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Vitamin D Supplementation and the Risk of Colds in Patients with Asthma

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Abbreviations:

respiratory tract infections- RTIs

inhaled corticosteroids- ICS

Asthma Control Test- ACT™

21-item Wisconsin Upper Respiratory Symptom Survey- WURSS-21©

Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness trial- VIDA

Lay Summary: Our study suggests that replacement of vitamin D levels does not affect the severity of colds but may increase the frequency of cold symptoms in select groups of patients with asthma, particularly when the dose of ICS is being reduced.

ABSTRACT

Background: Restoration of vitamin D sufficiency may reduce asthma exacerbations, events often associated with respiratory tract infections (RTIs) and cold symptoms.

Objective: To determine whether vitamin D supplementation reduces cold symptom occurrence and severity in adults with mild to moderate asthma and vitamin D insufficiency.

Methods: Colds were assessed in the AsthmaNet Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness (VIDA) trial, which randomized 408 adult patients to receive placebo or cholecalciferol (100,000 IU load plus 4,000 IU/day) for 28 weeks as add-on therapy. The primary outcome assessed cold symptom severity using daily Wisconsin Upper Respiratory Symptom Survey (WURSS)-21 scores.

Results: 203 participants experienced at least one cold. Despite achieving 25-hydroxyvitamin D levels of 41.9 ng/mL (95%CI, 40.1-43.7 ng/mL) by 12 weeks, vitamin D supplementation had no effect on the primary outcome, the average peak WURSS-21 scores [62.0 (95% CI 55.1-68.9; placebo) and 58.7 (95% CI 52.4-65.0; vitamin D), p = 0.39]. The rate of colds did not differ between groups (rate ratio [RR] 1.2, 95% CI 0.9 to 1.5); however, among African-Americans those receiving vitamin D vs. placebo had an increased rate of colds (RR 1.7, 95% CI 1.1-2.7, p = 0.02). This was also observed in a responder analysis of all subjects achieving vitamin D sufficiency regardless of treatment assignment (RR 1.4, 95% CI 1.1-1.7, p = 0.009).

Conclusion: In patients with mild-to-moderate asthma undergoing an ICS dose-reduction, these results do not support the use of vitamin D supplementation for the purpose of reducing cold severity or frequency.

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INTRODUCTION

Vitamin D insufficiency is common in the general population and has been linked to susceptibility to respiratory infections [1-4]. Physiologically, vitamin D alters the function of multiple cell types involved in both the innate and the adaptive immune systems, modulating pathways that can participate in the response to respiratory viral infections [5-9]. Given the results of these epidemiologic and physiologic studies, trials have been conducted to determine whether vitamin D supplementation reduces respiratory infections, but achieved mixed results. In children enrolled during the winter, vitamin D supplementation with 1,200 IU per day for 4 months reduced laboratory-confirmed influenza illnesses by 42% [10]. Likewise, ingestion of vitamin-D (300 IU/d)-fortified milk during the winter reduced the incidence of acute RTIs by 44% as assessed through questionnaires of children [11]. However, monthly vitamin D doses of 100,000 IU for 18 months failed to reduce reported and laboratory-confirmed upper RTIs in adults [12]. A meta-analysis of 11 randomized controlled trials indicated that vitamin D supplementation may prevent RTIs when administered daily rather than in high doses intermittently, although heterogeneity among the trials prevented a definitive conclusion [13]. Recently, a trial of weekly 10,000 IU of vitamin D3 for 2 months in the fall did not affect the viral load or clinical rate of colds, but reduced the incidence of laboratory-confirmed viral RTIs in healthy adults [14]. Although very few of these studies selectively enrolled patients with vitamin D insufficiency, the results collectively suggest that vitamin D supplementation may protect against RTIs, particularly when taken daily.

Patients with asthma are prone to more severe chest cold symptoms despite having similar rate of RTIs when compared to healthy co-habitants [15]. Because vitamin D insufficiency is also common in this population and may have independent effects on lung function and corticosteroid responsiveness [16], we recently completed a trial of vitamin D supplementation in patients with asthma and baseline 25-OH-D insufficiency [17]. Vitamin D supplementation taken daily for 28 weeks did not reduce the rates of first asthma treatment

failure or exacerbations, although it modestly spared the daily dose of inhaled corticosteroids (ICS) when the corticosteroid was tapered [17]. There was a trend for a reduction of the overall rate of exacerbations including multiple events per subject associated with assignment to Vitamin D supplementation (HR, 0.63 [95% CI, 0.39-1.01], P = .05). In a responder analysis, patients achieving vitamin D sufficiency at 12 weeks regardless of treatment assignment had a 40% reduction in overall exacerbations compared to placebo, with a 20% decrease noted for every 10 ng/mL improvement in 25-hydroxyvitamin D levels [17]. Because asthma exacerbations are frequently caused by viral RTIs [15, 18-20], we sought to determine whether vitamin D supplementation reduced severity and rate of acute RTIs (common colds) and the associated changes in asthma control in adults with mild to moderate asthma and vitamin D insufficiency. A portion of this work has been presented as a poster [21].

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METHODS

Study population

This analysis was a prospectively planned secondary analysis of a multi-center, randomized, double-blinded, placebo-controlled, clinical trial (VIDA - Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness) [17]. Briefly, 408 adult patients with mild-to-moderate asthma, baseline serum levels of 25-OH-D3 < 30 ng/mL and asthma symptoms despite low dose ICS were randomized to receive placebo or cholecalciferol for 28 weeks (100,000 IU once, then 4000 IU/d for 28 weeks) as add-on therapy in the background of a tapering ICS protocol.

Procedures

The visit structure and assessment of treatment failure, exacerbation, lung function, airway hyperresponsiveness, asthma symptoms, asthma control (measured by the *Asthma Control Test* (ACT) score [22]), asthma-specific quality of life, 25-hydroxyvitamin D levels, and ICS exposure have been previously described [17]. Cold symptoms were assessed using the 21-item *Wisconsin Upper Respiratory Symptom Survey* (WURSS-21), a validated instrument with a range of 0 to 140 points and a minimally important difference of 18.5 [23, 24]. Instructions on how to complete these surveys and their distribution occurred at the randomization visit, with reinforcement of its use at all subsequent visits occurring at 4 to 6 week intervals. Electronic diaries assessed asthma symptoms and asked “Did you have a cold today?”, which, if answered “yes”, participants were instructed to start completing WURSS-21 surveys daily. Survey completion continued until the first question on the survey (‘How sick do you feel today?’) was answered ‘Not sick’ for two days in a row. All completed surveys were returned to the study coordinator at the participant’s next study visit. Each participant was given 21 copies of the WURSS-21 to keep at home in the event that he/she experienced a cold event between visits.

Melanin-dependent skin pigmentation is a measure of sun exposure, which can correlate with endogenous production of 25-OH-D [25]. Melanin levels were estimated using a Smart

Probe 400 (IMS, Inc, Milford, CT), a spectrophotometer that measures degrees of pigmentation on a continuous scale from 0 to 100, 0 being absolute black and 100 being absolute white. Pigmentation measurements were made from the forehead, outer forearm, inner upper arm and abdomen, with two readings averaged and recorded at each location. We proposed that the difference between the forearm and abdominal readings would be a surrogate measure of degree of sun exposure. Skin pigmentation was measured before and after the 28 weeks of vitamin D supplementation.

Statistical analysis

Testing the primary hypothesis regarding the effect of Vitamin D supplementation on the severity of colds was addressed by fitting a repeated measures analysis of covariance (RM-ANCOVA) model to the peak WURSS-21 cold scores during each cold, allowing for multiple colds within each participant. Assuming that the incidence of colds was similar in our study to that seen in the Asthma Clinical Research Network Post-cold Asthma Control and Exacerbation (PAX) study [24], we estimated that 65 participants per group would experience at least one cold (32.4%). With this sample size we expected to have over 90% power to detect an effect size of 18, assuming that the power in our analyses was increased by the inclusion of multiple colds for each person (2-sided alpha 0.05, standard deviation 32).

In addition to evaluating the average peak cold score from each cold, the average score on day 1 and day 2 were also compared between the intervention and control groups. The rate of colds was compared between the treatment groups using Poisson regression. Each model included adjustment for center, African American race, and BMI>25 (similar to the parent trial [17]). Exploratory analyses to investigate the effect of treatment on cold severity and rate at different levels of baseline factors (African American race, BMI>25, baseline 25-hydroxyvitamin D level, cold season) were conducted via the inclusion of nested effects in the RM-ANCOVA and Poisson regression models.

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A responder analysis was performed to compare the cold severity and rate measures between those who became vitamin D sufficient (achieving a 25-hydroxyvitamin D level of at least 30 ng/ml 12 weeks post-randomization) vs. those who did not become vitamin D sufficient, regardless of treatment. This analysis was also performed using RM-ANCOVA and Poisson regression models as described above. In addition, 25-hydroxyvitamin D level at 12 weeks and change in the forearm to abdominal melanin pigmentation were evaluated as potential factors in each of these models. The impact of a RTI on the subsequent development of a treatment failure or exacerbation regardless of treatment assignment was assessed using Kaplan-Meier methods for the first event, and Poisson regression for the analysis of multiple events. The change in the ACT score during a cold was compared to the change in the ACT score throughout the duration of the study in those who did not experience a cold, this comparison was made using a RM-ANCOVA model adjusted for center, African American race, and BMI>25. All tests were two-sided with a p-value < 0.05 denoting significance. Without formal adjustment for the number of secondary analyses that were performed, the secondary results should be considered exploratory. All analyses were performed using SAS version 9.3 (SAS Institute Inc).

RESULTS

Baseline subject characteristics

Overall, 203 of the 408 (49.8%) participants experienced at least one self-reported cold during the course of the study. For subjects who developed a cold during the study, Table 1 shows the baseline characteristics prior to the cold, stratified by treatment assignment. For the original trial, there were no baseline characteristic differences noted between treatment assignments [17]. This randomization process was also successful when evaluating participants who had a cold during the course of the trial; the exceptions noted were small differences in baseline melanin (Table 1).

Cold severity and frequency

Figure 1 demonstrates the month of occurrence of the colds. The average peak WURSS-21 score for the group of subjects with colds was 61.3 (95% CI 57.6-65.0). We defined improvement of the RTI as the time until the WURSS-21 score was less than 50% of the peak value for two consecutive days [24]. The median time to improvement was 4 days with an interquartile range of 3-6 days. Participants with a cold had a decline in their ACT score (average -1.3, 95% CI -1.8 to -0.8) at the visit occurring after the cold, which was significantly different than the change in ACT scores over the course of the entire treatment period for subjects not experiencing a cold (0.2, 95% CI -0.4 to 0.8, $p < 0.001$, Figure 2, left panel). The minimally important difference for the ACT Score ranges between 2 and 3 depending on the methods and population studied [26]; having a cold increased the odds of having a decline in the ACT Score of at least 2 (OR 1.59, 95% CI 1.01 to 2.49, $p = 0.043$, Figure 2, right panel).

There were no significant differences between treatment groups in the adjusted models for the WURSS-21 scores on day 1, day 2, the sum of days 1-2, the sum of days 1-4, or the sum of days 1-7 (Figure 3A). The time course of the WURSS-21 scores is shown in Figure 3B, reflecting symptoms experienced by the participants during the first 14 days after the start of their colds, stratified by treatment assignment. The peak WURSS-21 cold score for participants

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assigned to placebo was 62.0 (95% CI 55.1-68.9) and 58.7 (95% CI 52.4-65.0) for subjects receiving vitamin D. This difference was not significant before or after adjustment for center, African-American race and BMI>25 (RM-ANCOVA p = 0.39). There were no differences between treatment groups in terms of the time to improvement, even when allowing for multiple colds per person.

Of those participants with at least one cold, the median number of colds per subject was 1 with an interquartile range of 1-2; seventeen subjects had 3 colds, 2 subjects had 4 colds and one subject had 5 colds. With respect to overall rate in the two treatment groups, there were 139 colds among the 207 subjects in the placebo group for a rate of 1.24 colds per person-year and 161 colds experienced by the 201 subjects receiving vitamin D with a rate of 1.48 colds per person-year. The rate ratio for the effect of vitamin D on the rate of colds was 1.2 with a 95% confidence interval of 0.9 to 1.5 (adjusted Poisson regression model p = 0.15). This effect was not different by center or BMI class; however, among African-American participants, those receiving vitamin D had a higher rate of colds than those receiving placebo (RR 1.7, 95% CI 1.1-2.7, p = 0.02).

Responder analysis

Despite enrollment of 217 of 408 subjects (53.2%) with baseline 25-hydroxyvitamin D levels less than 20 ng/mL, 82% of the vitamin-D assigned participants achieved sufficiency reaching a level greater than 30 ng/mL after 12 weeks of treatment with a mean level of 41.9 ng/mL (95%CI, 40.1-43.7 ng/mL); additionally, 9% of the placebo-treated subjects achieved 25-hydroxyvitamin D sufficiency [17]. The left panel of Figure 4 (blue bars) shows similar overall rates of colds in patients stratified by their baseline 25-hydroxyvitamin D levels. In a responder analysis comparing only those subjects who achieved sufficiency vs. those who did not, regardless of treatment assignment, achieving vitamin D sufficiency had no effect on any of the cold severity measures (p > 0.1 in all cases). Additionally as shown in the right panel of Figure 4 (red bars), Vitamin D responders had a higher rate of colds relative to non-responders (1.4,

95% CI 1.1-1.7, p = 0.009). Evaluating the level of 25-hydroxyvitamin D level achieved at 12 weeks post-randomization as a predictor of cold severity did not show a difference when evaluated as a main effect ($p > 0.4$ for all cold severity measures) or nested within cold season ($p > 0.1$ for all seasons). Additionally, adjustment by the change in the forearm to abdominal melanin pigmentation did not show significance ($p > 0.05$ in all cases).

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DISCUSSION

In symptomatic patients with mild-to-moderate asthma with baseline insufficiency of vitamin D and in the setting of ICS dose reduction [17], those assigned to an effective vitamin D supplementation regimen did not have less severe or frequent colds relative to subjects receiving placebo (Figures 3). Although this was a negative result, it is worth noting that the frequency of colds in this pre-specified analysis conferred over 90% power to observe an effect size that was smaller than the Minimal Important Difference for the survey instrument used. The observation period was slightly longer than 6 months, ensuring that each subject was followed during at least one cold season. Adjustment for season of enrollment or sun exposure did not change these results. We conclude that the lack of effect on cold severity in the overall study population is valid and unlikely to change without significant modification of the design.

A few caveats prevent broad generalizations of this study's results. These include the mild-to-moderate severity of the patient population studied. More severe patients with a history of frequent RTI-induced exacerbations might be an ideal population, with evaluation of respiratory samples during the course of the cold to confirm viral-associated events. Additionally, the ICS tapering protocol may have had unanticipated effects. For example, we hypothesized but did not observe (17) that achieving vitamin D sufficiency would allow for enhanced responsiveness to ICS with respect to lung function, due to the ability of vitamin D to influence steroid metabolism. Conversely, it is also possible that the change in ICS doses during the protocol influenced vitamin D metabolism and/or the expression of the vitamin D receptor and binding protein. With these considerations in mind, it is possible that we did not give enough vitamin D and that 25-hydroxyvitamin D levels in the serum do not reflect the changes relevant to airway epithelial innate immunity. This is unlikely in that the supplementation strategy used in this trial achieved 25-hydroxyvitamin D levels of 41.9 ng/mL (95%CI, 40.1-43.7 ng/mL) by 12 weeks [17], and epithelial cell conversion of 25-hydroxyvitamin D to the 1,25-dihydroxy active metabolite starts to plateau around 40 ng/mL; these levels are

sufficient for subsequent expression of cathelicidin and CD14 [27]. Future studies in this area should utilize a fixed dose of ICS (or none) and verify end-target effects of vitamin D supplementation, perhaps by including evaluation of changes in epithelial cell vitamin D-responsive gene expression.

We observed that achieving vitamin D sufficiency increased cold frequency. The direction of this effect is opposite to our hypothesis and appears to be driven by the subjects of African American race, who also had the lowest baseline vitamin D levels (mean 15.6 ng/mL, 95% CI 14.4-16.8 vs. 20.4 ng/mL, 95% CI 19.6-21.2 for all other races, reference (17)). This is also contrary in some ways to the observations that patients achieving vitamin D sufficiency have a lower overall rate of exacerbations (17). It is unlikely that vitamin D levels have any influence on the participants' exposure to respiratory viruses. One speculation is that patients with 25-hydroxyvitamin D levels less than 20 ng/mL may be more likely than those patients with higher levels to have asymptomatic upper respiratory tract infection when exposed to common cold viruses, and in this case replacement of vitamin D could reconstitute the inflammatory responses related to symptom development. This reconstitution could lead to a greater likelihood of upper airway symptoms, while also reducing the likelihood of lower airway infection and related risk of exacerbation. Of note, the median severity of the cold symptoms on a qualitative assessment was mild. Reconciling these possibilities would likely be best addressed in an inoculation study design, before and after vitamin D supplementation. In conclusion, the statistical power, frequency of study visits and lack of a signal in the current trial suggest that longer studies or those achieving higher levels are unlikely to change the conclusion that restoration of vitamin D sufficiency does not impact cold severity in patients with mild to moderate asthma undergoing an ICS dose reduction, and may increase the rate of symptomatic colds in patients with the lowest baseline levels of vitamin D.

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Table 1A: Baseline Characteristics of VIDA Randomized Participants with Colds - Categorical Variables

	Vitamin D (N=110)	Placebo (N=93)	Pbo vs. Vit D
Characteristic	**N (%)**	**N (%)**	**P-value**
Male	32 / 110 (29.1%)	24 / 93 (25.8%)	0.60[C]
Race: American Indian/Alaskan Native	1 / 110 (0.9%)	0 / 93 (0.0%)	0.14[F]
Asian/Pacific Islander	5 / 110 (4.5%)	4 / 93 (4.3%)	
Black	38 / 110 (34.5%)	21 / 93 (22.6%)	
White	53 / 110 (48.2%)	62 / 93 (66.7%)	
Hispanic	9 / 110 (8.2%)	4 / 93 (4.3%)	
Other	4 / 110 (3.6%)	2 / 93 (2.2%)	
OCS Response Period Improvement	14 / 92 (15.2%)	11 / 78 (14.1%)	0.84[C]
One or more asthma episodes in past year requiring ER or unscheduled office visit	40 / 110 (36.4%)	31 / 93 (33.3%)	0.65[C]
One or more overnight hospitalizations in past year due to asthma	5 / 110 (4.5%)	4 / 93 (4.3%)	1.00[F]
One or more courses of systemic corticosteroid therapy taken in past year for asthma	37 / 110 (33.6%)	30 / 93 (32.3%)	0.84[C]
Days of work, school, or housework missed in past year due to asthma: 0 days	65 / 110 (59.1%)	57 / 93 (61.3%)	0.24[C]
1 to 7 days	33 / 110 (30.0%)	20 / 93 (21.5%)	
> 7 days	12 / 110 (10.9%)	16 / 93 (17.2%)	
LTRA / 5LO Inhibitors used during past 12 months for asthma/allergies	32 / 110 (29.1%)	29 / 93 (31.2%)	0.75[C]
Oral Steroids used during past 12 months for asthma/allergies	39 / 110 (35.5%)	27 / 93 (29.0%)	0.33[C]
ICS (not including combination meds) used during past 12 months for asthma/allergies	55 / 110 (50.0%)	38 / 93 (40.9%)	0.19[C]
LABA and ICS combination meds used during past 12 months for asthma/allergies	59 / 109 (54.1%)	58 / 93 (62.4%)	0.24[C]
Vitamin D cutoff less than 20 ng/mL	63 / 110 (57.3%)	48 / 93 (51.6%)	0.42[C]
Season of Enrollment (using randomization date): Spring	29 / 110 (26.4%)	29 / 93 (31.2%)	0.75[C]
Summer	27 / 110 (24.5%)	24 / 93 (25.8%)	
Fall	29 / 110 (26.4%)	19 / 93 (20.4%)	
Winter	25 / 110 (22.7%)	21 / 93 (22.6%)	

OCS: Oral corticosteroid response to prednisone 40 mg PO qd for 5-7 days. LTRA: Leukotriene receptor antagonist. 5LO: 5 lypooxygenase. ICS: Inhaled corticosteroids. LABA: Long-acting beta agonist.

C Chisq test for differences in proportions between specified groups

F Fisher's Exact test for differences in proportions between specified groups

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Table 1B: Baseline Characteristics of VIDA Randomized Participants with Colds - Continuous Variables

	Vitamin D (N=110)			Placebo (N=93)			Pbo vs. Vit D
Characteristic	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**P-value**
Age (years)	110	39.6	12.1	93	39.2	12.8	0.85[T]
Duration of asthma (years since doctor first diagnosed)	110	24.9	13.2	93	25.0	13.4	0.94[T]
BMI (kg/m^2)	110	32.42	8.39	93	31.47	9.85	0.46[T]
Number of positive skin tests +	106	4.00	(2.00,6.00)	88	3.50	(2.00,6.00)	0.41[W]
AM Peak Flow 2-week average (liters/min)	110	401.5	97.3	93	393.1	106.6	0.56[T]
PM Peak Flow 2-week average (liters/min)	110	406.5	102.6	93	395.4	106.7	0.45[T]
AM Symptoms (average over 5 types)* 2-week average	110	0.36	0.27	93	0.40	0.36	0.34[T]
PM Symptoms (average over 5 types)* 2-week average	110	0.38	0.29	93	0.46	0.41	0.13[T]
Pre-bronch FEV_1 (liters)	110	2.62	0.76	93	2.61	0.83	0.98[T]
Pre-bronch FEV_1 % predicted	110	80.9	14.0	93	81.1	14.2	0.92[T]
Pre-bronch FEV_1/FVC ratio	110	0.73	0.09	93	0.71	0.09	0.24[T]
% Improvement in pre-bronch FEV_1 over OCS Response Period	92	-0.93	7.42	78	-0.17	8.04	0.52[T]
Imputed PC_{20} (mg/ml) ^	106	2.14	1.58	88	2.09	1.61	0.92[TL]
Sputum Eosinophils (%) +	90	0.25	(0.00,1.30)	80	0.25	(0.00,1.30)	0.81[W]
Maximum Post-Albuterol FEV_1 % predicted	110	91.61	14.30	92	93.16	13.98	0.44[T]
Maximum Reversibility (% change)	110	16.03	11.91	92	18.41	11.80	0.16[T]
Vitamin D (ng/mL)	110	18.05	(13.70,23.70)	93	19.70	(14.80,24.80)	0.29[W]
Melanin Level (Upper Inner Arm)	108	63.6	(51.4,68.1)	91	65.3	(61.5,67.5)	0.16[W]
Melanin Level (Outer Forearm)	107	56.7	(45.4,60.9)	92	58.3	(52.7,62.4)	0.04[W]
Melanin Level (Exposed Forehead)	108	56.0	(44.8,60.9)	92	58.2	(52.7,62.3)	0.02[W]
Melanin Level (Abdomen)	108	62.0	(45.8,68.0)	92	64.5	(57.6,68.8)	0.08[W]
ASUI Score	110	0.84	0.10	92	0.82	0.12	0.18[T]
ACT Score***	110	20.0	(17.0,22.0)	93	20.0	(17.0,22.0)	0.80[W]
Asthma control days 2-week average (proportion of controlled days)	110	0.20	0.27	93	0.17	0.24	0.39[T]
Asthma control days 2-week sum (# of controlled days)	110	2.81	3.75	93	2.38	3.39	0.39[T]
ABP Score	110	19.0	(13.0,26.0)	93	18.0	(13.0,28.0)	0.66[W]

OCS: Oral corticosteroid response to prednisone 40 mg PO qd for 5-7 days. PC20: Provocative concentration of methacholine that decreased FEV1 by 20%. Maximum reversibility after up to 8 puffs (360 mcg) of inhaled levalbuterol. ASUI: Asthma Symptom Utility Index. ACT: Asthma Control Test. ABP: Asthma Bother Profile.

* Symptoms scale: 0=Absent, 1=Mild, 2=Moderate, 3=Severe. Symptom types: Shortness of breath, Chest tightness, Wheezing, Cough, and Phlegm/Mucus.

*** Individual ACT questions are scaled 1 to 5, with higher values representing better asthma control. ACT score is sum of questions 1-5.

\+ Median (Q1,Q3) reported

^ Geometric mean (CV) reported

T T-test for differences between specified groups

TL T-test for differences between specified groups on log scale

W Wilcoxon rank-sum test for differences between specified groups

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Figure Legends

Figure 1: Number of colds per calendar month during the VIDA trial. This histogram includes multiple colds per subject.

Figure 2: Impact of the cold on asthma control. Changes in Asthma Control Test scores are shown in the left panel. Subjects' baseline measures were subtracted from the ACT measurement taken at the next scheduled study visit for those with colds or from the ACT value at the end of the trial for those without colds. The right panel shows the proportion of subject with a change in ACT scores that was greater than 2, the minimal important difference.

Figure 3: Cold symptom scores. The sum of the WURSS-21 cold scores on days 1-2, days 1-4 and days 1-7 are shown, stratified by treatment assignment (Panel A, red for placebo and blue for Vitamin D). These scores are reported daily with the time course shown for the first 14 days after the start of the cold (Panel B). The number of observations for each day is included, with an expected decrease in sample size due to the resolution of some colds prior to the 14-day window. In addition to the peak scores for single day measures, Data are presented as mean ± SE.

Figure 4: Number of colds per person-year stratified by 25-hydroxyvitamin D level collected at baseline (blue bars) or after completing 12 of 28 weeks of treatment (red bars).

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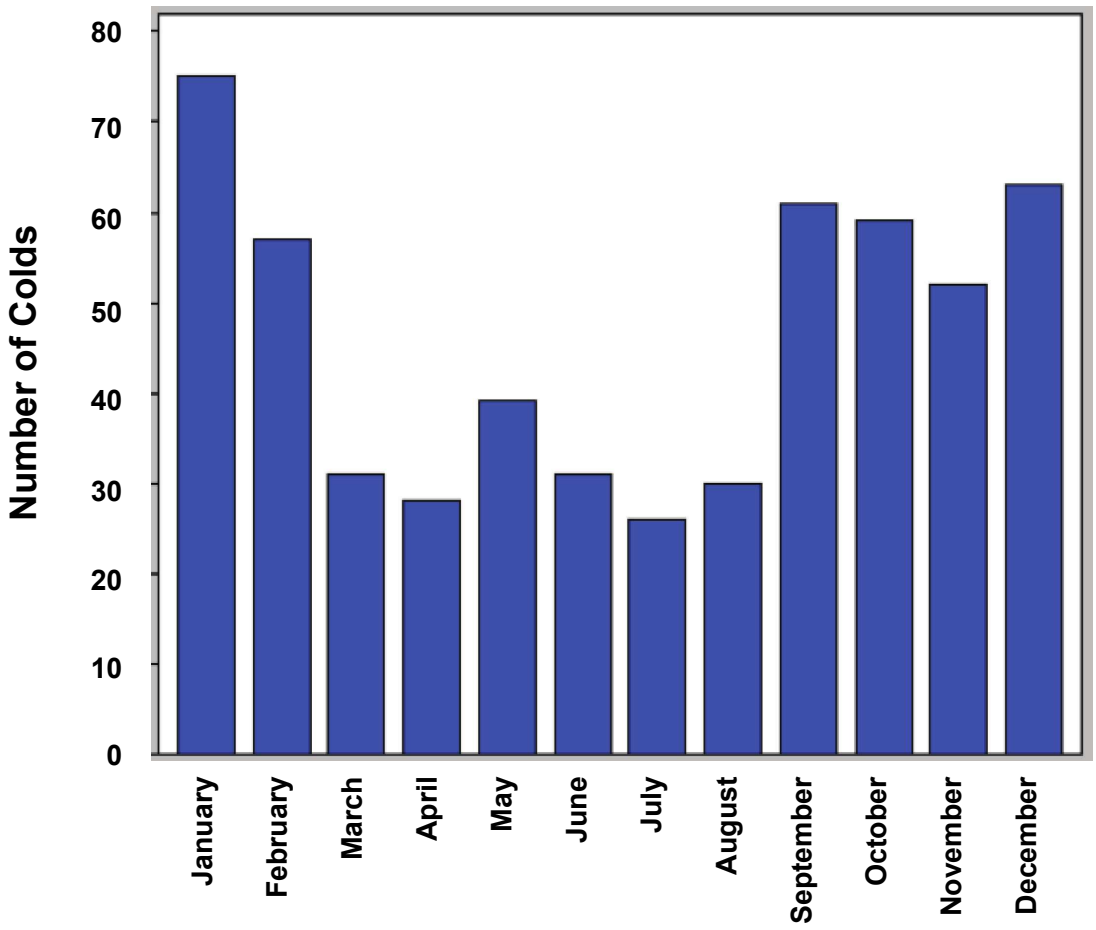
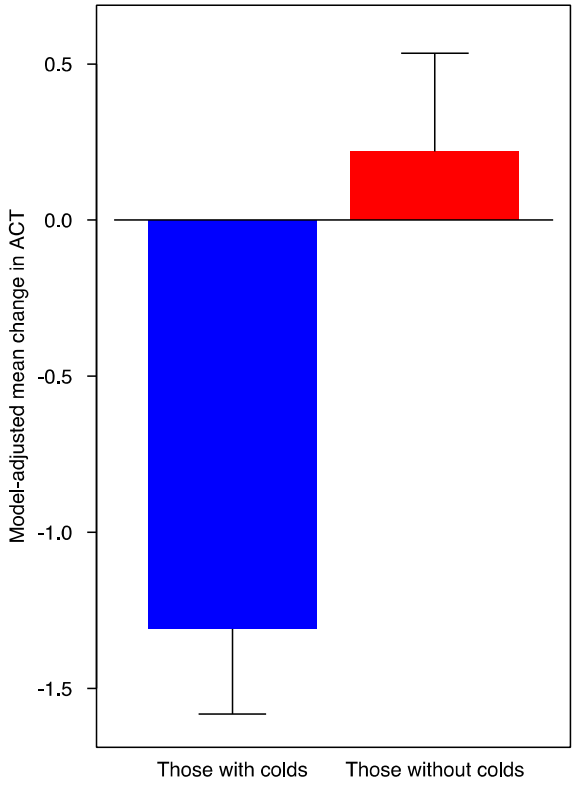
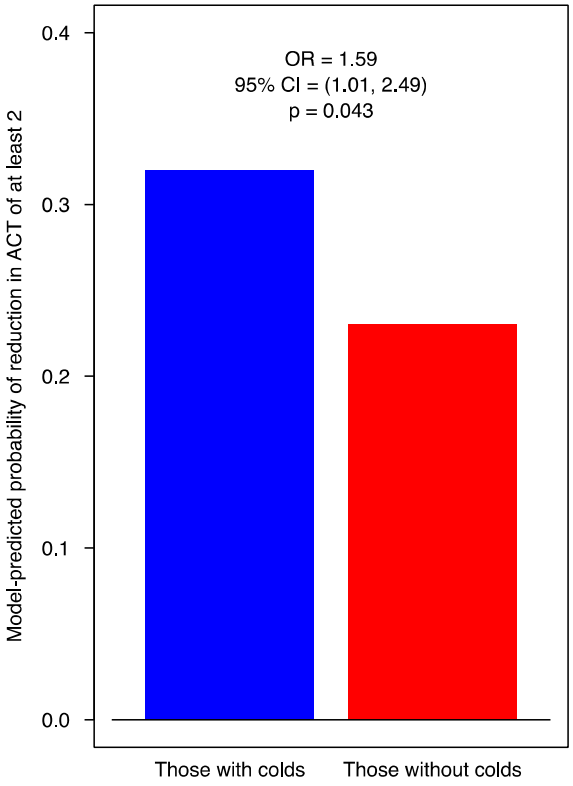
Denlinger *et al.*, Figure 1



Denlinger *et al.*, Figure 2





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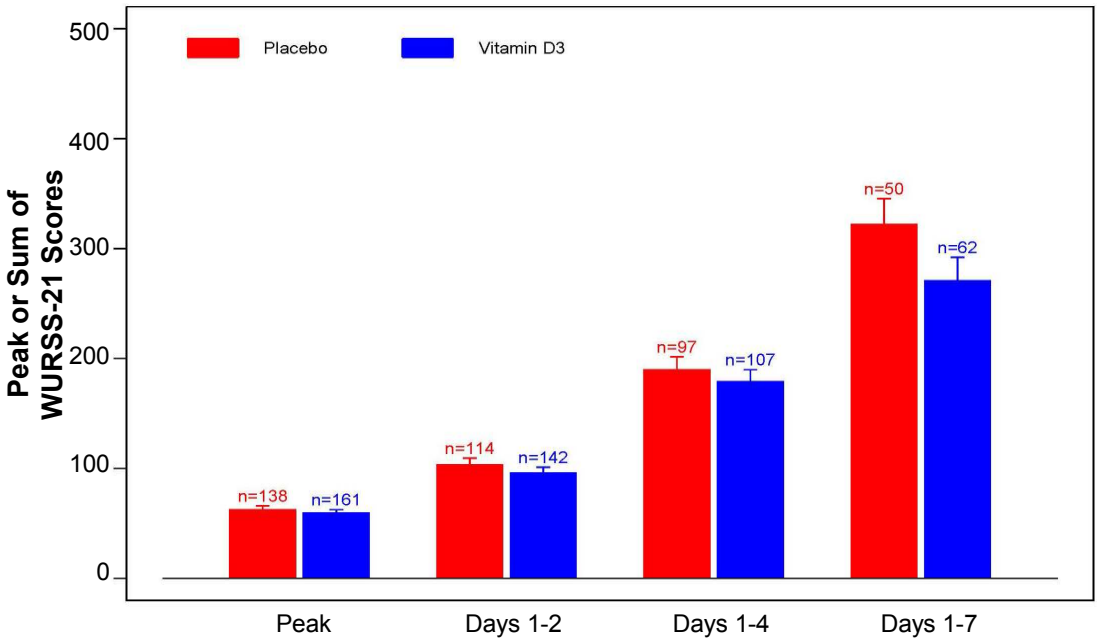
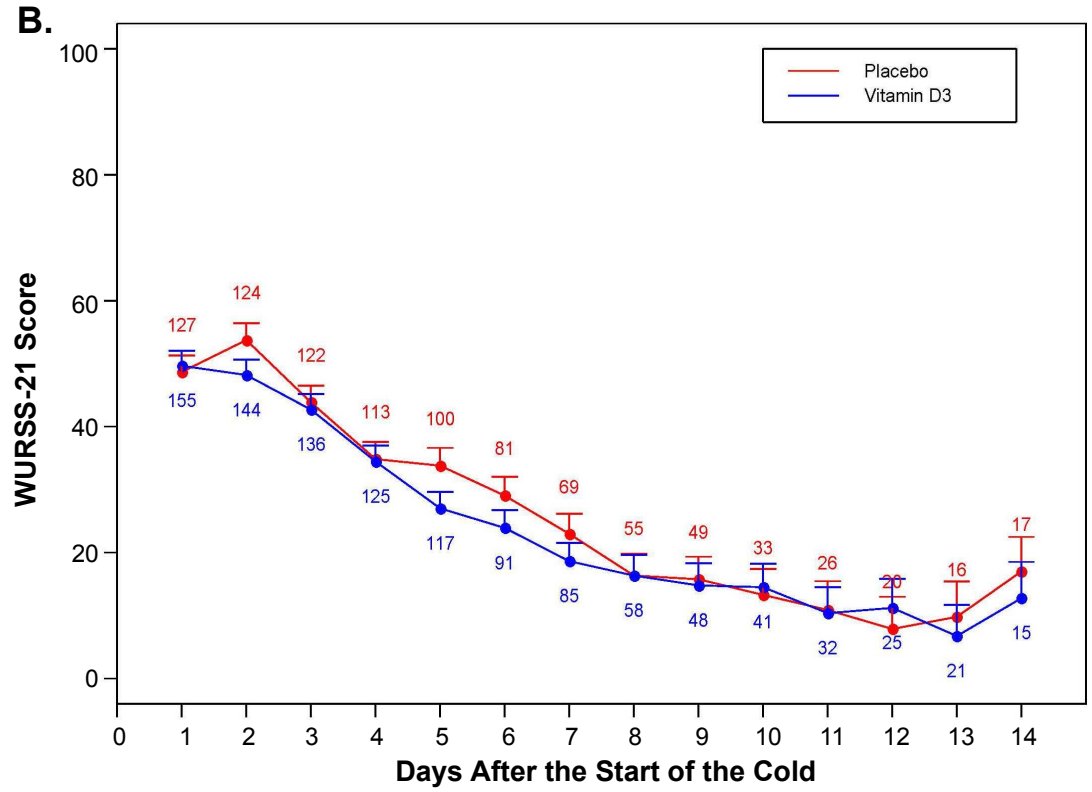
Denlinger *et al.*, Figure 3

A.



B.



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Denlinger *et al.*, Figure 4