Vitamin D supplements for fracture prevention in schoolchildren in Mongolia: analysis of secondary outcomes from a multicentre, double-blind, randomised, placebo-controlled trial

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Summary

Background Vitamin D supplementation has been shown to increase total hip areal bone mineral density in healthy children and adolescents. We aimed to investigate whether supplementing schoolchildren living in Mongolia with weekly vitamin D_3 for 3 years affected fracture risk.

Methods We did a multicentre, double-blind, randomised, placebo-controlled trial across 18 public schools in Ulaanbaatar, Mongolia. Schoolchildren were eligible if they were aged 6–13 years at screening, had a negative QuantiFERON-TB Gold In-tube assay (QFT) result, were not hypersensitive to vitamin D or immunocompromised, did not use vitamin D supplements, did not have clinical signs of rickets, and had no intention of leaving Ulaanbaatar within 3 years. Participants were randomly assigned (1:1) to receive either vitamin D (oral dose of 14 000 international units [IU] vitamin D_3, once per week) or placebo for 3 years using permuted block randomisation stratified by school of attendance. Participants, care providers, and all trial staff were masked to group assignment during the intervention. Prespecified secondary outcomes were incidence of fractures and adverse events, ascertained using questionnaires. The fracture and safety analyses included participants who completed at least one follow-up fracture questionnaire. We estimated adjusted risk ratios (RRs) and 95% CIs using generalised linear models with binomial distribution and a log link function with adjustment for school of attendance. The trial is registered with ClinicalTrials.gov, NCT02276755, and the intervention ended in May, 2019.

Findings Between Sept 2, 2015, and March 20, 2017, 11 475 children were invited to participate in the study and 8851 were recruited and randomly assigned to receive either vitamin D (n=4418) or placebo (n=4433). 8348 participants were included in the fracture and safety analyses (4176 [94·5%] in the vitamin D group and 4172 [94·1%] in the placebo group). Of these, 4125 (49·4%) were female, 4223 (50·6%) were male, and 7701 (92·2%) were of Khalkh ancestry. Median age was 9·2 years (IQR 8·0–10·7) and 7975 (95·5%) participants had baseline serum 25-hydroxyvitamin D concentrations less than 50 nmol/L. During a median follow-up of 3·0 years (IQR 2·9–3·1), 268 (6·4%) participants in the vitamin D group and 253 (6·1%) in the placebo group reported one or more fractures (adjusted RR 1·10, 95% CI 0·93–1·29; p=0·27). Incidence of adverse events did not differ between study groups.

Interpretation Oral vitamin D supplementation at a dose of 14 000 IU/week for 3 years was safe, but did not influence fracture risk in schoolchildren living in Mongolia who had a high baseline prevalence of vitamin D deficiency.

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Introduction

Around a third of children and adolescents sustain at least one fracture before the age of 18 years, with the risk peaking around the time of the pubertal growth spurt.[1,2] Impacts range from temporary limitation of activity to hospitalisation and occasionally permanent disability.[3] Injury prevention is one strategy to address this problem,[4] but a complementary approach relates to the development of interventions to improve bone strength in childhood.[5] The potential for vitamin D supplementation to achieve this end has attracted considerable attention because of the physiological role of its active metabolite calcitriol in supporting calcium absorption.[6] Observational studies investigating associations between low vitamin D status and increased fracture risk have yielded inconsistent findings.[7] A meta-analysis of individual participant data from 1439 healthy children participating in nine randomised controlled trials[8] reported a small positive effect of vitamin D on total hip areal bone mineral density but no statistically significant effects of vitamin D

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Research in context

Evidence before this study

We searched PubMed from database inception to Sept 30, 2023, for randomised controlled trials published in any language evaluating effects of vitamin D supplementation on bone mineral content, bone mineral density, and fracture risk in HIV-uninfected schoolchildren, using the terms "vitamin D AND [bone OR fracture] AND child* AND randomized controlled trial". A meta-analysis of individual participant data from 1439 children not infected with HIV participating in nine randomised controlled trials reported a small positive effect of vitamin D on total hip areal bone mineral density but no statistically significant effects of vitamin D on total body bone mineral content or on bone mineral density at the femoral neck, lumbar spine, or forearm after 1 year of supplementation. We did not find any randomised controlled trials investigating fracture outcomes in children.

Added value of this study

To our knowledge, this study is the first phase 3 randomised controlled trial to investigate the effects of vitamin D supplementation on fracture risk in children with a high prevalence of vitamin D deficiency. Weekly oral supplementation with 14 000 international units of vitamin D_3 for 3 years elevated mean serum 25-hydroxyvitamin D (25[OH]D) concentrations and suppressed mean serum concentrations of parathyroid hormone in Mongolian schoolchildren. However, the intervention did not influence fracture risk, either in the study population as a whole or in the large subgroup of participants with baseline serum 25(OH)D concentrations of less than 25 nmol/L.

Implications of all the available evidence

Taken together with null findings from another, recently completed, phase 3 randomised controlled trial of weekly oral vitamin D supplementation undertaken in South African schoolchildren, our findings suggest that weekly vitamin D supplementation without concomitant calcium supplementation does not have a role in the reduction of fracture risk in children.

on total body bone mineral content or on bone mineral density at the femoral neck, lumbar spine, or forearm after 1 year of supplementation. Randomised controlled trials investigating the effects of vitamin D on children's fracture risk are lacking, as are randomised controlled trials investigating the effects of vitamin D on bone outcomes in children with baseline serum 25-hydroxyvitamin D (25[OH]D) concentrations of less than 50 nmol/L.

To address this evidence gap, we undertook a phase 3 randomised controlled trial of weekly oral vitamin D supplementation for 3 years in 8851 schoolchildren aged 6–13 years living in Mongolia, a setting with a particularly high fracture burden,[9] where vitamin D deficiency is also widely prevalent.[10] The primary outcome for the trial was incidence of tuberculosis infection; results for this outcome were null.[11] In this Article, we aimed to assess whether vitamin D supplementation affected incidence of bone fracture and serum concentrations of 25(OH)D in all participants; radial speed of sound (SOS) Z scores in a subset of participants who took part in a nested substudy; and serum concentrations of biochemical parameters: parathyroid hormone (PTH), calcium, albumin, total alkaline phosphatase (ALP), and bone-specific ALP (BALP) in a smaller subset of participants.

See Online for appendix

For the **online version of the protocol** see https://www.nejm.org/doi/suppl/10.1056/NEJMoa1915176/suppl_file/nejmoa1915176_protocol.pdf

Methods

Study design and participants

We did a parallel, two-arm, double-blind, individually randomised, placebo-controlled trial in 18 public schools in Ulaanbaatar, Mongolia. Detailed information about the methods has been published previously.[11,12] Briefly, we invited parents and guardians of children attending the participating schools to provide written informed consent for their child's participation in the trial, and then invited children to give written informed assent to participate. School attendance is compulsory in Mongolia. Inclusion criteria were age 6–13 years at screening and attendance at a participating school. Exclusion criteria were a positive QuantiFERON-TB Gold In-tube assay (QFT; Qiagen, Venlo, The Netherlands) result at baseline; presence of conditions associated with vitamin D hypersensitivity (ie, primary hyperparathyroidism or sarcoidosis), being immunocompromised (ie, taking immunosuppressant medication or receiving cytotoxic therapy); use of vitamin D supplements; presence of clinical signs of rickets (all participants were screened for rickets via physical examination by a study doctor); intention to move from Ulaanbaatar within 3 years of enrolment; and known HIV seropositivity at screening. The trial was approved by institutional review boards of the Mongolian Ministry of Health, Mongolian National University (Ulaanbaatar, Mongolia), and Harvard T H Chan School of Public Health (Boston, MA, USA; reference number 14-0513), and monitored by an external data and safety monitoring board. Study personnel are listed in the appendix (pp 2–4). The original and final versions of the full trial protocol, including the statistical analysis plans, are freely available online.

Randomisation and masking

We used computer-generated permuted block randomisation, stratified by school of attendance, to randomly assign participants (1:1) to receive one soft-gel capsule per week containing either vitamin D or placebo. The allocation sequence was generated by PK and accessed via an email attachment by an independent researcher at Brigham and Women's Hospital (Boston,

MA, USA), who supervised the bottling and labelling of the study medication; neither of these individuals was involved with data collection.

Vitamin D and placebo capsules had identical appearance and taste. Allocation was concealed from participants, care providers, and all trial staff (including senior investigators and those assessing outcomes) during the intervention. Participants were notified of their allocation after the trial was completed. Staff and investigators were masked until the database was locked and the statistical analysis commenced (in June, 2019). The success of masking was not assessed.

Procedures

All eligible participants received weekly doses of either 14 000 international units (IU) of vitamin D_3 or placebo. We purchased the study capsules from Tishcon Corp (Westbury, NY, USA). During school terms, study participants had weekly face-to-face visits during which they received the study capsule and adverse events were recorded. During school holidays, either children were given a single bolus dose of up to 42 000 IU (for holidays of up to 2 weeks) or study staff travelled to participants' homes to administer medication, or parents and guardians were supplied with sufficient trial medication to cover the holiday period, along with instructions on its storage and administration. The intervention ended after 3 years of supplementation, or in May, 2019, for participants who were randomly allocated after May, 2016.

At baseline, participants' parents or guardians completed a questionnaire detailing their child's socioeconomic circumstances, lifestyle, and dietary factors influencing vitamin D status, and intake of foods previously shown to be major contributors to dietary calcium intake in urban Mongolia.[13] Participating children's height was then measured with a portable stadiometer (SECA, Hamburg, Germany), and their weight was measured with a digital floor scale (SECA). In a subset of 1465 participants attending one of 14 participating schools, randomly selected with stratification by school year to ensure equal representation from students in year 2 to year 6, SOS was measured at the distal one third of the radius (ie, at the point midway between the elbow and the end of the middle finger) with a Sunlight MiniOmni portable bone sonometer (BeamMed, Petah Tikva, Israel) according to the manufacturer's instructions.[14] This methodology measures bone strength rather than bone mineral density, and other factors such as trabecular connectivity, elasticity, and microarchitecture contribute to the sonometry reading.[15] Radial SOS was measured on the non-dominant arm, unless it was injured, in which case measurement was done on the dominant arm. Finally, a blood sample was drawn for QFT testing and for separation and storage of serum, to measure 25(OH)D concentrations (in all participants) and calcium, albumin, PTH, total ALP, and BALP (in 100 participants randomly selected from the subgroup of 1465 participants).

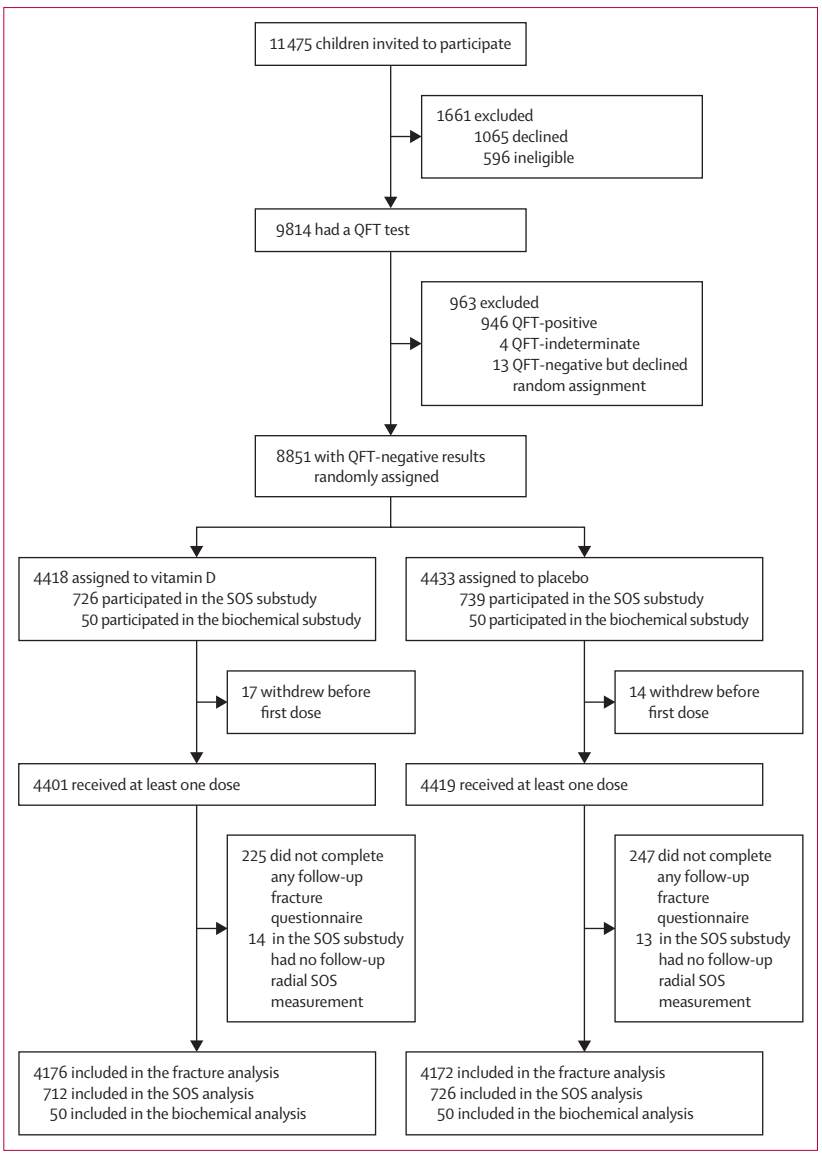

Figure: **Trial profile**
QFT=QuantiFERON-TB Gold In-tube assay. SOS=speed of sound.

At the 2-year and 3-year follow-ups, history of fractures was recorded for all participants using a questionnaire, with the questions answered by children (appendix p 11). Repeat radial SOS measurements were taken at the 1-year, 2-year, and 3-year follow-ups, using the same method as the one used at baseline. At the 3-year follow-up, a second blood sample was drawn to measure the biochemical parameters.

Serum 25(OH)D concentrations were calculated with an enzyme-linked fluorescent assay (VIDAS 25OH Vitamin D Total, bioMérieux, Marcy-l'Étoile, France). The total coefficient of variation was 7·9%, the mean bias was 7·7% from DEQAS standards, and the limit of detection

For **DEQAS** see http://www.deqas.org

was 20·2 nmol/L. Values below the limit of detection were classified as less than 20·2 nmol/L. Non-zero 25(OH)D values were standardised using a published method,[16] using a set of 40 serum samples provided by DEQAS (the Vitamin D External Quality Assessment Scheme). Serum concentrations of PTH, calcium,

	Fracture analysis			SOS analysis			Biochemical analysis		
	Total (n=8348)	Vitamin D (n=4176)	Placebo (n=4172)	Total (n=1438)	Vitamin D (n=712)	Placebo (n=726)	Total (n=100)	Vitamin D (n=50)	Placebo (n=50)
Age, years	9·2 (8·0–10·7)	9·2 (8·0–10·7)	9·2 (8·1–10·7)	9·5 (8·1–10·8)	9·4 (8·1–10·8)	9·5 (8·2–10·7)	9·2 (7·9–10·4)	9·5 (8·0–10·5)	9·0 (7·9–9·9)
Sex									
Male	4223 (50·6%)	2151 (51·5%)	2072 (49·7%)	735 (51·1%)	360 (50·6%)	375 (51·7%)	49 (49·0%)	23 (46·0%)	26 (52·0%)
Female	4125 (49·4%)	2025 (48·5%)	2100 (50·3%)	703 (48·9%)	352 (49·4%)	351 (48·3%)	51 (51·0%)	27 (54·0%)	24 (48·0%)
Ethnicity									
Khalkh	7701 (92·2%)	3838 (91·9%)	3863 (92·6%)	1320 (91·8%)	646 (90·7%)	674 (92·8%)	87 (87·0%)	43 (86·0%)	44 (88·0%)
Other	647 (7·8%)	338 (8·1%)	309 (7·4%)	118 (8·2%)	66 (9·3%)	52 (7·2%)	13 (13·0%)	7 (14·0%)	6 (12·0%)
Parental education*									
Secondary school or lower	4579 (54·9%)	2267 (54·3%)	2312 (55·4%)	866 (60·2%)	421 (59·1%)	445 (61·3%)	61 (61·0%)	32 (64·0%)	29 (58·0%)
University or polytechnic	3769 (45·1%)	1909 (45·7%)	1860 (44·6%)	572 (39·8%)	291 (40·9%)	281 (38·7%)	39 (39·0%)	18 (36·0%)	21 (42·0%)
Type of residence									
Ger (yurt)	3091 (37·0%)	1555 (37·2%)	1536 (36·8%)	605 (42·1%)	314 (44·1%)	291 (40·1%)	47 (47·0%)	25 (50·0%)	22 (44·0%)
House without central heating	3231 (38·7%)	1586 (38·0%)	1645 (39·4%)	614 (42·7%)	289 (40·6%)	325 (44·8%)	38 (38·0%)	16 (32·0%)	22 (44·0%)
House with central heating	2026 (24·3%)	1035 (24·8%)	991 (23·8%)	219 (15·2%)	109 (15·3%)	110 (15·2%)	15 (15·0%)	9 (18·0%)	6 (12·0%)
Home ownership	6594 (79·0%)	3310 (79·3%)	3284 (78·7%)	1091 (75·9%)	542 (76·1%)	549 (75·6%)	81 (81·0%)	43 (86·0%)	38 (76·0%)
Monthly household income, US$†	842·8 (537·3)	847·4 (549·5)	838·1 (524·7)	764·9 (435·5)	776·8 (432·3)	753·3 (438·7)	745·5 (510·7)	746·6 (528)	744·4 (498·2)
Calcium intake, mg/day†	382 (228–625)	389 (229–628)	375 (227–623)	378 (215–625)	388 (228–631)	370 (203–617)	388 (221–620)	445 (251–665)	359 (221–559)
Calcium intake, <500 mg/day	5191/8090 (64·2%)	2582/4053 (63·7%)	2609/4037 (64·6%)	889/1375 (64·6%)	451/687 (65·6%)	438/689 (63·6%)	62/98 (63·3%)	30/49 (61·2%)	32/49 (65·3%)
BMI-for-age Z score†	0·2 (1·1)	0·2 (1·0)	0·2 (1·1)	0·1 (1·0)	0·1 (1·0)	0·1 (1·0)	0·2 (0·9)	0·1 (0·9)	0·3 (1)
Height-for-age Z score†	−0·3 (1·0)	−0·3 (1·0)	−0·3 (1·0)	−0·4 (1·0)	−0·3 (1·0)	−0·4 (1·0)	−0·4 (1·1)	−0·4 (1·1)	−0·5 (1·1)
Serum 25(OH)D concentration, nmol/L†§	27·0 (22·9–36·0)	27·0 (23·0–35·9)	27·0 (22·9–36·1)	26·9 (22·5–35·4)	26·9 (22·4–35·3)	26·9 (22·5–35·7)	26·9 (24·3–35·6)	27·0 (24·5–36·3)	26·9 (22·9–35·6)
Serum 25(OH)D concentration‡									
<25 nmol/L	2664 (31·9%)	1323 (31·7%)	1341 (32·2%)	518 (36·0%)	248 (34·8%)	270 (37·2%)	34 (34·0%)	15 (30·0%)	19 (38·0%)
25–49·9 nmol/L	5311 (63·7%)	2671 (64·0%)	2640 (63·3%)	863 (60·0%)	434 (61·0%)	429 (59·1%)	60 (60·0%)	31 (62·0%)	29 (58·0%)
50–74·9 nmol/L	359 (4·3%)	174 (4·2%)	185 (4·4%)	56 (3·9%)	29 (4·1%)	27 (3·7%)	6 (6·0%)	4 (8·0%)	2 (4·0%)
≥75 nmol/L	10 (0·1%)	7 (0·2%)	3 (0·1%)	1 (0·1%)	1 (0·1%)	0	0	0	0
Missing	4	1	3	0	0	0	0	0	0
Radial SOS Z score	..	..	..	−0·6 (0·1)	−0·5 (1·1)	−0·6 (1·1)	−0·7 (1·1)	−0·8 (1·2)	−0·6 (1·1)
Radial SOS, m/s	..	..	..	3635·1 (122·0)	3639·5 (122·6)	3630·9 (121·4)	3619·3 (125·1)	3609·5 (133·2)	3629 (116·9)
Adjusted serum calcium concentration, mmol/L	..	..	..	..	..	..	2·24 (2·17–2·30)	2·24 (2·17–2·30)	2·24 (2·20–2·29)
Serum PTH concentration, pmol/L	..	..	..	..	..	..	4·4 (3·4–6·5)	4·2 (3·3–6·4)	4·8 (3·7–6·6)
Serum total ALP concentration, IU/L	..	..	..	..	..	..	285·0 (232·0–333·3)	280·2 (239·6–325·7)	298·3 (222·6–337·4)
Serum bone-specific ALP concentration, IU/L	..	..	..	..	..	..	25·3 (19·5–30·1)	25·8 (19·6–30·0)	24·4 (19·3–31·8)

Data are n (%), median (IQR), mean (SD), n/N (%), or n. 25(OH)D=25-hydroxyvitamin D. ALP=alkaline phosphatase. IU=international unit. PTH=parathyroid hormone. SOS=speed of sound. *Highest educational level attained by either parent. †For the fracture analysis, household income was missing for one participant in the vitamin D group; calcium intake was missing for 123 participants in the vitamin D group and 135 participants in the placebo group; BMI-for-age Z score was missing for one participant in the placebo group; height-for-age Z score was missing for one participant in the placebo group; and serum 25(OH)D concentration was missing for one participant in the vitamin D group and three participants in the placebo group. For the SOS analysis, household income was missing for one participant in the placebo group; and calcium intake was missing for 25 participants in the vitamin D group and 37 participants in the placebo group. For the biochemical analysis, calcium intake was missing for one participant in the vitamin D group and one participant in the placebo group. ‡Deseasonalised 25(OH)D concentrations.

Table 1: **Demographic and baseline characteristics**

albumin, and total ALP were measured with the cobas e 411 analyser (Roche Diagnostics, Indianapolis, IN, USA) in the ISO 15189-accredited integrated clinical laboratory at the National Second Central Hospital, Ulaanbaatar, Mongolia. Albumin-adjusted calcium (mmol/L) was calculated as:

$$\text{total calcium (mmol/L)} + 0{\cdot}02 \times (40 - \text{albumin [g/L]})$$

Serum concentrations of BALP were obtained at the Global Laboratory, Ulaanbaatar, Mongolia, using MicroVue bone alkaline phosphatase enzyme immunoassay kits (Quidel, San Diego, CA, USA), according to the manufacturer's instructions.

Outcomes

The primary outcome of the trial was the proportion of children who were QFT-positive at the manufacturer-recommended threshold of 0·35 IU/mL IFN-γ at the end of the study.[11] Fracture incidence was a prespecified secondary outcome of the trial (added in a protocol amendment dated Aug 15, 2017). Post-hoc secondary outcomes measured in the subgroup of 1465 participants were radial SOS Z scores (adjusted for age and sex) and unadjusted SOS Z scores. These two outcomes were also added in the protocol amendment dated Aug 15, 2017, but with the outcome specified as bone mineral density rather than bone strength. We therefore considered them as exploratory. Serum concentrations of PTH, albumin-adjusted calcium, total ALP, and BALP were additional, post-hoc secondary outcomes measured in the subgroup of 100 participants. Safety outcomes for the overall population are reported elsewhere;[11] in this Article, we report those that occurred in participants who completed at least one follow-up fracture questionnaire. Safety endpoints were death, serious adverse events, adverse events resulting in the discontinuation of the trial regimen, and adverse events of special interest (ie, hypercalcaemia, hypervitaminosis D, and renal stones).

Statistical analysis

We calculated that 8850 randomly allocated participants were needed to detect a 25% reduction in the proportion of children with a positive QFT result at the 3-year follow-up with 80% power and a 5% type I error rate, assuming a 2% annual risk of tuberculosis infection, 18% loss to follow-up, and 5% indeterminate QFT results at the 3-year follow-up. The sample size for the fracture analysis was based on feasibility—ie, all participants completing at least one follow-up fracture questionnaire were included. The sample sizes for the SOS substudy and for the biochemical substudy were also based on feasibility.

All analyses were done according to intention to treat in those with at least one follow-up questionnaire or measurement, with a 5% significance level. We did not adjust for multiple testing of secondary outcomes. Missing data were not imputed; participants with missing data for a given outcome were excluded from the analysis of that outcome.

Proportions of participants reporting one or more fractures were analysed using generalised linear models with binomial distribution and a log link function with adjustment for school of attendance as a fixed effect. Treatment effects are presented as adjusted risk ratios (RRs) with 95% CIs. Radial SOS measurements were converted to Z scores on the basis of age-matched and sex-matched reference values, as previously described.[14] Radial SOS Z scores and raw SOS measurements were analysed using mixed models for repeated measures (MMRM) with random effects for individuals and mixed effects for treatment, time, and treatment-by-time interaction, adjusted for school of attendance. Mean changes in values from baseline were analysed using a maximum likelihood-based repeated measures approach in combination with the Newton-Raphson algorithm. Analyses included a random effect for students and fixed categorical effects of treatment, visit (year), school, and treatment-by-visit interaction, as well as the fixed continuous covariates of baseline value. A compound symmetry covariance structure was used to model the within-participant errors to prevent this analysis failing to converge. The containment method was used to compute denominator degrees of freedom. Significance tests were based on least-squares means using a two-sided α of 0·05 (two-sided 95% CIs). The analyses using MMRM were exploratory and focused on comparing the treatment effects at each annual visit as well as an overall trend. Least squares means with 95% CIs were reported for treatment differences at each annual follow-up timepoint. Statistical significance of treatment effects was reported for each follow-up timepoint and for the overall treatment-by-time

	Vitamin D group (n=4176)	Placebo group (n=4172)	Adjusted risk ratio (95% CI)*	p value	$p_{interaction}$†
Overall	268/4176 (6·4%)	253/4172 (6·1%)	1·10 (0·93–1·29)	0·27	NA
Sex	..	..	..	..	0·60
Male	183/2151 (8·5%)	164/2072 (7·9%)	1·11 (0·91–1·35)	0·30	..
Female	85/2025 (4·2%)	89/2100 (4·2%)	0·99 (0·75–1·30)	0·92	..
Baseline serum 25(OH)D concentration‡	..	..	..	..	0·67
<25 nmol/L	82/1323 (6·2%)	73/1341 (5·4%)	1·13 (0·84–1·50)	0·42	..
≥25 nmol/L	186/2852 (6·5%)	180/2828 (6·4%)	1·08 (0·90–1·31)	0·41	..
Calcium intake	..	..	..	..	0·94
<500 mg/day	169/2582 (6·5%)	162/2609 (6·2%)	1·11 (0·91–1·36)	0·29	..
≥500 mg/day	91/1471 (6·2%)	84/1428 (5·9%)	1·07 (0·81–1·41)	0·63	..

Data are n/N (%), unless otherwise stated. *Adjusted for random effects of school of attendance. †p value for treatment-by-subgroup interaction. ‡Deseasonalised 25(OH)D concentrations. 25(OH)D=25-hydroxyvitamin D. NA=not applicable.

Table 2: **Proportion of participants reporting one or more bone fractures of any type**

	Vitamin D group (n=712)	Placebo group (n=726)	Adjusted mean difference (95% CI)*	p value for timepoint	Overall p value†	$p_{interaction}$
Overall	..	..	..	..	0·11	NA
1 year	−0·79 (1·22); 668	−0·88 (1·18); 680	0·08 (−0·04 to 0·21)	0·19	..	..
2 years	−1·06 (1·27); 629	−0·99 (1·17); 649	−0·06 (−0·19 to 0·07)	0·35	..	..
3 years	−0·96 (1·22); 671	−0·92 (1·19); 686	−0·06 (−0·18 to 0·07)	0·36	..	..
Sex	..	..	..	..	..	0·90
Male	..	..	..	..	0·19	..
1 year	−0·80 (1·26); 339	−0·89 (1·22); 353	0·07 (−0·11 to 0·25)	0·44	..	..
2 years	−1·03 (1·27); 322	−1·04 (1·18); 332	−0·01 (−0·19 to 0·17)	0·91	..	..
3 years	−1·11 (1·28); 336	−1·02 (1·21); 358	−0·13 (−0·31 to 0·05)	0·14	..	..
Female	..	..	..	..	0·27	..
1 year	−0·77 (1·19); 329	−0·86 (1·14); 327	0·09 (−0·08 to 0·27)	0·29	..	..
2 years	−1·09 (1·26); 307	−0·95 (1·17); 317	−0·12 (−0·30 to 0·06)	0·19	..	..
3 years	−0·80 (1·14); 335	−0·80 (1·15); 328	0·01 (−0·17 to 0·18)	0·95	..	..
Baseline serum 25(OH)D concentration‡	..	..	..	..	..	0·87
<25 nmol/L	..	..	..	..	0·57	..
1 year	−0·81 (1·18); 233	−0·87 (1·11); 254	0·05 (−0·16 to 0·25)	0·66	..	..
2 years	−1·09 (1·23); 217	−1·06 (1·24); 241	−0·02 (−0·23 to 0·19)	0·86	..	..
3 years	−1·03 (1·20); 232	−0·95 (1·16); 255	−0·08 (−0·29 to 0·12)	0·42	..	..
≥25 nmol/L	..	..	..	..	0·18	..
1 year	−0·77 (1·25); 435	−0·88 (1·22); 426	0·12 (−0·04 to 0·27)	0·14	..	..
2 years	−1·04 (1·29); 412	−0·95 (1·13); 408	−0·07 (−0·23 to 0·08)	0·36	..	..
3 years	−0·92 (1·23); 439	−0·89 (1·20); 431	−0·04 (−0·19 to 0·12)	0·65	..	..
Calcium intake	..	..	..	..	..	0·16
<500 mg/day	..	..	..	..	0·15	..
1 year	−0·77 (1·23); 423	−0·91 (1·19); 409	0·14 (−0·02 to 0·30)	0·088	..	..
2 years	−1·02 (1·24); 406	−1·02 (1·18); 401	0·01 (−0·15 to 0·17)	0·89	..	..
3 years	−0·97 (1·22); 441	−0·98 (1·22); 431	0·01 (−0·15 to 0·16)	0·95	..	..
≥500 mg/day	..	..	..	..	0·63	..
1 year	−0·84 (1·20); 223	−0·86 (1·13); 237	0·03 (−0·18 to 0·24)	0·80	..	..
2 years	−1·12 (1·34); 213	−0·96 (1·17); 235	−0·12 (−0·33 to 0·09)	0·27	..	..
3 years	−0·91 (1·22); 222	−0·81 (1·13); 245	−0·09 (−0·30 to 0·12)	0·39	..	..

Data are mean (SD); n, unless otherwise stated. 25(OH)D=25-hydroxyvitamin D. NA=not applicable. SOS=speed of sound. *Adjusted for baseline value and school of attendance. †A p-value for treatment-by-time interaction. ‡Deseasonalised 25(OH)D concentrations.

Table 3: **Radial SOS Z scores in SOS substudy**

interaction. Serum concentrations of biochemical parameters were analysed using linear regression with adjustment for baseline values and school of attendance; least squares means for intergroup differences are presented with 95% CI. We also did an exploratory analysis of ln-transformed biochemical data, with intergroup differences presented as adjusted geometric mean ratios with 95% CI.

We did prespecified subgroup analyses for fracture incidence, SOS Z scores, and biochemical outcomes by sex (male *vs* female), baseline deseasonalised 25(OH)D concentration (<25 nmol/L *vs* ≥25 nmol/L), and calcium intake (<500 mg/day *vs* ≥500 mg/day). The primary p values for subgroup analyses were the overall p values (ie, those associated with the interaction between follow-up timepoint and treatment allocation). Statistical significance of subgroup effects was calculated using separate MMRM models but with the additional inclusion of a treatment-by-subgroup interaction term.

Calcium intakes were calculated as previously described,[12] on the basis of parental responses to a one-off food frequency questionnaire administered in March, 2018, which captured participants' frequency of intake of calcium-containing foods, and the calcium content of those foods, based on food composition data compiled from the analysis of their calcium content. Serum 25(OH)D concentrations were adjusted for seasonal variation before analysis using a sinusoidal model, as previously described.[4] We did all statistical analyses using SAS (version 9.4 or higher). The trial is registered with ClinicalTrials.gov, NCT02276755.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of this report.

Results
Between Sept 2, 2015, and March 20, 2017, 11475 children were invited to participate in the study. After excluding 1661 participants, 9814 underwent QFT testing, and 8851 had a negative QFT result. Of 8851 participants, 4418 were randomly assigned to receive vitamin D and 4433 to receive placebo (figure). 8348 participants (4176 [94·5%] in the vitamin D group and 4172 [94·1%] in the placebo group) completed at least one follow-up fracture questionnaire and were included in the analysis of fracture outcomes. 726 (16·4%) participants assigned to the vitamin D group and 739 (16·7%) participants assigned to the placebo group participated in the SOS substudy, and 50 participants from each group provided serum samples for biochemical analysis. The median age of participants who completed at least one follow-up questionnaire was 9·2 years (IQR 8·0–10·7); 4125 (49·4%) were female, 4223 (50·6%) were male, 7701 (92·2%) were of Khalkh ancestry, and 647 (7·8%) were of another ethnicity (table 1). Mean baseline serum 25(OH)D concentration was 29·6 nmol/L (SD 10·5) in the vitamin D group and 29·6 nmol/L (10·6) in the placebo group; 7975 (95·5%) participants had baseline 25(OH)D concentrations of less than 50 nmol/L and 2664 (31·9%) participants had 25(OH)D concentrations of less than 25 nmol/L. Baseline characteristics were well balanced across the vitamin D and placebo groups (table 1; appendix p 5). Median follow-up was 3·0 years (IQR 2·9–3·1), and the median age at trial completion was 12·2 (11·1–13·7) years.

677 fractures occurred in 521 participants (incidence 266 events per 10000 children per year), of which 461 (68·1%) affected the upper limb, 163 (24·1%) affected the lower limb, and 53 (7·8%) occurred at other sites (appendix p 7). 268 (6·4%) participants in the vitamin D group and 253 (6·1%) participants in the placebo group had at least one fracture (adjusted RR 1·10, 95% CI 0·93–1·29; p=0·27; table 2). Subgroup analyses for this outcome showed no statistically significant effect modification by sex, baseline 25(OH)D concentration, or calcium intake ($p_{interaction}$>0·05; table 2). No intergroup differences in the proportion of participants reporting one or more fractures were seen for radiographically confirmed or plaster cast-treated events, for fractures arising at different sites, or for fractures associated with different degrees of trauma (appendix p 7).

712 (98·1%) of 726 participants in the vitamin D group and 726 (98·2%) of 739 participants in the placebo group had at least one follow-up radial SOS measurement (figure). Allocation to the vitamin D group versus placebo group did not influence radial SOS Z scores or unadjusted SOS values, either overall or in subgroups defined by sex, baseline 25(OH)D concentration, or calcium intake (table 3; appendix p 8).

	Vitamin D group (n=50)	Placebo group (n=50)	Adjusted mean difference (95% CI)*	p value	$p_{interaction}$
25(OH)D, nmol/L					
Overall	72·1 (23·8); 50	26·1 (14·9); 50	46·7 (39·0 to 54·4)	<0·0001	NA
Sex	..	..	..	..	0·34
Male	76·4 (21·1); 23	25·2 (11·5); 26	50·7 (41·1 to 60·2)	<0·0001	..
Female	68·4 (25·7); 27	27·1 (18·1); 24	43·1 (31·4 to 54·8)	<0·0001	..
Baseline serum 25(OH)D concentration†	..	..	..	..	0·91
<25 nmol/L	68·7 (10·5); 15	26·6 (19·9); 19	45·3 (34·3 to 56·2)	<0·0001	..
≥25 nmol/L	73·5 (27·6); 35	25·8 (11·2); 31	46·5 (36·1 to 56·8)	<0·0001	..
Calcium intake	..	..	..	..	0·77
<500 mg/day	71·6 (19·4); 30	22·3 (10·2); 32	47·9 (40·3 to 55·5)	<0·0001	..
≥500 mg/day	75·2 (28·6); 19	33·9 (19·4); 17	55·4 (37·3 to 73·5)	<0·0001	..
Parathyroid hormone, pmol/L					
Overall	4·0 (1·9); 50	5·4 (3·2); 50	−1·4 (−2·5 to −0·4)	0·0075	NA
Sex	..	..	..	..	0·62
Male	4·1 (2·2); 23	5·8 (3·5); 26	−1·2 (−2·6 to 0·1)	0·073	..
Female	4·0 (1·7); 27	4·9 (2·9); 24	−1·1 (−2·3 to 0·0)	0·051	..
Baseline serum 25(OH)D concentration†	..	..	..	..	0·035
<25 nmol/L	4·1 (1·3); 15	6·4 (3·8); 19	−2·5 (−4·2 to −0·9)	0·0047	..
≥25 nmol/L	4·1 (2·2); 35	4·8 (2·7); 31	−0·8 (−2·0 to 0·4)	0·19	..
Calcium intake	..	..	..	..	0·030
<500 mg/day	4·3 (1·8); 30	6·0 (3·5); 32	−2·1 (−3·4 to −0·8)	0·0020	..
≥500 mg/day	3·6 (2·1); 19	3·9 (1·9); 17	0·1 (−1·4 to 1·5)	0·92	..
Albumin-adjusted calcium, mmol/L					
Overall	2·30 (0·08); 50	2·27 (0·13); 50	0·02 (−0·02 to 0·06)	0·24	NA
Sex	..	..	..	..	0·68
Male	2·31 (0·08); 23	2·24 (0·15); 26	0·03 (−0·05 to 0·10)	0·49	..
Female	2·30 (0·09); 27	2·29 (0·09); 24	0·01 (−0·03 to 0·05)	0·57	..
Baseline serum 25(OH)D concentration†	..	..	..	..	0·010
<25 nmol/L	2·27 (0·06); 15	2·21 (0·16); 19	0·10 (0·01 to 0·20)	0·037	..
≥25 nmol/L	2·32 (0·09); 35	2·30 (0·09); 31	0·00 (−0·03 to 0·04)	0·95	..
Calcium intake	..	..	..	..	0·56
<500 mg/day	2·30 (0·09); 30	2·25 (0·15); 32	0·03 (−0·02 to 0·08)	0·25	..
≥500 mg/day	2·31 (0·07); 19	2·29 (0·10); 17	0·03 (−0·02 to 0·08)	0·19	..

(Table 4 continues on next page)

Analysis of biochemical outcomes included 50 participants in the vitamin D group and 50 participants in the placebo group (figure). Mean serum 25(OH)D concentration at trial completion was 72·1 nmol/L (SD 23·8) in the vitamin D group and 26·1 nmol/L (14·9) in the placebo group (mean difference 46·7 nmol/L, 95% CI 39·0–54·4; table 4). Participants in the vitamin D group had lower PTH concentrations than those in the placebo group at the 3-year follow-up (adjusted mean difference −1·4 pmol/L, 95% CI −2·5 to −0·4; p=0·0075; table 4). The effect of vitamin D on PTH concentrations was not modified by sex ($p_{interaction}$=0·62), but it was modified by baseline 25(OH)D concentration and calcium intake, with greater vitamin D-induced reductions in

	Vitamin D group (n=50)	Placebo group (n=50)	Adjusted mean difference (95% CI)*	p value	$p_{interaction}$
(Continued from previous page)					
Total ALP, IU/L					
Overall	308·4 (107·9); 50	332·8 (118·7); 50	−20·1 (−63·9 to 23·7)	0·36	NA
Sex	..	..	..	..	0·97
Male	342·1 (101·7); 23	368·8 (134·6); 26	−24·4 (−81·2 to 32·4)	0·39	..
Female	279·7 (106·4); 27	293·9 (85·3); 24	−10·8 (−59·1 to 37·5)	0·65	..
Baseline serum 25(OH)D concentration†	..	..	..	..	0·030
<25 nmol/L	280·9 (107·4); 15	369·9 (155·4); 19	−38·7 (−132·3 to 54·8)	0·40	..
≥25 nmol/L	320·2 (107·5); 35	310·1 (84·3); 31	13·4 (−30·6 to 57·4)	0·54	..
Calcium intake	..	..	..	..	0·10
<500 mg/day	305·0 (108·9); 30	339·6 (124·6); 32	−48·1 (−104·7 to 8·6)	0·094	..
≥500 mg/day	316·9 (110·9); 19	310·9 (104·4); 17	38·9 (−41·9 to 119·8)	0·33	..
Bone-specific ALP, IU/L					
Overall	31·5 (10·7); 50	30·9 (12·8); 50	−0·2 (−4·8 to 4·4)	0·93	NA
Sex	..	..	..	..	0·38
Male	34·7 (9·6); 23	35·2 (14·9); 26	−5·4 (−12·2 to 1·4)	0·12	..
Female	28·8 (10·9); 27	26·3 (8·0); 24	2·7 (−1·9 to 7·3)	0·24	..
Baseline serum 25(OH)D concentration†	..	..	..	..	0·036
<25 nmol/L	27·6 (11·0); 15	34·4 (17·6); 19	−4·8 (−12·7 to 3·1)	0·22	..
≥25 nmol/L	33·2 (10·2); 35	28·8 (8·4); 31	3·9 (−0·7 to 8·5)	0·094	..
Calcium intake	..	..	..	..	0·023
<500 mg/day	30·6 (11·6); 30	31·9 (14·1); 32	−4·3 (−10·7 to 2·0)	0·17	..
≥500 mg/day	33·1 (9·4); 19	28·4 (10·3); 17	8·9 (1·5 to 16·4)	0·022	..

Data are mean (SD); n, unless otherwise stated. 25(OH)D=25-hydroxyvitamin D. ALP=alkaline phosphatase. IU=international unit. NA=not applicable. *Adjusted for baseline value and school of attendance. †Deseasonalised 25(OH)D concentrations.

Table 4: **Serum concentrations of biochemical parameters in the biochemical substudy at the 3-year follow-up**

PTH seen in participants having baseline 25(OH)D concentrations of less than 25 nmol/L (*vs* ≥25 nmol/L; $p_{interaction}$=0·035) and calcium intake of less than 500 mg/day (*vs* ≥500 mg/day; $p_{interaction}$=0·030). Allocation to the vitamin D group versus placebo group did not influence albumin-adjusted serum calcium concentrations overall (p=0·24). The effect of vitamin D on albumin-adjusted serum calcium concentrations was not modified by sex ($p_{interaction}$=0·68) or calcium intake ($p_{interaction}$=0·56), but it was modified by baseline 25(OH)D concentration, with a greater vitamin D-induced increase seen in participants having baseline serum 25(OH)D concentrations of less than 25 nmol/L (*vs* ≥25 nmol/L; $p_{interaction}$=0·010). No overall effect of allocation was seen on total serum ALP (p=0·36) or BALP (0·93) concentrations. The effect of vitamin D on both parameters was not modified by sex ($p_{interaction}$>0·05), but it was modified by baseline 25(OH)D concentrations, with greater vitamin D-induced reductions seen in participants having baseline serum 25(OH)D concentrations of less than 25 nmol/L (*vs* ≥25 nmol/L; $p_{interaction}$≤0·036). The effect of vitamin D on BALP was also modified by calcium intake, with greater vitamin D-induced reductions seen in those with calcium intake of less than 500 mg/day (*vs* ≥500 mg/day; $p_{interaction}$=0·023). However, the effect of vitamin D on total ALP was not modified by calcium intake ($p_{interaction}$=0·10). Analyses of ln-transformed data showed similar results (appendix pp 9–10).

The incidence of adverse events was similar in participants in the vitamin D and placebo groups, and none were judged to have been caused by the study preparation (appendix p 6).

Discussion

We present findings of the largest randomised controlled trial to investigate the effects of vitamin D supplementation on the risk of bone fracture in children. Vitamin D deficiency and low calcium intake (ie, <500 mg/day) were common among participants at baseline, and weekly oral administration of 14000 IU vitamin D_3 was effective in elevating serum 25(OH)D concentrations to 75 nmol/L or higher. In a subset of participants with available serum samples for biochemical analyses, allocation to vitamin D was associated with reduced serum PTH concentrations (irrespective of baseline vitamin D status) and suppression of serum concentrations of total ALP and BALP in participants with a baseline serum 25(OH)D concentration of less than 25 nmol/L. However, the intervention did not affect fracture risk or radial SOS Z scores, either in the study population as a whole or in subgroups of participants with low baseline vitamin D status or low calcium intake.

Null results in our trial for outcomes relating to fracture incidence and bone strength are consistent with those of our trial in schoolchildren in Cape Town, South Africa,[17] and with those of trials in adults, which suggest that vitamin D does not reduce fracture risk in the absence of concomitant calcium supplementation.[18] The lack of concomitant calcium supplementation in our trial might have been particularly impactful on the outcome because 62·2% of participants had calcium intake of less than 500 mg/day—ie, the minimum recommended amount during childhood and adolescence.[19] However, no effect of vitamin D on fracture risk or radial SOS Z scores was seen in the subgroup of participants with higher calcium intake.

Suppression of serum PTH concentrations in response to vitamin D supplementation probably reflects correction of secondary hyperparathyroidism associated with participants' very low vitamin D status at baseline. Vitamin D-induced suppression of BALP in participants with the lowest baseline 25(OH)D concentrations might indicate an effect of vitamin D in reducing bone remodelling secondary to the reduction in serum PTH concentration; however, we saw no intergroup differences in bone mineral density or fracture risk even when the analysis was restricted to those with a baseline 25(OH)D concentration of less than 25 nmol/L.

Our study has several strengths. The double-blind trial design is the gold standard for evaluating effectiveness of an intervention because it minimises the potential for bias and confounding to operate. The 3-year duration of the study provided ample time for any effects of vitamin D to manifest, and the proportion of participants without follow-up fracture data was low and similar between groups (5·5% in the vitamin D group *vs* 5·9% in the placebo group), providing assurance that data missingness is unlikely to have introduced bias. Fracture incidence was high at 266 events per 10 000 children per year—more than double that reported in a Norwegian cohort of 193 540 children aged 0–12 years (128 events per 10 000 children per year).[3] Together with the large sample size, this incidence provided a high degree of statistical power to detect an effect of the intervention. The lower bound of the 95% CI for the adjusted RR was 0·93, indicating with 97·5% certainty that any reduction in fracture risk is no greater than 7%: our null findings can therefore be regarded as definitive. The consistent lack of effect of vitamin D supplementation on both radial SOS Z scores and fracture outcomes is indicative that our null results are likely to be valid.

Our study also has some limitations. We used radial quantitative ultrasound to measure bone strength rather than dual energy x-ray absorptiometry measurement of bone mineral density, which is the gold standard. The low cost, simplicity of performance, mobility, and lack of exposure to ionising radiation made this alternative attractive. SOS Z scores are associated with fracture risk in adults,[20] and low SOS values are associated with increased fracture risk in children.[21] We only investigated a single dose of vitamin D, which was given at weekly intervals without concomitant calcium supplementation; thus, our findings do not exclude the possibility that daily dosing, with or without concomitant calcium supplementation, might be effective. We measured serum 25(OH)D concentrations using an enzyme-linked fluorescent assay with a limit of detection of 20·2 nmol/L, rather than liquid chromatography with tandem mass spectrometry, which is the gold standard. Accordingly, we were unable to distinguish children with baseline 25(OH)D concentrations of less than 12·5 nmol/L versus those with concentrations of 12·5–25·0 nmol/L. However, the potential for analytical bias was minimised by standardisation of our assay with a reference set of serum samples, as recommended by the Vitamin D Standardization Program.[16] Estimation of participants' calcium intake was based on parental recall, rather than a prospectively completed food frequency questionnaire, which might have compromised the accuracy of this assessment. Our findings also relate to a specific geographical and ethnic locale, which might limit their generalisability. Finally, this Article focused on the analysis of secondary outcomes, exploring several potential effect modifiers, without correction for multiple testing. Bone strength and markers of bone turnover were not prespecified outcomes, and results of these analyses should be considered as exploratory.

Contributors

DG and ARM conceived the study and contributed to the study design and protocol development. DG led the trial implementation, with support from UB, ETser, SE, C-EA, NY, BD, MA, ETsen, BO, BJ, and DE. BD and MA did and supervised the conduct of biochemical assays. DG, PK, and ARM drafted the statistical analysis plan. DG, UB, ETser, SE, BD, and MA managed the data. DG, PK, and ARM accessed and verified the underlying data reported in the manuscript. PK did the statistical analyses. ARM wrote the first draft of the manuscript. All authors made substantive comments thereon and approved the final version for submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

ARM declares receipt of funding to support vitamin D research from Pharma Nord, DSM Nutritional Products, Thornton & Ross, and Hyphens Pharma. ARM also declares receipt of vitamin D capsules for clinical trial use from Pharma Nord, Synergy Biologics, and Cytoplan; support for attending meetings from Pharma Nord and Abiogen Pharma; receipt of consultancy fees from DSM Nutritional Products and Qiagen; receipt of a speaker fee from the Linus Pauling Institute (Corvallis, OR, USA); participation on data and safety monitoring boards for the VITALITY trial (PACTR20200989766029) and the trial of Vitamin D and Zinc Supplementation for Improving Treatment Outcomes Among COVID-19 Patients in India (NCT04641195); and unpaid work as a programme committee member for the Vitamin D Workshop. All other authors declare no competing interests.

Data sharing

Anonymised data can be requested after publication from the corresponding authors to be shared subject to the approval of all institutional review boards.

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