Original Article

The Effect of Vitamin D and Inhaled Corticosteroid Treatment on Lung Function in Children

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At a Glance Commentary: This is the first study to suggest that vitamin D sufficiency in patients treated with inhaled corticosteroids.is associated with improved lung function in

patients with mild to moderate persistent asthma. When treating patients with persistent asthma with inhaled corticosteroids, vitamin D levels should be monitored.

ABSTRACT

Rationale: Low vitamin D levels are associated with asthma and decreased airway responsiveness. Treatment with inhaled corticosteroids improves airway responsiveness and asthma control.

Objective: To assess the effect of vitamin D levels on pre-bronchodilator forced expiratory volume in 1 second (FEV_1), bronchodilator response (BDR), and responsiveness to methacholine (PC_{20}) in asthmatics treated with inhaled corticosteroids.

Methods: We measured 25-hydroxyvitamin D levels in the serum of children with persistent asthma at the time of enrollment in the Childhood Asthma Management Program. We divided subjects into the vitamin D sufficiency (>30 ng/ml), insufficiency (20-30 ng/ml), and deficiency (<20 ng/ml) groups. Covariates included age, treatment, gender, BMI, race, history of emergency department visits, hospitalizations, and season that vitamin D specimen was drawn. Our main outcome measures were change in pre-bronchodilator FEV_1, BDR, and PC_{20} from enrollment to 8-12 months.

Results: Of the 1024 subjects, 663 (65%) were vitamin D sufficient, 260 (25%) were insufficient, and 101 (10%) were deficient. Vitamin D deficient subjects were more likely to be older, be African American and have higher BMI compared to the vitamin D sufficient and insufficient subjects. In the inhaled corticosteroid treatment group, pre-bronchodilator FEV_1 increased from randomization to 12 months by 140 ml in the vitamin D deficient group

while prebronchodilator FEV_1 increased by 330 ml in the vitamin D insufficiency group and 290 ml in the vitamin D sufficiency group (p=0.0072), in adjusted models.

Conclusion: In asthmatic children treated with inhaled corticosteroids, vitamin D deficiency is associated with poorer lung function than children with vitamin D insufficiency or sufficiency.

Abstract Word Count: 249

Key Words: asthma, vitamin D, lung function, bronchodilator response, forced expiratory volume, children

Abbreviations:

BMI: Body Mass Index

CAMP: Childhood Asthma Management Program

ED: Emergency Department

FEV_1: Forced expiratory volume in one second

FVC: Forced vital capacity

NAEPP: National Asthma Education and Prevention Program

PC20: Provocative concentration of methacholine producing a 20% decline in FEV_1

INTRODUCTION

The prevalence of both asthma, the most common chronic illness in children,[1] and vitamin D deficiency have dramatically increased in recent years, suggesting they may be linked.[2, 3] Multiple studies have supported the hypothesis that asthma and vitamin D deficiency are related,[2, 3] but few studies have examined the direct effects of vitamin D levels and corticosteroid treatment on lung function in children with asthma.

Low levels of vitamin D are associated with reduced lung function in adults. An analysis of cross-sectional data from the Third National Health and Nutrition Examination Survey found that serum vitamin D was associated with forced expiratory volume in 1 second (FEV_1) in a general population.[4] Li et al found that in adults with asthma, serum vitamin D levels were positively correlated with FEV_1, FEV_1 percent predicted, and the ratio of FEV_1/forced vital capacity (FVC).[5] In children, low vitamin D levels have been found to be associated with increased frequency of asthma exacerbations[6] and increased markers of allergy and asthma severity.[7, 8]

Treatment with inhaled corticosteroids improves airway responsiveness and asthma control.[9] Furthermore, use of inhaled corticosteroids is inversely correlated with vitamin D levels.[10] An experimental model of corticosteroid resistance suggested that vitamin D may restore the immunosuppressive function of dexamethasone.[10] Thus, vitamin D supplementation may further accentuate the anti-inflammatory function of corticosteroids in patients with asthma.[10] If vitamin D levels improve lung function in children, then treatment with inhaled corticosteroids may potentiate this effect, but this has not been demonstrated clinically.

We hypothesize that vitamin D levels may modulate the effect of inhaled corticosteroids on lung function and airway responsiveness. The objectives of this study were to assess whether vitamin D levels modulate the effect of inhaled corticosteroids on pre-bronchodilator (pre-BD) FEV_1, bronchodilator response to inhaled beta-agonists (BDR), and methacholine challenge test results (PC_{20}).

PATIENTS AND METHODS

Design

We conducted an analysis using data from the Childhood Asthma Management Program (CAMP), a multi-center trial of 1041 children with mild to moderate persistent asthma between the ages of five and 12 years who were randomly assigned to receive budesonide (inhaled corticosteroid), nedocromil, or placebo. Details of the CAMP clinical trial have been published.[9] The institutional review board at the eight participating institutions approved the study.[9]

Data Collection

Nurse coordinators obtained spirometry measurements on the subjects before and after bronchodilator at randomization and at 12 months. BDR was calculated at each visit as FEV_1 ([post-bronchodilator FEV_1 – pre-bronchodilator FEV_1]/pre-bronchodilator FEV_1). The subjects' airway responsiveness to methacholine was measured by calculating the concentration of methacholine that caused a 20 percent decrease in the FEV_1 at randomization and 8 months after randomization (PC_{20} was not measured at the 12 month post-randomization visit). The concentration that provoked a 20% decrease from post-diluent FEV_1 was obtained by linear interpolation of logarithmic dose-response curve expressed as PC_{20}..Race/ethnicity, family income, and parental education were determined by

parental self-report. Body mass index (BMI) was calculated using height and weight measurements at randomization.

Serum levels of 25-hydroxyvitamin D (referred to as vitamin D) are thought to be the best circulating biomarker of vitamin D metabolic status and reflect contributions from all sources of vitamin D, including diet and sun exposure.[11] A single measurement of vitamin D was obtained on 1024 subjects (98% of enrolled subjects) using a radioimmunoassay method using stored serum samples that had been frozen since randomization,[12, 13] as previously reported.[6] We categorized vitamin D levels into deficient (≤ 20 ng/ml), insufficient (20-30 ng/ml), and sufficient (> 30 ng/ml) based on previous studies.[14]

Our main outcome measures were the change in BDR and pre-bronchodilator FEV_1 from randomization to 12 months and log PC_{20} between randomization and 8 months. We chose to study the change in our outcome measurements over 8-12 months in order to capture the effects of both treatment and vitamin D level on lung function. We chose to study the first 8-12 months of the CAMP clinical trial because the maximum effect of inhaled corticosteroids on BDR was seen at 12 months and vitamin D levels were available at randomization.[9]

Statistical Analyses

Analyses were conducted in SAS version 9.1 (SAS Institute, Cary, NC, 2007). In bivariate analyses, we evaluated the association of vitamin D sufficiency, insufficiency, or deficiency and independent variables. We studied the association of vitamin D sufficiency, insufficiency, or deficiency with our main outcome measures pre-bronchodilator FEV1, BDR, and log PC20. We studied the association of the change in each of our outcome measures from randomization to 8 months (PC_{20}) or 1 year (pre-bronchodilator FEV_1, BDR)

in all of the treatment groups. In multivariate analyses using least squares means regression, we built forced-entry models with the variables significant at $p \leq 0.20$, which included age, race, BMI, history of ED visit, gender, and season that vitamin D specimen was drawn. Variables significant at $p \leq 0.10$ were retained in the final multivariable models.

RESULTS

Baseline

Of the 1041 subjects in the trial, 1024 (98%) subjects had serum vitamin D measurements at randomization, and 663 (65%) of these subjects were vitamin D sufficient, 260 (25%) were vitamin D insufficient, and 101 (10%) were vitamin D deficient. As shown in Table I, the subjects in the vitamin D deficient group were older than the subjects in vitamin D sufficient and insufficient groups (mean age 9.71 years versus 8.76 years and 9.10 years, $p < 0.0001$). The mean weight of subjects with vitamin D deficiency was 39.0 kg, which was significantly more than vitamin D sufficient and insufficient subjects who weighed 32.1 kg and 34.5 kg respectively, $p<0.0001$. The mean height of vitamin D deficient subjects was 138 cm, which was significantly taller than vitamin D sufficient and insufficient subjects who had a mean height of 132 cm and 135 cm respectively, $p=0.0003$. Vitamin D deficient subjects had higher BMI at 19.8 kg/m2 compare to 17.8 kg/m2 in vitamin D sufficient subjects and 18.5 kg/m2 in vitamin D insufficient subjects, $p<0.0001$. African American subjects (35%) were more likely to be vitamin D deficient than the Caucasian (5%), Hispanic (10%), and other (11%) subjects ($p<0.0001$). Fewer subjects in the inhaled corticosteroid treatment group were vitamin D deficient (7%) compared to the nedocromil (12%) and placebo (11%) groups ($p=0.03$). Subjects who had their blood drawn for vitamin D levels in the summer or fall were more likely to be in the vitamin D sufficient group, with

77% of subjects who had vitamin D levels drawn in the summer being in the vitamin D sufficient group and 67% for subjects who had levels drawn in the fall. In comparison, 59% of subjects who had vitamin D levels drawn in the winter and 54% of subjects with levels drawn in the spring were in the vitamin D sufficient group ($p<0.0001$). There were no differences in vitamin D sufficiency, insufficiency, or deficiency by gender, parental education, household income, or history of hospitalizations. Subjects who had a history of experiencing ED visits were more likely to be vitamin D sufficient (59% were vitamin D sufficient while 30% were vitamin D insufficient), however, of subjects who did not have a history of ED visits, 67% were vitamin D sufficient and 23% were vitamin D insufficient, $p=0.026$.

Follow-up

As shown in Table II, there are no differences in pre-bronchodilator FEV_1, BDR, log PC_{20} at 8 to 12 months by vitamin D sufficiency, insufficiency, or deficiency groups. Even after stratifying by treatment group, there are no differences in these parameters.

No differences were seen in the change in pre-bronchodilator FEV1, BDR, log PC20 at 8 to 12 months when comparing the vitamin D groups when all treatment groups were combined. Furthermore, the change in BDR and PC_{20} were similar for the budesonide, nedocromil, and placebo groups

Table III shows the change in pre-bronchodilator FEV_1 by vitamin D categories in the entire CAMP population over the first year of the trial. In subjects treated with inhaled corticosteroids, adjusted (age, gender, race, BMI, history of ED visit, season that vitamin D specimen was drawn) least squares regression demonstrated that being vitamin D sufficient or insufficient was associated with greater pre-bronchodilator FEV_1 change over 12 months

compared with the vitamin D deficient group. When treated with inhaled corticosteroids while being vitamin D sufficient, subjects experienced an increase of 0.30 liters in pre-bronchodilator FEV_1, whereas when treated with inhaled corticosteroids, vitamin D insufficient subjects experienced an increase of 0.31 liters, and subjects who were vitamin D deficient experienced an increase of 0.14 liters in prebronchodilator FEV_1 ($p=0.0072$). We conducted a similar analysis with FEV1 percent predicted as the main outcome and we found similar results. When treated with inhaled corticosteroids while being vitamin D sufficient, subjects experienced an increase of 5.2% in pre-bronchodilator FEV_1 percent predict whereas when treated with inhaled corticosteroids, vitamin D insufficient subjects experienced an increase of 6.1%, and subjects who were vitamin D deficient experienced an decrease of 1.5% in prebronchodilator FEV_1 percent predicted ($p=0.036$). Figure 1 depicts the change in pre-bronchodilator FEV_1 and pre-bronchodilator FEV1 percent predicted from randomization to 12 months in the subjects treated with inhaled corticosteroids for the vitamin D deficiency, insufficiency, and sufficiency groups, while adjusting for age, gender, race, BMI, history of ED visit. Adjusted (age, gender, race, BMI, history of ED visit, season that vitamin D level was drawn) least squares regression demonstrated that in the inhaled corticosteroid group, the change in BDR decreased by 0.035 over 12 months for subjects who were vitamin D sufficient while the change in BDR decreased by 0.057 in subjects who were vitamin D insufficient, and increased by 0.0053 for subjects who were vitamin D deficient; however, this finding did not reach statistical significance ($p=0.10$). We explored whether there was as linear relationship between vitamin D level and change in pre-bronchodilator FEV_1, BDR, and PC20, and did not find a relationship after adjusting for age, gender, race, BMI, history of ED visit, and season that vitamin D level was drawn.

DISCUSSION

Prior work in children has supported a role for vitamin D in preventing asthma exacerbations in children in the CAMP trial, especially those children treated with inhaled corticosteroids.[6] Our current study found that children with asthma who are deficient in vitamin D levels have less improvement in pre-bronchodilator FEV_1 over the course of one year when treated with inhaled corticosteroids as compared to children who are sufficient in vitamin D. These findings support the hypothesis that vitamin D supplementation may enhance the anti-inflammatory function of corticosteroids in asthma patients.

Strengths of our study include a well characterized cohort of children with asthma, ascertainment of vitamin D levels at randomization, and carefully measured lung function measures. Our bivariate results that found older age, African American race, and higher BMI are associated with lower vitamin D levels have been seen in previous studies.[14, 15] Multiple previous studies have found that inhaled corticosteroids improve lung function.[16] Our finding that children who are vitamin D deficient are more likely to have lower lung function is consistent with a previous study that demonstrated that in children with exercise-induced bronchoconstriction, lower vitamin D levels were associated with reduced lung function.[17] Our study's result that asthmatic children who are vitamin D sufficient have improved lung function is also supported by other studies. Searing et al found that vitamin D levels were associated with FEV_1 percent predicted and FEV_1/FVC ratio, however, they had a small sample size of 59 subjects with spirometric results and they did not have longitudinal measures.[10] The apparent paradox of the decrease in BDR over time in vitamin D sufficient versus deficient subjects is appropriate because as pre-bronchodilator FEV_1 increases, BDR decreases (i.e. subjects are maximally dilated at baseline).[18]

Our findings are supported by Sutherland et al who found that reduced vitamin D levels are associated with impaired lung function especially in adults who are not being treated with inhaled corticosteroids.[19] The authors suggested that vitamin D supplementation could be especially beneficial in patients who are not treated with inhaled corticosteroids.[19] In vitro studies also support the findings of our study. Searing et al found that vitamin D potentiates glucocorticoid action in peripheral blood mononuclear cells in vitro.[10]

Despite the strengths of our study, some caveats deserve mention. We chose to study children who are vitamin D deficient compared to children who are insufficient and sufficient; however, the sample size of children who were vitamin D deficient was relatively small with 101 subjects. The number of subjects who were vitamin D deficient and in the inhaled corticosteroid arm was even smaller. Nevertheless, this sample size is larger than previous studies.[10] Furthermore, a high proportion of the vitamin D deficient group is African American, and in addition, a high proportion of ICS resistant asthmatics are African American. This finding is consistent with vitamin D biology where high melanin content in the skin limits UVB light absorption, which is the major biologic source of vitamin D. Race and skin color are not confounders in our analysis since they are in the causal pathway defining low vitamin D.[20]

In addition, our sample size was not large enough to conduct our analyses stratified by race, although we did adjust for race in our analyses. Based on the biology described above, this is probably an over adjustment and hence conservative. Future prospective studies will help address these questions. Other limitations include that we only studied vitamin D levels at one time point; given the low reproducibility of vitamin D levels this would likely be a null bias and would have biased our results in a direction of not finding a significant

effect of vitamin D on lung function. A prospective study to validate findings is needed. Furthermore, we did not find a dose-response relationship between vitamin D levels and change in FEV1, BDR, or PC20; however, we did not expect to be able to assess a dose-response relationship because the CAMP population does not have a full range of vitamin D levels in the vitamin D sufficiency category with a mean level of 37.8 ng/ml [SD 15.7].

In conclusion, vitamin D sufficiency in patients treated with inhaled corticosteroids is associated with improved lung function in patients with mild to moderate persistent asthma. Monitoring vitamin D levels and/or supplementing with vitamin D could be considered during inhaled corticosteroid treatment for patients with asthma.

CAMP Credit Roster

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References:

1. Moorman JE, Rudd RA, Johnson CA, et al. National surveillance for asthma--United States, 1980-2004. *MMWR Surveill Summ.* 2007;56(8):1-54.
2. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? *J Allergy Clin Immunol.* Nov 2007;120(5):1031-1035.
3. Camargo CA, Jr., Ingham T, Wickens K, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics.* Jan 2011;127(1):e180-187.
4. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin d and pulmonary function in the third national health and nutrition examination survey. *Chest.* Dec 2005;128(6):3792-3798.
5. Li F, Peng M, Jiang L, et al. Vitamin D Deficiency Is Associated with Decreased Lung Function in Chinese Adults with Asthma. *Respiration.* Dec 1 2010.
6. Brehm JM, Schuemann B, Fuhlbrigge AL, et al. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J Allergy Clin Immunol.* Jul 2010;126(1):52-58 e55.
7. Brehm JM, Celedon JC, Soto-Quiros ME, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med.* May 1 2009;179(9):765-771.
8. Devereux G, Litonjua AA, Turner SW, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am J Clin Nutr.* Mar 2007;85(3):853-859.
9. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med.* 2000;343(15):1054-1063.
10. Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DY. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. *J Allergy Clin Immunol.* May 2010;125(5):995-1000.
11. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr.* Feb 2005;135(2):317-322.
12. Hollis BW, Kamerud JQ, Selvaag SR, Lorenz JD, Napoli JL. Determination of vitamin D status by radioimmunoassay with an 125I-labeled tracer. *Clin Chem.* Mar 1993;39(3):529-533.
13. Hollis BW, Napoli JL. Improved radioimmunoassay for vitamin D and its use in assessing vitamin D status. *Clin Chem.* Nov 1985;31(11):1815-1819.
14. Holick MF. Vitamin D deficiency. *N Engl J Med.* Jul 19 2007;357(3):266-281.
15. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-2004. *Pediatrics.* Sep 2009;124(3):e362-370.
16. O'Byrne PM, Pedersen S, Busse WW, et al. Effects of early intervention with inhaled budesonide on lung function in newly diagnosed asthma. *Chest.* Jun 2006;129(6):1478-1485.
17. Chinellato I, Piazza M, Sandri M, et al. Vitamin D serum levels and exercise-induced bronchoconstriction in children with asthma. *Eur Respir J.* Nov 11 2010.
18. Sharma S, Litonjua AA, Tantisira KG, et al. Clinical predictors and outcomes of consistent bronchodilator response in the childhood asthma management program. *J Allergy Clin Immunol.* 2008;122(5):921-928 e924.
19. Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DY. Vitamin D levels, lung function, and steroid response in adult asthma. *Am J Respir Crit Care Med.* Apr 1 2010;181(7):699-704.

20. Armas LA, Dowell S, Akhter M, et al. Ultraviolet-B radiation increases serum 25-hydroxyvitamin D levels: the effect of UVB dose and skin color. *J Am Acad Dermatol.* Oct 2007;57(4):588-593.

21. Epstein AM, Ayanian JZ, Keogh JH, et al. Racial disparities in access to renal transplantation--clinically appropriate or due to underuse or overuse? 2000;343(21).

Table I. Baseline demographic variables stratified by Vitamin D deficiency (≤20ng/ml), insufficiency (20-30ng/ml), and sufficiency (>30ng/ml). For continuous measures, we provide means and standard deviations in brackets.

N=1024	Vitamin D sufficient n=663	Vitamin D insufficiency n=260	Vitamin D deficient n=101	p
Age, years [SD]	8.76 [2.10]	9.10 [2.17]	9.71 [1.98]	<0.0001
Treatment group				0.03
Inhaled corticosteroid	71% (216)	23% (69)	7% (20)	
Nedocromil	59% (182)	29% (89)	12% (36)	
Placebo	64% (265)	25% (182)	11% (45)	
Gender				0.39
Male	66% (405)	24%(146)	10% (60)	
Female	62% (258)	28%(114)	10% (41)	
Weight, kg [SD]	32.1 [11.2]	34.5 [12.5]	39.0 [14.3]	<0.0001
Height, cm [SD]	132.4 [13.7]	134.8 [14.1]	138.0 [13.3]	0.0003
Body Mass Index kg/m^2[SD]	17.8 [3.2]	18.5 [3.7]	19.8 [4.3]	<0.0001
Race				<0.0001
Caucasian	72% (507)	23% (159)	5% (34)	
African American	34% (46)	31% (41)	35% (47)	
Hispanic	63% (62)	27% (26)	10% (10)	
Other	52% (48)	37% (34)	11% (10)	
Education				0.81
High School or less	66% (121)	24% (43)	10% (19)	
Some College	65% (542)	26% (216)	10% (82)	
Income				0.42
<$30,000	64% (152)	25% (59)	12% (28)	
≥$30,000	65% (488)	26% (192)	9% (66)	
History ED visits				0.026
Absent	67% (457)	23% (155)	10% (66)	
Present	59% (206)	30% (105)	10% (35)	
Hospitalization history				0.88
Absent	65% (598)	25%(232)	10% (90)	
Present	63% (65)	27% (28)	11% (11)	
Season that vitamin D level was drawn				<0.0001
Winter	59% (126)	24% (52)	17% (36)	
Spring	54% (181)	33% (112)	13% (43)	
Summer	77% (222)	18% (51)	6% (16)	
Fall	67% (124)	25% (47)	8% (14)	

Table II. Lung function by vitamin D deficiency at 8 months (log PC20) to 12 months (Prebronchodilator FEV_1, BDR). N=1024.

		Pre-bronchodilator FEV_1 (liters/second) at 12 months	p	BDR at 12 months	p	Log PC20 at 8 months	p
Inhaled corticosteroid	Vitamin D sufficient n=210	1.93 [0.73]	0.88	0.073 [0.06]	0.45	4.91 [8.40]	0.55
	Vitamin D insufficient n=66	2.01 [0.65]		0.072 [0.071]		4.22 [7.95]	
	Vitamin D deficient n=20	1.97 [0.43]		0.085 [0.083]		6.35 [11.45]	
Nedocromil	Vitamin D sufficient n=180	1.84 [0.55]	0.95	0.10 [0.087]	0.83	5.42 [9.81]	0.58
	Vitamin D insufficient N=85	1.90 [0.57]		0.11 [0.11]		3.47 [6.54]	
	Vitamin D deficient n=36	1.85 [0.54]		0.11 [0.13]		5.85 [9.57]	
Placebo	Vitamin D sufficient n=255	1.85 [0.53]	0.33	0.10 [0.094]	0.52	3.23 [5.83]	0.30
	Vitamin D insufficient n= 99	1.88 [0.58]		0.12 [0.13]		3.03 [5.10]	
	Vitamin D deficient n=43	1.94 [0.67]		0.12 [0.096]		4.56 [8.35]	

Table III. Change in pre- bronchodilator FEV_1 between randomization and 12 months in liters/second by vitamin D deficiency. N=1024. *Adjusted for age, sex, BMI, history of ED visit, race, and season that vitamin D specimen was drawn. Reference group is Vitamin D sufficient group.

Treatment Group	Vitamin D sufficient Mean change in pre-bronchodilator FEV_1 n=663	Vitamin D insufficiency Mean change in pre-bronchodilator FEV_1 n=260	p-value*	Vitamin D deficient Mean change in pre-bronchodilator FEV_1 n=101	p-value*
Inhaled corticosteroid n=305	0.30 [0.023]	0.33 [0.031]	0.45	**0.14 [0.057]**	**0.0072**
Nedocromil n=307	0.19 [0.039]	0.17 [0.028]	0.18	0.25 [0.023]	0.83
Placebo n=412	0.23 [0.020]	0.24 [0.025]	0.54	0.16 [0.033]	0.06

Figure I. Change in pre-bronchodilator FEV1 (Figure 1A) and pre-bronchodilator FEV1 percent predicted (Figure 1B) from randomization to 12 months for the vitamin D deficiency (solid line, n=20), insufficiency (dotted line, n=69), and sufficiency (dashed line, n=216) groups, while adjusting for age, gender, race, BMI, history of ED visit, and season that vitamin D level was drawn in patients treated with inhaled corticosteroids. The differences in pre-bronchodilator FEV1 and pre-bronchodilator FEV1 percent predicted for the vitamin D groups were obtained with multivariate analyses using least squares means regression. As demonstrated in Figure 1B, the change in pre- bronchodilator FEV1 for the vitamin D deficiency group (p=0.0072) is significantly less than the vitamin D sufficient group (reference group). The change in pre-bronchodilator FEV1 for the vitamin D insufficiency group is not significantly different from the vitamin D sufficient group (p=0.45). There were no significant differences in baseline pre-bronchodilator FEV_1 values between the groups at randomization. Figure 1B shows similar results for pre-bronchodilator FEV1 percent predicted in subjects treated with inhaled corticosteroids. Vitamin D sufficient subjects experienced an increase of 5.2% in pre-bronchodilator FEV1 percent predicted, vitamin D insufficient subjects experienced an increase of 6.1%, and subjects who were vitamin D deficient experienced an decrease of 1.5% in prebronchodilator FEV1 percent predicted (p=0.036 compared to vitamin D sufficient group).