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

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To the Editor:

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 randomised imbalanced placebo-controlled trial reported that vitamin D supplementation improved asthma control, but not lung function measures, after 2 months of treatment. In that trial, children were not selected based on low vitamin D levels, asthma management was not standardised across treatment arms, and a low dose of vitamin D (800 IU per 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 randomised, double-blind, parallel, placebo-controlled clinical trial (NCT02687815) [5]. Based on published literature, we hypothesised 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 $ng \cdot mL^{-1}$. 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 seven US 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 US 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 $ng \cdot mL^{-1}$ but $\geqslant 10$ $ng \cdot mL^{-1}$ (until 21 July, 2017) or $\geqslant 14$ $ng \cdot mL^{-1}$ (after that date, following a protocol amendment). Entry criteria included 1) physician-diagnosed asthma for $\geqslant 1$ year; 2) $\geqslant 1$ severe asthma exacerbation in the previous year [6]; 3) use of asthma medications for at least 6 months in the previous year; 4) forced expiratory volume in one second (FEV_1) $\geqslant 70\%$ of predicted; and 5) 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, 4000 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 $\geqslant 12$ years). Eligible participants were screened between February of 2016 and March of 2019 and enrolled if they met inclusion criteria. After a 4-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 randomised.

After screening, 219 participants entered a 4-week run-in phase, of whom 192 were randomised (96 each to the vitamin D and placebo groups). The reasons for 27 participants dropping out after the run-in period included nonadherence to study medications, failure to schedule a randomisation visit, an asthma

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Vitamin D supplementation, compared with placebo, had no significant effect on percent predicted lung function measures (FEV1, FVC or FEV1/FVC), asthma control, or asthma-related quality of life in children with asthma and low vitamin D levels https://bit.ly/3ibbT4u

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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: four subjects in the placebo arm had a vitamin D level <10 $ng \cdot mL^{-1}$ at any visit (n=2) or between 10 and 13 $ng \cdot mL^{-1}$ at two visits (n=2) and were thus referred to a pediatric endocrinologist for evaluation and treatment, and six subjects (four in the vitamin D arm and two 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 randomisation and exit visits, and were thus included in the current analysis. Mean±SD duration of follow-up for these 176 study participants was 315±42 days.

Spirometry was conducted with an EasyOne (NDD Medical Technologies, Andover, MA, USA) spirometer, following American Thoracic Society/European Respiratory Society recommendations [7]. Percent predicted lung function measures (FEV_1, forced vital capacity (FVC) and FEV_1/FVC) were calculated at the baseline and exit visits, based on the Global Lung Function Initiative data [8]. Asthma control was assessed using the Asthma Control Test (ACT, score 5–25) for participants aged ⩾12 years, and the Childhood Asthma Control Test (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: $ACT' = c \times (ACT - a)/(b - a)$, where a denotes the ACT minimum score; b denotes the ACT maximum score; and c denotes the C-ACT maximum score.

The standardised version of the Paediatric 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 randomisation 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 randomisation 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 randomisation and exit visits. In a sensitivity analysis, we excluded 12 participants in the vitamin D

TABLE 1 Multivariable analysis of vitamin D supplementation, compared with placebo, and change in (Δ) lung function measures and asthma outcomes

Outcome of interest	β (95% CI)	
	Unadjusted	Adjusted[#]
Lung function measures		
Δ % predicted FEV_1	−0.63 (−4.72, 3.46)	−0.51 (−4.69, 3.67)
Δ % predicted FVC	−0.43 (−3.80, 2.93)	−0.57 (−3.95, 2.82)
Δ % predicted FEV_1/FVC	0.03 (−2.57, 2.62)	0.30 (−2.30, 2.89)
Δ FEV_1/FVC (%)	0.05 (−2.23, 2.33)	0.25 (−2.03, 2.54)
Asthma-related outcomes		
Δ Asthma control test	−0.17 (−1.27, 0.93)	−0.06 (−1.18, 1.06)
Δ 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. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

treatment arm who had a serum vitamin D level <30 ng·mL^{-1} at the exit visit, obtaining similar results (data not shown).

Our results are not generalisable to children with asthma and very low vitamin D levels (*e.g.* <10 ng·mL^{-1}). 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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Trial registration: Clinicaltrials.gov identifier NCT02687815. Requests for de-identified data from this clinical trial should be made to the corresponding author. Following completion of a signed data access agreement for a specified purpose (*e.g.* a meta-analysis), researchers whose proposed used of the data has been approved will receive de-identified data for study participants and a data dictionary for this clinical trial, starting on 15 December, 2020.

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