

Vitamin D for Growth and Rickets in Stunted Children: A Randomized Trial

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abstract

BACKGROUND AND OBJECTIVES: Vitamin D is essential for healthy development of bones, but little is known about the effects of supplementation in young stunted children. Our objective was to assess the effect of vitamin D supplementation on risk of rickets and linear growth among Afghan children.

METHODS: In this double-blind, placebo-controlled trial, 3046 children ages 1 to 11 months from inner-city Kabul were randomly assigned to receive oral vitamin D₃ (100 000 IU) or placebo every 3 months for 18 months. Rickets Severity Score was calculated by using wrist and knee radiographs for 631 randomly selected infants at 18 months, and rickets was defined as a score >1.5. Weight and length were measured at baseline and 18 months by using standard techniques, and z scores were calculated.

RESULTS: Mean (95% confidence interval [CI]) serum 25-hydroxyvitamin D (seasonally corrected) and dietary calcium intake were insufficient at 37 (35–39) nmol/L and 372 (327–418) mg/day, respectively. Prevalence of rickets was 5.5% (placebo) and 5.3% (vitamin D): odds ratio 0.96 (95% CI: 0.48 to 1.92); *P* = .9. The mean difference in height-for-age z score was 0.05 (95% CI: –0.05 to 0.15), *P* = .3, although the effect of vitamin D was greater for those consuming >300 mg/day of dietary calcium (0.14 [95% CI: 0 to 0.29]; *P* = .05). There were no between-group differences in weight-for-age or weight-for-height z scores.

CONCLUSIONS: Except in those with higher calcium intake, vitamin D supplementation had no effect on rickets or growth.



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Dr Crowe designed the analysis plan, analyzed the data, and drafted the manuscript; Prof Mughal made substantial contributions to the conceptualization and design of the study and drafted the manuscript; Dr Maroof was the trial manager, managed the implementation of the study, and revised the manuscript critically for important intellectual content; Dr Berry led the analysis of blood 25-hydroxyvitamin D and parathyroid hormone, made a substantial contribution to the interpretation of the data, and revised the manuscript critically for important intellectual content; Dr Kaleem led the analysis of the wrist and knee radiographs, made a substantial contribution to the interpretation of the data, and revised the manuscript critically for important intellectual content; Dr Abburu led the analysis of the dietary data, made a substantial contribution to the interpretation of the data, and revised the manuscript critically for important intellectual content; (Continued)

WHAT'S KNOWN ON THIS SUBJECT: Few trials have been used to examine whether vitamin D supplementation can prevent rickets or improve growth. Vitamin D supplementation potentially prevents rickets in children deficient in vitamin D and increases height in subpopulations of young teenagers and premature infants.

WHAT THIS STUDY ADDS: In a highly stunted population insufficient (not deficient) in vitamin D and calcium using vitamin D supplementation every 3 months, there was no statistically significant reduction in rickets or improved growth. In those with calcium intake >300mg/day, height improved.

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Afghanistan, a low-income country, has one of the highest rates of child mortality among children <5 years of age in the region.¹ Although improvements in nutrition and the alleviation of poverty have led to a reduction in mortality in recent years,² undernutrition still poses a big threat to the health of Afghan children, with one of the highest prevalence of childhood stunting ranging from 40%³ to >80% in some districts.⁴ Factors associated with stunting include sanitation, food insecurity, and low dietary diversity,^{2,4} and children in Afghanistan <5 years have high rates of anemia and deficiencies in vitamins A and D.³

Vitamin D is essential for children achieving optimal linear growth and development of bones.⁵ Nutritional rickets is a condition in which there is impaired mineralization of the growth plate and osteoid in a growing child. It can lead to deformities of the lower limbs and pelvis and in severe cases is associated with fragility fractures.^{6,7} Deficiency in vitamin D or dietary calcium intake, or a combination of both these factors, can cause nutritional rickets.⁶ Vitamin D deficiency arises when there is inadequate exposure of the skin to sunlight or insufficient dietary intake.^{8,9} Besides being a major cause of rickets and osteomalacia, vitamin D deficiency might also lead to impaired growth. Randomized control trials of vitamin D supplementation revealed improvements in growth in premature low birth weight neonates in India¹⁰ and in school-aged children (11–13 years) in Mongolia.¹¹ The duration of vitamin D supplementation and follow-up in these 2 trials was only 6 months, and it is not clear whether a longer period of vitamin D supplementation as bolus doses in young children undergoing rapid periods of growth (6–24 months) leads to greater improvements in growth or prevents cases of rickets. Additionally, daily

and weekly home supplementation regimens often have poor adherence^{12,13} and bolus doses implemented during regular child health contacts (eg, vaccination) are important supplementation methods for programmatic purposes.

Vitamin D deficiency and malnutrition are common problems in Afghanistan,^{3,14} making it an ideal study population in which to examine the effects of vitamin D on bones and growth, which may be relevant to other low- and middle-income countries (LMICs). Here, we assess the effect of vitamin D supplementation on the risk of rickets, as measured by the Thacher radiologic score (hereafter known as the Rickets Severity Score [RSS]), and growth parameters of children who participated in a randomized controlled trial in Afghanistan. Chronically low dietary calcium intake, with or without vitamin D deficiency or insufficiency, also leads to rickets in a growing child.⁶ Therefore, we have also examined the role that dietary calcium intake may have in the causation of rickets.

METHODS

Study Design

A more detailed description of the trial methods, including the trial profile, has been published elsewhere.¹⁵ Briefly, this trial was a community-based, double-blind, randomized, placebo-controlled parallel trial that was conducted between November 2007 and June 2009 in 5 inner-city districts of Kabul, Afghanistan. The primary objective of the trial was to evaluate the effect of quarterly supplementation of 100 000 IU (2.5 mg) of cholecalciferol (vitamin D₃) on the incidence and/or severity of childhood pneumonia. A priori secondary objectives of the study were to assess the effect of vitamin D₃ supplementation on the risk of rickets and linear growth among children.

Approvals, Consent, and Registration

The study protocol was approved by the ethics and review board of the Ministry of Public Health of Afghanistan (reference: 422328) and the ethics committee of the London School of Hygiene and Tropical Medicine (application 5117). Thumbprint or signature consent from the mother, father, or other head of the household was obtained after either parent read the consent form or it was explained to him or her by the field-worker. This study was registered at www.clinicaltrials.gov (identifier NCT00548379).

Participants

The children enrolled in the study mainly were from socioeconomically deprived inner-city districts in Kabul and aged 1 to 11 months. A total of 3060 children were assessed for eligibility and 3046 children were randomly assigned to the vitamin D ($n = 1524$) or placebo group ($n = 1522$).

Randomization

An independent statistician individually randomized unique identification numbers in blocks of 20 to the vitamin D or placebo group by use of a random number generator with the SAS (SAS Institute, Inc, Cary, NC) routine.

Intervention

We prepared 2.5 mg of vitamin D₃ (cholecalciferol) dissolved in 1 mL of olive oil (vitamin D) or 1 mL of olive oil alone (placebo) in sealed plastic syringes. The vitamin D in olive oil and placebo syringes were identical in appearance, and all families and study personnel, including the clinicians, were blinded to the group allocation of the child. Vitamin D or placebo was given by the field-worker to the child on a quarterly basis; doses were given in November 2007, February 2008, May 2008, August 2008, and December 2008, and the final (sixth) dose was given in March

2009. The field-workers were unaware of whether the upcoming syringe was vitamin D or placebo; therefore, allocation was concealed.

Measurements

At recruitment, data on demography, socioeconomic characteristics of the household, and medical history of the child were collected. Principal component analyses of household characteristics and assets were used to measure a wealth index, and this was divided into quintiles as a measure of the socioeconomic status of a household.

Dietary Intake of Energy, Protein, and Calcium

Twice throughout the study (once in the winter and then in the summer months), mothers (or the main caregiver) completed a semiquantitative food frequency questionnaire (FFQ) that was used to estimate the child's intake of a list of 56 commonly consumed foods over the past week (Supplemental Information). Dietary calcium <300 mg/day was used as a cut point to define deficiency.⁶

Adverse Events

There were no adverse events reported in the study. Of the children who had serum concentration of 25-hydroxyvitamin D (25-OH-D) measured, only 5 in the vitamin D and 1 in the placebo group had 25-OH-D >250 nmol/L (indicative of being at risk for hypercalcemia). None of these children had serum calcium measured.

Anthropometry

Measurement of length or height and weight were performed while the children were wearing light or no clothing and were collected from the children at recruitment and 18 months later (Supplemental Information).

Radiographs

There were 641 sets of radiographs of the wrist and knee obtained from a subset of children by use of a simple random sample. The radiographs were evaluated by a consultant pediatric radiologist (M.K.) who was blinded to the group allocation using the RSS¹⁶ for radiologic grading of active nutritional rickets (Supplemental Information). Of the 641 sets of radiographs, 10 could not be evaluated because of reasons such as poor image quality, and so the RSS was available for 631 children (321 in the vitamin D group and 310 in placebo group).

Measurement of Serum 25(OH)D and Parathyroid Hormone

Five times over the 18 months of the study, ~120 to 140 blood samples (60–70 from the vitamin D group and 60–70 from the placebo group) were randomly collected each time from blocks of children. The timing of the blood samples was to allow for measurement of both the pharmacodynamic and seasonal changes in 25(OH)D concentrations.

Serum 25(OH)D was measured by the Immunodiagnostic Systems (IDS)–iSYS multidiscipline automated chemiluminescent assay (IDS Holdings PLC, Tyne and Wear, United Kingdom), and serum intact parathyroid hormone (PTH) was measured by using the IDS intact PTH enzyme-linked immunosorbent assay kit (IDS) at Manchester Royal Infirmary (Supplemental Information).

Power Calculation

The trial sample size was based on the outcome measure of the first episode of pneumonia.¹⁵

Statistical Analyses

Of the 3046 children allocated in the trial, anthropometric measurements were available for 2103 children and an RSS score was available for 631 children (Supplemental Fig 3).

Serum concentrations of 25(OH)D and PTH were log transformed to normalize distributions and difference in the geometric mean concentrations between the vitamin D and placebo group were assessed by using linear regression analysis.

Logistic regression was used to assess the risk of rickets (RSS >1.5) in the vitamin D compared with the placebo group. The difference in mean RSS and the mean z score of height for age, weight for age, and weight for height was assessed by using multiple linear regression. Heterogeneity in the effect of vitamin D on RSS and anthropometric measurements by the subgroup of calcium intake (<300, ≥300 mg/day)⁶ was assessed by using a standard χ^2 test. This was also done for subgroups of calcium expressed as mg/1000 kcal (<459, ≥459 mg/1000 kcal). In a sensitivity analysis, the between-group differences in the anthropometric z scores were repeated, controlling for the respective baseline values.

All statistical analyses were performed by using Stata statistical software (Stata Corp, College Station, TX), version 15. Two-sided *P* values <.05 were considered statistically significant.

RESULTS

Characteristics of children for the placebo and vitamin D groups are shown in Table 1. The average age at enrollment was 6 months, and there were slightly more boys than girls in the trial. More than half of the infants were being breastfed at recruitment, and 10% of infants in both the vitamin D and placebo groups were from the poorest households. There was a similar degree of underweight (12%), stunting (13%), and wasting (7%) in the vitamin D and placebo groups. The dietary intake (including breast milk) of energy, protein, and calcium were similar between the groups, and the percentage of children with intakes of calcium

TABLE 1 Baseline Characteristics of the Children in the Trial by Allocation

	Placebo (<i>n</i> = 1522)	Vitamin D (<i>n</i> = 1524)
Sex		
Boys	780 (51.3)	811 (53.2)
Girls	742 (48.8)	713 (46.8)
Child age at recruitment	6.2 ± 3.1 ^a	6.2 ± 3.2
<2 mo	111 (7.3)	132 (8.7)
2–5 mo	537 (35.3)	510 (33.5)
6–12 mo	874 (57.4)	882 (57.9)
Breastfeeding at recruitment		
Yes	865 (56.8)	900 (59.1)
No	617 (40.5)	584 (38.3)
Not known	40 (2.6)	40 (2.6)
Socioeconomic status, fifths		
Poorest	159 (10.4)	164 (10.8)
Very poor	266 (17.5)	262 (17.2)
Poor	247 (16.2)	226 (14.8)
Less poor	227 (14.9)	226 (14.8)
Least poor	235 (15.4)	254 (16.7)
Not known	388 (25.5)	392 (25.7)
No. indoor smokers in household		
None	887 (58.3)	893 (58.6)
≥1	476 (31.3)	459 (30.1)
Not known	159 (10.4)	172 (11.3)
Length-for-age z score	−0.6 ± 1.4	−0.6 ± 1.4
≥−1	918 (60.3)	944 (61.9)
−2 to > −1	319 (21.0)	301 (19.8)
<−2	212 (13.9)	200 (13.1)
Not known	73 (4.8)	79 (5.2)
Wt-for-age z score	−0.6 (1.2)	−0.7 ± 1.2
≥−1	969 (63.7)	945 (62.0)
−2 to > −1	368 (24.2)	372 (24.4)
<−2	176 (11.6)	185 (12.1)
Not known	9 (0.6)	22 (1.4)
Height-for-wt z score	−0.3 ± 1.2	−0.3 ± 1.2
≥−1	1059 (69.6)	1069 (70.1)
−2 to > −1	289 (19.0)	251 (16.5)
<−2	98 (6.4)	118 (7.7)
Not known	76 (5.0)	86 (5.6)
Daily dietary intake ^b		
Total energy intake, kcal	704.3 ± 326.8	713.4 ± 336.3
Dietary protein intake, g	21.2 ± 10.1	21.5 ± 10.4
Dietary calcium intake, mg	370.3 ± 272.3	374.3 ± 279.0

All values are *n* (%), except when noted otherwise.

^a Values are mean ± SD, all such values.

^b Dietary intake values were available for 1197 in the placebo and 1186 in the vitamin D group.

considered deficient (<300 mg/day) was 50.5% and 50.6% in the vitamin D group and placebo group, respectively.

The geometric mean (95% confidence interval [CI]) serum concentrations of 25(OH)D in a random sample of ~120 infants from the placebo and vitamin D groups throughout 5 time points in the study are shown in Fig 1. Mean serum 25(OH)D was higher in the vitamin D group compared with the placebo group after the first dose of

vitamin D supplement (115 vs 39 nmol/L; *P* < .001), second dose (49 vs 28 nmol/L; *P* < .001), and the third dose (94 vs 47 nmol/L; *P* < .001) of vitamin D supplement. There was no difference in mean 25(OH)D concentration between the vitamin D and placebo group at the last time point (>4 months after the sixth and final dose of vitamin D). The mean serum 25(OH)D in the subgroup of the placebo group who had 25(OH)D measured was 28 nmol/L in the winter months and 47 nmol/L in

summer months, giving a seasonally corrected mean 25(OH)D of 37 nmol/L (95% CI: 35 to 39) throughout the trial period. In the placebo group, 26%, 55%, 55%, 21%, and 7% were <30 nmol/L in rounds 1, 2, 3, 4, and 5, respectively.

Among the placebo group, PTH increased during the winter months (December 2007 to January 2008 and January to February 2008) and was significantly higher than in the vitamin D group at these 2 time points; 2.6 vs 1.8 pmol/L, *P* = .004 and 3.8 vs 2.3 pmol/L, *P* < .001, respectively (Fig 2). There was no difference in PTH between the placebo and vitamin D group at the other time points.

The proportion of children with an RSS of 0 did not differ significantly between the vitamin D and placebo groups (67% vs 69%), and only a single child in the placebo group had an RSS of 10 (Table 2). The mean RSS, although lower in the vitamin D group, did not differ significantly between the vitamin D and placebo group (0.46 vs 0.35; *P* = .086). The proportion of children with an RSS indicative of rickets also did not differ between the 2 groups (5.5% vs 5.3%; *P* = .9). The mean RSS was lower in the vitamin D group, but this was not statistically significant by intake of dietary calcium.

The mean height-for-age, weight-for-age, and weight-for-height z scores did not differ significantly between the vitamin D and placebo groups for all children and for those with <300 mg/day dietary calcium (Table 3). However, the mean height for age for children with a calcium intake ≥300 mg/day revealed a slight improvement (mean difference 0.14 [95% CI: 0 to 0.29]; *P* = .05); the test for interaction by calcium intake was not statistically significant (*P* = .355). Mean height-for-age, weight-for-age, and weight-for-height z scores did not differ significantly between the vitamin D and placebo groups for

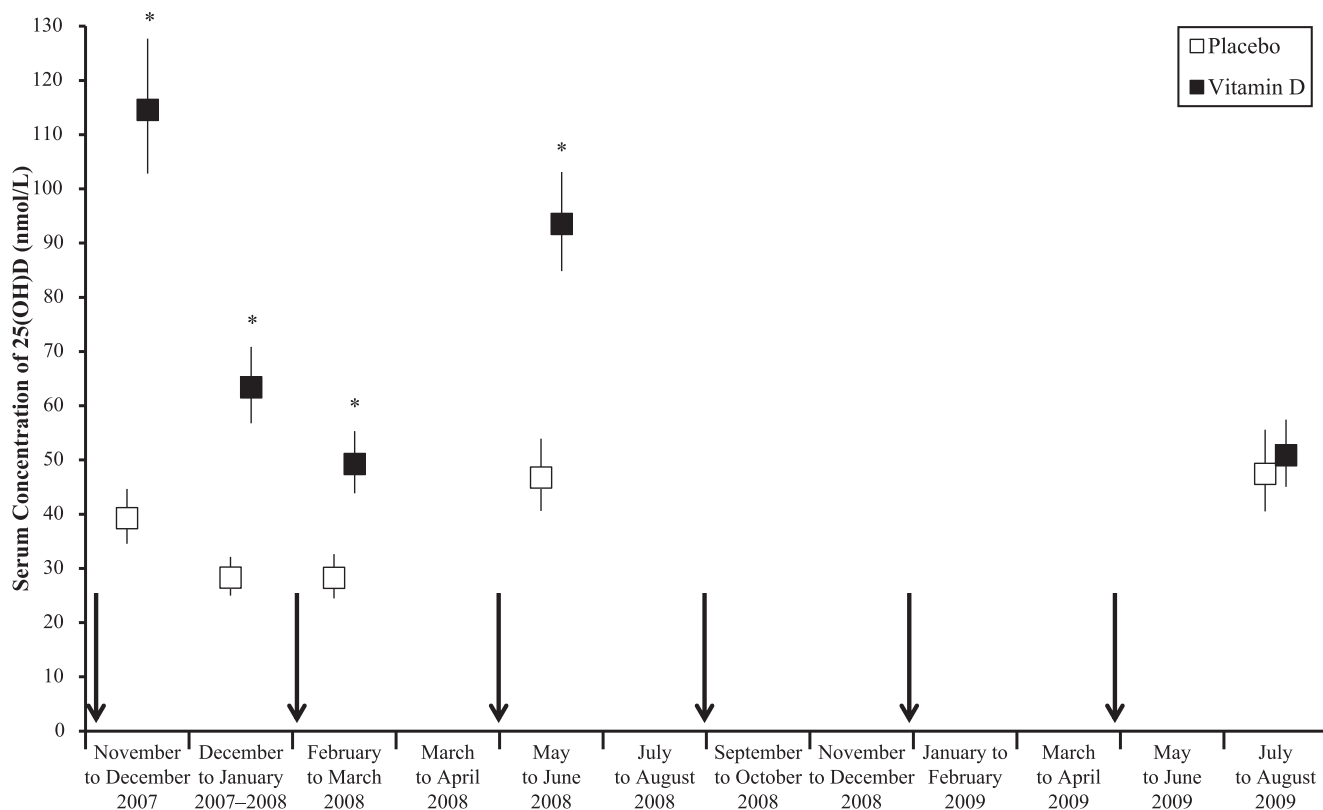


FIGURE 1

Geometric mean (95% CI) serum concentrations of 25(OH)D in the placebo and vitamin D group over the duration of the study. Arrows indicate when the bolus dose of vitamin D or placebo was administered. * $P < .001$ for difference between placebo and vitamin D.

children with a calcium intake <459 mg/1000 kcal or those with a calcium intake ≥ 459 mg/1000 kcal (Supplemental Table 4).

It made little difference to the results if the analysis for the anthropometric z scores included an adjustment for baseline values or if growth velocity (centimeter change in height per year) was used (results not shown).

DISCUSSION

Six bolus doses of 2.5 mg of vitamin D every 3 months given to young highly stunted children with insufficient vitamin D status and calcium intake did not have a significant effect on the prevalence of rickets over a period of 18 months. There was also no significant effect on growth except in a subgroup with a high intake of calcium.

The lack of an effect of vitamin D supplementation on the risk of rickets in this trial may have been due to several factors. The overall prevalence of rickets at the end of the trial was lower than anticipated (5%), meaning this study may have been insufficiently powered to detect a statistically significant difference between the groups. Nutritional rickets arises when there is inadequate absorption of dietary calcium due to vitamin D deficiency and/or dietary calcium deficiency or when there is vitamin D insufficiency and dietary calcium deficiency.⁶ These factors result in inadequate dietary calcium absorption leading to a fall in serum calcium, which in turn elevates PTH. This secondary hyperparathyroidism increases renal phosphate wastage, resulting in chronic hypophosphatemia. In a growing child, chronic

hypophosphatemia causes rickets through failure of maturation and mineralization of the growth plate, as well as impaired mineralization of osteoid matrix.^{6,17} High rates (73%) of vitamin D deficiency have previously been reported in young Afghan children,^{3,14} but in this study, the seasonally corrected mean serum 25(OH)D in the subgroup of the placebo group who had 25(OH)D measured was 37 nmol/L (95% CI: 35 to 39) throughout the trial period; thus, they would be considered vitamin D insufficient rather than deficient. The estimated mean dietary calcium intake in this population was 372 (SD 276) mg/day meaning that this population would be considered insufficient not deficient. Although the mean winter PTH concentrations were not above the assay reference range, some of the children may have developed

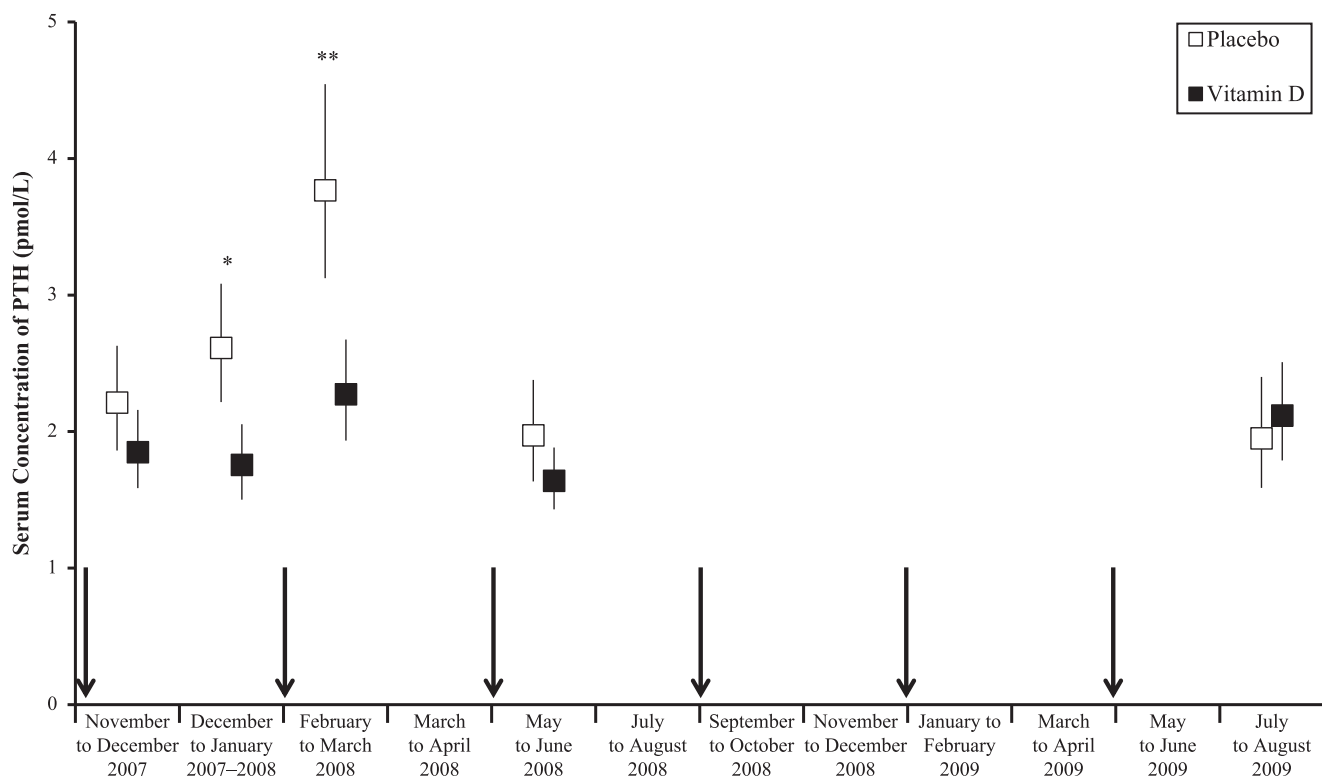


FIGURE 2

Geometric mean (95% CI) serum concentrations of PTH in the placebo and vitamin D group over the duration of the study. Arrows indicate when the bolus dose of vitamin D or placebo was administered. * $P < .01$ for difference between placebo and vitamin D; ** $P < .001$ for difference between placebo and vitamin D.

secondary hyperparathyroidism in the winter months. These findings emphasize the importance of calcium deficiency in combination with vitamin D deficiency or insufficiency in the etiology of rickets.⁶

There may be other reasons why differences in rickets between groups may not have been detected. A one-

year follow-up of Kenyan children who received inpatient treatment of severe acute malnutrition revealed that the presence of rickets (13% of the cohort) was associated with increased linear growth compared with children without rickets.¹⁸ Therefore, the impaired growth in this study population, as demonstrated by the high prevalence

of stunting, may have contributed to the low rates of rickets irrespective of their level of vitamin D. It is also possible that some features of rickets may be masked in undernourished children. These findings are important for interventions aimed to prevent stunting in LMICs and indicate that for the purpose of growth and rickets prevention, community-level vitamin D supplementation programs alone may not be cost-effective for such populations.

TABLE 2 Effect of Vitamin D Supplementation on RSS at 18 Months in Intention-To-Treat Analysis

	Placebo ($n = 310$)	Vitamin D ($n = 321$)	P
Range	0–10	0–3	—
Median (IQR)	0 (0–1)	0 (0–0.5)	—
Mean (95% CI)	0.46 (0.36 to 0.56)	0.35 (0.28 to 0.42)	.086
Rickets, n (%)			
RSS ≤ 1.5	293 (94.5)	304 (94.7)	—
RSS > 1.5	17 (5.5)	17 (5.3)	—
Risk of rickets, OR (95% CI)	1.0 (reference)	0.96 (0.48 to 1.92)	.917
RSS, mean (95% CI)			
Calcium < 300 mg/day ($n = 265$)	0.57 (0.37 to 0.77)	0.39 (0.28 to 0.50)	.106
Calcium ≥ 300 mg/day ($n = 270$)	0.44 (0.31 to 0.57)	0.29 (0.20 to 0.39)	.081

Dietary calcium was available for 268 children in the placebo ($n = 126$ with calcium < 300 mg/day and $n = 142$ with calcium ≥ 300 mg/day) and 267 children in the vitamin D group ($n = 139$ with calcium < 300 mg/day and $n = 128$ with calcium ≥ 300 mg/day). OR, odds ratio; —, not applicable.

In the few existing trials of vitamin D supplementation for improving growth, results are inconsistent and are not easily comparable to our population. Some reporting a lack of effect of vitamin D supplementation on growth of children may be criticized as being underpowered¹⁹ or of insufficient duration.²⁰ Ganmaa et al¹¹ reported an increase in height of almost 1 cm in older school-aged (11–13 years) children in Mongolia

TABLE 3 Anthropometric z Scores at 18 Months by Allocation

	Placebo (<i>n</i> = 1032), Mean ± SD	Vitamin D (<i>n</i> = 1071), Mean ± SD	Mean (95% CI) Difference	<i>P</i>	<i>P</i> Heterogeneity
Height-for-age z score					0.355
All children	−2.21 ± 1.15	−2.16 ± 1.12	0.05 (−0.05 to 0.15)	.300	
Calcium intake <300 mg/d	−2.41 ± 1.14	−2.36 ± 1.08	0.05 (−0.10 to 0.19)	.517	
Calcium intake ≥ 300 mg/d	−2.12 ± 1.11	−1.98 ± 1.09	0.14 (0 to 0.29)	.050	
Wt-for-age z score					0.817
All children	−1.35 ± 1.00	−1.31 ± 0.95	0.04 (−0.04 to 0.13)	.323	
Calcium intake <300 mg/d	−1.51 ± 0.98	−1.45 ± 0.96	0.06 (−0.07 to 0.18)	.358	
Calcium intake ≥ 300 mg/d	−1.24 ± 0.98	−1.16 ± 0.93	0.08 (−0.04 to 0.20)	.208	
Wt-for-height z score					0.757
All children	−0.25 ± 0.97	−0.25 ± 0.94	0 (−0.08 to 0.08)	.979	
Calcium intake <300 mg/d	−0.31 ± 0.95	−0.29 ± 0.95	0.02 (−0.11 to 0.14)	.807	
Calcium intake ≥ 300 mg/d	−0.18 ± 0.93	−0.19 ± 0.93	−0.01 (−0.13 to 0.11)	.846	

Height was available for 1029 children in the placebo and 1066 children in the vitamin D group; dietary calcium was available for 907 children in the placebo (*n* = 443 with calcium <300 mg/day and *n* = 464 with calcium ≥300 mg/day) and 924 children in the control group (*n* = 479 with calcium <300 mg/day and *n* = 445 with calcium ≥300 mg/day).

supplemented with 800 IU (20 µg) of vitamin D plus milk daily for 6 months compared to milk alone and no effect on 9- to 11-year-old children. Kumar et al¹⁰ also found a greater length-for-age z score in premature low birth weight infants after 6 months of supplementation with 1400 IU/week (35 µg/week) of vitamin D to breast milk compared to breast milk alone. In trials in Mongolia¹¹ and India,¹⁰ researchers used daily and weekly supplementation, respectively, whereas in our trial, young children were administered bolus doses of vitamin D every 3 months. Differences in the effectiveness of vitamin D for the daily and weekly versus bolus doses have been described for other outcomes such as acute respiratory tract infections²¹ and bone outcomes.²² This has been attributed to the finding that high circulating concentrations of 25(OH)D after bolus dosing may downregulate activity of enzymes that synthesize and degrade the active form of vitamin D, 1,25-dihydroxyvitamin D, leading to lower concentrations of this metabolite in extrarenal tissues.²³ This in turn may have attenuated the effect of vitamin D on the growth of these young children by reducing intestinal calcium absorption. Other differences in the trial population and design may have contributed to the contrasting

findings. Our population is more typical of the highly malnourished populations in LMICs, although the proportion of children who were vitamin D or calcium deficient was low.

Strengths of this trial include being the largest sample size relative to other studies in children, a long follow-up time, vitamin D and placebo supplements being administered to the children directly, radiographic screening of rickets, and use of a validated RSS. The findings are generalizable to Kabul and most of Afghanistan's urban population. Serum 25(OH)D and PTH were not measured in all children who had radiographic screening for rickets, making it difficult to know whether the cases of rickets were caused by vitamin D deficiency. Serum concentrations of alkaline phosphatase (that are raised above the reference range in rickets) are used as a screening marker for diagnosis of vitamin D deficiency²⁴ but were not measured. Lastly, the relative validity of the FFQ used in this study has not been assessed, and there was no information on the volume and nutritional composition of breast milk from women in Afghanistan, so estimates from Gambian women were used,²⁵ which may have underestimated the contribution of calcium from breast

milk, thus reducing the negative effects of vitamin D deficiency.

CONCLUSIONS

Among these young Afghan children who were mostly vitamin D and calcium insufficient, there was no effect of a bolus vitamin D supplementation given every 3 months for 18 months on the risk of rickets and growth except for those who had a high intake of calcium, who had marginally better growth. In future research studies of rickets and growth in undernourished children, researchers need to consider both the vitamin D dosing regimens as well as calcium supplementation.

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ABBREVIATIONS

CI: confidence interval
 FFQ: food frequency questionnaire
 IDS: Immunodiagnostic Systems
 LMIC: low- and middle-income country
 PTH: parathyroid hormone
 RSS: Rickets Severity Score
 25(OH)D: 25-hydroxyvitamin D

Drs Walraven, Masher, and Chandramohan made substantial contributions to the conceptualization and design of the study and revised the manuscript critically for important intellectual content; Dr Manaseki-Holland made substantial contributions to the conceptualization and design of the study, directed the study execution, and drafted the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

A deidentified individual participant data set (including data dictionaries) on which the conclusions of the article rely will be made available after publication to researchers who provide a methodologically sound proposal for use. Proposals should be submitted to Dr Crowe (f.crowe@bham.ac.uk).

This trial has been registered at www.clinicaltrials.gov (identifier NCT00548379).

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REFERENCES

1. UN Inter-agency Group for Child Mortality Estimation. Most recent stillbirth, child and adolescent mortality estimates. Available at: <https://childmortality.org/wp-content/uploads/2019/10/UN-IGME-Child-Mortality-Report-2019.pdf>. Accessed January 10, 2019
2. Levitt E, Kostermans K, Laviolette L, Mbuya N. *Malnutrition in Afghanistan: Scale, Scope, Causes, and Potential Response*. Washington, DC: World Bank; 2011
3. Afghanistan Ministry of Public Health; UNICEF. *National Nutrition Survey Afghanistan*. Kabul: Afghanistan Ministry of Public Health; 2013
4. Akseer N, Bhatti Z, Mashal T, et al. Geospatial inequalities and determinants of nutritional status among women and children in Afghanistan: an observational study. *Lancet Glob Health*. 2018;6(4):e447–e459
5. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357(3):266–281
6. Munns CF, Shaw N, Kiely M, et al. Global consensus recommendations on prevention and management of nutritional rickets. *Horm Res Paediatr*. 2016;85(2):83–106
7. Pettifor JM, Prentice A. The role of vitamin D in paediatric bone health. *Best Pract Res Clin Endocrinol Metab*. 2011;25(4):573–584
8. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. *Chem Biol*. 2014;21(3):319–329
9. Prentice A. Nutritional rickets around the world. *J Steroid Biochem Mol Biol*. 2013;136(1):201–206
10. Kumar GT, Sachdev HS, Chellani H, et al. Effect of weekly vitamin D supplements on mortality, morbidity, and growth of low birthweight term infants in India up to age 6 months: randomised controlled trial. *BMJ*. 2011;342:d2975
11. Ganmaa D, Stuart JJ, Sumberzul N, et al. Vitamin D supplementation and growth in urban Mongol school children: results from two randomized clinical trials. *PLoS One*. 2017;12(5):e0175237
12. Gallo S, Jean-Philippe S, Rodd C, Weiler HA. Vitamin D supplementation of Canadian infants: practices of Montreal mothers. *Appl Physiol Nutr Metab*. 2010;35(3):303–309
13. Vervel C, Zegboud F, Boutignon H, Tjani JC, Walrant-Debray O, Garabédian M. Fortified milk and supplements of oral vitamin D. Comparison of the effect of two doses of vitamin D (500 and 1,000 IU/d) during the first trimester of life [in French]. *Arch Pediatr*. 1997;4(2):126–132
14. Manaseki-Holland S, Zulf Mughal M, Bhutta Z, Qasem Shams M. Vitamin D status of socio-economically deprived children in Kabul, Afghanistan. *Int J Vitam Nutr Res*. 2008;78(1):16–20
15. Manaseki-Holland S, Maroof Z, Bruce J, et al. Effect on the incidence of pneumonia of vitamin D supplementation by quarterly bolus dose to infants in Kabul: a randomised controlled superiority trial. *Lancet*. 2012;379(9824):1419–1427
16. Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Manaster BJ, Reading JC. Radiographic scoring method for the assessment of the severity of nutritional rickets. *J Trop Pediatr*. 2000;46(3):132–139
17. Mughal MZ. Rickets. *Curr Osteoporos Rep*. 2011;9(4):291–299
18. Ngari MM, Thitiri J, Mwalekwa L, et al. The impact of rickets on growth and morbidity during recovery among children with complicated severe acute malnutrition in Kenya: a cohort study. *Matern Child Nutr*. 2018;14(2):e12569
19. Ala-Houhala M, Koskinen T, Koskinen M, Visakorpi JK. Double blind study on the need for vitamin D supplementation in prepubertal children. *Acta Paediatr Scand*. 1988;77(1):89–93
20. Schou AJ, Heuck C, Wolthers OD. A randomized, controlled lower leg growth study of vitamin D

- supplementation to healthy children during the winter season. *Ann Hum Biol.* 2003;30(2):214–219
21. Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ.* 2017;356:i6583
22. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA.* 2010;303(18):1815–1822
23. Vieth R. How to optimize vitamin D supplementation to prevent cancer, based on cellular adaptation and hydroxylase enzymology. *Anticancer Res.* 2009;29(9):3675–3684
24. Tiosano D, Hochberg Z. Hypophosphatemia: the common denominator of all rickets. *J Bone Miner Metab.* 2009;27(4):392–401
25. Prentice A. Regional Variations in the Composition of Human Milk. In: Jensen RG, ed. *Handbook of Milk Composition.* London, United Kingdom: Academic Press; 1995:115–221

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