

# Influence of Vitamin D Supplementation on Growth, Body Composition, and Pubertal Development Among School-aged Children in an Area With a High Prevalence of Vitamin D Deficiency

## A Randomized Clinical Trial

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**IMPORTANCE** Vitamin D deficiency (defined as 25-hydroxyvitamin D [25(OH)D] <20 ng/mL) is prevalent among children living in temperate climates and has been reported to associate independently with stunting, obesity, and early activation of the hypothalamic-pituitary-gonadal axis. Phase 3 randomized clinical trials to investigate the influence of long-term vitamin D replacement on growth, body composition, and pubertal development of school-aged children with vitamin D deficiency are lacking.

**OBJECTIVE** To determine whether weekly oral vitamin D supplementation influences linear growth, body composition, or pubertal development in school-aged children living in a setting where vitamin D deficiency is highly prevalent.

**DESIGN, SETTING, AND PARTICIPANTS** This secondary analysis of a double-blind, placebo-controlled randomized clinical trial was conducted from June 2016 to June 2019 at 18 grade schools in Ulaanbaatar, Mongolia. School-aged children (6 to 13 years at baseline) attending participating schools were included. Exclusion criteria included a positive QuantiFERON-TB Gold in-tube assay result, conditions or medications associated with altered vitamin D metabolism, use of vitamin D supplements, signs of rickets, or intention to move from Ulaanbaatar within 4 years. Of 11 475 children invited to participate in the study, 9814 underwent QFT testing, and 8851 with negative results were included in the study. All but 1 participant in the placebo group completed follow-up and were included in the present analysis. Data were analyzed from November 2021 to February 2022.

**INTERVENTIONS** Weekly oral doses of vitamin D<sub>3</sub>, 14 000 IU, (n = 4418), or placebo (n = 4433) for 3 years.

**MAIN OUTCOMES AND MEASURES** Mean z scores for height for age, body mass index for age, and waist-to-height ratio; mean percentage body fat, fat mass, and fat-free mass; and mean Tanner scores for pubertal development.

**RESULTS** Of 8851 participants, 4366 (49.3%) were female, and 8165 (92.2%) were of Khalkh ethnicity; the mean (SD) age was 9.4 (1.6) years. A total of 8453 participants (95.5%) were vitamin D deficient at baseline, and mean end-of-study 25(OH)D concentrations among participants randomized to vitamin D vs placebo were 31.0 vs 10.7 ng/mL (mean difference, 20.3; 95% CI; 19.9-20.6). However, vitamin D supplementation did not influence mean height for age, body mass index for age, waist-to-height ratio, percentage body fat, fat mass, fat-free mass, or Tanner scores, either overall or within subgroups defined by baseline 25(OH)D concentration less than 10 ng/mL vs 10 ng/mL or greater, estimated calcium intake less than 500 mg/d vs 500 mg/d or greater, or male vs female sex.

**CONCLUSIONS AND RELEVANCE** In school-aged children in this study with low baseline vitamin D status, oral vitamin D<sub>3</sub> supplementation at a dose of 14 000 IU per week for 3 years was effective in elevating 25(OH)D concentrations but did not influence growth, body composition, or pubertal development.

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The US Institute of Medicine recommends maintenance of 25(OH)D concentrations of 20 ng/mL or higher (to convert to nanomoles per liter, multiply by 2.496) to support optimal skeletal health in children.<sup>1</sup> Vitamin D affects growth by promoting adequate bone mineralization and mass and influences somatic growth and macronutrient metabolism through regulation of the cell cycle and cell proliferation.<sup>2</sup> It may also exert effects on body composition via effects on myocyte function and development<sup>3</sup> and by regulating insulin signaling, adipogenesis, and adipocyte apoptosis.<sup>4</sup> Through its actions on macrophage, dendritic, and T cell function, vitamin D is a potent mediator of innate and adaptive immunity,<sup>5</sup> and vitamin D deficiency may contribute to systemic inflammation.<sup>6</sup> Thus, by modulating diverse physiological pathways, vitamin D status is a potentially important determinant of growth, body composition, and metabolic health—a concept supported by the observation that these diverse axes are simultaneously perturbed in animal models of vitamin D deficiency.<sup>7</sup> Given the high global prevalence of vitamin D deficiency<sup>8</sup> and the rising prevalence of cardiometabolic disease,<sup>9</sup> there is interest in evaluating the potential relationship between vitamin D status—an actionable target for supplementation and fortification—and measures of metabolic health and fitness.

A potential role for vitamin D supplementation in improving anthropometric and metabolic outcomes is supported by findings of increased lean mass, decreased fat mass, and decreased body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) in long-term follow-up with infants who received vitamin D supplementation<sup>10,11</sup> and observational studies reporting independent associations between vitamin D deficiency and underweight and stunting in infants and toddlers<sup>12</sup>; lower lean mass,<sup>13</sup> slowed growth,<sup>14</sup> childhood obesity<sup>15-17</sup>; and precocious puberty.<sup>18</sup> Findings of observational studies may be explained by confounding or reverse causation, and randomized clinical trials of vitamin D supplementation are required to evaluate causality. We have previously reported results of a phase 2 randomized clinical trial showing that a 6-month course of vitamin D supplementation increased height gain in 113 Mongolian children aged 12 to 15 years with vitamin D deficiency.<sup>19</sup> We therefore wished to verify this finding by conducting a definitive phase 3 randomized clinical trial of sustained vitamin D replacement in a similar population and extend the investigation to test for potential effects of vitamin D on BMI, body composition, and pubertal development.

## Methods

### Study Design, Setting, Participants, and Randomization

We conducted a parallel 2-arm double-blind individually randomized placebo-controlled trial from June 2016 to June 2019 in 18 public schools in Ulaanbaatar, Mongolia, as previously described.<sup>20</sup> The primary outcome of the trial was acquisition of latent tuberculosis infection. This study assessed the effects of the intervention on prespecified secondary outcomes relating to growth, body composition, and pubertal development.

## Key Points

**Question** Does oral vitamin D replacement influence linear growth, body composition, or pubertal development in school-aged children living in areas with a high prevalence of vitamin D deficiency?

**Findings** This secondary analysis of a randomized clinical trial including 8851 children with a high prevalence of vitamin D deficiency at baseline found that oral vitamin D supplementation was effective in elevating 25(OH)D levels into the physiological range. However, this intervention had no impact on height for age, body mass index, body composition, or pubertal development, either in the study population as a whole or within subgroups defined by baseline 25(OH)D concentration, estimated calcium intake, and sex.

**Meaning** In this study, weekly oral administration of vitamin D for 3 years did not influence linear growth, body composition, or pubertal development among school-aged children with a high prevalence of vitamin D deficiency at baseline.

Principal inclusion criteria were ages 6 to 13 years at screening and attendance at a participating school; principal exclusion criteria were a positive QuantiFERON-TB Gold in-tube assay (QFT) result, presence of conditions associated with vitamin D hypersensitivity (primary hyperparathyroidism or sarcoidosis) or immunocompromise (taking immunosuppressant medication or cytotoxic therapy), use of vitamin D supplements, signs of rickets (all participants were screened for rickets via physical examination by a pediatrician), or intention to move from Ulaanbaatar within 4 years of enrollment. Of 11 475 children invited to participate in the study, 9814 underwent QFT testing, and 8851 with negative results were included in the study. All but 1 participant in the placebo group completed follow-up and were included in the present analysis. Eligible participants were individually randomized to receive a weekly capsule containing 14 000 IU vitamin D<sub>3</sub> or placebo for 3 years with a 1-to-1 allocation ratio and stratification by school of attendance. Treatment allocation was concealed from participants, clinicians, and all trial staff (including senior investigators and those assessing outcomes) so that the double-blinding was maintained. Each child and their parent or guardian provided written informed assent and consent, respectively, prior to participation. Because Khalkha is the largest ethnic group in Mongolia (constituting more than 80% of the population), Khalkh vs non-Khalkh ethnicity was gathered by interview. The study was approved by institutional review boards of the Mongolian Ministry of Health, Mongolian National University, and Harvard T. H. Chan School of Public Health. The study report followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. Data were analyzed from November 2021 to February 2022. The trial protocol can be found in [Supplement 1](#).

### Baseline Procedures

At baseline, participants' parents were asked to complete questionnaires detailing their socioeconomic circumstances, lifestyle, and dietary factors influencing vitamin D status, including intake of foods previously shown to be major contributors

to dietary calcium intake in urban Mongolia.<sup>21</sup> Participating children's height was then measured using a portable stadiometer (seca GmbH & Co), weight was measured using a digital floor scale (seca GmbH & Co), waist circumference was measured using a tape measure, and percentage body fat, fat mass, and fat-free mass were determined using the SC-331S body composition analyzer (Tanita). Finally, a blood sample was drawn for separation and storage of serum for determination of baseline 25(OH)D concentrations.

### Follow-up Procedures

During school terms, study participants had weekly in-person visits at which time study medication was administered and adverse events were recorded. During school holidays, either children were given a single bolus dose of up to 36 000 IU (shorter holidays), study staff traveled to participants' homes to administer medication, or parents were supplied with sufficient trial medication to cover the holiday period, along with instructions on its storage and administration. Weight, height, waist circumference, and body composition were reassessed at 12, 24, and 36 (end of study) months' follow-up using the same methods as at baseline. Pubertal status was evaluated at 3-year follow-up in a randomly selected subset of 1356 participants who completed Tanner self-assessment questionnaires.<sup>22</sup> A second blood sample was drawn from all participants at 3-year follow-up for separation and storage of serum for determination of end-of-study 25(OH)D concentrations.

### Measurement of Vitamin D Status

Concentrations of 25(OH)D were determined in serum samples from baseline and 3-year follow-up using the VIDAS 25OH Vitamin D total enzyme-linked fluorescent assay (bio-Mérieux). These measurements were validated and standardized using standards provided by the Vitamin D External Quality Assessment Scheme.<sup>23</sup> Total coefficient of variation was 7.9%, mean bias was 7.7%, and the limit of quantitation was 8.1 ng/mL. Nonzero 25(OH)D values were standardized using a published method,<sup>24</sup> using a set of 40 serum samples provided by the Vitamin D External Quality Assessment Scheme (DEQAS). Values below the limit of quantitation were classified as less than 8.1 ng/mL.

### Outcomes

The primary anthropometric outcome of interest was mean height-for-age *z* score at 1, 2, and 3 years' follow-up. Secondary outcomes were mean BMI-for-age *z* score; mean waist-to-height ratio *z* score; mean percentage body fat; mean fat mass; mean fat-free mass; mean Tanner scores for pubic hair (male and female), external genitalia (male only), and breast development (female only); the proportion of participants reaching menarche by the end of the trial (female only); and mean age at onset of menarche (female individuals who had reached menarche by the end of the trial only).

### Sample Size and Statistical Methods

The sample size calculation was based on the power needed to detect a clinically significant effect of the intervention on

the primary end point (incident latent tuberculosis infection) as described previously.<sup>20</sup> Estimated calcium intake values were calculated on the basis of parental responses to a 1-time food frequency questionnaire administered in March 2018 (eTable 1 in Supplement 2), which captured participants' frequency of intake of certain calcium-containing foods and the calcium content of those foods based on food composition data compiled from analysis of their calcium content.<sup>21</sup> Anthropometric measurements and data on participants' age and sex were then used to compute *z* scores for height for age, BMI for age, and waist-to-height ratio for age using the who2007 Shiny App (Canadian Pediatric Endocrine Group) based on 2007 World Health Organization growth reference data for children aged 5 to 19 years.<sup>25</sup>

Serum 25(OH)D values were adjusted for seasonal variation prior to analysis using a sinusoidal model.<sup>26</sup> Anthropometric and body composition outcomes were analyzed overall and in each subgroup using mixed models for repeated measures with fixed effects for treatment and time and treatment-by-time interaction adjusted for school of attendance and random effects for individuals. Adjusted treatment mean differences at different time points were presented with 95% CIs, and significance tests were conducted for the treatment effect at each time point and the overall treatment-by-time interaction. Where overall *P* values were less than the significance threshold of .05, we applied a Benjamini Hochberg procedure with a 5% false discovery rate<sup>27</sup> to the relevant family of *P* values to adjust for multiple comparisons. End-of-study pubertal development analyses were done using general linear models with gaussian distribution and identity link function for all outcomes except for the proportion of female participants menstruating at the end of the trial, which was analyzed using binomial distribution and log link function. Prespecified subgroup analyses were conducted according to participants' sex (male vs female), estimated calcium intake (<500 mg/d vs ≥500 mg/d), baseline deseasonalized 25(OH)D concentration (<10 ng/mL vs ≥10 ng/mL), and baseline *z* scores (−2.00 vs ≥−2.00 for height for age and <−2.00 vs −2.00 to 1.00 vs 1.01 to 2.00 vs >2.00 for BMI for age and waist-to-height ratio, percentage body fat, fat mass, and fat-free mass). An exploratory subgroup analysis was conducted according to participants' age at baseline (≤8 vs >8 years) in response to a reviewer request. The primary *P* values for outcome modeling were the overall *P* values, that is, those associated with the interaction between follow-up time point and treatment allocation.

## Results

### Participants

Of 8851 children with negative QFT results who were included in the trial (mean [SD] age, 9.4 [1.6] years; 4366 [49.3%] female; 8165 [92.2%] of Khalkh ethnicity), 4418 were randomly assigned to receive vitamin D<sub>3</sub> and 4433 to receive placebo, all but 1 of whom (allocated to placebo) had anthropometry data available at baseline and contributed to the current analysis (Figure). Table 1 shows baseline characteristics of par-

ticipants contributing data to analyses of anthropometric outcomes. Mean (SD) baseline serum 25(OH)D concentration was 11.9 (4.2) ng/mL; 8453 participants (95.5%) had 25(OH)D levels less than 20 ng/mL and 2813 (31.8%) less than 10 ng/mL. Baseline prevalence of stunting was 3.7%; underweight, 1.2%; overweight, 4.5%; and obesity, 1.1%. Baseline characteristics were balanced between participants randomized to vitamin D vs placebo, both for those contributing data to anthropometric analyses and for the subset of 1356 participants whose pubertal status was assessed at the end of the trial (eTable 2 in Supplement 2). End-of-trial anthropometric outcomes were available for 8128 participants (91.8% of those randomized). Mean (SD) end-of-trial serum 25(OH)D was 31.0 (9.1) ng/mL in the treatment group and 10.7 (5.3) in the placebo group (mean difference, 20.3; 95% CI, 19.9-20.6). End-of-study 25(OH)D levels were 20 ng/mL or higher in 3528 participants randomized to vitamin D (89.8%) vs 187 randomized to placebo (5.6%).

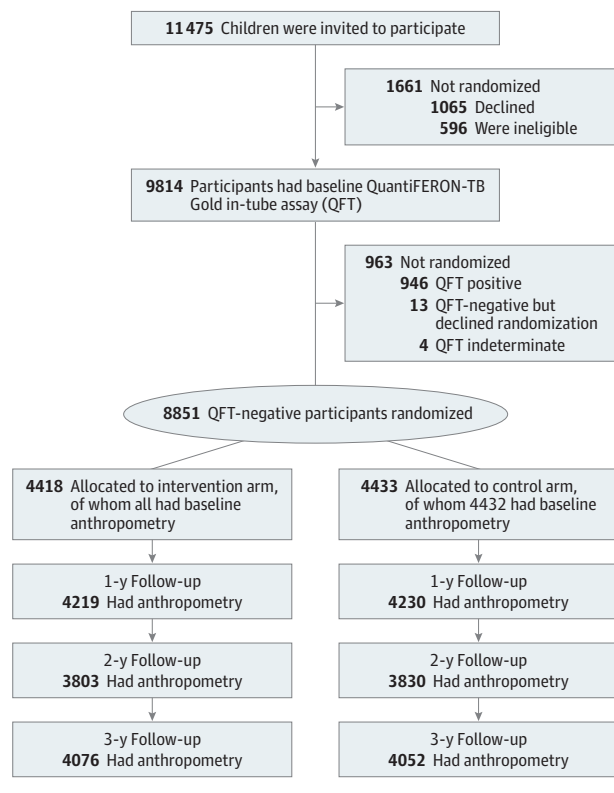
### Outcomes

Allocation to vitamin D vs placebo did not influence mean height-for-age z score, either overall or within subgroups defined by male vs female sex, age at baseline 8 years or younger vs older than 8 years, estimated calcium intake less than 500 vs 500 or more mg/d, baseline 25(OH)D concentration less than 10 vs 10 or more ng/mL, or presence vs absence of stunting at baseline (Table 2). Similarly, no effect of the intervention was seen on mean BMI-for-age z score (Table 3), mean waist-to-height ratio z score (eTable 3 in Supplement 2), mean percentage body fat (eTable 4 in Supplement 2), mean fat mass (eTable 5 in Supplement 2), or mean fat-free mass (eTable 6 in Supplement 2), either overall or by subgroups defined by sex, age, estimated calcium intake, baseline 25(OH)D concentration, or baseline anthropometry. Among the subset of 1356 participants in whom end-of-trial pubertal development was assessed, no interarm differences were seen in mean Tanner scores for pubic hair (male and female), external genitalia (male only), or breast development (female only), either overall or within subgroups defined by calcium intake and baseline 25(OH)D concentration (Table 4). When Tanner scores were dichotomized to distinguish prepubertal vs pubertal status (Tanner score 1 vs 2-5, respectively), the proportions of participants reporting Tanner score 2 to 5 did not differ between study arms, either overall or by subgroup (eTable 7 in Supplement 2). The proportion of female participants reaching menarche by the end of the trial did not differ between arms, either overall or by subgroup. Among female participants who reached menarche by the end of the trial, no difference in mean age at onset of menarche was seen between arms, either overall or by subgroup (Table 4).

### Discussion

We present results of what is to our knowledge the first phase 3 randomized clinical trial to investigate whether vitamin D supplementation influences child growth, body composition, or pubertal development. Vitamin D deficiency was highly prevalent in the study population at baseline, and a substan-

Figure. Participant Flow Diagram



tial and sustained increased in 25(OH)D levels was achieved among participants randomized to the intervention arm of the study. However, vitamin D supplementation did not influence any anthropometric or developmental outcome studied, either in the trial population as a whole or in subgroups defined by baseline vitamin D status, sex, calcium intake, or baseline anthropometric status.

To our knowledge, there have been only 2 other randomized clinical trials conducted to evaluate effects of vitamin D on growth and development in school-aged children, both of which we conducted, also in Mongolia. In those studies, where the baseline prevalence of vitamin D deficiency was also very high, we observed a greater increase in stature among children randomized to vitamin D vs placebo.<sup>19</sup> This contrasts with the null findings from the current trial. Differing results from the 2 trials may relate to differences in participant age (children aged 6 to 13 years at enrollment in the current trial vs 12 to 15 years in our previous studies) or outcome (height-for-age z scores in the current trial vs change in absolute height previously). Additionally, the duration of vitamin D supplementation and follow-up in our previous trials was only 2 to 6 months, and doses of vitamin D administered were lower at 300 to 800 IU per day; it is therefore possible that the longer period of vitamin D supplementation (3 years), the weekly dosing regimen, or the higher dose of vitamin D administered (14 000 IU per week) in the current trial may have been less effective in boosting growth than the shorter, lower-dose daily

Table 1. Baseline Characteristics of Participants by Allocation

Characteristic	No. (%)		
	Overall (n = 8851)	Placebo (n = 4432)	Vitamin D (n = 4418)
Age, mean (SD), y	9.4 (1.6)	9.4 (1.6)	9.4 (1.6)
Female	4366 (49.3)	2224 (50.2)	2142 (48.5)
Male	4485 (50.7)	2209 (49.8)	2276 (51.5)
Ethnic origin <sup>a</sup>			
Khalkh	8165 (92.2)	4103 (92.6)	4062 (91.9)
Non-Khalkh	686 (7.8)	330 (7.4)	356 (8.1)
Parental education <sup>b</sup>			
≤Secondary school	4858 (54.9)	2457 (55.4)	2401 (54.3)
≥University/polytechnic school	3993 (45.1)	1976 (44.6)	2017 (45.7)
Type of residence			
Ger (yurt)	3271 (37.0)	1628 (36.7)	1643 (37.2)
House without central heating	3387 (38.3)	1722 (38.9)	1665 (37.7)
House with central heating	2193 (24.8)	1083 (24.4)	1110 (25.1)
Home ownership, yes	6963 (78.7)	3470 (78.3)	3493 (79.1)
Monthly household income, mean (SD), \$ <sup>c</sup>	848 (579)	846 (604)	851 (554)
Household environmental tobacco smoke <sup>d</sup>	3143 (35.5)	1573 (35.5)	1570 (35.5)
Child actively smoking	47 (0.5)	21 (0.5)	26 (0.6)
BMI-for-age z score, mean (SD) <sup>e</sup>	0.2 (1.1)	0.2 (1.1)	0.2 (1.0)
Height-for-age z score, mean (SD) <sup>e</sup>	-0.3 (1.0)	-0.3 (1.0)	-0.3 (1.0)
Serum 25(OH)D, mean (SD), ng/mL <sup>c,e</sup>	11.9 (4.2)	11.9 (4.2)	11.9 (4.2)
Serum 25(OH)D, ng/mL <sup>c,e</sup>			
<10	2813 (31.8)	1420 (32.1)	1393 (31.5)
10-19.9	5640 (63.7)	2812 (63.5)	2828 (64.0)
20-29.9	381 (4.3)	193 (4.4)	188 (4.3)
≥30	12 (0.1)	4 (0.1)	8 (0.2)

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index.

SI conversion factor: To convert 25(OH)D to nmol/L, multiply by 2.496.

<sup>a</sup> Because Khalkha is the largest ethnic group in Mongolia (constituting more than 80% of the population), Khalkh vs non-Khalkh ethnicity was gathered by interview.

<sup>b</sup> Highest educational level attained by either parent.

<sup>c</sup> Household income missing for 1 participant in each arm; baseline BMI-for-age z score missing for 1 participant in placebo arm; baseline height-for-age z score missing for 1 participant in placebo arm; baseline serum 25(OH)D missing for 4 participants in placebo arm and 1 participant in vitamin D arm.

<sup>d</sup> Defined as 1 or more people in the household smoking indoors.

<sup>e</sup> Baseline 25(OH)D values deseasonalized.

intervention previously investigated. Head-to-head studies directly comparing the effects of different vitamin D supplementation regimens on anthropometric outcomes are needed to resolve this discrepancy.

Our trial has several strengths. Its large size afforded ample power to detect small differences in anthropometric outcomes. In contrast with several recent phase 3 trials of vitamin D supplementation,<sup>28-30</sup> our study population had a high baseline prevalence of vitamin D deficiency; null effects of the intervention cannot therefore be attributed to a paucity of participants with low vitamin D status at baseline. The supplementation regimen we used was highly effective in correcting this among participants randomized to the intervention arm of the trial. Weekly administration of vitamin D<sub>3</sub> allowed us to directly observe and optimize adherence during term-time while avoiding large fluctuations in 25(OH)D that may result from larger and more widely spaced bolus doses used in some other studies and potential enzymatic dysregulation that could attenuate vitamin D's pharmacological activity.<sup>31,32</sup> Other important strengths of our study were the high retention rate (91.7% over 3 years) and standardization of serum 25(OH)D measurements.

### Limitations

Our trial also has limitations. One such relates to our need to recruit children across different age groups—spanning 6 to 13 years at baseline and 9 to 15 at end-of-trial—to ensure ad-

equately power for studying the primary end point (latent tuberculosis infection). This is relevant because child growth and development trajectories differ by age: increases in height, weight, and accretion of lean mass accelerate considerably during early adolescence,<sup>33</sup> as do levels of growth hormone and insulin-like growth factor 1, which have been postulated to interact with vitamin D to stimulate growth.<sup>34</sup> A second limitation relates to our use of self-assessed pubertal status as opposed to Tanner staging performed by a health care professional, which involves examination of pubic hair (male and female), genitalia (male), and breasts (female). Major issues with acceptability of such examinations would have seriously compromised recruitment to the study since many children and their parents would likely have concerns about such assessments. Thus, use of self-assessment questionnaires maximized participation and generalizability of our findings. Due to the double-blind design of our study, any imprecision introduced by use of self-assessment is likely to be equally distributed between trial arms and should not therefore have introduced bias. A third limitation relates to the fact that 25(OH)D concentrations were only established at baseline and at 3 years; as a result, seasonal fluctuations in 25(OH)D concentrations during follow-up would not have been captured. However, we highlight that steady state 25(OH)D concentrations among participants randomized to the intervention arm of the trial are likely to have been attained within 2 to 3 months of initiating supplementation. Given the high degree of ad-

Table 2. Mean Height-for-Age z Scores by Allocation, Overall and by Subgroup

Group	Follow-up time point, y	Mean (SD); No.		Adjusted mean difference (95% CI) <sup>a</sup>	P value for time point	Overall P value <sup>b</sup>
		Placebo	Vitamin D			
Overall	1	-0.29 (1.00); 4230	-0.30 (1.00); 4219	-0.01 (-0.02 to 0.01)	.24	.45
	2	-0.27 (1.00); 3830	-0.30 (1.00); 3803	-0.01 (-0.03 to 0.00)	.17	
	3	-0.17 (1.00); 4052	-0.17 (1.02); 4076	0.00 (-0.02 to 0.01)	.80	
By sex						
Female	1	-0.35 (1.02); 2126	-0.34 (0.99); 2036	-0.01 (-0.04 to 0.01)	.20	.48
	2	-0.34 (1.00); 1927	-0.32 (0.99); 1851	-0.01 (-0.03 to 0.02)	.66	
	3	-0.22 (0.99); 2043	-0.19 (0.98); 1975	0.00 (-0.02 to 0.02)	.84	
Male	1	-0.23 (0.98); 2104	-0.26 (1.00); 2183	0.00 (-0.02 to 0.02)	.77	.49
	2	-0.21 (1.01); 1903	-0.29 (1); 1952	-0.01 (-0.03 to 0.00)	.14	
	3	-0.12 (1.03); 2009	-0.16 (1.05); 2101	0.00 (-0.02 to 0.01)	.64	
By age at baseline, y						
≤8	1	-0.24 (1.00); 1076	-0.24 (0.92); 1079	-0.02 (-0.05 to 0.01)	.12	.42
	2	-0.21 (0.99); 1040	-0.21 (0.94); 1049	-0.01 (-0.04 to 0.01)	.37	
	3	-0.13 (1.03); 1027	-0.11 (0.98); 1056	-0.02 (-0.04 to 0.01)	.21	
>8	1	-0.31 (1.00); 3239	-0.32 (1.02); 3216	-0.01 (-0.02 to 0.01)	.52	.52
	2	-0.30 (1.01); 2868	-0.34 (1.01); 2822	-0.01 (-0.03 to 0.01)	.22	
	3	-0.19 (1.00); 3106	-0.20 (1.03); 3094	0.00 (-0.02, 0.02)	.90	
By calcium intake						
<500 mg/d	1	-0.30 (1.00); 2171	-0.30 (1.02); 2161	-0.01 (-0.03 to 0.01)	.50	.42
	2	-0.29 (1.01); 1973	-0.33 (1.01); 1927	-0.01 (-0.03 to 0.01)	.23	
	3	-0.19 (1.02); 2141	-0.18 (1.02); 2143	0.00 (-0.02 to 0.02)	.71	
≥500 mg/d	1	-0.25 (0.99); 1210	-0.27 (0.98); 1261	-0.01 (-0.03 to 0.01)	.50	.42
	2	-0.24 (1.01); 1095	-0.27 (0.98); 1151	-0.01 (-0.03 to 0.01)	.23	
	3	-0.10 (1.01); 1194	-0.14 (1.01); 1241	0.00 (-0.02 to 0.02)	.71	
By baseline 25(OH)D concentration, ng/mL <sup>c</sup>						
<10	1	-0.33 (1.02); 1348	-0.31 (0.98); 1340	0.01 (-0.02 to 0.03)	.56	.90
	2	-0.33 (1.02); 1223	-0.32 (0.98); 1212	0.00 (-0.02 to 0.03)	.75	
	3	-0.24 (1.00); 1305	-0.21 (1.00); 1290	0.01 (-0.02 to 0.04)	.46	
≥10	1	-0.28 (0.99); 2878	-0.29 (1.00); 2878	-0.02 (-0.03 to 0.00)	.08	.20
	2	-0.25 (1.00); 2604	-0.29 (1.01); 2590	-0.02 (-0.03 to 0.00)	.07	
	3	-0.14 (1.01); 2744	-0.16 (1.02); 2785	-0.01 (-0.02 to 0.01)	.43	
By presence/absence of stunting <sup>d</sup> at baseline						
Present	1	-2.37 (0.60); 164	-2.38 (0.41); 149	-0.04 (-0.13 to 0.05)	.43	.78
	2	-2.30 (0.62); 155	-2.28 (0.51); 144	-0.01 (-0.10 to 0.08)	.78	
	3	-2.10 (0.72); 153	-2.13 (0.62); 140	-0.04 (-0.13 to 0.05)	.37	
Absent	1	-0.21 (0.92); 4065	-0.22 (0.93); 4070	-0.02 (-0.06 to 0.02)	.38	.56
	2	-0.19 (0.93); 3674	-0.23 (0.93); 3659	-0.02 (-0.06 to 0.02)	.31	
	3	-0.10 (0.94); 3898	-0.10 (0.96); 3936	-0.01 (-0.05 to 0.03)	.62	

Abbreviation: 25(OH)D, 25-hydroxyvitamin D.

SI conversion factor: To convert 25(OH)D to nmol/L, multiply by 2.496.

<sup>a</sup> Adjusted for random effects of school and individual.<sup>b</sup> P value for treatment-by-time interaction.<sup>c</sup> 25(OH)D values deseasonalized.<sup>d</sup> Stunting was defined as weight-for-height z score <-2.00.

herence achieved by directly observing administration of study supplements, we anticipate that the large interarm difference in end-of-study 25(OH)D levels noted at 3-year follow-up is likely to have been sustained throughout follow-up. A fourth limitation relates to exclusion of children who were found to have QFT-positive results at baseline: this design feature potentially reduces the generalizability of our findings, although baseline demographic and anthropometric charac-

teristics were similar for children with QFT positive vs negative results at screening.

## Conclusions

In conclusion, this prespecified secondary analysis of a randomized clinical trial found that oral vitamin D<sub>3</sub> supplementen-

Table 3. Mean BMI<sup>a</sup>-for-Age z Scores by Allocation, Overall and by Subgroup

Group	Follow-up time point, y	Mean (SD), No.		Adjusted mean difference (95% CI) <sup>b</sup>	P value for time point	Overall P value <sup>c</sup>
		Placebo	Vitamin D			
Overall	1	0.17 (1.08); 4229	0.16 (1.08); 4219	0.00 (-0.01 to 0.02)	.70	.95
	2	0.19 (1.08); 3829	0.16 (1.09); 3803	0.00 (-0.02 to 0.02)	.90	
	3	0.15 (1.11); 4051	0.14 (1.12); 4076	0.00 (-0.02 to 0.02)	.76	
By sex						
Male	1	0.31 (1.11); 2104	0.26 (1.11); 2183	0.01 (-0.02 to 0.04)	.47	.91
	2	0.31 (1.13); 1903	0.23 (1.12); 1952	0.01 (-0.02 to 0.03)	.66	
	3	0.22 (1.17); 2009	0.16 (1.17); 2101	0.00 (-0.02 to 0.03)	.72	
Female	1	0.03 (1.03); 2125	0.06 (1.03); 2036	0.00 (-0.03 to 0.02)	.96	.78
	2	0.07 (1.02); 1926	0.10 (1.05); 1851	-0.01 (-0.03 to 0.02)	.71	
	3	0.08 (1.04); 2042	0.13 (1.07); 1975	0.01 (-0.02 to 0.03)	.50	
By age at baseline, y						
≤8	1	0.35 (1.09); 1076	0.33 (1.02); 1079	0.03 (-0.01 to 0.06)	.17	.17
	2	0.38 (1.11); 1040	0.37 (1.08); 1049	0.04 (0.00 to 0.07)	.05	
	3	0.35 (1.16); 1027	0.36 (1.13); 1056	0.04 (0.00 to 0.07)	.06	
>8	1	0.11 (1.07); 3239	0.11 (1.09); 3216	0.00 (-0.02 to 0.02)	.76	.50
	2	0.12 (1.07); 2868	0.09 (1.08); 2822	-0.02 (-0.04 to 0.01)	.15	
	3	0.08 (1.08); 3106	0.07 (1.11); 3094	-0.01 (-0.03 to 0.01)	.42	
By calcium intake						
<500 mg/d	1	0.16 (1.08); 2171	0.16 (1.07); 2161	0.01 (-0.02 to 0.03)	.54	.94
	2	0.18 (1.08); 1973	0.17 (1.06); 1927	0.00 (-0.02 to 0.03)	.76	
	3	0.14 (1.11); 2141	0.15 (1.10); 2143	0.01 (-0.02 to 0.03)	.69	
≥500 mg/d	1	0.18 (1.06); 1210	0.20 (1.10); 1261	0.00 (-0.03 to 0.04)	.77	.96
	2	0.19 (1.07); 1095	0.22 (1.12); 1151	0.01 (-0.02 to 0.04)	.61	
	3	0.16 (1.09); 1194	0.21 (1.16); 1241	0.00 (-0.03 to 0.03)	.94	
By baseline 25(OH)D concentration, mg/ML						
<10	1	0.08 (1.08); 1347	0.14 (1.05); 1340	0.00 (-0.02 to 0.02)	.83	.86
	2	0.07 (1.08); 1222	0.15 (1.06); 1212	-0.01 (-0.03 to 0.02)	.61	
	3	0.04 (1.10); 1304	0.10 (1.11); 1290	0.00 (-0.02 to 0.03)	.76	
≥10	1	0.22 (1.08); 2878	0.17 (1.09); 2878	-0.26 (-0.47 to -0.05)	.01	.01 <sup>d</sup>
	2	0.24 (1.08); 2604	0.17 (1.10); 2590	-0.26 (-0.49 to -0.04)	.02	
	3	0.20 (1.10); 2744	0.16 (1.13); 2785	-0.25 (-0.46 to -0.05)	.02	
By baseline BMI <sup>a</sup> category						
Underweight <sup>e</sup>	1	-2.05 (0.61); 48	-2.27 (0.53); 54	0.00 (-0.04 to 0.04)	.98	1.00
	2	-1.95 (0.72); 39	-2.20 (0.59); 47	0.00 (-0.04 to 0.03)	.86	
	3	-1.97 (0.84); 49	-2.18 (0.76); 55	0.00 (-0.04 to 0.03)	.88	
Normal range <sup>f</sup>	1	-0.16 (0.76); 3381	-0.16 (0.74); 3386	0.05 (-0.01 to 0.11)	.12	.29
	2	-0.14 (0.79); 3072	-0.14 (0.79); 3085	0.04 (-0.02 to 0.10)	.22	
	3	-0.17 (0.83); 3240	-0.16 (0.85); 3270	0.06 (0.00 to 0.12)	.05	
Overweight <sup>g</sup>	1	1.35 (0.50); 562	1.40 (0.48); 542	0.02 (-0.05 to 0.09)	.55	.92
	2	1.37 (0.56); 508	1.41 (0.57); 471	0.02 (-0.06 to 0.09)	.67	
	3	1.30 (0.63); 536	1.36 (0.63); 525	0.02 (-0.05 to 0.09)	.58	
Obese <sup>h</sup>	1	2.55 (0.65); 238	2.51 (0.59); 237	0.04 (-0.13 to 0.20)	.68	.93
	2	2.50 (0.61); 210	2.48 (0.60); 200	0.04 (-0.14 to 0.22)	.65	
	3	2.37 (0.65); 226	2.34 (0.61); 226	-0.01 (-0.18 to 0.16)	.92	

Abbreviations: BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D.

SI conversion factor: To convert 25(OH)D to nmol/L, multiply by 2.496.

<sup>a</sup> Calculated as weight in kilograms divided by height in meters squared.

<sup>b</sup> Adjusted for random effects of school and individual.

<sup>c</sup> P value for treatment-by-time interaction.

<sup>d</sup> After adjustment for multiple comparisons using the Benjamini-Hochberg

procedure, this P value was .14.

<sup>e</sup> Defined as BMI-for-age z score <-2.00.

<sup>f</sup> Defined as BMI-for-age z score -2.00 to 1.00.

<sup>g</sup> Defined as BMI-for-age z score 1.01 to 2.00.

<sup>h</sup> Defined as BMI-for-age z score >2.00.

Table 4. End-of-Study Stage of Pubertal Development by Allocation and Sex, Overall and by Subgroup

Outcome measure	Subgroup	Mean (SD); No.		Adjusted mean difference (95% CI) <sup>a</sup>	P value	Adjusted risk ratio (95% CI) <sup>a</sup>	P value
		Placebo	Vitamin D				
<b>Male</b>							
Pubic hair, Tanner score							
Overall	NA	2.02 (1.06); 358	2.06 (1.04); 337	0.06 (−0.10 to 0.22)	.48	NA	NA
Calcium intake	<500 mg/d	1.96 (1.05); 192	2.09 (1.05); 184	0.15 (−0.06 to 0.36)	.17	NA	NA
	≥500 mg/d	2.04 (1.09); 97	2.01 (1.01); 104	0.04 (−0.26 to 0.34)	.79	NA	NA
Baseline 25(OH)D concentration, ng/mL	<10 ng/mL	2.31 (1.15); 129	2.21 (1.13); 98	0.09 (−0.21 to 0.39)	.56	NA	NA
	≥10 ng/mL	1.86 (0.98); 229	2.00 (0.99); 239	0.14 (−0.04 to 0.32)	.13	NA	NA
External genitalia, Tanner score							
Overall	NA	2.18 (1.02); 358	2.14 (0.98); 337	−0.04 (−0.19 to 0.11)	.59	NA	NA
Calcium intake	<500 mg/d	2.11 (1.01); 192	2.14 (0.97); 184	0.04 (−0.16 to 0.24)	.70	NA	NA
	≥500 mg/d	2.26 (1.01); 97	2.15 (1.02); 104	−0.05 (−0.34 to 0.24)	.74	NA	NA
Baseline 25(OH)D concentration, ng/mL	<10 ng/mL	2.36 (1.04); 129	2.31 (1.08); 98	0.06 (−0.23 to 0.34)	.70	NA	NA
	≥10 ng/mL	2.09 (1.04); 229	2.07 (0.93); 239	−0.01 (−0.18 to 0.17)	.94	NA	NA
<b>Female</b>							
Pubic hair, Tanner score							
Overall	NA	2.08 (1.08); 327	2.13 (0.99); 334	0.05 (−0.11 to 0.20)	.57	NA	NA
Calcium intake	<500 mg/d	2.07 (1.09); 168	2.15 (0.99); 196	0.06 (−0.15 to 0.28)	.57	NA	NA
	≥500 mg/d	2.09 (1.07); 104	2.17 (1.03); 88	0.05 (−0.25 to 0.34)	.75	NA	NA
Baseline 25(OH)D concentration, ng/mL	<10 ng/mL	2.22 (1.12); 125	2.16 (1.01); 135	−0.10 (−0.35 to 0.15)	.43	NA	NA
	≥10 ng/mL	2.00 (1.04); 202	2.12 (0.97); 199	0.12 (−0.08 to 0.31)	.25	NA	NA
Breast development, Tanner score							
Overall	NA	2.61 (0.93); 327	2.69 (0.94); 334	0.07 (−0.07 to 0.21)	.33	NA	NA
Calcium intake	<500 mg/d	2.62 (0.95); 168	2.72 (0.97); 196	0.08 (−0.12 to 0.28)	.44	NA	NA
	≥500 mg/d	2.63 (0.92); 104	2.55 (0.84); 88	−0.12 (−0.67 to 0.14)	.20	NA	NA
Baseline 25(OH)D concentration, ng/mL	<10 ng/mL	2.67 (0.97); 125	2.69 (0.97); 135	0.01 (−0.22 to 0.24)	.92	NA	NA
	≥10 ng/mL	2.57 (0.90); 202	2.69 (0.93); 199	0.11 (−0.07 to 0.29)	.24	NA	NA
Proportion menstruating, No./total No.							
Overall	NA	160/327	161/334	NA	NA	1.00 (0.86 to 1.17)	.96
Calcium intake	<500 mg/d	79/168	100/196	NA	NA	0.96 (0.78 to 1.19)	.73
	≥500 mg/d	53/104	40/88	NA	NA	1.17 (0.80 to 1.72)	.41
Baseline 25(OH)D concentration, ng/mL	<10 ng/mL	72/125	67/135	NA	NA	1.05 (0.86 to 1.29)	.64
	≥10 ng/mL	88/202	84/199	NA	NA	0.90 (0.73 to 1.11)	.33
Age at menarche, y							
Overall	NA	12.19 (1.14); 160	12.20 (1.14); 161	−0.04 (−0.29 to 0.21)	.75	NA	NA
Calcium intake	<500 mg/d	12.05 (1.18); 79	12.22 (1.19); 100	0.07 (−0.27 to 0.42)	.67	NA	NA
	≥500 mg/d	12.34 (1.02); 53	12.15 (1.10); 40	−0.38 (−0.82 to 0.06)	.09	NA	NA
Baseline 25(OH)D concentration, ng/mL	<10 ng/mL	12.42 (1.16); 72	12.31 (1.12); 67	−0.10 (−0.49 to 0.29)	.62	NA	NA
	≥10 ng/mL	12.01 (1.10); 88	12.13 (1.15); 94	0.02 (−0.30 to 0.34)	.91	NA	NA

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; NA, not applicable.

SI conversion factor: To convert 25(OH)D to nmol/L, multiply by 2.496.

<sup>a</sup> Adjusted for random effects of school and individual.

tation at a dose of 14 000 IU per week was effective in elevating 25(OH)D concentrations in a large population of Mongolian school-aged children with low baseline vitamin D status. However, this intervention did not influ-

ence growth, body composition, or pubertal development, either in the study population as a whole or within subgroups having the lowest baseline 25(OH)D concentrations or calcium intake values.

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