Original Article

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

Ann Chen Wu, MD, MPH,1-3 Kelan Tantisira, MD, MPH,3-5 Lingling Li,1,3 Anne L. Fuhlbrigge, MD, MS,3,4 Scott T. Weiss, MD, MS,3-5 and Augusto Litonjua MD, MPH3-5 for the Childhood Asthma Management Program Research Group*

1. Center for Child Health Care Studies, Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA
2. Department of Pediatrics, Children’s Hospital, Boston, MA
3. Harvard Medical School, Boston, MA
4. Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital, Boston, MA
5. Center for Genomic Medicine, Department of Medicine, Brigham and Women’s Hospital, Boston, MA

Address correspondence to:
Ann Wu, MD, MPH
Department of Population Medicine
133 Brookline Avenue, 6th Floor
Boston, MA 02215-5301
Phone: 617-509-9823
Fax: 617-859-8112
Email: ann.wu@childrens.harvard.edu
Contributions:

Conception and design: ACW, KT, STW

Acquisition of data: STW, AL, ALF

Analysis and interpretation: ACW, KT, STW, AL, LL, ALF

Drafting and revising the manuscript for important intellectual content: ACW, KT, STW, AL, LL, ALF

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*Members of the CAMP Research Group are detailed at the end of this manuscript.

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Short Running Head: Vitamin D and Inhaled Corticosteroids in Asthmatics

Subject Category: 1.11 Clinical Asthma

Word count: 2359

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$_1$
The prevalence of both asthma, the most common chronic illness in children, and vitamin D deficiency have dramatically increased in recent years, suggesting they may be linked. Multiple studies have supported the hypothesis that asthma and vitamin D deficiency are related, 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. 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). In children, low vitamin D levels have been found to be associated with increased frequency of asthma exacerbations and increased markers of allergy and asthma severity.

Treatment with inhaled corticosteroids improves airway responsiveness and asthma control. Furthermore, use of inhaled corticosteroids is inversely correlated with vitamin D levels. An experimental model of corticosteroid resistance suggested that vitamin D may restore the immunosuppressive function of dexamethasone. Thus, vitamin D supplementation may further accentuate the anti-inflammatory function of corticosteroids in patients with asthma. 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\(_1\) \([\text{post-bronchodilator FEV}_1 – \text{pre-bronchodilator FEV}_1]/\text{pre-bronchodilator FEV}_1\). 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. 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, as previously reported. We categorized vitamin D levels into deficient (≤ 20 ng/ml), insufficient (20-30 ng/ml), and sufficient (> 30 ng/ml) based on previous studies.

Our main outcome measures were the change in BDR and pre-bronchodilator FEV₁ from randomization to 12 months and log PC₂₀ 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.

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 (PC₂₀) or 1 year (pre-bronchodilator FEV₁, 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 ≤ 0.20, which included age, race, BMI, history of ED visit, gender, and season that vitamin D specimen was drawn. Variables significant at p ≤ 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 FEV$_1$, BDR, log PC$_{20}$ 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. 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. Multiple previous studies have found that inhaled corticosteroids improve lung function. 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.

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. 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).
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.\textsuperscript{19} The authors suggested that vitamin D supplementation could be especially beneficial in patients who are not treated with inhaled corticosteroids.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.
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Members of the CAMP Research Group:

Clinical centers

**ASTHMA, Inc, Seattle, WA:** Paul Williams, MD (Principal Investigator); Mary V. Lasley, MD (Co-Director); Tamara Chinn, MSN, ARNP (Coordinator). Michele Hinatsu, MSN, ARNP; Clifton T. Furukawa, MD; Leonard C. Altman, MD; Frank S. Virant, MD; Michael S. Kennedy, MD; Jonathan W. Becker, MD; Stephen Tilles, MD; Miranda MacLaren. C. Warren Bierman, MD (1992-1997); Dan Crawford, RN (1996-2002); Thomas DuHamel (1991-2004); Heather Eliassen, BA (1996-1999); Babi Hammond (1996-1999); Dominick A. Minotti, MD (1992-2003); Chris Reagan (1992-2003); Gail Shapiro (1991-2006, Principal Investigator); Marian Sharpe, RN (1992-1994); Ashley Tatum, MD (2004-2007); Grace White (1991-2007). Timothy G. Wighton, PhD (1994-1998).


**The Hospital for Sick Children, Toronto, Ontario, Canada:** Hartmut Grasemann, MD (Principal Investigator); Melody Miki, RN, BSN (Coordinator); Padmaja Subbarao, MD; Ian MacLusky, MD, FRCP (Director 1999-2007); Joe Reisman, MD, FRCP(C), MBA (Director, 1996-1999); Henry Levison, MD, FRCP(C) (Director, 1992-1996); Anita Hall, RN (Coordinator, 1993-2007). Yola Benedet (1994-1999); Susan Carpenter, RN (1998-2001); Jennifer Chay (2004); Michelle Collinson, RN (1994-1998);

Johns Hopkins Asthma & Allergy Center, Baltimore, MD: N. Franklin Adkinson, Jr, MD (Director); Deborah Bull, LPN (Coordinator); Stephanie Philips, RN. Peyton Eggleston, MD (Co-Director, 1991-2004); Karen Huss, DNSc (Co-Investigator, 1991-2004); Leslie Plotnick, MD (Co-Investigator, 1991-1999); Margaret Pulisifer, PhD (Co-Investigator, 1993-2004); Cynthia Rand, PhD (Co-Investigator, 1991-2004). Elizabeth Aylward, PhD (1991-2004), Nancy Bollers, RN (Coordinator, 1993-2004); Kathy Pessaro (2004-2007); Barbara Wheeler, RN, BSN (Coordinator, 1991-1999).

National Jewish Health, Denver, CO: Stanley Szefler, MD (Director); Harold S. Nelson, MD (Co-Director); Bruce Bender, PhD (Co-Investigator); Ronina Covar, MD (Co-Investigator); Andrew Liu, MD (Co-Investigator); Joseph Spahn, MD (Co-Investigator); D Sundström (Coordinator); Melanie Phillips; Michael P. White; Melanie Gleason, PA-C; Marzena Krawiec, MD; Gary Larsen, MD; Gayle Spears, PA-C. Kristin Brelsford (1997-1999); Jessyca Bridges (1995-1999); Jody Ciacco (1993-1996); Michael Eltz (1994-1995); Jeryl Feeley, MA (Coordinator, 1992-1995); Michael Flynn (1995-1996); Tara Junk-Blanchard (1997-2000); Joseph Hassell (1992-1998); Marcia Hefner (1992-1994); Caroline Hendrickson, RN (1995-1998; Coordinator, 1995-1997); Daniel Hettleman, MA (1995-1996); Charles G. Irvin, PhD (1992-1998); Alan Kamada, PharmD (1994-1997); Sai Nimmagadda, MD (1993-1996); Kendra Sandoval (1995-1997); Jessica Sheridan (1994-1995); Trela Washington (1993-1997); Eric Willcutt, MA (1996-1997). We also thank the pediatric allergy/immunology and pulmonary fellows for their participation (Ivan Cardona, MD; Kirstin Carel, MD; Jayna Doshi, MD; Rich Hendershot, MD; Jeffrey Jacobs, MD; Neal Jain, MD; June-ku Brian Kang, MD; Tracy Kruzick, MD; Harvey Leo, MD; Beth Macomber, MD; Jonathan Malka, MD; Chris Mjaanes, MD; John Prpich, MD; Lora Stewart, MD; Ben Song, MD; Grace Tamesis, MD).


University of New Mexico, Albuquerque, NM: H. William Kelly, PharmD (Director); Aaron Jacobs (Co-Investigator); Hengameh H. Raissy, PharmD, PhC (Co-Investigator); Mary Spicher, RN (Coordinator). Christina Batson. Robert Annett, PhD (Co-Investigator, 1993-2004); Teresa Archibeque (1994-1999); Naim Bashir, MD (Co-Investigator, 1998-2005); H. Selda Bereket (1995-1998); Marisa Braun (1996-1999); Carrie Bush (1995-1999); Shannon

**Washington University, St. Louis, MO:** Robert C. Strunk, MD (Director); Leonard Bacharier, MD (Co-Investigator); Gordon R. Bloomberg, MD (Co-Investigator); Denise Rodgers, RPFT (Coordinator). Ellen Albers (1999-2003); James M. Corry, MD (Co-Investigator, 1995-2004); Karen DeMuth (2006-2007); Lila Kertz, MSN, RN, CPNP (2005-2007); Valerie Morgan, RRT (2004-2007); Cynthia Moseid (2007); Tina Oliver-Welker, CRTT (1993-2007); Deborah K. White, RPFT, RRT (1993-2007).

**Resource centers**

**Data Coordinating Center, The Johns Hopkins University, Baltimore, MD:** James Tonascia, PhD (Director). Patricia Belt; Karen Collins; Betty Collison; Ryan Colvin, MPH; John Dodge; Michele Donithan, MHS; Cathleen Ewing; Rosetta Jackson; Hope Livingston; Jill Meinert; Girlie Reyes; Michael Smith; Alice L. Sternberg, ScM; Mark L. Van Natta, MHS; Annette Wagoner; Laura Wilson, ScM; Robert Wise, MD; Katherine Yates, ScM.

**Project Office, National Heart, Lung, and Blood Institute, Bethesda, MD:** Virginia Taggart, MPH (Project Officer); Lois Eggers; James Kiley, PhD; Howard Moore; Gang Zheng, PhD. Paul Albert, PhD (1991-1999); Suzanne Hurd, PhD (1991-1999); Sydney Parker, PhD (1991-1994); Pamela Randall (1992-2003); Margaret Wu, PhD (1991-2001).

**Committees**

**Data and Safety Monitoring Board:** Michelle Cloutier, MD; John Connett, PhD; Leona Cuttler, MD; Frank Gilliland, MD, PhD. Clarence E. Davis, PhD (1993-2003); Howard Eigen, MD (1993-2009, Chair); David Evans, PhD (1993-2007); Meyer Kattan, MD (1993-2007); Rogelio Menendez, MD (1993-2007); F. Estelle R. Simons, MD (1993-2007); Sanford Leikin, MD (1993-1999).
Steering Committee: Robert Strunk, MD (Study Chair); N. Franklin Adkinson, MD; Robert Annett, PhD (1992-1995, 1997-1999); Bruce Bender, PhD; Mary Caesar, MHS (1994-1996); Reuben Cherniack, MD (Study Chair 1993-2007); Thomas R. DuHamel, PhD (1992-1994, 1996-1999); Anne Fuhlbrigge, MD; Hartmut Grasemann, MD; H. William Kelly, PharmD; Henry Levison, MD (1992-1996); Alan Lincoln, PhD (1994-1995); Ian MacLusky, MD (1999-2006); Bennie McWilliams, MD (1992-1998); Curtis L. Meinert, PhD; Sydney Parker, PhD (1991-1994); Joe Reisman, MD, FRCP(C), MBA (1991-1999); Denise Rodgers; Kay Seligsohn, PhD (1996-1997); Gail G. Shapiro, MD (1991-2006); Marian Sharpe (1993-1994); D Sundström (1998-1999); Stanley Szeefler, MD; Virginia Taggart, MPH; Martha Tata, RN (1996-1998); James Tonascia, PhD; Scott Weiss, MD, MS; Barbara Wheeler, RN, BSN (1993-1994); Paul Williams, MD; Robert Wise, MD; Robert Zeiger, MD, PhD
References:


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.

<table>
<thead>
<tr>
<th>N=1024</th>
<th>Vitamin D sufficient n=663</th>
<th>Vitamin D insufficiency n=260</th>
<th>Vitamin D deficient n=101</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Treatment group</td>
<td></td>
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<td>Inhaled corticosteroid</td>
<td>71% (216)</td>
<td>23% (69)</td>
<td>7% (20)</td>
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<td>Nedocromil</td>
<td>59% (182)</td>
<td>29% (89)</td>
<td>12% (36)</td>
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<tr>
<td>Placebo</td>
<td>64% (265)</td>
<td>25% (182)</td>
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<td>24% (146)</td>
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<td>Female</td>
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<td>28% (114)</td>
<td>10% (41)</td>
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<tr>
<td>Weight, kg [SD]</td>
<td>32.1 [11.2]</td>
<td>34.5 [12.5]</td>
<td>39.0 [14.3]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Height, cm [SD]</td>
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<td>134.8 [14.1]</td>
<td>138.0 [13.3]</td>
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<tr>
<td>Body Mass Index kg/m² [SD]</td>
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<td>18.5 [3.7]</td>
<td>19.8 [4.3]</td>
<td>&lt;0.0001</td>
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<tr>
<td>Race</td>
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<td>&lt;0.0001</td>
</tr>
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<td>Caucasian</td>
<td>72% (507)</td>
<td>23% (159)</td>
<td>5% (34)</td>
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<tr>
<td>African American</td>
<td>34% (46)</td>
<td>31% (41)</td>
<td>35% (47)</td>
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<tr>
<td>Hispanic</td>
<td>63% (62)</td>
<td>27% (26)</td>
<td>10% (10)</td>
<td></td>
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<tr>
<td>Other</td>
<td>52% (48)</td>
<td>37% (34)</td>
<td>11% (10)</td>
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<tr>
<td>High School or less</td>
<td>66% (121)</td>
<td>24% (43)</td>
<td>10% (19)</td>
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<tr>
<td>Some College</td>
<td>65% (542)</td>
<td>26% (216)</td>
<td>10% (82)</td>
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<td>25% (59)</td>
<td>12% (28)</td>
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<tr>
<td>≥$30,000</td>
<td>65% (488)</td>
<td>26% (192)</td>
<td>9% (66)</td>
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<tr>
<td>History ED visits</td>
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</tr>
<tr>
<td>Absent</td>
<td>67% (457)</td>
<td>23% (155)</td>
<td>10% (66)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>59% (206)</td>
<td>30% (105)</td>
<td>10% (35)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization history</td>
<td></td>
<td></td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>Absent</td>
<td>65% (598)</td>
<td>25% (232)</td>
<td>10% (90)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>63% (65)</td>
<td>27% (28)</td>
<td>11% (11)</td>
<td></td>
</tr>
<tr>
<td>Season that vitamin D level was drawn</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Winter</td>
<td>59% (126)</td>
<td>24% (52)</td>
<td>17% (36)</td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td>54% (181)</td>
<td>33% (112)</td>
<td>13% (43)</td>
<td></td>
</tr>
<tr>
<td>Summer</td>
<td>77% (222)</td>
<td>18% (51)</td>
<td>6% (16)</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>67% (124)</td>
<td>25% (47)</td>
<td>8% (14)</td>
<td></td>
</tr>
</tbody>
</table>
Table II. Lung function by vitamin D deficiency at 8 months (log PC20) to 12 months (Prebronchodilator FEV$_1$, BDR). N=1024.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Vitamin D sufficient n=210</th>
<th>Prebronchodilator FEV$_1$ (liters/second) at 12 months</th>
<th>p</th>
<th>BDR at 12 months</th>
<th>p</th>
<th>Log PC20 at 8 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled corticosteroid</td>
<td></td>
<td>1.93 [0.73]</td>
<td>0.88</td>
<td>0.073 [0.06]</td>
<td>0.45</td>
<td>4.91 [8.40]</td>
<td>0.55</td>
</tr>
<tr>
<td>Vitamin D sufficient n=210</td>
<td></td>
<td>2.01 [0.65]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D insufficient n=66</td>
<td></td>
<td>1.97 [0.43]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D deficient n=20</td>
<td></td>
<td>1.97 [0.43]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nedocromil</td>
<td></td>
<td>1.84 [0.55]</td>
<td>0.95</td>
<td>0.10 [0.087]</td>
<td>0.83</td>
<td>5.42 [9.81]</td>
<td>0.58</td>
</tr>
<tr>
<td>Vitamin D sufficient n=180</td>
<td></td>
<td>1.90 [0.57]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D insufficient N=85</td>
<td></td>
<td>1.85 [0.54]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D deficient n=36</td>
<td></td>
<td>1.85 [0.54]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>1.85 [0.53]</td>
<td>0.33</td>
<td>0.10 [0.094]</td>
<td>0.52</td>
<td>3.23 [5.83]</td>
<td>0.30</td>
</tr>
<tr>
<td>Vitamin D sufficient n=255</td>
<td></td>
<td>1.88 [0.58]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D insufficient n=99</td>
<td></td>
<td>1.94 [0.67]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D deficient n=43</td>
<td></td>
<td>1.94 [0.67]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table III. Change in prebronchodilator FEV₁ 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.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Vitamin D sufficient Mean change in prebronchodilator FEV₁ n=663</th>
<th>Vitamin D insufficiency Mean change in prebronchodilator FEV₁ n=260</th>
<th>p-value*</th>
<th>Vitamin D deficient Mean change in prebronchodilator FEV₁ n=101</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled corticosteroid n=305</td>
<td>0.30 [0.023]</td>
<td>0.33 [0.031]</td>
<td>0.45</td>
<td>0.14 [0.057]</td>
<td>0.0072</td>
</tr>
<tr>
<td>Nedocromil n=307</td>
<td>0.19 [0.039]</td>
<td>0.17 [0.028]</td>
<td>0.18</td>
<td>0.25 [0.023]</td>
<td>0.83</td>
</tr>
<tr>
<td>Placebo n=412</td>
<td>0.23 [0.020]</td>
<td>0.24 [0.025]</td>
<td>0.54</td>
<td>0.16 [0.033]</td>
<td>0.06</td>
</tr>
</tbody>
</table>
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 FEV1 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).