Supplemental Information

PARTICIPANTS

The inclusion criteria were infants aged 1 to 11 months living in the study region. The exclusion criteria were families who were expected to move away from the study region in the next 18 months, diagnosis with rickets or treatment with vitamin D in the past 3 months, or diagnosis of kwashiorkor or marasmus.

DIETARY INTAKE OF ENERGY, PROTEIN, AND CALCIUM

The mean daily intakes of energy (kilocalorie), protein, and calcium were calculated by multiplying the frequency of consumption by standard portion sizes and the calorie, protein, and calcium content of the food or beverage, derived mainly from the *Food Composition Table for Afghanistan*[26] but supplemented with values from *McCance and Widdowson's Composition of Foods Integrated Dataset*[27] when appropriate. The mothers were asked to report whether they were breastfeeding their infants at the time they completed the FFQ. Breastfeeding was defined as "any breastfeeding," and there were no children being exclusively breastfed at the time the FFQs were completed. For any infant who was being breastfed, an extra 506 kcal, 7.5 g of protein, and 120 mg of calcium were added to the daily intake. Values for the volume and nutritional composition of breast milk were derived from studies conducted in parts of the Gambia[28] because no published values were available from Afghanistan. The average of the 2 dietary assessments were used to calculate the intake of energy, protein, and calcium. Dietary questionnaires were completed by 2702 children, and after excluding dietary intake data for children with implausible intakes, dietary data were available for 2383 children. For children with an RSS, dietary data were available for 535 children and for 1831 with an anthropometric measurement at the end of the study.

RADIOGRAPHS

The RSS is used to report the radiographic features of rickets, such as the widening of the growth plate, degree of lucency, and irregular margins at the metaphyses. The wrist was scored for both the radius and the ulna taking into account the presence of fraying, irregularity of the metaphyseal margin, and extent of concave cupping. On the knee radiograph, both the distal femur and proximal tibia were scored for the degree of lucency, the widening of the zone of provisional calcification, and the proportion of the growth plate that was affected. The RSS ranged from 0 (normal) to 10 (severe).[29] Nineteen of the radiographs (covering the full range of severity of rickets) were also reported by a consultant in pediatric bone disorders (M.Z.M). Overall, the agreement between the reporting of the 19 radiographs was moderate ($\kappa = 0.49$; $P = .007$).

ANALYSIS OF 25(OH)D AND PTH

Up to 5 mL of venous blood was drawn and stored on ice until it was transferred to the clinic where the samples were centrifuged and the serum was aliquoted into tubes for storage at −20°C.

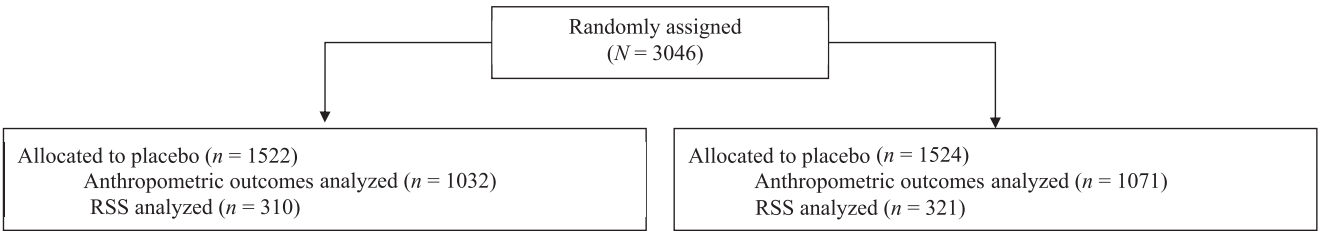
Serum 25(OH)D levels were measured on 632 blood samples (332 from vitamin D and 300 from the placebo group) by the IDS-iSYS multidiscipline automated chemiluminescent assay (IDS) at Manchester Royal Infirmary (Supra-Regional Vitamin D Reference Laboratories accredited to ISO9001: 2000 and ISO13485:2003 and participating in the Vitamin D External Quality Assessment Scheme). A serum 25(OH) level of >50 is considered vitamin D sufficiency, levels between 30 and 50 nmol/L are considered as vitamin D insufficiency, and levels <30 nmol/L are considered as vitamin D deficiency.[30]

Serum intact PTH was measured by using the IDS intact PTH enzyme-linked immunosorbent assay kit (IDS) normal adult reference range 0.8 to 3.9 pmol/L, sensitivity 0.06 pmol/L, and intraassay and interassay coefficients of variation 4% and 6%, respectively (manufacturer's values). All laboratory technicians were blinded to the group allocation.

ANTHROPOMETRY

The length or height of the child was determined to the nearest 0.1 cm with the use of height or length

measuring boards (United Nations Children's Fund), and the child's weight was measured to within 10 g by using electronic SECA scales (United Nations Children's Fund). Measurements were collected in duplicate, and the average was used in the analysis. The anthropometric measurements were converted to *z* scores by using the World Health Organization growth reference.[31]



SUPPLEMENTAL FIGURE 3
Trial profile.

SUPPLEMENTAL TABLE 4 Anthropometric *z* Scores at 18 Month by Allocation

	Placebo (*n* = 1032), Mean ± SD	Vitamin D (*n* = 1071), Mean ± SD	Mean (95% CI) Difference	*P*	*P* Heterogeneity
Height-for-age *z* score					.807
All children	−2.21 + 1.15	−2.16 + 1.12	0.05 (−0.05 to 0.15)	.300	
Calcium intake <459 mg per 1000 kcal	−2.41 ± 1.17	−2.33 ± 1.08	0.08 (−0.07 to 0.22)	.287	
Calcium intake ≥459 mg per 1000 kcal	−2.10 ± 1.06	−2.00 ± 1.11	0.10 (−0.04 to 0.25)	.157	
Wt-for-age *z* score					.65
All children	−1.35 ± 1.00	−1.31 ± 0.95	0.04 (−0.04 to 0.13)	.323	
Calcium intake <459 mg per 1000 kcal	−1.52 ± 0.99	−1.43 ± 0.93	0.08 (−0.04 to 0.21)	.175	
Calcium intake ≥459 mg per 1000 kcal	−1.22 ± 0.96	−1.18 ± 0.97	0.04 (−0.08 to 0.17)	.497	
Wt-for-height *z* score					.386
All children	−0.25 + 0.97	−0.25 + 0.94	0 (−0.08 to 0.08)	.979	
Calcium intake <459 mg per 1000 kcal	−0.33 ± 0.93	−0.29 ± 0.94	0.04 (−0.08 to 0.16)	.541	
Calcium intake ≥459 mg per 1000 kcal	−0.16 ± 0.94	−0.20 ± 0.93	−0.04 (−0.16 to 0.09)	.539	

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 and 924 children in the control group.

SUPPLEMENTAL REFERENCES

26. Food, Agriculture, Animal Husbandry and Information Management and Policy Unit. *Food Composition Table for Afghanistan*. Kabul, Afghanistan: Food and Agriculture Organization; 2004
27. Public Health England. *McCance and Widdowson's Composition of Foods Integrated Dataset*. London, United Kingdom: Crown Copyright; 2015
28. Prentice A. Nutritional rickets around the world. *J Steroid Biochem Mol Biol*. 2013;136(1):201–206
29. 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
30. 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
31. World Health Organization. *WHO Anthro for Personal Computers, Version 3.2.2, 2011: Software for Assessing Growth and Development of the World's Children [computer program]*.Geneva, Switzerland: World Health Organization; 2010. Available at: https://www.who.int/childgrowth/software/en/. Accessed July 12, 2017