys, but also demonstrates that this negative effect is exacerbated by low serum vitamin D. While further research is needed to confirm this finding, and whether vitamin D supplementation can confer clinical benefits on future bone health, our data suggests that children, in particular boys, with asthma who have frequent exacerbations requiring OCS treatment may benefit from a vitamin D assessment and that vitamin D supplementation in these children may help to preserve bone mineral density.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BMA	Bone mineral accretion
BMD	Bone mineral density
CAMP	Childhood Asthma Management Program
DEXA	Dual-energy radiograph absorptiometry
ICS	Inhaled corticosteroid
OCS	Oral corticosteroid
PTH	Parathyroid hormone

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Clinical Implications

Corticosteroid use in asthma is associated with a reduction in BMA. Vitamin D insufficiency is also associated with decreased BMD. However, the interaction between vitamin D and corticosteroids in asthma is not well understood.

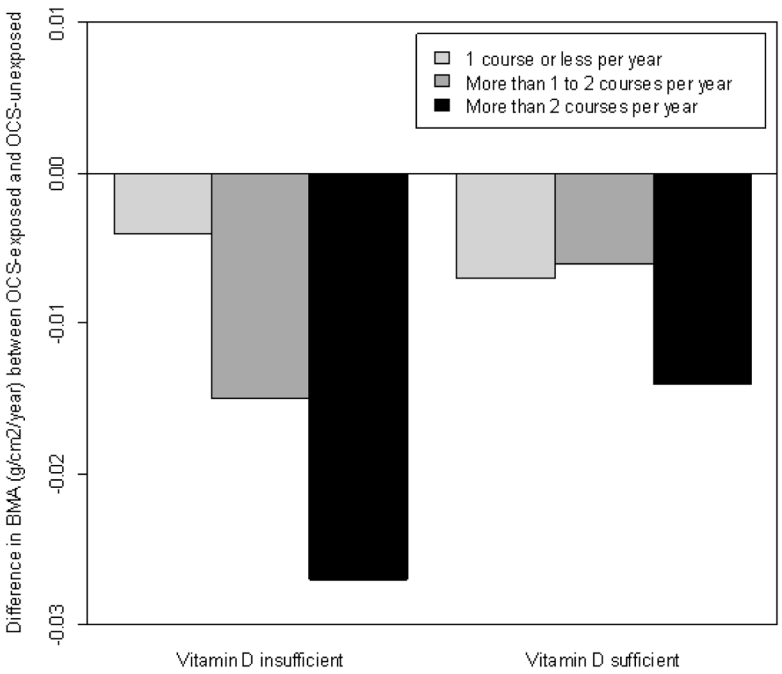

Figure 1.

Difference in BMA between OCS-exposed and OCS-unexposed in boys, by category of OCS exposure and vitamin D sufficiency status. Vitamin D insufficient boys who were exposed to more than 2 OCS courses per year had twice the difference in BMA compared to the vitamin D sufficient boys.

Table I

Baseline characteristics

Baseline characteristics (n=780)				
	Vitamin D ≤30 ng/ml		**Vitamin D >30 ng/ml**	
N (%)	289 (37.0)		491 (63.0)	
Male (%)	176 (60.9)		306 (62.3)	
Age, mean (SD), years	9.2 (2.1)		8.8 (2.1)	
Height, mean (SD), cm	135.6 (13.9)		132.9 (13.5)	
BMI percentile, median (IQR), kg/m^2	76.9 (49.0, 93.1)		68.0 (42.9, 88.9)	
BMD, median (IQR), g/cm^2				
Baseline	0.64 (0.59, 0.72)		0.63 (0.57, 0.69)	
Vitamin D, median (IQR), ng/ml	24.0 (19.6, 27.5)		41.9 (35.2, 52.5)	
Exposure to passive smoking, n(%)	60 (20.8)		130 (26.4)	
Race/Ethnicity, n (%)				
White	158 (54.7)		380 (77.4)	
Black	71 (24.6)		28 (5.7)	
Hispanic	26 (9.0)		46 (9.4)	
Other	34 (11.8)		37 (7.5)	
Tanner stage, n (% within sex)				
Baseline	**Male**	**Female**	**Male**	**Female**
Stage 1	117 (67.2)	81 (71.6)	220 (72.6)	131 (70.8)
Stage 2	40 (23.0)	14 (12.4)	69 (22.8)	37 (20.0)
Stage 3	13 (7.5)	9 (8.0)	9 (3.0)	12 (6.5)
Stage 4	4 (2.3)	7 (6.2)	5 (1.6)	4 (2.2)
Stage 5	0 (0)	2 (1.8)	0 (0)	1 (0.5)
At 4 years follow-up				
Stage 1	29 (16.7)	8 (7.3)	86 (28.5)	18 (9.9)
Stage 2	46 (26.4)	26 (23.9)	72 (23.8)	41 (22.5)
Stage 3	25 (14.4)	25 (23.0)	37 (12.3)	43 (23.6)
Stage 4	31 (17.8)	20 (18.3)	38 (12.6)	34 (18.7)
Stage 5	43 (24.7)	30 (27.5)	69 (22.8)	46 (25.3)

Table II

Bone mineral accretion by corticosteroid exposures and vitamin D sufficiency

Bone mineral accretion by corticosteroid exposures and vitamin D sufficiency											
By randomization to budesonide treatment group											
		Boys					**Girls**				
		n	**BMA, median, g/cm2/year**		**Coefficient (95% CI)**	**p***	**n**	**BMA*, median, g/cm2/year**		**Coefficient (95% CI)**	**p***
Vitamin D ≤30 ng/ml	No budesonide	137	0.038	0.034*	0.004 (−0.002, 0.010)	0.17	80	0.059	0.061*	−0.003 (−0.012, 0.006)	0.53
	Budesonide	39	0.045	0.041*			33	0.059	0.051*		
Vitamin D >30 ng/ml	No budesonide	204	0.032	0.031*	−0.004 (−0.007, 0.000)	0.07	128	0.052	0.060*	−0.002 (−0.009, 0.005)	0.62
	Budesonide	102	0.034	0.033*			57	0.063	0.064*		
Vitamin D x Budesonide, p						0.53					0.79
By cumulative ICS											
Vitamin D ≤30 ng/ml	No ICS	101	0.040	0.038*	−0.001 (−0.004, 0.002)	0.50	60	0.063	0.064*	−0.002 (−0.007, 0.002)	0.33
	≤3 year-equivalent of daily ICS	32	0.028	0.030*			20	0.054	0.051*		
	>3 year-equivalent of daily ICS	43	0.045	0.042*			33	0.058	0.052*		
Vitamin D >30 ng/ml	No ICS	155	0.035	0.032*	−0.003 (−0.005, −0.001)	**0.007**	86	0.052	0.060*	−0.002 (−0.005, 0.002)	0.40
	≤3 year-equivalent of daily ICS	48	0.031	0.028*			43	0.058	0.060*		
	>3 year-equivalent of daily ICS	103	0.033	0.033*			56	0.062	0.065*		
Vitamin D x ICS, p						0.48					0.90
By cumulative OCS											
Vitamin D ≤30 ng/ml	No OCS	31	0.049	0.046*	−0.005 (−0.008, −0.002)	**<0.001**	26	0.058	0.065*	0.000 (−0.004, 0.004)	0.94
	≤1 course per year	88	0.045	0.048*			54	0.049	0.063*		
	1–2 courses per year	36	0.034	0.029*			17	0.044	0.042*		
	>2 courses per year	21	0.022	0.032*			16	0.065	0.062*		
Vitamin D >30 ng/ml	No OCS	62	0.040	0.037*	−0.001 (−0.003, 0.001)	0.20	29	0.050	0.059*	0.000 (−0.004, 0.003)	0.91

Bone mineral accretion by corticosteroid exposures and vitamin D sufficiency											
By randomization to budesonide treatment group											
		Boys					Girls				
		n	BMA, median, g/cm2/year		Coefficient (95% CI)	p*	n	BMA*, median, g/cm2/year		Coefficient (95% CI)	p*
	≤1 course per year	156	0.033	0.031*			96	0.040	0.063*		
	1–2 courses per year	56	0.034	0.029*			33	0.044	0.058*		
	>2 courses per year	32	0.026	0.028*			27	0.062	0.063*		
Vitamin D x OCS, p						**0.02**					0.77

*Adjusted for baseline BMD, age, race, height, BMI percentile, Tanner stage.

Table III

BMD z-scores in boys by vitamin D sufficiency status.

BMD z-scores in boys						
		Boys				
		n	**ZBMD*, median (IQR), (g/cm2)**		**Coefficient (95% CI)**	**p****
Vitamin D ≤30 ng/ml	No OCS	31	0.391	0.053 *	−0.178 (−0.279, −0.077)	**<0.001**
	≤1 course per year	88	0.001	−0.010 *		
	1–2 courses per year	36	0.022	0.121 *		
	>2 courses per year	21	−0.428	−0.063 *		
Vitamin D >30 ng/ml	No OCS	62	−0.275	−0.065 *	−0.039 (−0.122, 0.043)	0.35
	≤1 course per year	156	−0.131	−0.180 *		
	1–2 courses per year	56	−0.185	−0.057 *		
	>2 courses per year	32	−0.397	−0.250 *		
Vitamin D x OCS, p						**0.04**

* Adjusted for baseline BMD, age, race, height, BMI percentile, Tanner stage