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Vitamin D Oral Replacement in Children With Obesity Related Asthma: VDORA1 Randomized Clinical Trial

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Children with asthma and obesity are more likely to have lower vitamin D levels, but the optimal replacement dose is unknown in this population. The objective of this study is identifying a vitamin D dose in children with obesity-related asthma that safely achieves serum vitamin D levels of ≥40 ng/mL. This prospective multisite randomized controlled trial recruited children/adolescents with asthma and body mass index ≥85% for age/sex. Part 1 (dose finding), evaluated 4 oral vitamin D regimens for 16 weeks to identify a replacement dose that achieved serum vitamin D levels ≥40 ng/mL. Part 2 compared the replacement dose calculated from part 1 (50,000 IU loading dose with 8,000 IU daily) to standard of care (SOC) for 16 weeks to identify the proportion of children achieving target serum 25(OH)D level. Part 1 included 48 randomized participants. Part 2 included 64 participants. In Part 1, no SOC participants achieved target serum level, but 50–72.7% of participants in cohorts A-C achieved the target serum level. In part 2, 78.6% of replacement dose participants achieved target serum level compared with none in the SOC arm. No related serious adverse events were reported. This trial confirmed a 50,000 IU loading dose plus 8,000 IU daily oral vitamin D as safe and effective in increasing serum 25(OH)D levels in children/adolescents with overweight/obesity to levels ≥40 ng/mL. Given the critical role of vitamin D in many conditions complicating childhood obesity, these data close a critical gap in our understanding of vitamin D dosing in children.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Children with obesity-related asthma are more likely to have low vitamin D levels. Vitamin D has anti-inflammatory potential, but the pharmacokinetics of vitamin D in children with overweight/obesity must be defined before therapeutic trials can occur.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What dose of oral vitamin D supplementation is needed to safely achieve 25(OH)D levels ≥ 40 ng/mL in children with vitamin D deficiency and obesity-related asthma?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This multisite trial establishes that a 50,000 IU loading dose of oral vitamin D plus 8,000 IU daily can safely raise children's 25(OH)D serum values to potentially anti-inflammatory levels.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Children with obesity and vitamin D deficiency require higher than standard of care vitamin D dosing, which may be beneficial for many disorders in addition to asthma.

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Asthma is one of the most common chronic childhood illnesses, placing a high burden on families and society.[1] Similarly, increasing numbers of children have overweight/obesity, which complicates many childhood conditions, including asthma.[2] Adipose tissue is a physical impediment to lung expansion and produces pro-inflammatory cytokines contributing to airway hyper-reactivity.[3] Multiple studies report an inverse relationship between asthma severity and vitamin D levels, which may be related to the anti-inflammatory properties of vitamin D.[4,5] Low serum vitamin D levels (25(OH)D) are common in adults and children with both overweight/obesity and asthma.[6–8] Correcting low vitamin D could improve asthma control in children with overweight/obesity.

Vitamin D supplementation studies have not shown a clear benefit in asthma control in either adults or children to date.[9,10] This may be due to uncertainty around the optimal 25(OH)D levels to target for anti-inflammatory effects.[11] Weiss and Litonjua note that levels far greater than the 20 ng/mL for bone health may be necessary to achieve anti-inflammatory effects and propose levels in the 40–60 ng/mL range.[11] Studies such as the Childhood Asthma Management Program and others suggest that 25(OH)D levels ≥ 40 ng/mL should be targeted in children and adolescents to achieve anti-inflammatory effects.[4,12] However, lack of pharmacokinetic (PK) data to inform vitamin D supplementation dosing that would reach this anti-inflammatory level in children with overweight/obesity remains a critical gap in managing asthma and other conditions where vitamin D has therapeutic potential. Here, we report the outcomes of the Vitamin D Oral Replacement in Asthma (VDORA1) multisite randomized clinical trial designed to identify a vitamin D oral supplementation dose in children with obesity-related asthma that safely achieves serum vitamin D levels of ≥ 40 ng/mL.[13,14]

METHODS

Trial design and participants

VDORA1 is a prospective, randomized open label clinical trial conducted in 17 centers across the United States to evaluate the PKs and safety of oral vitamin D supplementation in children with asthma and overweight/obesity to identify a vitamin D dose that achieves serum 25(OH)D levels greater than 40 ng/mL. The study was comprised of dose finding (part 1) and dose confirming (part 2) parts. Participant enrollment occurred between 2019 and 2021. The University of Arkansas for Medicine Sciences served as the overseeing single Institutional Review Board for the 17 participating sites.

Study procedures are detailed in the protocol manuscript.[13] Inclusion criteria were: age 6 to less than 18 years; physician-diagnosed asthma; body mass index (BMI) ≥ 85th percentile for age and sex; serum 25(OH)D level of 10–≤ 30 ng/mL at screening; ability to swallow pills; and signed consent/assent. Female subjects of child-bearing potential could not be pregnant or lactating and must agree to practice adequate birth control methods. Children with known diseases of calcium metabolism, renal insufficiency, liver disorders, and those on medications that may impact vitamin D absorption were excluded. Additional exclusion criteria are detailed in the published protocol.[13]

Study procedures

In both parts of the study, participants received oral vitamin D3 gelatin capsules (BioTech Pharmacal, Fayetteville, AR) for 16 weeks. Serum 25(OH)D levels were collected and analyzed by a central laboratory prior to initiating vitamin D supplementation and monthly through week 28 to assess changes in 25(OH)D levels after active supplementation stopped. In part 1, participating children were randomized using a 1:1:1:1 scheme to receive one of four oral vitamin D dosing regimens (**Table S1**) for 16 weeks. A 2-compartment population PK model with linear absorption and elimination kinetics was used in part 1, reported in a separate manuscript, to inform the dose selection to be used in part 2. Part 2 participants were randomized 2:1 to receive either the replacement dose derived from part 1 (50,000 IU loading dose plus 8,000 IU daily dose) or a standard of care dose (SOC; 600 IU per day). Participants received SOC rather than a placebo control due to ethical concerns if treatment was denied to children known to be vitamin D deficient or insufficient. Adverse events (AEs) were tabulated including serious AEs (SAE) and participants withdrawn from treatment due to an AE. Urine calcium/creatinine (Ca/Cr) ratios were monitored for safety purposes, with withdrawal and primary care provider referral of any participant with multiple ratios > 0.37.

Study staff reviewed the participants' daily respiratory symptom, AEs, and vitamin D adherence diaries monthly. Additionally, the Asthma Control Test (ACT), or child Asthma Control Test (c-ACT), was used to assess asthma symptoms at baseline and monthly during the 16-week intervention.[15,16]

Statistical analysis

Demographic and baseline characteristics were tabulated overall, by dose regimens, and by study phase. Categorical variables were summarized by frequency and percent, whereas continuous measures of the descriptive statistics included means, standard deviations, median, 25th and 75th percentiles, as appropriate. For each dose group, we estimated the proportion of participants who achieved a vitamin D level of greater than or equal to 40 ng/mL at 16-weeks with the corresponding 95% confidence interval (CI) along with a one-sample test of proportion. Additionally for part 2, we used a one-sample test of proportion to analyze the overall proportion of participants with 25(OH)D ≥ 40 ng/mL at 16 weeks for each group separately, and we tested the difference in the proportions of participants with 25(OH)D ≥ 40 ng/mL across the 2 vitamin D dose regimens (50,000 IU loading dose plus 8,000 IU daily dose vs. 600 IU per day) using a two-sided z-test with a significance level of 0.05. We report the difference in proportions along with the 95% CI and *P* value. The relationship between vitamin D dose cohort in part 2 with changes in asthma symptom scoring measured by the ACT for ages 12–17 years and c-ACT for ages 6–11 years old were summarized and evaluated separately using a Wilcoxon sum-rank test statistic. Asthma symptom days (ASDs) were summarized at baseline and at 16 weeks and was compared across the dose groups using an analysis of covariance adjusting for baseline ASD values.

RESULTS

Study population

During the dose-finding part 1 (dose-finding) of this study, 78 eligible participants were assessed; 25 did not meet inclusion criteria at screening or baseline visit (**Figure S1**). Four were lost to follow-up and one withdrew consent. Ultimately, 48 participants were randomized to receive 1 of 4 possible vitamin D dose regimens (**Table S1**). The mean age was 12.3 years and mean BMI was 31.6 kg/m^2, with 54% of participants having a baseline BMI > 99th percentile for age and sex.

For part 2 (dose-confirming), 88 participants were assessed for eligibility and 64 participants were ultimately randomized (**Figure 1**). The mean age was 12 years and mean baseline BMI was 30.6 kg/m^2, with 41% of participants having a BMI > 99th percentile for age and sex. For both part 1 and part 2, key demographic characteristics were similar across the dose cohorts (**Table 1**).

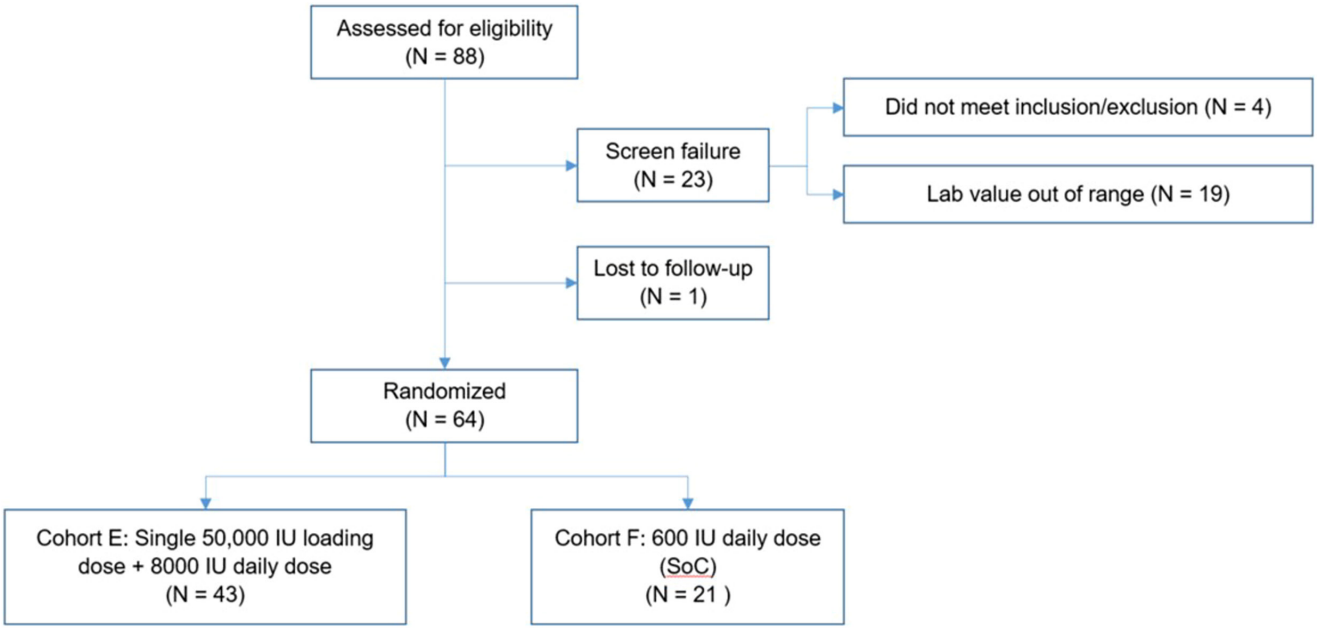

Figure 1 Part 2 – Dose confirming phase – Consolidated Standards of Reporting Trials (CONSORT) diagram outlining participant flow. SoC, standard of care.

Part 1: 25(OH)D outcomes

As detailed in **Table 2**, no participants in the SOC dose (600 IU daily, cohort D) achieved the target serum 25(OH)D level of ≥ 40 ng/mL. However, in the higher dose cohorts, 50.0–72.7% of participants achieved the target level. Specifically, in cohort A (50,000 IU loading dose followed by 6,000 IU daily) 67% (8/12; 95% CI: 39.1%, 86.2%) achieved serum 25(OH)D level of ≥ 40 ng/mL, with a mean increase of 23.2 ± 14.2 ng/mL. In cohort B (50,000 IU loading dose plus 10,000 IU daily) 73% (8/11; 95% CI: 43.4%, 90.3%) achieved serum 25(OH)D level of ≥ 40 ng/mL, with a mean increase of 31.3 ± 20.1 ng/mL. In cohort C (6,000 IU daily) 50% (5/10; 95% CI 23.7%, 76.3%) achieved serum 25(OH)D level of ≥ 40 ng/mL, with a mean increase of 27.8 ± 18.9 ng/mL. PK analysis of these data identified an optimal dose of 50,000 IU loading dose plus 8,000 IU daily for part 2 of the trial.

Part 2: 25(OH)D Outcomes

The descriptive summaries and proportion of participants achieving 25(OH)D ≥ 40 ng/mL are also presented in **Table 2**. As baseline, the overall average 25(OH)D level was 17.3 ng/mL with a standard deviation of 5.8 ng/mL. As expected, there were zero participants with 25(OH)D ≥ 40 ng/mL at baseline. The average baseline 25(OH)D across the 2 cohorts was not statistically different with mean difference of 1.4 ng/mL (95% CI: −1.71, 4.59; $P = 0.36$). At 16 weeks, 42 of 43 participants from cohort E (replacement dose: 50,000 IU loading dose plus 8,000 IU daily) had blood samples available for vitamin level determination whereas cohort B (600 IU daily standard of care dosing) had 3 participants with missing blood samples. The average 25(OH)D level among participants in cohort E was 58.4 ng/mL compared with 17.8 ng/mL in cohort F. The difference in 25(OH)D at visit 6 (16 weeks) was highly significant with mean difference of 40.5 ng/mL (95% CI: 32.8, 48.2; $P < 0.0001$). In cohort E, 78.6% of participants (33/42; 95% CI: 64.1%, 88.3%) achieved the target serum 25(OH)D level of ≥ 40 ng/mL, with a mean change in 25(OH)D of 40.1 ± 22.9 ng/mL (**Table 2**). As expected, the test statistic based on a one-sided z-test was highly significant with $P < 0.0001$. In contrast, cohort F had no participants that (0/18; 95% CI: 0, 17.6) achieved the target serum 25(OH)D level of ≥ 40 ng/mL, with a mean change in 25(OH)D of 1.2 ± 6.0 ng/mL. The test in difference of proportions across the two cohorts was highly significant ($P < 0.0001$).

Clinical and secondary outcomes

Clinical and secondary outcomes during part 2 showed no significant differences in the change c-ACT/ACT scores and ASDs between cohort E (added supplementation) and cohort F (SOC). Specifically, the average change c-ACT scores from baseline to 16 weeks among participants randomized to cohort E was 1.6 (95% CI: −0.1, 3.2) compared with 0.8 (95% CI: −1.7, 3.4) among those randomized to cohort F (**Table S2**). The median difference in c-ACT change scores across the two groups was determined based on Hodges-Lehmann estimation (median difference = 0; 95% CI: −3, 2) and was not statistically significant based on the Wilcoxon rank-sum test with $P = 0.9846$. Similarly, there was no statistical difference in the change ACT scores (median difference = 0; 95% CI: −2, 3). Asthma symptom days at end of study treatment (i.e., week 16) were similar across the groups with 25.1 ± 8.8 ASDs for cohort E compared with 26.1 ± 12.4 ASDs for cohort F, which are not significantly different with $P = 0.6027$ (**Table S3**).

Safety outcomes

Overall, 64.3% of participants (72/112) reported an AE during the study (**Table 3**). Only 3.6% (4/112) and 2.7% (3/112)

Table 1 Participant characteristics

Variables	Part 1: Dose finding					Part 2: Dose confirming		
	Cohort A (*N* = 13)	Cohort B (*N* = 12)	Cohort C (*N* = 11)	Cohort D (*N* = 12)	Total (*N* = 48)	Cohort E (*N* = 43)	Cohort F (*N* = 21)	Total (*N* = 64)
Female, *N* (%)	6 (46)	7 (58)	5 (45)	5 (42)	23 (48)	20 (47)	10 (48)	30 (47)
Age, mean ± SD	12.8 ± 3.1	12.3 ± 3.4	11.5 ± 3.6	12.5 ± 2.9	12.3 ± 3.2	12.2 ± 2.5	11.7 ± 2.6	12 ± 2.5
Ethnicity, *N* (%)								
Hispanic	5 (38)	2 (17)	2 (18)	1 (8)	10 (21)	7 (16)	3 (14)	10 (16)
Non-Hispanic	7 (54)	10 (83)	8 (73)	10 (83)	35 (73)	33 (77)	18 (86)	51 (80)
Unknown/prefer not to answer	1 (8)	0 (0)	1 (9)	1 (8)	3 (6)	3 (7)	0 (0)	3 (5)
Race, *N* (%)								
Black or African American	6 (46)	4 (33)	5 (45)	6 (50)	21 (44)	15 (35)	9 (43)	24 (38)
White	4 (31)	5 (42)	3 (27)	5 (42)	17 (35)	19 (44)	10 (48)	29 (45)
Other	3 (23)	3 (25)	3 (27)	1 (8)	10 (21)	9 (21)	2 (10)	11 (17)
RUCAM code, *N* (%)								
Metropolitan	13 (100)	10 (83)	9 (82)	11 (92)	43 (90)	32 (74)	17 (81)	49 (77)
Non-Metropolitan	0 (0)	2 (17)	2 (18)	1 (8)	5 (10)	11 (26)	4 (19)	15 (23)
BMI at baseline (visit 2) Mean ± SD	33.9 ± 8.4	29.7 ± 6.4	30.1 ± 4.3	32.2 ± 9.2	31.6 ± 7.4	30.8 ± 6.9	30.3 ± 8.2	30.6 ± 7.3
BMI-percentile, *N* (%)								
≥ 85th to < 95th	3 (23)	2 (17)	2 (18)	3 (25)	10 (21)	9 (21)	5 (24)	14 (22)
≥ 95th to < 99th	4 (31)	3 (25)	2 (18)	3 (25)	12 (25)	16 (37)	8 (38)	24 (38)
≥ 99th	6 (46)	7 (58)	7 (64)	6 (50)	26 (54)	18 (42)	8 (38)	26 (41)
Urine Ca+/Cr ratio > 0.37, *N* (%)[a]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)

Part 1: Cohort A (single 50,000 IU loading dose +6,000 IU daily dose); cohort B (Single 50,000 IU loading dose +10,000 IU daily dose; cohort C (6,000 IU daily dose); cohort D (600 IU daily dose, standard of care comparator); part 2 cohort E (single 50,000 IU loading dose +8,000 IU daily dose); cohort F (600 IU daily dose, standard of care comparator).
BMI, body mass index; Ca/Cr, calcium/creatinine; RUCAM, Rural-Urban Commuting Area Method.
[a]Calcium/creatinine ratio was collected at screening.

experienced an AE related to vitamin D or study procedures, respectively (detailed in **Table 3**). Related AEs included nausea, abdominal pain, headache, increased urine Ca/Cr ratio, bruising at venipuncture site, and dizziness with venipuncture. Reported SAEs were rare (3.6%; 4/112) and none were related to vitamin D or study procedures. Of the 43 participants in cohort E receiving the loading dose of 50,000 IU followed by 8,000 IU daily, only 2 participants recorded serum concentrations of 25(OH)D > 100 ng/mL. One participant peaked at 107 ng/mL and the other at 110 ng/mL. In terms of asthma exacerbation, 15.2% of participants (17/112) reported asthma exacerbation during the study. From part 1, there were 3 participants each that reported an asthma exacerbation from cohorts A, B, and D, whereas 4 participants from cohort C had an asthma exacerbation. From part 2, one participant from cohort E compared with 3 from cohort F reported an event; however, each asthma exacerbation event was not deemed related to vitamin D or study procedures.

DISCUSSION

This study demonstrates that a loading dose of 50,000 IU followed by a daily dose of 8,000 IU of vitamin D over 16 weeks is safe and effective in achieving serum 25(OH)D levels ≥ 40 ng/mL in children with obesity-related asthma, with 78.6% of children on this dose achieving the target level. Conversely, none of the children reached target 25(OH)D levels on SOC dosing at 600 IU daily. In total, we obtained monthly 25(OH)D serum levels in 112 children over 28 weeks who were given at least daily oral vitamin D over 16 weeks. This provides a wealth of information of vitamin D uptake, metabolism, and safety in a specific population at high risk for having low vitamin D levels. There were no clinically significant SAEs related to study procedures or vitamin D supplementation, no evidence of hypercalciuria, and no participants with serum 25(OH)D levels surpassing 150 ng/mL. This is consistent with previous studies demonstrating no increase in hypercalcemia in the general population from high dose vitamin D supplementation alone.[17] Because studies suggest vitamin D toxicity does not occur until levels surpass 150 ng/mL, the replacement dose used in this study allowed serum concentrations of 25(OH)D to remain in a safe range.[18] Overall, this study demonstrates that children and adolescents with overweight/obesity can safely increase their vitamin D levels to the 40–60 ng/mL range felt to be necessary for an anti-inflammatory effect on this 16-week dosing

Table 2 Descriptive statistics and 25(OH) D measurements ≥40 ng/mL by study visit

	Visit 2 (baseline)	Visit 6 (week 16)		Δ(25(OH) D)[a]
			Measurements ≥40 ng/mL	
	Mean ± SD	Mean ± SD	*N* (%) with 95% CI	Mean ± SD
Part 1: Dose finding				
Cohort A (*n* = 13)	18.3 ± 6.5	44.3 ± 16.6	8 (66.7) [39.1, 86.2]	23.2 ± 14.2
Cohort B (*n* = 12)	20.8 ± 7.2	52.9 ± 19.4	8 (72.7) [43.4, 90.3]	31.3 ± 20.1
Cohort C (*n* = 11)	19.0 ± 5.2	47.4 ± 17.6	5 (50.0) [23.7, 76.3]	27.8 ± 18.9
Cohort D (*n* = 12)	17.6 ± 5.8	22.4 ± 6.4	0 (0) [0, 24.2]	4.8 ± 4.8
Total (*N* = 48)	18.9 ± 6.2	41.3 ± 19.2	21 (46.7) [32.9, 60.9]	21.3 ± 18.2
Part 2: Dose confirming				
Cohort E (*n* = 43)	17.7 ± 6.0	58.4 ± 23.7	33 (78.6) [64.1, 88.3]	40.1 ± 22.9
Cohort F (*n* = 21)	16.3 ± 5.2	17.8 ± 4.8	0 (0) [0, 17.6]	1.2 ± 6.0
Total (*N* = 64)	17.3 ± 5.8	46.2 ± 27.4	33 (55.0) [42.5, 66.9]	28.3 ± 26.4

Part 1: cohort A: single 50,000 IU loading dose +6,000 IU daily dose had one missing observation at visits 2 and 6; cohort B: single 50,000 IU loading dose +10,000 IU daily dose had one missing observation at visit 6; cohort C: 6,000 IU daily dose had one missing observation at visit 6; cohort D: 600 IU daily dose (standard of care comparator group) had no missing data; part 2: cohort E (single 50,000 IU loading dose +8,000 IU daily dose); cohort F (600 IU daily dose, standard of care comparator).
CI, confidence interval.
[a]$\Delta(25(OH)\ D) = 25(OH)\ D_{visit\ 6} - 25(OH)\ D_{visit\ 2}$.

Table 3 Adverse events

	AEs *N* (%)	Related to vitamin D AEs *N* (%)	Related to procedure AEs *N* (%)	SAEs *N* (%)	Related to Vitamin D SAEs *N* (%)	Related to procedure SAEs *N* (%)
Part 1: Dose finding						
Cohort A (*N* = 13)	11 (85)	0 (0)	1 (8)	0 (0)	0 (0)	0 (0)
Cohort B (*N* = 12)	9 (75)	3 (25)	0 (0)	1 (8)	0 (0)	0 (0)
Cohort C (*N* = 11)	11 (100)	0 (0)	0 (0)	1 (9)	0 (0)	0 (0)
Cohort D (*N* = 12)	10 (83)	0 (0)	1 (8)	1 (8)	0 (0)	0 (0)
Total (*N* = 48)	41 (85)	3 (6)	2 (4)	3 (6)	0 (0)	0 (0)
Part 2: Dose confirming						
Cohort E (*N* = 43)	19 (44)	1 (2)	0	0	0	0
Cohort F (*N* = 21)	12 (57)	0	1 (5)	1 (5)	0	0
Total (*N* = 64)	31 (48)	1 (2)	1 (2)	1 (2)	0	0

Part 1: Cohort A (single 50,000 IU loading dose +6,000 IU daily dose); cohort B (single 50,000 IU loading dose +10,000 IU daily dose; cohort C (6,000 IU daily dose); cohort D (600 IU daily dose, standard of care comparator); Part 2: cohort E (single 50,000 IU loading dose +8,000 IU daily dose); cohort F (600 IU daily dose, standard of care comparator). Related AEs included nausea, abdominal pain, headache, increased urine Ca/Cr ratio, bruising at venipuncture site, and dizziness with venipuncture.
AEs, adverse events; Ca/Cr, calcium/creatinine; SAE, serious adverse event.

regimen. This is of critical importance given the role of vitamin D in health and disease and the previous gaps in our understanding of vitamin D PKs in children with overweight/obesity.

Prior to our study, there was no consensus on the recommended dose of vitamin D to achieve sufficiency in children and adolescents with overweight/obesity, nor whether the high doses of vitamin D that may be required to achieve an ideal 25(OH) D level would do so at the cost of toxicity. Previous studies in children and adolescents with overweight/obesity have demonstrated that higher loading doses of oral vitamin D may be indicated in children and adolescents with higher body fat given their lower rise in serum vitamin D levels compared with children and adolescents with a normal BMI, consistent with our PK analysis in this study showing that doses much higher than standard of care are needed for children and adolescents with overweight/obesity and asthma.[19,20] The prevalence of vitamin D deficiency in children with overweight/obesity in the United States varies based on geographic location, time of year, skin color, and the definition of vitamin D deficiency utilized.[18] Some major clinical consensus guidelines define vitamin D deficiency as a 25(OH)D level <20 ng/mL, insufficiency as between 20 and 30 ng/mL, and sufficiency as >30 ng/mL.[17,18] However, both the Pediatric Endocrine Society and the American Academy of Pediatrics suggest the definition of deficiency to be a 25(OH)D level <12 ng/mL, insufficiency between 12 and 20 ng/mL, and sufficiency as >20 ng/mL.[21] Multiple studies have revealed the prevalence of vitamin D deficiency in children with overweight/obesity to be >50% when a cutoff of <20 ng/mL is utilized.[22,23]

Knowing the appropriate approach to replacement in this group is vital, particularly if the goal is to decrease life-long inflammatory conditions.

Over the past decade, vitamin D has been proposed as a protective factor and potential therapy in many chronic medical conditions, particularly those associated with or exacerbated by overweight/obesity. For example, several studies show that vitamin D supplementation has a modest effect on preventing the progression of pre-diabetes to diabetes in adults, especially in participants that are vitamin D deficient at baseline.[24,25] Population studies have also shown an association between vitamin D deficiency and a higher risk of several inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel diseases.[26–32] However, studies have shown no benefit of vitamin D supplementation in several disease states, raising concern about the therapeutic role of vitamin D as treatment for anything but bone disorders.[33] Importantly, those studies were performed in adults with established disease. The potential for vitamin D as a prophylactic anti-inflammatory agent started in childhood has yet to be studied rigorously. The results of this study, while focused on children with overweight/obesity and asthma, may therefore have much broader implications for future pediatric clinical trials on vitamin D as a therapy in children and adolescents with overweight/obesity and a variety of comorbidities associated with both overweight/obesity and vitamin D deficiency.

Asthma symptoms and exacerbations were exploratory end points of the study. Although a previous study of vitamin D supplementation in children with asthma showed no benefit, the study population was not enriched for the comorbidity of overweight/obesity.[9] In our study, ACT and c-ACT (**Table S2**) demonstrated participants in all cohorts had similar levels of control at enrollment and at the conclusion of study treatment. Mean ACT/c-ACT scores of greater than 19 for all cohorts at each visit suggests that for most participants, their asthma was well-controlled at baseline and throughout the study. Although there were slight changes in ACT/c-ACT scores from baseline to the conclusion of study treatment, none of the cohorts experienced a minimal clinically important difference in ACT/c-ACT score (ACT ≥ 3 points / c-ACT ≥ 2 points).[34,35] The slight change in score could be due to the Hawthorne effect resulting in improved adherence with baseline asthma medications as a result of participating in an asthma clinical trial.[36] Despite mean ACT/c-ACT scores reflecting overall good control, participants reported a relatively high number of ASDs (**Table S3**), which may be attributable to the increased sensitivity of asthma symptom diaries.[37] Asthma exacerbations were similar across cohorts in both parts of the study. Fewer exacerbations were seen in part 2 than in part 1, regardless of cohort, which is likely due to part 2 being conducted after the onset of coronavirus disease 2019 when pediatric asthma exacerbations were significantly decreased nationwide.[38] Importantly, this study was not powered to detect a clinical impact of vitamin D supplementation on asthma control, so any interpretation of these results should be undertaken with caution. The VDORA study team is currently exploring future therapeutic trial options to evaluate the effect of normalizing vitamin D levels in children and adolescents with obesity and asthma on asthma symptoms, using the doses identified in this study.

The starting points selected in part 1, which included only one loading dose, may not capture all possible safe, effective oral vitamin D dosing and the dose tested in part 2 was calculated based on PK modeling rather than a dose directly tested in part 1. Additionally, although it is likely that children with overweight/obesity and asthma have similar vitamin D PKs than children with overweight/obesity who do not have asthma, the results of this study may not apply to other children and adolescents with overweight/obesity. Because BMI may not reflect true adiposity, there was likely a wide variation in the volume of distribution in this cohort which could impact 25(OH)D levels. There are also several limitations to consider regarding asthma outcomes in this study, including a lack of testing, such as spirometry, to confirm physician-diagnosed asthma. Most participants' ACT/c-ACT scores indicated well-controlled asthma throughout the trial, which may have limited the effect of vitamin D supplementation on asthma symptoms.

CONCLUSIONS

The VDORA1 multisite randomized clinical trial identified and confirmed that a 50,000 IU loading dose plus 8,000 IU daily of oral vitamin D is safe and effective in increasing the serum 25(OH)D levels in children and adolescents with overweight/obesity to levels ≥ 40 ng/mL. Given the critical role of vitamin D in many conditions complicated by childhood obesity, these data close a critical gap in our understanding of vitamin D dosing in children with overweight/obesity and lays the foundation for future therapeutic trials.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

B.O., L.J., M.M., J.L., A.S., F.P., M.G., M.G., and J.S. designed the research, performed the research, and wrote the manuscript. J.L. and S.O. designed the research, analyzed the data, performed the research, and wrote the manuscript. Z.H. analyzed the data and wrote the manuscript. S.B., B.E., L.F., D.H., A.J., L.K., D.L., T.P., M.H.A., C.S., J.T., and B.W. performed the research and wrote the manuscript.

DATA ACCESS, RESPONSIBILITY, AND ANALYSIS

Dr. Ounpraseuth had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

Data can be made available on request and will also be uploaded into the NIH DASH repository.

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