Vitamin D replacement in children with acute wheeze: a dose-escalation study

Received: 28 Oct 2021
Accepted: 31 Jan 2022

To the Editor:

Meta-analyses report protective effects of vitamin D supplementation against asthma exacerbations and acute respiratory infections in adults [1–3], but data relating to effects of vitamin D on risk of preschool wheeze and asthma attacks in childhood are more limited [4]. In preparation for a randomised controlled trial (RCT) of vitamin D in children with recurrent preschool wheeze or school-age asthma, we carried out a dose-escalation study to find the daily vitamin D_3 supplementation regimen that is most effective in elevating circulating 25-hydroxyvitamin D (25(OH)D) concentrations in these children. We hypothesised that daily oral vitamin D_3 supplementation of 1000 IU would be more effective than 400 IU (UK recommendation [5]) in elevating the circulating 25(OH)D concentration to $\geqslant$75 nmol·L^{-1} at 3 months in vitamin-D-insufficient children with recurrent preschool wheeze or school-age asthma.

Children were recruited from primary and secondary care if they were aged 1–4 years with $\geqslant$2 self-reported episodes of acute wheeze requiring unscheduled healthcare attendances in the preceding year (preschool children), or aged 5–12 years with doctor-diagnosed asthma and $\geqslant$1 self-reported asthma attack requiring an unscheduled healthcare attendance in the preceding year (school children). Exclusion criteria were baseline 25(OH)D level $\geqslant$75 nmol·L^{-1}, concurrent vitamin D supplementation, or a history of other chronic or acute respiratory or systemic conditions. Approval was by Brent Ethics Committee (ref 16/LO/1218). Written informed consent was obtained from parents of all children, with assent additionally obtained from children aged $\geqslant$7 years.

Oral vitamin D_3 (Fultium-D_3 drops; Internis Pharmaceuticals Ltd) was initially administered at a dose of 400 IU·day^{-1} for 3 months (phase 1). The dose was increased to 1000 IU·day^{-1} for a further 3 months (phase 2) if the 25(OH)D concentration at the end of phase 1 was <150 nmol·L^{-1}; otherwise, no dosing increment was applied during phase 2. Concentrations of 25(OH)D_2 and 25(OH)D_3 in capillary blood were measured from a fingerprick at baseline and at the end of phases 1 and 2 using liquid chromatography with tandem mass spectrometry and summed to give the total circulating 25(OH)D concentration [6]. Nasal epithelial lining fluid was sampled at baseline and at the end of phases 1 and 2 using nasosorption [7]. Nasal concentrations of cytokines and chemokines were determined using a multiplex assay (Meso Scale Discovery, #15050D). At baseline, body weight was measured with a validated scale. Children aged 5–12 years completed a baseline childhood asthma control test (c-ACT) under their parent's/legal guardian's supervision. The volume of residual vitamin D_3 supplement was assessed at the end of phases 1 and 2.

Co-primary outcomes were the proportions of participants attaining 25(OH)D $\geqslant$75 nmol·L^{-1} at the end of phases 1 and 2. Secondary outcomes were mean concentrations of 25(OH)D in capillary blood and concentrations of inflammatory mediators in nasal epithelial lining fluid. The proportions of children attaining serum 25(OH)D concentrations $\geqslant$75 nmol·L^{-1} or $\geqslant$100 nmol·L^{-1} at the end of phases 1 *versus* 2 were compared using McNemar's test. Mean 25(OH)D levels and c-ACT score by visits were compared using paired t-tests. Univariate linear regression was applied to determine independent predictors (body weight and age) of the response to vitamin D supplementation during phases 1 and 2. End-phase mean cytokine and chemokine concentrations were compared using paired t-tests with correction for multiple comparisons using the Benjamini and Hochberg method with a false discovery rate of 5% [8].

Shareable abstract (@ERSpublications)
Vitamin D supplementation at the current UK recommended level (400 IU·day^{-1}) or enhanced supplementation (1000 IU·day^{-1}) failed to achieve adequate levels of vitamin D (>75 nmol·L^{-1}) in vitamin-D-insufficient children with acute wheeze https://bit.ly/3J43Ouo

Cite this article as: Stefanidis C, Bush A, Newby C, *et al*. Vitamin D replacement in children with acute wheeze: a dose-escalation study. *ERJ Open Res* 2022; 8: 00609-2021 [DOI: 10.1183/23120541.00609-2021].

40 children had baseline 25(OH)D <75 nmol·L^{-1} and were offered vitamin D, of whom eight withdrew from the study (withdrew consent/assent or consistently failed to attend scheduled study visits and did not reply to telephone calls) and one was excluded from statistical analyses as dosing was unchanged during phase 2. Mean±SD baseline body weight for all children was 27.8±17.4 kg (n=31), with 15.4±2.7 kg for preschool children (n=15) and 39.5±17.2 kg for school children (n=16). At baseline, 12 out of 16 (75%) school children had uncontrolled asthma (c-ACT score ⩽19), and four out of 16 (25%) had controlled asthma (c-ACT score >19). 11 out of 31 (35.5%) children attained 25(OH)D ⩾75 nmol·L^{-1} at the end of phase 1 *versus* 16 out of 31 (51.6%) at the end of phase 2 (p=0.06). All children who attained 25(OH)D ⩾75 nmol·L^{-1} at the end of phase 1 maintained 25(OH)D ⩾75 nmol·L^{-1} at the end of phase 2. Four out of 31 (12.9%) children (all preschool children) attained 25(OH)D ⩾100 nmol·L^{-1} at the end of phase 1 *versus* 12 out of 31 (38.7%) (10 preschool children and two school children) at the end of phase 2 (p=0.13). Mean 25(OH)D concentration increased from baseline to the end of phase 1 (mean change 23.6 nmol·L^{-1}, 95% CI 15.1–32.1 nmol·L^{-1}; p<0.001) and from the end of phase 1 to the end of phase 2 (mean change 12.7 nmol·L^{-1}, 95% CI 1.4–23.9 nmol·L^{-1}; p=0.03) (figure 1).

10 out of 15 (66.7%) and 11 out of 15 (73.3%) preschool children attained 25(OH)D ⩾75 nmol·L^{-1} at the end of phases 1 and 2, respectively (p>0.99). One out of 16 (6.3%) and five out of 16 (31.3%) school children attained 25(OH)D ⩾75 nmol·L^{-1} at the end of phases 1 and 2, respectively (p=0.13). We reasoned that a greater proportion of preschool children *versus* school children attaining 25(OH)D ⩾75 nmol·L^{-1} might arise as a consequence of differences in body weight and age, as reported elsewhere [9]. We found that the 25(OH)D response to vitamin D supplementation during phases 1 or 2 was not associated with body weight (mean difference per additional kg of body weight during phase 1 was −0.2 nmol·L^{-1}, 95% CI −0.9 to 0.4 nmol·L^{-1}, p=0.47; mean difference per additional kg of body weight during phase 2 was −0.1 nmol·L^{-1}, 95% CI −1.1 to 0.1 nmol·L^{-1}, p=0.12). The 25(OH)D response to vitamin D supplementation during phase 1 was not associated with age (mean difference per additional year of age was 0.7 nmol·L^{-1}, 95% CI −2.5 to 3.9 nmol·L^{-1}; p=0.66). However, there was a trend for an inverse association between the 25(OH)D response to vitamin D supplementation during phase 2 with age (mean difference per additional year of age was −3.3 nmol·L^{-1}, 95% CI −6.7 to 0.1 nmol·L^{-1}; p=0.06). In preschool children, mean circulating 25(OH)D concentration increased from baseline to the end of phase 1 (mean change 28.7 nmol·L^{-1}, 95% CI 11.9–45.4 nmol·L^{-1}; p=0.002) and from the end of phase 1 to the end of phase 2 (mean change 24.3 nmol·L^{-1}, 95% CI 4.0–44.6 nmol·L^{-1}; p=0.02). In school children, mean circulating 25(OH)D concentration increased significantly from baseline to the end of phase 1 (mean change 18.9 nmol·L^{-1}, 95% CI 11.9–25.9 nmol·L^{-1}; p<0.001), but no increase was seen between the end of phase 1 and the end of phase 2 (mean change 1.7 nmol·L^{-1}, 95% CI −8.3 to 11.8 nmol·L^{-1}; p=0.72) (figure 1). No participant experienced hypervitaminosis D (25(OH)D >220 nmol·L^{-1}) or any adverse reaction. The highest 25(OH)D concentrations were 181 nmol·L^{-1} in a school child at the end of phase 1,

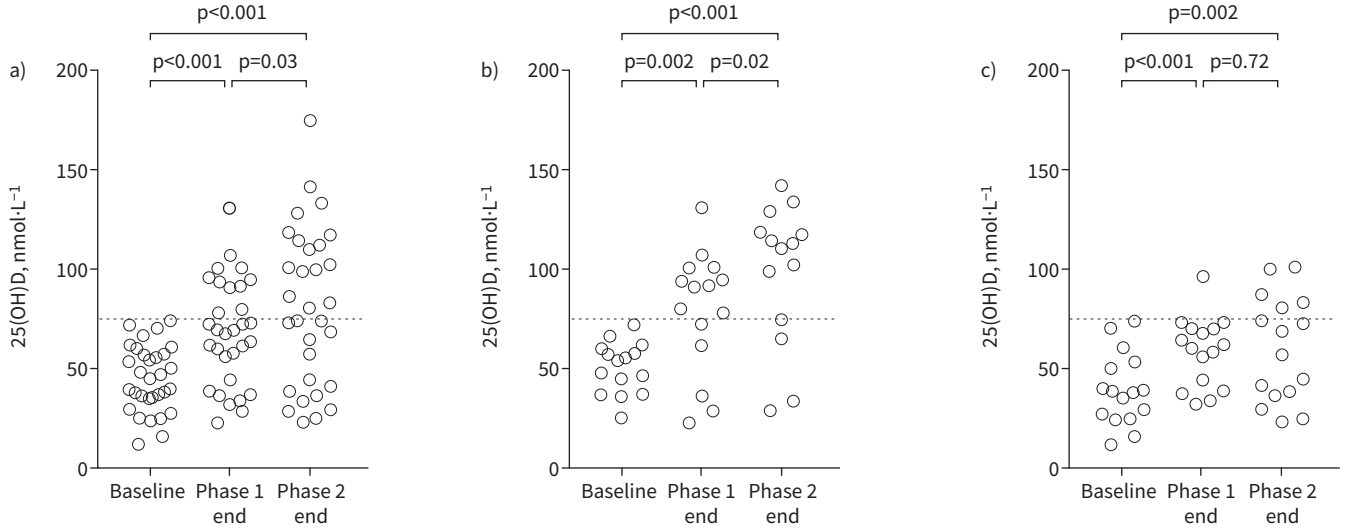

FIGURE 1 25-hydroxyvitamin D (25(OH)D) concentrations by study time-point in a) all participants (n=31), b) the subset of participants with preschool wheeze (n=15) and c) the subset of participants with school-age asthma (n=16). The dotted line represents the threshold denoting optimal 25(OH)D concentration (>75 nmol·L^{-1}). p-values from paired t-tests.

and 175 nmol·L^{-1} in a preschool child at the end of phase 2. Mean c-ACT score was not associated with baseline 25(OH)D concentration, or with the response to vitamin D supplementation during phases 1 or 2 ($p \geqslant 0.19$). There were no statistically significant changes in nasal epithelial lining fluid cytokines or chemokines.

The volume of vitamin D_3 supplement returned at the end of phase 1 was higher than the expected volume based on 100% adherence in 10 out of 13 (76.9%) school children and in seven out of 14 (50.0%) preschool children. At the end of phase 2, two out of seven (28.6%) preschool children returned their vitamin D_3 supplement with a higher residual volume than was compatible with 100% adherence. Only a limited number of vials were handed back at the end of phases 1 (27 vials) and 2 (12 vials).

Neither vitamin D replacement regimen investigated was particularly effective in elevating 25(OH)D concentrations to $\geqslant$75 nmol·L^{-1} in vitamin-D-insufficient children with preschool wheeze or asthma: nearly half the children failed to attain 25(OH)D concentration $\geqslant$75 nmol·L^{-1} after 3 months of supplementation with 1000 IU vitamin D_3. A greater proportion of preschool children attained 25(OH)D concentrations $\geqslant$75 nmol·L^{-1} at the end of phases 1 (10 out of 15 *versus* one out of 16) and 2 (11 out of 15 *versus* five out of 16) compared to school children ($p \geqslant 0.001$). A daily oral dose of 400 IU vitamin D safely elevated circulating 25(OH)D levels by a mean of 23.6 nmol·L^{-1} at 3 months. Escalation of this dose to 1000 IU·day^{-1} resulted in a further mean increase of 12.7 nmol·L^{-1}. Stratification of the analysis by age group revealed that increases in 25(OH)D were higher among preschool *versus* school children.

The main strength of the study is the prospective, individual tailoring of supplementation and the use of a fingerprick to measure 25(OH)D levels, which was well tolerated. We acknowledge that we did not record information on prescribed asthma treatments. Additionally, we highlight the fact that we excluded children who received vitamin D supplementation at the time of enrolment as they were more likely to have a circulating 25(OH)D concentration $\geqslant$75 nmol·L^{-1}; this may have limited the generalisability of our findings. The main limitation related to monitoring adherence: weighing returned bottles only reveals what medication has not been taken, and we cannot know if the missing drops were taken regularly, all at once before return (dose-dumping) or discarded. Better adherence in preschool *versus* school children may therefore explain their higher attained 25(OH)D levels. Alternatively, children with asthma may have dysregulated vitamin D metabolism associating with a blunted 25(OH)D response to vitamin D_3 supplementation, as recently reported in adults [10]. Finally, reference ranges for 25(OH)D levels are based on requirements to support optimal bone health; the levels needed to support optimal immune function are unknown.

Our data have implications for the design of RCTs of vitamin D supplementation in preschool wheeze and school-age asthma. It cannot be assumed that conventional supplementation will achieve adequate levels in all participants. Given the safety data here, it would seem reasonable initially to supplement children who are vitamin D deficient with 1000 IU rather than 400 IU·day^{-1}, since this regimen resulted in higher mean attained 25(OH)D levels without increasing risk of hypervitaminosis D; it may be that doses of >1000 IU·day^{-1} are needed to prevent exacerbations. The use of smart phone applications for remote direct observation of daily vitamin D_3 supplement intake may be an inexpensive method to address adherence accurately and allow researchers to prompt participants with poor adherence [11]. Financial incentives or rewards for those whose adherence can be documented remotely can optimise adherence and encourage patients to complete the study as per protocol [12].

Christos Stefanidis[1], Andrew Bush[2], Christopher Newby[1], Chinedu Nwokoro[1], Susan Liebeschuetz[3], Imogen P. Skene[4], Christopher J. Griffiths[1] and Adrian R. Martineau[1]

[1]Asthma UK Centre for Applied Research; Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK. [2]Asthma UK Centre for Applied Research; Imperial College and Royal Brompton Hospital, Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London, London, UK. [3]Dept of Paediatrics, Newham University Hospital, London, UK. [4]Emergency Department Research Office, Royal London Hospital, Whitechapel, London, UK.

Corresponding author: Christos Stefanidis (c.stefanidis@outlook.com)

Provenance: Submitted article, peer reviewed.

Acknowledgements: The authors thank all the children and their parents/carers who participated in the research.

Author contributions: C. Stefanidis, A. Bush, A.R. Martineau and C.J. Griffiths conceived the study and contributed to study design. C. Stefanidis, A. Bush, A.R. Martineau, C.J. Griffiths, C. Nwokoro, S. Liebeschuetz and I.P. Skene participated in implementation of the study. C. Stefanidis, A. Bush, A.R. Martineau, C.J. Griffiths and C. Newby performed data analysis. C. Stefanidis, A. Bush and A.R. Martineau wrote the first draft of the article; all other authors critically reviewed it and approved the final version.

Conflict of interest: All authors have nothing to disclose.

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