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Vitamin D supplementation, lung function, and asthma control in children with asthma and low vitamin D levels

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SUMMARY

Observational studies have shown that low vitamin D levels are linked to worse lung function and poor asthma control in children with asthma. We hypothesized that vitamin D supplementation would improve function, disease control, and quality of life in children with asthma (ages 6–16 years) and vitamin D levels below 30 ng/ml. We tested this hypothesis in a secondary analysis of data from the Vitamin D Kids Asthma Study (VDKA), a randomized, double-blind, parallel, placebo-controlled clinical trial. Each participant in the VDKA was randomly assigned to either daily placebo capsules or daily vitamin D3 (4,000 IU) plus low-dose inhaled fluticasone propionate. Of the 192 randomized participants, 176 were included in the analysis of change

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in percent predicted lung function measures (FEV₁, FVC, and FEV₁/FVC) and asthma control scores. Of these 176 participants, 94 were also included in the analysis of change in asthma-related quality of life scores, as they were 10 years and older. Linear regression was used for the multivariable analysis of vitamin D supplementation and each outcome, which was adjusted for study site, race, sex, and time in the study. In this analysis, vitamin D supplementation was not significantly associated with change in any outcome (lung function measures, asthma control, or asthma-related quality of life) between the randomization and exit visits. Our results do not support recommending vitamin D supplementation to improve lung function, asthma control, or asthma-related quality of life in children with asthma and vitamin D levels below 30 ng/ml.

Trial registration: clinicaltrials.gov identifier: [NCT02687815](https://clinicaltrials.gov/ct2/show/study/NCT02687815)

Keywords

Asthma; children; clinical trials; vitamin D; lung function; asthma; children

Observational studies have shown that low vitamin D levels are associated with decreased lung function, worse asthma control, and lower quality of life in children with asthma [1–3]. Moreover, a small randomized imbalanced placebo-controlled trial reported that vitamin D supplementation improved asthma control -but not lung function measures- after two months of treatment. In that trial, children were not selected based on low vitamin D levels, asthma management was not standardized across treatment arms, and a low dose of vitamin D (800 IU/day) was used in the treatment arm [4].

We recently reported that vitamin D supplementation, compared to placebo, had no significant effects on preventing severe asthma exacerbations in children with persistent asthma and low vitamin D levels who participated in the Vitamin D Kids Asthma Study (VDKA), a randomized, double-blind, parallel, placebo-controlled clinical trial ([NCT02687815](https://clinicaltrials.gov/ct2/show/study/NCT02687815)) [5]. Based on published literature, we hypothesized that high-dose vitamin D supplementation would improve lung function, asthma control, and asthma-related quality of life in children with asthma and vitamin D levels below 30 ng/ml. We tested this hypothesis in a secondary analysis of data from the VDKA.

Subject recruitment and the design of the VDKA were recently described in detail [5]. In brief, children were recruited from 7 U.S. sites. The study protocol was approved by the institutional review board at each participating institution, and an independent data and safety monitoring board appointed by the U.S. National Heart, Lung and Blood Institute monitored the study. Written parental consent was obtained for participating children, from whom written assent was also obtained.

Eligible participants were children with asthma, aged 6 to 16 years, with serum vitamin D levels <30 ng/mL but ≥10 ng/mL (until July 21, 2017) or ≥14 ng/mL (after that date, following a protocol amendment). Entry criteria included **i.** physician-diagnosed asthma for ≥1 year; **ii.** ≥1 severe asthma exacerbation in the previous year [6]; **iii.** use of asthma medications for at least 6 months in the previous year; **iv.** forced expiratory volume in one second (FEV₁) ≥70% of predicted; and **v.** either bronchodilator responsiveness or, in those

without bronchodilator responsiveness, increased airway responsiveness to methacholine. Exclusion criteria included chronic respiratory disorders other than asthma, chronic oral corticosteroid therapy, severe asthma, and inability to perform adequate spirometry.

Each participant in the VDKA was randomly assigned to either daily placebo capsules or daily vitamin D3, 4,000 IU (Pharmavite LLC), plus inhaled fluticasone propionate (88 µg twice per day in children aged 6–11 years and 110 µg twice per day in children ≥12 years). Eligible participants were screened between February of 2016 and March of 2019 and enrolled if they met inclusion criteria. After a four-week run-in period in which participants received placebo capsules plus inhaled fluticasone and as-needed inhaled albuterol (prior medications were discontinued), those who met inclusion criteria at entry and during run-in were randomized.

After screening, 219 participants entered a four-week run-in phase, of whom 192 were randomized (96 each to the vitamin D and placebo groups). The reasons for 27 participants dropping out after the run-in period included nonadherence with study medications, failure to schedule a randomization visit, an asthma exacerbation or medication changes during run-in, and withdrawal. Of the 192 participants, 181 (94.3%) completed the trial (88 [49%] in the vitamin D group and 93 [51%] in the placebo group). As per protocol, study medications were stopped in 10 subjects: 4 subjects in the placebo arm had a vitamin D level <10 ng/ml at any visit (n=2) or between 10 and 13 ng/ml at two visits (n=2) and were thus referred to a pediatric endocrinologist for evaluation and treatment, and 6 subjects (4 in the vitamin D arm and 2 in the placebo arm) had ≥3 severe asthma exacerbations [5]. All subjects were followed up under intention to treat principles. Of the 181 subjects who completed the trial, 176 subjects (86 in the vitamin D group and 90 in the placebo group) had adequate lung function measures and data on asthma control scores at the randomization and exit visits, and were thus included in the current analysis. Mean duration of follow-up for these 176 study participants was 315 (± 42) days.

Spirometry was conducted with an EasyOne (NDD Medical Technologies, Andover, Mass) spirometer, following American Thoracic Society/European Respiratory Society recommendations [7]. Percent predicted lung function measures (FEV₁, FVC and FEV₁/FVC) were calculated at the baseline and exit visits, based on the Global Lung Function Initiative [GLI] data [8]. Asthma control was assessed using the Asthma Control Test (ACT, score=5–25) for participants aged ≥12 years, and the Childhood ACT (C-ACT, score=0–27) for participants aged <12 years. A change of 2–3 points in the ACT or C-ACT has been suggested as clinically meaningful [9]. Because ACT and C-ACT score have different ranges, a linear transformation was adopted for the ACT score (ACT') before combining it with the C-ACT score, as follows: $ACT' = c \cdot (ACT - a) / (b - a)$, where **a** denotes the ACT minimum score; **b** denotes the ACT maximum score; and **c** denotes the C-ACT maximum score.

The standardized version of the pediatric asthma quality of life questionnaire (PAQLQ) was used to measure health-related quality of life in 94 children aged 10 years (45 and 49 in the vitamin D and placebo arms, respectively). This questionnaire contains 23 questions

with three domains: symptoms, activity limitation and emotional function (score=1–7, with a higher score indicating a better quality of life) [10].

Our outcomes of interest were change in percent predicted lung function measures, change in the ACT[®]/C-ACT scores, and change in PAQLQ scores between the randomization and exit visits. Linear regression was used for the multivariable analysis of vitamin D supplementation and each outcome, which was adjusted for study site, race (white or Caucasian, Black or African American, and other), sex, and time in the study.

At the randomization visit, participants in the vitamin D supplementation arm were more likely to be female ($P=0.07$). There were no differences in other demographic characteristics, lung function measures, asthma control, or asthma-related quality of life between subjects in the two treatment arms at $P < 0.10$ (data not shown).

Table 1 shows the results of the multivariable linear regression analysis of vitamin D supplementation and the outcomes of interest. In this analysis, vitamin D supplementation was not significantly associated with change in any outcome (lung function measures, asthma control, or asthma-related quality of life) between the randomization and exit visits. In a sensitivity analysis, we excluded 12 participants in the vitamin D treatment arm who had a serum vitamin D level <30 ng/ml at the exit visit, obtaining similar results (data not shown).

Our results are not generalizable to children with asthma and very low vitamin D levels (e.g., <10 ng/ml). We may have also lacked statistical power to detect small differences in the outcomes between treatment arms, but it is unlikely that such differences would be clinically relevant. For example, the 95% confidence interval for our effect estimate for change in the asthma control test (-0.06 points) did not include a change of at least 2 points (ranging from -1.18 points to 1.06 points).

In summary, vitamin D supplementation, compared with placebo, had no significant effect on percent predicted lung function measures (FEV_1 , FVC, or FEV_1/FVC), asthma control, or asthma-related quality of life in children with asthma and low vitamin D levels. Our results do not support recommending vitamin D supplementation to improve lung function, asthma control, or asthma-related quality of life in this population.

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Conflicts of interest: Dr. Celedón has received Asmanex[®] from Merck for another NIH-funded study, unrelated to the current work. Dr. Guilbert reports personal fees from the American Board of Pediatrics (Pediatric Pulmonary

Sub-board), GSK, and TEVA; grants from Astra-Zeneca and Novartis, grants and personal fees from Sanofi/Regeneron, and other support from UpToDate; all unrelated to the current work. Dr. Phipatanakul has served as consultant for GSK, Genentech, Novartis, Regeneron, Sanofi, and Teva; has received clinical trial support or medications from Genentech, Novartis, Regeneron, Sanofi, Circassia, Monaghan, Thermo Fisher, Alk Abello, Lincoln Diagnostics, GSK, Kaleo, and Merck; and reports funding to the institution by Genentech, Regeneron, Novartis, and the US NIH; all for projects unrelated to the current work. Dr. Cabana is a member of the United States Preventive Services Task Force (USPSTF). The contents of this manuscript do not necessarily represent the views of the USPSTF.

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Table 1

-Multivariable analysis of vitamin D supplementation, compared with placebo, and change in () lung function measures and asthma outcomes

	Unadjusted	Adjusted*
Outcome of interest	β (95% confidence interval)	
Lung function measures		
% predicted FEV ₁	-0.63 (-4.72, 3.46)	-0.51 (-4.69, 3.67)
% predicted FVC	-0.43 (-3.80, 2.93)	-0.57 (-3.95, 2.82)
% predicted FEV ₁ /FVC	0.03 (-2.57, 2.62)	0.30 (-2.30, 2.89)
FEV ₁ /FVC (%)	0.05 (-2.23, 2.33)	0.25 (-2.03, 2.54)
Asthma-related outcomes		
Asthma control test	-0.17 (-1.27, 0.93)	-0.06 (-1.18, 1.06)
Asthma-related quality of life [†]	0.19 (-0.20, 0.57)	0.12 (-0.27, 0.51)

* All models adjusted for sex, race, study site, and days in the study (range:162 to 359 days).

[†] Available in children 10 years and older