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Vitamin D₃ Therapy in Subjects with Asthma Complicated by Sinonasal Disease: Secondary Analysis of the VIDA Trial

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Trial Registration

ClinicalTrials.gov NCT01248065

Keywords

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To the Editor

Our recent Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma (VIDA) clinical trial (NCT01248065) revealed that vitamin D₃ supplementation in adults with persistent asthma and vitamin D insufficiency (serum 25-hydroxyvitamin D <30 ng/mL) did not reduce the rate of asthma treatment failures.¹ Inadequate vitamin D status has been implicated in the pathogenesis of chronic sinonasal disease which frequently co-exists with asthma.^{2, 3} In this pre-specified secondary analysis of the VIDA trial, we aimed to investigate the effects of vitamin D₃ supplementation on sinonasal disease and asthma control in patients having symptomatic asthma and vitamin D insufficiency.

For a complete description of the study methods, refer to this article's Online Repository at www.jacionline.org. Briefly, 408 adult patients with symptomatic asthma and vitamin D insufficiency were randomized to receive placebo (n=207) or oral vitamin D₃ (n=201) in addition to a stable dose of inhaled corticosteroids for 12 weeks. A sinonasal questionnaire (SNQ) was used at baseline to indicate the presence of sinonasal disease (defined as score 1.0).⁴

Of the 408 subjects, 242 (59.3%) had chronic sinonasal disease at baseline. Baseline clinical characteristics were similar across the groups (Table E1). Vitamin D₃ treatment led to substantial improvements in the 25(OH)vitamin D levels in subjects with (42.0 ng/mL, 95%CI 40.2–43.7) and without sinonasal disease (40.8 ng/mL, 95%CI 38.7–43.0, both p<0.001 compared to baseline, Fig 1A). Blacks and non-Blacks responded similarly to vitamin D₃ supplementation (Fig 1B).

There was no difference in the proportion of subjects with baseline sinonasal disease (SNQ 1.0) between those randomized to receive vitamin D₃ or placebo (Fig. 1A). While vitamin D₃ supplementation for 12 weeks was associated with a significant decrease (8.4%) in the percentage of subjects with sinonasal disease (p=0.03), a similar reduction (8.2%) was also observed in the placebo group (p=0.02). The magnitude of decrease was comparable between groups (p=0.56), suggesting that vitamin D₃ was no better than placebo in relieving sinonasal symptoms (Fig. 1C). This finding was corroborated by the lack of change in SNQ scores after 12 weeks - vitamin D₃ (-0.14, 95%CI -0.23–(-)0.06) and placebo groups (-0.14, 95%CI -0.21–(-)0.07) (p=0.97) (Fig. 1D).

In an exploratory analysis, 59 Blacks assigned to the vitamin D₃ group, 28 (47.5%) had SNQ 1.0 after 12 weeks compared to 16/63 (25.4%) in the placebo group, which is lower than the baseline (Fig. 1E). The rate of sinonasal disease in those receiving vitamin D₃ was not improved when compared with placebo (p=0.01). By contrast, the rates of sinonasal disease in non-Black subjects after 12 weeks were similar between the vitamin D₃ and placebo groups (p=0.17).

A multivariate analysis was performed to determine the rates of asthma treatment failures and exacerbations in those subjects with sinonasal disease and those without (Table 1A). Among those receiving vitamin D₃, asthma exacerbations occurred in 23/123 (18.7%) subjects having sinonasal disease in comparison with 5/78 (6.4%) without the disease (adjusted RR 2.9, 95%CI 1.1–7.7, p=0.03). By contrast, the rate of asthma exacerbations was not significantly different among subjects with or without sinonasal disease after receiving placebo (adjusted RR 0.9, 95%CI 0.5–1.6, p=0.68). In Blacks with sinonasal disease who received vitamin D₃, 13/36 (36.1%) experienced asthma exacerbations whereas only 2/27 (7.4%) exacerbations occurred in blacks without the disease (adjusted RR 5.3, 95%CI 1.1–25.1, p=0.04). No such association was observed in non-Blacks receiving vitamin D₃ (adjusted RR 1.8, 95%CI 0.5–6.6, p=0.41) or in those in the placebo group.

We further measured the rates of asthma treatment failure and exacerbation between subjects taking vitamin D₃ and those receiving placebo stratified by the presence or absence of sinonasal disease (Table 1B). The rates of asthma exacerbations were significantly lower in subjects treated with vitamin D₃ with no sinonasal disease (adjusted RR 0.3, 95%CI 0.1–0.7, p=0.01), but not in those with the disease (adjusted RR 0.9, 95%CI 0.5–1.7, p=0.80). A reduced risk of exacerbation in non-Blacks without sinonasal disease receiving vitamin D₃ was observed (adjusted RR 0.2, 95%CI 0.1–0.9, p=0.03). Blacks without sinonasal disease receiving vitamin D₃ appeared to have a similar trend toward lower risk for exacerbation (adjusted RR 0.2, 95%CI 0.05–1.1, p=0.06). There was no effect on asthma treatment failures stratified by the presence or absence of sinonasal disease.

Our data show that vitamin D₃ repletion does not positively influence the course of sinonasal disease in patients with asthma. Decreased risk of asthma exacerbation associated with vitamin D₃ was only seen in those without sinonasal disease. On the other hand, sinonasal disease was associated with a significantly greater rate of asthma exacerbation in Black subjects taking vitamin D₃ while no such relationship was seen in non-Blacks. These findings imply interplay of race and genetic variance on the response to vitamin D₃.^{5, 6}

There are several notable limitations to this study. Caution is needed in interpreting the present data given the small sample size of Blacks and the nature of subgroup analysis with limited power. Further, the SNQ may not have adequate sensitivity to detect a response to vitamin D₃ therapy and the score of 1.0 may not represent the optimal cutpoint. Lastly, it remains unknown whether a 12-week course of treatment with vitamin D₃ is sufficient to impact chronic sinonasal disease.

In summary, correction of vitamin D insufficiency in patients with symptomatic asthma and sinonasal disease did not lead to improved clinical outcomes. In fact, we observed a higher risk of asthma exacerbations in those with sinonasal disease, especially in blacks, suggesting potential deleterious effects of high dose vitamin D in some populations. Clinicians should keep this in mind when using supplements in these populations but be cautious with this interpretation given the relatively small number of Blacks in this study. Conversely, vitamin D₃ was associated with a lower risk of asthma exacerbation in asthma patients without sinonasal disease. Overall, vitamin D₃ supplementation in the setting of patients with

symptomatic asthma needs to take into account the underlying phenotype of sinonasal disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

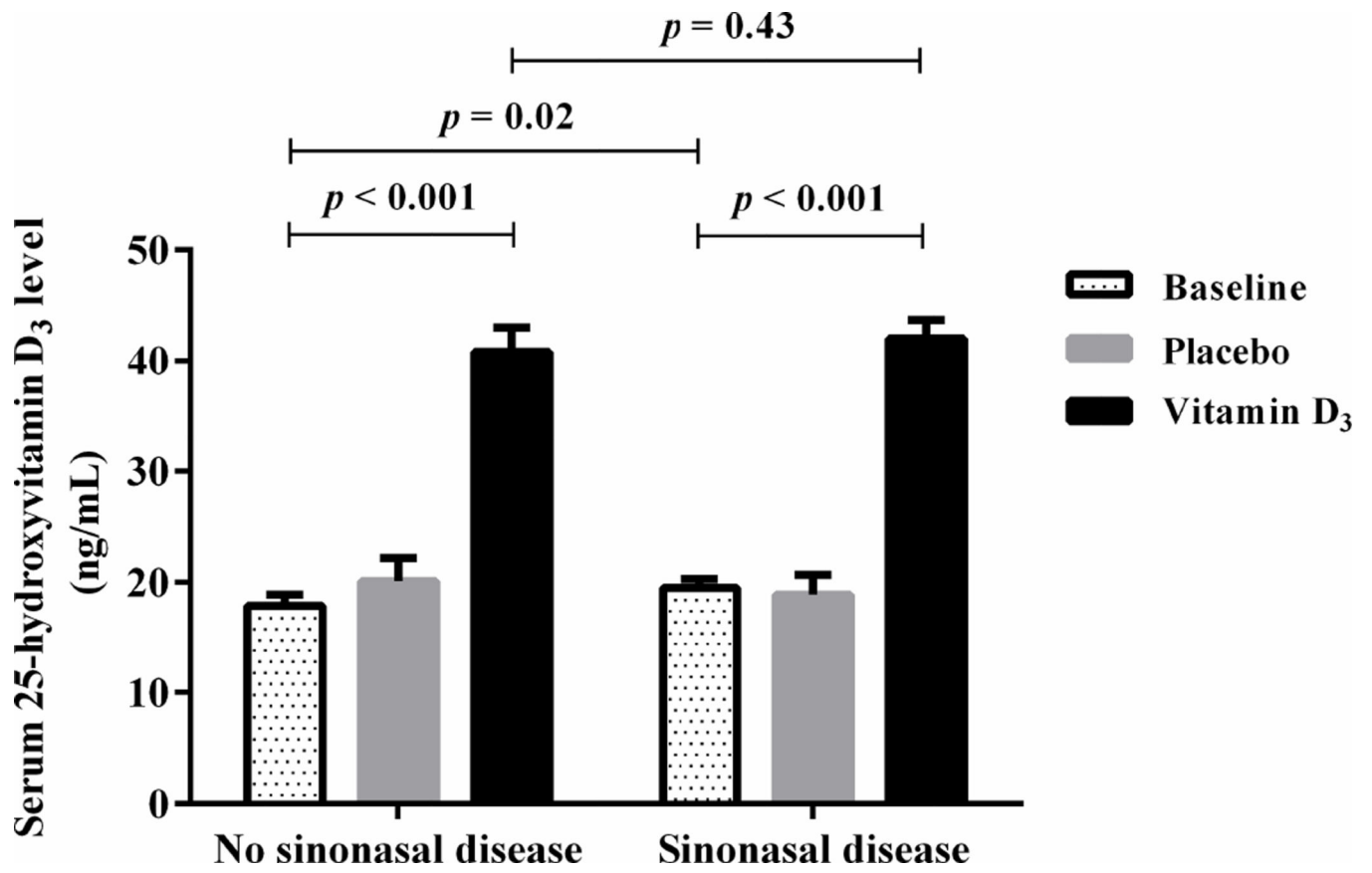
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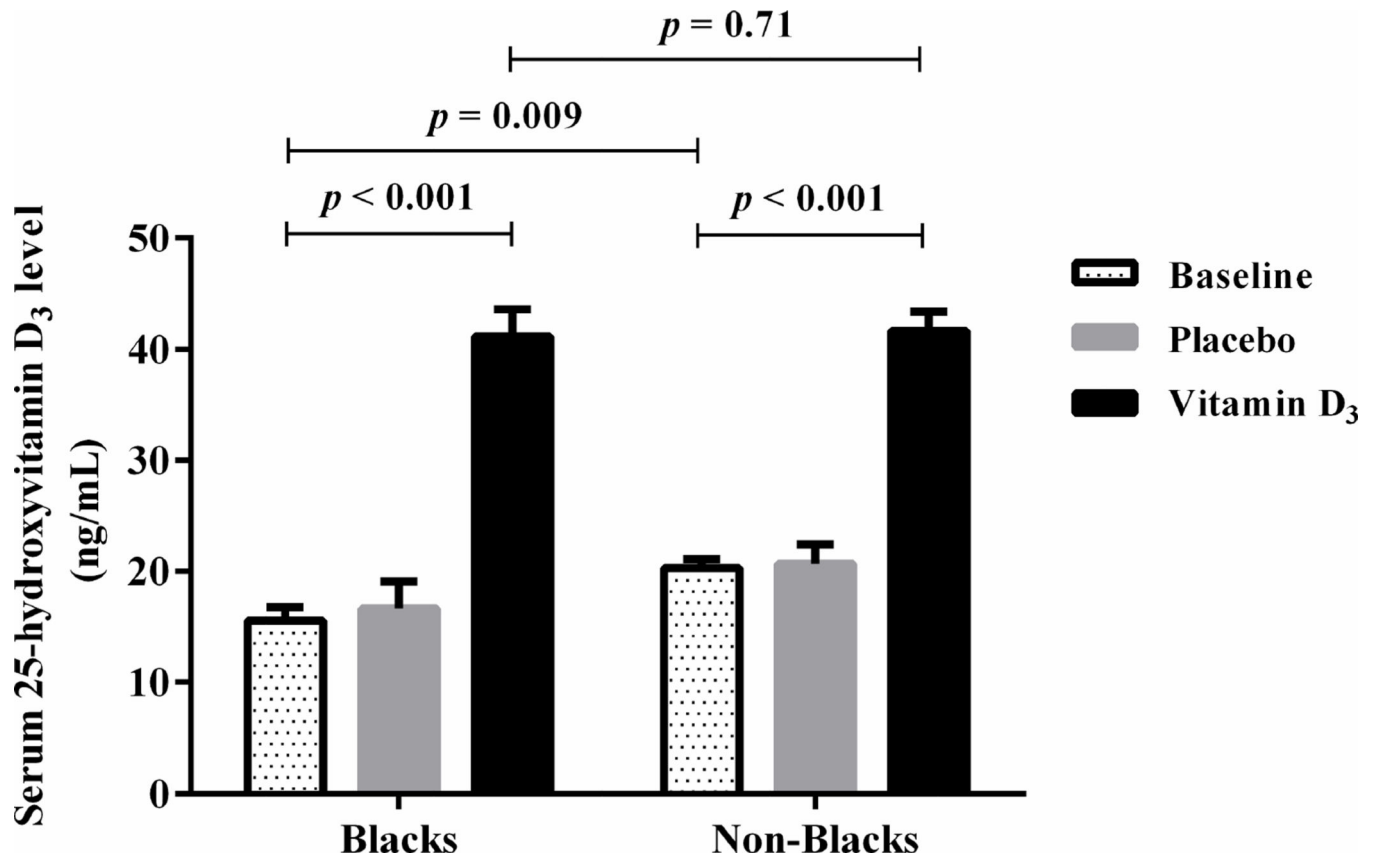
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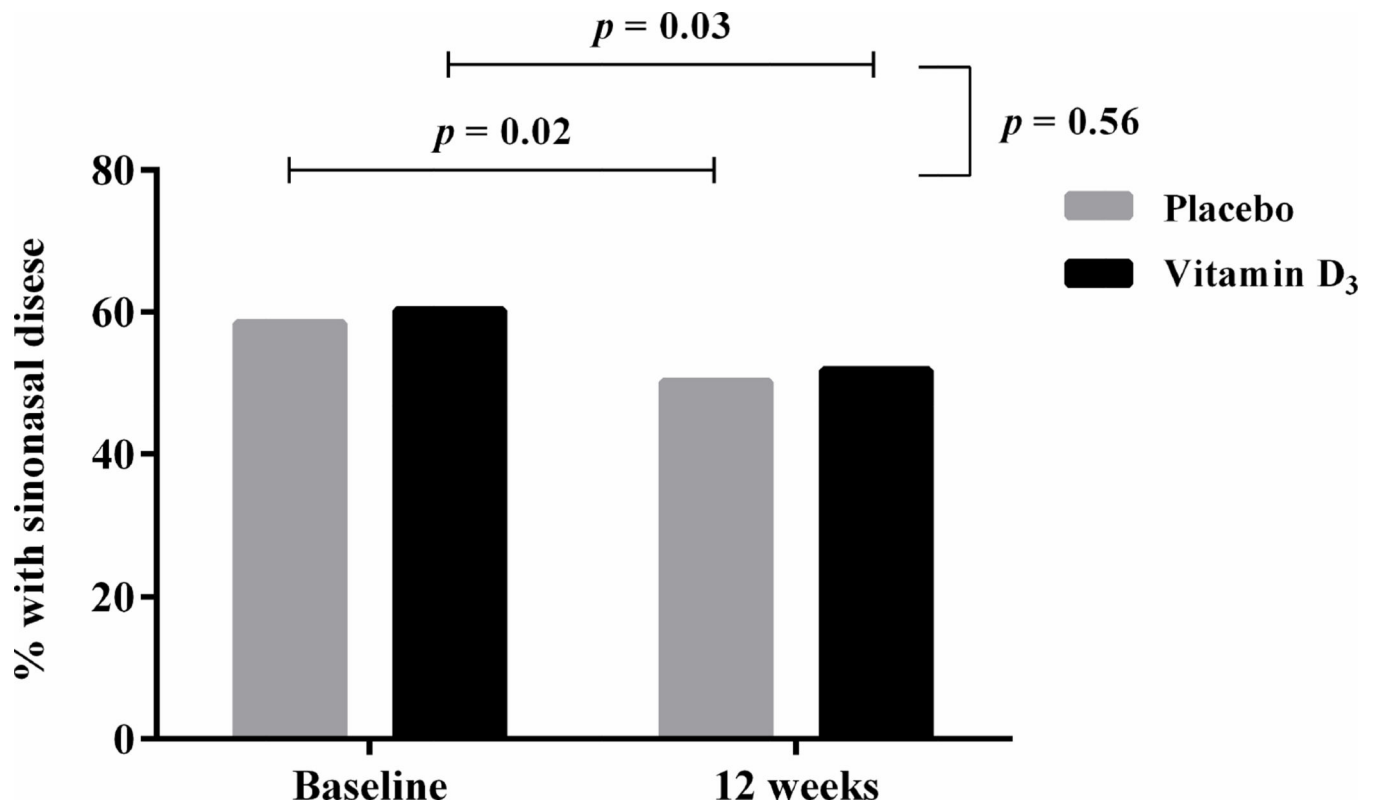
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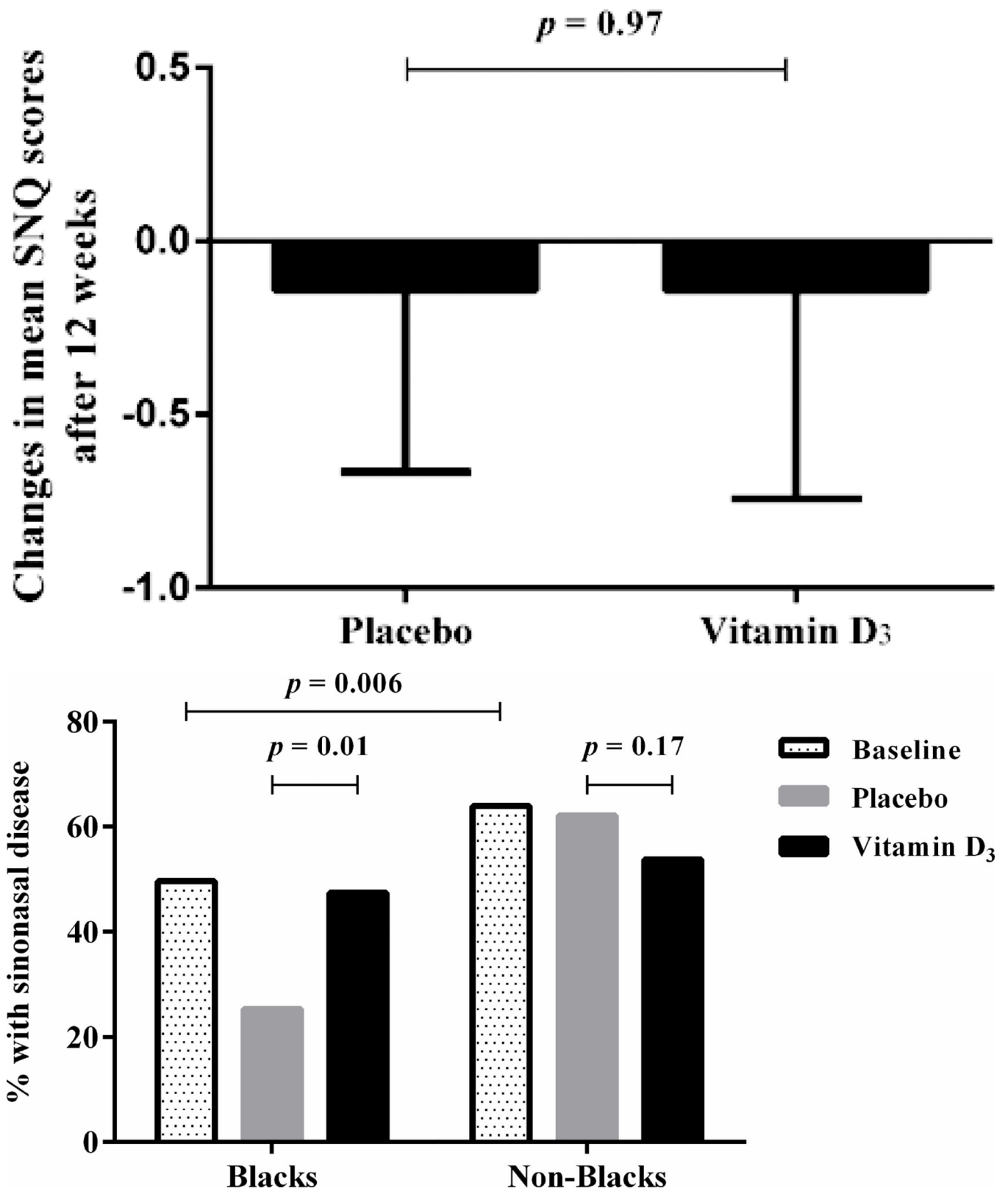


Fig 1.

Responses to vitamin D₃ supplementation in asthmatics with and without sinonasal disease. **A**, Baseline 25-hydroxyvitamin D levels were compared to the levels 12 weeks after randomization to placebo or vitamin D₃ in those with sinonasal disease and without the disease. **B**, Similar comparison between black and non-black subjects. Data are represented as mean ± SD. **C**, Changes in the percentage of sinonasal disease in placebo and vitamin D₃ groups. **D**, Changes in SNQ scores in response to vitamin D₃ and placebo. **E**, Response to vitamin D₃ and placebo in black and non-black subjects with sinonasal disease.

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Table 1

Multivariate adjusted risks of asthma treatment failure and exacerbation

Outcome	Vitamin D ₃ (n = 201)				Placebo (n = 207)			
	Event rate (per person-year)		Adjusted * RR (95% CI)	p value	Event rate (per person-year)		Adjusted * RR (95% CI)	p value
	Sinonasal disease	No sinonasal disease			Sinonasal disease	No sinonasal disease		
Overall	0.59	0.57	1.1 (0.7-1.8)	0.74	0.70	0.80	0.9 (0.6-1.5)	0.82
Asthma treatment failure								
Non-Blacks	0.45	0.47	1.0 (0.5-2.1)	0.98	0.62	0.64	1.0 (0.5-1.8)	0.89
Blacks	0.93	0.75	1.2 (0.6-2.7)	0.61	0.96	1.00	0.9 (0.5-1.9)	0.85
Overall	0.35	0.12	2.9 (1.1-7.7)	0.03	0.36	0.46	0.9 (0.5-1.6)	0.68
Asthma exacerbation								
Non-Blacks	0.21	0.11	1.8 (0.5-6.6)	0.41	0.35	0.42	1.0 (0.4-2.3)	0.97
Blacks	0.67	0.14	5.3 (1.1-25.1)	0.04	0.38	0.52	0.6 (0.2-1.7)	0.33

Outcome	No sinonasal disease (n = 166)				Sinonasal disease (n = 242)			
	Event rate (per person-year)		Adjusted * RR (95% CI)	p value	Event rate (per person-year)		Adjusted * RR (95% CI)	p value
	Vitamin D ₃	Placebo			Vitamin D ₃	Placebo		
Overall	0.57	0.80	0.7 (0.4-1.2)	0.24	0.59	0.70	0.8 (0.5-1.3)	0.43
Asthma treatment failure								
Non-Blacks	0.47	0.64	0.6 (0.3-1.3)	0.19	0.45	0.62	0.8 (0.4-1.3)	0.33
Blacks	0.75	1.00	0.7 (0.3-1.6)	0.43	0.93	0.96	1.0 (0.5-2.0)	0.95
Overall	0.12	0.46	0.3 (0.1-0.7)	0.01	0.35	0.36	0.9 (0.5-1.7)	0.80
Asthma exacerbation								
Non-Blacks	0.11	0.42	0.2 (0.1-0.9)	0.03	0.21	0.35	0.6 (0.2-1.2)	0.14

B. Relative rate ratios between subjects assigned to receive vitamin D3 and placebo

Outcome	No sinonasal disease (n = 166)		Sinonasal disease (n = 242)		Adjusted * RR (95% CI)	p value
	Event rate (per person-year) Vitamin D ₃	Adjusted * RR (95% CI)	Event rate (per person-year) Vitamin D ₃	Adjusted * RR (95% CI)		
Blacks	0.14	0.52 (0.05-1.1)	0.67	0.38 (0.7-5.5)	2.0	0.17

* Poisson regression models adjusted for partnership, body mass index, black race, baseline % predicted FEV1, baseline asthma symptoms, and baseline 25-hydroxyvitamin D level. See the Methods section for definitions of asthma treatment failure and asthma exacerbation in this article's Online Repository at www.jacionline.org.