BMJ Open Sport & Exercise Medicine

Influence of vitamin D supplementation on muscle strength and exercise capacity in South African schoolchildren: secondary outcomes from a randomised controlled trial (ViDiKids)

Keren Middelkoop,[1,2] Lisa Micklesfield,[3,4] Stephanie Hemmings,[5] Neil Walker,[6] Justine Stewart,[1,2] David A Jolliffe,[7] Amy E Mendham,[4,8] Jonathan C Y Tang,[9,10] Cyrus Cooper,[11,12] Nicholas C Harvey,[11,12] Robert J Wilkinson,[13,14,15] Adrian R Martineau [5]

To cite: Middelkoop K, Micklesfield L, Hemmings S, *et al*. Influence of vitamin D supplementation on muscle strength and exercise capacity in South African schoolchildren: secondary outcomes from a randomised controlled trial (ViDiKids). *BMJ Open Sport & Exercise Medicine* 2024;**10**:e002019. doi:10.1136/bmjsem-2024-002019

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjsem-2024-002019).

Accepted 23 August 2024

Linked

► http://dx.doi.org/10.1136/bmjsem-2024-002018

Check for updates

© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Dr Adrian R Martineau;
a.martineau@qmul.ac.uk

ABSTRACT

Objective To determine whether vitamin D supplementation influences grip strength, explosive leg power, cardiorespiratory fitness and risk of exercise-induced bronchoconstriction (EIB) in South African schoolchildren.

Methods Substudy (n=450) in Cape Town schoolchildren aged 8–11 years nested within a phase 3 randomised placebo-controlled trial (ViDiKids). The intervention was weekly oral doses of 10 000 IU vitamin D_3 (n=228) or placebo (n=222) for 3 years. Outcome measures were serum 25-hydroxyvitamin D_3 ($25(OH)D_3$) concentrations, grip strength, standing long jump distance, peak oxygen uptake (VO_{2peak}, determined using 20 m multistage shuttle run tests) and the proportion of children with EIB, measured at end-study.

Results 64.7% of participants had serum 25(OH) D_3 concentrations <75 nmol/L at baseline. At 3-year follow-up, children randomised to vitamin D versus placebo had higher mean serum $25(OH)D_3$ concentrations (97.6 vs 58.8 nmol/L, respectively; adjusted mean difference 39.9 nmol/L, 95% CI 36.1 to 43.6). However, this was not associated with end-study differences in grip strength, standing long jump distance, VO_{2peak} or risk of EIB.

Conclusion A 3-year course of weekly oral supplementation with 10 000 IU vitamin D_3 elevated serum $25(OH)D_3$ concentrations in South African schoolchildren but did not influence muscle strength, exercise capacity or risk of EIB.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Observational studies have reported that vitamin D deficiency is associated with reduced muscle strength and peak oxygen uptake and increased risk of exercise-induced bronchoconstriction (EIB) in children. Randomised controlled trials (RCTs) of vitamin D supplementation to improve children's muscle strength and cardiorespiratory fitness have yielded conflicting results.

WHAT THIS STUDY ADDS

⇒ This RCT, conducted in South African schoolchildren aged 8–11 years at baseline, found that a 3-year course of weekly oral supplementation with 10 000 IU vitamin D_3 improved vitamin D status but had no effect on grip strength, standing long jump distance, peak oxygen uptake or risk of EIB.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Taken together with null results from another phase 3 RCT of vitamin D supplementation conducted in Mongolian children, our findings do not suggest that weekly oral vitamin D supplementation exerts clinically significant effects on muscle strength or exercise tolerance in schoolchildren in whom rickets have been excluded.

INTRODUCTION

Muscle strength and exercise tolerance positively correlate with physical and mental health during childhood and are associated with reduced risk of cardiometabolic disease in adulthood.[1–4] Vitamin D is essential for the normal development and function of the cardiorespiratory system and skeletal muscle.[5–7] Deficiency in this fat-soluble micronutrient—indicated by low circulating concentrations of 25-hydroxyvitamin D (25(OH)D)—is widespread among children in both higher-income and lower-income countries.[8–11] Observational studies have linked vitamin D deficiency in children and adolescents to reduced muscle strength and cardiorespiratory fitness[12 13] and increased risk of exercise-induced bronchoconstriction (EIB),[14] which may limit exercise capacity. Numerous randomised controlled trials (RCTs) in adults have revealed positive effects

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2024-002019 on 26 September 2024. Downloaded from http://bmjopensem.bmj.com/ on October 7, 2024 at Imperial College London Library. Protected by copyright.

of vitamin D supplementation on muscle strength and power, with meta-analyses reporting a modest benefit overall.[15] However, analogous studies in children are less numerous and have yielded inconsistent outcomes. For example, an RCT of vitamin D supplementation conducted in Tunisia in vitamin D deficient male soccer players aged 8–15 years reported improvements in long jump distance, sprint and shuttle run outcomes[16] while a UK study in girls aged 12–14 years showed that vitamin D supplements enhanced movement efficiency, with indications of better jumping velocity and grip among participants randomised to intervention.[17] However, RCTs in children and adolescents living in Denmark,[18 19] the USA,[20] Israel[21] and Lebanon[22] have not found significant effects of vitamin D supplementation on grip strength, leg press strength or swimming performance. No such trials have yet been conducted in Africa; moreover, there is a lack of large, multicentre trials examining the impact of prolonged (greater than 1 year) vitamin D supplementation on muscle strength, cardiorespiratory fitness and risk of EIB in children living in any setting.

Given these limitations of the existing evidence base, we took the opportunity to generate new data in this area during the conduct of a phase 3 RCT of weekly vitamin D supplementation involving a total of 1682 children attending primary schools in Cape Town, South Africa. The primary objective was to determine whether this intervention would decrease the risk of incident tuberculosis (TB) infection, as indicated by the conversion of an interferon-gamma release assay from negative at baseline to positive at 3-year follow-up; null findings for this outcome have been reported elsewhere.[23] The current paper reports findings of a substudy nested within the main trial, which tested the hypotheses that vitamin D supplementation would improve grip strength, standing long jump distance, peak oxygen uptake (VO_{2peak}) and reduce risk of EIB in a subset of 450 participants aged 8–11 years at baseline.

METHODS

Trial design, setting, approvals and registration

We conducted a multicentre phase 3 individually randomised placebo-controlled trial in 23 government schools in Cape Town, South Africa, as previously described.[23–25] The primary outcome was the acquisition of latent TB infection; the current manuscript reports the effects of the intervention on prespecified secondary outcomes relating to muscle strength and cardiorespiratory outcomes measured at 3-year follow-up in a subset of 450 participants who took part in a nested substudy. The trial was sponsored by Queen Mary University of London and registered on the South African National Clinical Trials Register (DOH-27-0916-5527) and ClinicalTrials.gov (ref NCT02880982).

Participants

Inclusion criteria for the main trial were enrolment in grades 1–4 at a participating school; aged 6–11 years at screening and written informed assent/consent to participate in the main trial provided by children and their parent/legal guardian, respectively. Exclusion criteria for the main trial were a history of previous latent TB infection, active TB disease or any chronic illness other than asthma (including known or suspected HIV infection) prior to enrolment; use of any regular medication other than asthma medication; use of vitamin D supplements at a dose of more than 400 IU/day in the month before enrolment; plans to move away from study area within 3 years of enrolment; inability to swallow a placebo soft gel capsule with ease and clinical evidence of rickets or a positive QuantiFERON-TB Gold Plus (QFT-Plus) assay result at screening. Additional inclusion criteria for the substudy were enrolment in grade 4 at a participating school; additional exclusion criteria for the substudy were the presence of an injury or disability limiting the ability to run with maximum effort and the inability to perform spirometry at baseline. Trial staff who determined whether subjects were eligible for inclusion in the trial were unaware of which group the next subject would be allocated to, that is, allocation was concealed.

Enrolment and baseline assessments

Parents or legal guardians were invited to provide written informed consent for their child to participate in the main trial during a home visit, unless their child was eligible for the substudy, in which case they were invited to provide written informed consent for their child to participate in both the main trial and the substudy until a total of 450 substudy participants were randomised. If parents/legal guardians consented, they were asked to provide details of their child's dietary intake of foods containing vitamin D and calcium in the previous month, which were captured on an electronic case report form as previously described.[24] Their children were then invited to provide written assent to participate in the main trial±the substudy (if eligible) at a school-based visit. If they agreed, a clinically trained member of the study team screened them for symptoms and signs of rickets. For all participants, a blood sample was taken for a QFT-Plus assay (Qiagen, Hilden, Germany) and separation and storage of serum for determination of 25(OH) D concentrations as described below. Participants were reviewed when baseline QFT-Plus results were available. Those with a positive QFT-Plus result were excluded from the trial and screened for active TB. Those with an indeterminate QFT-Plus result were excluded from the trial without screening for active TB. Those with a negative QFT-Plus result were deemed eligible to participate and underwent measurement of weight (using a digital floor scale, Charder Medical) and height (using a portable HM200P stadiometer, Charder Medical). For substudy participants, grip strength was measured as described elsewhere[26] using a portable dynamometer (Takei Digital Grip Strength Dynamometer, Model T.K.K.5401); the best of two readings for the dominant hand were recorded, except where injury precluded measurement,

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2024-002019 on 26 September 2024. Downloaded from http://bmjopensem.bmj.com/ on October 7, 2024 at Imperial College London Library. Protected by copyright.

where strength of the non-dominant hand was measured. Standing long jump distance was measured as described elsewhere[27] using a DiCUNO measuring tape, with the best of two readings recorded. Validity and reliability of the Takei Digital Grip Strength Dynamometer for measurement of grip strength, and of the standing long jump for measurement of lower body muscular power have both been demonstrated in schoolchildren studied in other settings.[28 29] Spirometry was performed according to European Respiratory Society/American Thoracic Society standards[30] using a portable spirometer (SpiroUSB, Carefusion, San Diego, USA). A 20 m multistage shuttle run test was then conducted using freely available recorded instruction (Shuttle run bleep test, www.bleeptests.com, accessed on 26 March 2024) until volitional exhaustion. Two lines were marked 20 m apart and an audible 'bleep' signalled to participants the speed required to run between them. The number of completed laps was recorded and used to derive VO_{2peak} as described below. Spirometry was repeated 3–5 min after completion of the shuttle run test to detect EIB.

Randomisation and blinding

Eligible and assenting children whose parents consented to their participation in the trial were individually randomised to receive a weekly capsule containing vitamin D_3 or placebo for 3 years, with a one-to-one allocation ratio and randomisation stratified by school of attendance, as previously described.[23] Full details are supplied in online supplemental file 1. The randomisation list was computer generated by a statistician (Prof Richard Hooper, Queen Mary University of London) prior to the start of recruitment. This list was held by the Data Monitoring Committee during the conduct of the trial. Concealment of allocation was achieved by ensuring that no trial staff (including those who assessed eligibility) had access to the trial randomisation list. All participants and their parents/guardians, and all trial personnel, including principal investigators and all those who had contact with study participants, including those who assessed outcomes, were blinded to participant allocation during the conduct of the trial.

Intervention

Study medication comprised a 3-year course of weekly soft gel capsules manufactured by the Tishcon Corporation (Westbury, New York, USA), containing either 0.25 mg (10 000 international units) cholecalciferol (vitamin D_3) in olive oil (intervention arm) or olive oil without any vitamin D_3 content (placebo arm). A slightly lower dose was employed in this trial as compared with the sister trial in Mongolia (which investigated the effects of administering 14 000 IU vitamin D_3 weekly),[31] as we anticipated that South African participants' baseline vitamin D status would be higher than in Mongolia and that accordingly a lower dose of vitamin D would be needed to optimise vitamin D status of South African participants, randomised to the intervention arm. Active and placebo capsules had identical appearance and taste. Vitamin D_3 content of active capsules was confirmed by the manufacturer using high-performance liquid chromatography (LC). Capsules were taken under direct observation of study staff during the school term time. During the summer holidays (8 weeks), packs containing eight doses of study medication were provided for administration by parents, together with a participant diary. Following shorter school holidays (≤4 weeks) and/or if participants missed one or more doses of study medication during term time, up to four 'catch-up' doses were administered at the first weekly visit attended following the missed dose(s). During the initial national lockdown for COVID-19 in South Africa (27 March 2020–1^{t} May 2020), participants did not receive any study medication. During subsequent school closures due to COVID-19, two rounds of 8-week holiday packs were provided to participants, which were sufficient to cover their requirements until schools reopened.

Outcomes

The primary outcome for the main trial, reported elsewhere,[23] was the QuantiFERON-TB Gold Plus result at the manufacturer-recommended 0.35 IU/mL threshold at the end of the study. The following secondary outcomes were assessed for substudy participants at 3-year follow-up: maximal grip strength (kg), standing long jump distance (cm), VO_{2peak} (mL/kg/min, derived from shuttle run performance) and the proportion of participants with EIB, defined as a ≥10% decrease in forced expiratory volume in 1 s after completion versus before the shuttle run test.[32]

Laboratory assessments

Biochemical analyses were performed at the Bioanalytical Facility, University of East Anglia (Norwich, UK) according to manufacturers' instructions and under Good Clinical and Laboratory Practice conditions. Serum concentrations of 25(OH)D_3 were measured using LC tandem mass spectrometry (LC-MS/MS) as previously described.[10] 25(OH)D_3 was calibrated using standard reference material SRM972a from the National Institute of Science and Technology (NIST), and the assay showed linearity between 0 and 200 nmol/L. The inter-assay/intra-assay coefficient of variation across the assay range was ≤9%, and the lower limit of quantification was 0.1 nmol/L. The assay showed <6% accuracy bias against NIST reference method on the vitamin D external quality assessment (DEQAS) scheme (http://www.deqas.org/; accessed on 18 March 2024). QFT-Plus assays were performed by the Bio Analytical Research Corporation South Africa (Johannesburg, South Africa) according to the manufacturer's instructions.

Sample size

The sample size for the main trial was predicated on the power to detect an effect of the intervention on the primary outcome (the proportion of children with

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2024-002019 on 26 September 2024. Downloaded from http://bmjopensem.bmj.com/ on October 7, 2024 at Imperial College London Library. Protected by copyright.

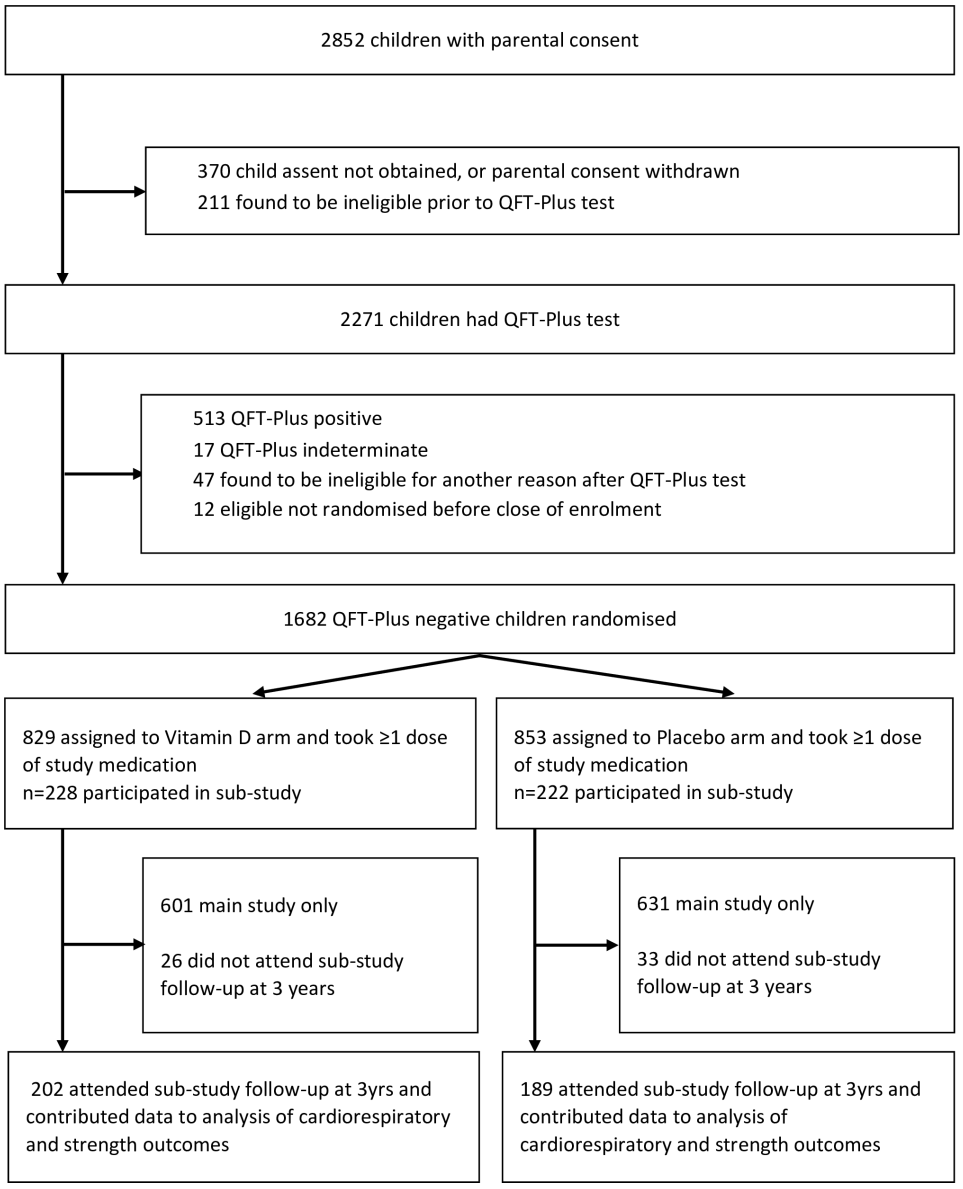

Figure 1 Participant flow diagram. QFT-Plus, QuantiFERON-TB Gold Plus.

a positive QFT-Plus assay result at 3-year follow-up), as previously described.[23] Sample size for the substudy was predicated on power to detect an effect of the intervention on bone mineral content: assuming 29% loss to follow-up at year 3, we calculated that enrolment of 450 participants would provide 88% power to detect a difference of 0.35 SDs between arms for mean bone mineral content, at either site investigated at the 5% significance level.

Statistical analyses

Statistical analyses were performed by using Stata software (V.17.0; StataCorp) according to intention to treat. Values of $p<0.05$ were considered to be statistically significant. VO_{2peak} was calculated from the number of completed laps on shuttle run tests using a published formula.[33] Effects of treatment on continuous outcomes measured at 3-year follow-up were analysed using multilevel mixed models with random effects of school and individual and with the treatment effect at baseline constrained to be zero to reflect the randomisation, where applicable. Proportions of children with EIB at 3-year follow-up were analysed using a mixed-effects logistic regression model, with treatment allocation as the sole fixed effect and school attended as a random intercept and adjustment for presence versus absence of EIB at baseline. Prespecified subgroup analyses were conducted to determine whether the effect of vitamin D supplementation was modified by sex (male vs female), baseline deseasonalised $25(OH)D_3$ concentration, calculated using a sinusoidal model as previously described[34] (<75 vs ≥75 nmol/L) and estimated calcium intake (< vs ≥ median value of 466 mg/day, calculated as previously described).[24] These were performed by repeating efficacy analyses with the inclusion of an interaction term between allocation (to

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2024-002019 on 26 September 2024. Downloaded from http://bmjopensem.bmj.com/ on October 7, 2024 at Imperial College London Library. Protected by copyright.

Table 1 Participants' baseline characteristics, overall and by allocation

		Overall (n=450)	Vitamin D arm (n=228)	Placebo arm (n=222)
Mean age, years (SD) (range)		10.1 (0.7) (8.2 to 11.9)	10.2 (0.7) (8.2 to 11.9)	10.0 (0.6) (8.5 to 11.9)
Sex, n (%)	Female	234 (52.0)	116 (50.9)	118 (53.2)
	Male	216 (48.0)	112 (49.1)	104 (46.8)
Ethnic origin*	Xhosa, n (%)	424 (96.4)	214 (96.0)	210 (96.8)
	Other, n (%)	16 (3.6)	9 (4.0)	7 (3.2)
Type of residence	Brick, n (%)	230 (51.1)	121 (53.1)	109 (49.1)
	Informal, n (%)	220 (48.9)	107 (46.9)	113 (50.9)
Parental education†	None, n (%)	-	-	-
	Primary school, n (%)	24 (5.3)	16 (7.0)	8 (3.6)
	Secondary school or higher, n (%)	426 (94.7)	212 (93.0)	214 (96.4)
Mean monthly household income, ZAR1000 (SD)		1.6 (2.3)	1.5 (2.7)	1.6 (1.9)
Household environmental tobacco smoke, n (%)		47 (10.4)	28 (12.3)	19 (8.6)
Mean maximal grip strength, kg (SD)‡		13.9 (3.4)	14.2 (3.6)	13.7 (3.1)
Mean standing long jump distance, cm (SD)‡		120.0 (18.4)	121.7 (18.5)	118.2 (18.1)
Mean VO_{2peak}, mL/kg/min (SD)‡		40.5 (3.2)	40.5 (3.0)	40.5 (3.3)
Exercise-induced bronchospasm, proportion (%)‡		79/448 (17.6)	38/228 (16.7)	41/220 (18.6)
Mean serum $25(OH)D_3$, nmol/L (SD) (range)§		70.0 (13.5) (24.9–112.5)	70.4 (12.1) (43.2–101.3)	69.6 (14.9) (24.9–112.5)
Serum $25(OH)D_3$ categories, n (%)§	<25 nmol/L	1 (0.3)	0 (0.0)	1 (0.6)
	25–49.9 nmol/L	20 (5.5)	7 (3.7)	13 (7.4)
	50–74.9 nmol/L	214 (59.0)	114 (61.0)	100 (56.8)
	≥75 nmol/L	128 (35.3)	66 (35.3)	62 (35.2)

*Ethnicity data missing in 5 participants in both the vitamin D and placebo arms.
†Highest level of education of at least 1 parent.
‡Data missing in 2 participants in the placebo arm.
§Serum $25(OH)D_3$ concentrations deseasonalised; data missing in 41 participants in the vitamin D arm and 46 participants in the placebo arm.
$25(OH)D_3$, 25-hydroxyvitamin D_3; VO_{2peak}, peak oxygen consumption; ZAR, South African Rand.

vitamin D vs placebo) and each posited effect-modifier with the presentation of the p value associated with this interaction term. Given the number of potential effect modifiers and secondary outcome measures, these analyses are considered exploratory. Interim safety assessments, where independent data monitoring committee (IDMC) members reviewed accumulating serious adverse event data, were performed at 6-monthly intervals. At each review, the IDMC recommended continuation of the trial. No interim efficacy analysis was performed.

Patient and public involvement

The ViDiKids trial was designed in consultation with the local Community Advisory Board (CAB)—a committee of local community stakeholders. Plans for enrolment and implementation of the study protocol were discussed with the school principals, staff and parent bodies prior to study initiation. Collaborative relationships with participating schools meant that the staff assisted in addressing study challenges, especially those that arose as a result of the COVID-19 pandemic. Dissemination of study results to the CAB, the school staff and parent bodies by a team including a staff member fluent in the local language is ongoing.

Equity, diversity and inclusion statement

This trial recruited a group of participants who are under-represented in research (schoolchildren in South Africa). Participation was open to children of any gender, race/ethnicity/culture and socioeconomic level. The author team is gender-balanced and nationality-balanced and includes junior researchers and perspectives from multiple disciplines. Subgroup analyses were conducted to detect gender differences in response to vitamin D supplementation.

RESULTS

Participants

2852 children were screened for eligibility to participate in the main trial from March 2017 to March 2019, of whom

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2024-002019 on 26 September 2024. Downloaded from http://bmjopensem.bmj.com/ on October 7, 2024 at Imperial College London Library. Protected by copyright.

Table 2 Maximal grip strength and standing long jump distance at 3-year follow-up by allocation: overall and by subgroups

		Vitamin D: mean value, kg (SD) (n)	Placebo: mean value, kg (SD) (n)	Adjusted mean difference (95% CI)*	P value	P for interaction
Grip strength						
Overall		20.9 (5.1) (201)	20.6 (5.2) (188)	−0.19 (−0.94 to 0.55)	0.61	--
By sex	Male	22.0 (5.5) (96)	21.3 (5.9) (89)	0.04 (−1.24 to 1.32)	0.95	0.57
	Female	19.8 (4.4) (105)	20.0 (4.4) (99)	−0.38 (−1.22 to 0.46)	0.37	
By baseline 25(OH)D concentration†	<75 nmol/L	20.6 (4.7) (103)	21.1 (5.3) (96)	−0.51 (−1.58 to 0.56)	0.35	0.14
	≥75 nmol/L	21.7 (6.2) (60)	20.5 (5.3) (54)	0.74 (−0.64 to 2.12)	0.30	
By calcium intake	<median‡	20.9 (4.6) (93)	20.9 (5.5) (97)	−0.25 (−1.43 to 0.94)	0.68	0.65
	≥median‡	21.0 (5.6) (102)	20.5 (4.8) (88)	−0.12 (−1.02 to 0.78)	0.79	
		Vitamin D: mean value, cm (SD) (n)	**Placebo: mean value, cm (SD) (n)**	**Adjusted mean difference (95% CI)***	**P value**	**P for interaction**
Long jump distance						
Overall		128.2 (22.1) (201)	122.1 (21.0) (188)	3.58 (−0.00 to 7.16)	0.0502	--
By sex	Male	140.5 (20.3) (96)	132.7 (20.2) (89)	5.89 (0.80 to 10.99)	0.02	0.32
	Female	117.0 (17.2) (105)	112.6 (17.0) (99)	2.58 (−1.47 to 6.62)	0.21	
By baseline 25(OH)D concentration†	<75 nmol/L	130.0 (24.4) (93)	124.7 (20.7) (97)	1.14 (−3.76 to 6.05)	0.65	0.62
	≥75 nmol/L	126.7 (19.3) (102)	119.9 (21.2) (88)	3.66 (−2.54 to 9.86)	0.25	
By calcium intake	<median‡	129.97 (24.39) (93)	124.70 (20.72) (97)	3.33 (−1.67 to 8.33)	0.19	0.98
	≥median‡	126.73 (19.35) (102)	119.86 (21.21) (88)	3.86 (−1.32 to 9.03)	0.14	

*Adjusted for baseline value and school of attendance.
†Serum 25(OH)D_3 concentrations deseasonalised.
‡Median value 466 mg/day.
25(OH)D_3, 25-hydroxyvitamin D_3.

2271 underwent QFT testing: 1682 (74.1%) QFT-negative children were randomly assigned to receive vitamin D_3 (829 participants) or placebo (853 participants) as previously described.[23] 450/1682 (26.8%) participants in the main trial also participated in the substudy, of whom 228 vs 222 participants were allocated to the vitamin D versus placebo arms, respectively (figure 1). Table 1 shows the baseline characteristics of participants contributing data to analyses of cardiorespiratory and strength outcomes: overall, mean age was 10.1 years, 52.0% were female and mean deseasonalised baseline serum 25(OH)D concentration was 70.0 nmol/L (SD 13.5 nmol/L). These and other baseline characteristics were well balanced between substudy participants randomised to vitamin D versus

Table 3 VO_{2peak} at 3-year follow-up by allocation: overall and by subgroups

		Vitamin D arm: mean value, mL/kg/min (SD) (n)	Placebo arm: mean value, mL/kg/min (SD) (n)	Adjusted mean difference (95% CI)*	P value	P for interaction
Overall		37.2 (4.1) (200)	37.1 (4.1) (187)	0.24 (−0.15 to 0.63)	0.23	
By sex	Male	39.0 (3.2) (95)	39.2 (3.4) (89)	−0.02 (−0.56 to 0.53)	0.95	0.22
	Female	35.5 (4.1) (105)	35.2 (3.8) (98)	0.47 (−0.06 to 1.00)	0.08	
By baseline 25(OH)D concentration†	<25 nmol/L	36.6 (4.5) (103)	36.7 (3.9) (95)	0.50 (−0.06 to 1.06)	0.08	0.28
	≥25 nmol/L	37.7 (3.9) (59)	37.5 (4.2) (54)	−0.01 (−0.75 to 0.74)	0.98	
By calcium intake	<median‡	37.5 (3.7) (92)	37.4 (4.3) (97)	0.19 (−0.32 to 0.70)	0.47	0.87
	≥median‡	36.8 (4.5) (102)	36.6 (4.0) (87)	0.25 (−0.36 to 0.87)	0.42	

*Adjusted for baseline value and school of attendance.
†Serum 25(OH)D_3 concentrations deseasonalised.
‡Median value 466 mg/day.
25(OH)D_3, 25(OH)D_3, 25-hydroxyvitamin D_3.

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2024-002019 on 26 September 2024. Downloaded from http://bmjopensem.bmj.com/ on October 7, 2024 at Imperial College London Library. Protected by copyright.

Table 4 Proportion of participants with exercise-induced bronchoconstriction at 3-year follow-up by allocation: overall and by subgroup

		Vitamin D: proportion (%)	Placebo: proportion (%)	Adjusted OR (95% CI)*	P value	P for interaction
Overall		29/200 (14.50)	16/187 (8.56)	1.92 (0.99 to 3.73)	0.053	
By sex	Male	13/95 (13.68)	5/89 (5.62)	2.86 (0.95 to 8.61)	0.06	0.32
	Female	16/105 (15.24)	11/98 (11.22)	1.48 (0.65 to 3.41)	0.35	
By baseline 25(OH)D concentration†	<75 nmol/L	14/103 (13.59)	8/95 (8.42)	1.82 (0.70 to 4.72)	0.22	0.39
	≥75 nmol/L	7/59 (11.86)	2/54 (3.70)	3.49 (0.69 to 17.68)	0.13	
By calcium intake	<median‡	13/92 (14.13)	4/97 (4.12)	3.86 (1.17 to 12.70)	0.03	0.08
	≥median‡	14/102 (13.73)	12/87 (13.79)	1.04 (0.44 to 2.46)	0.93	

*Adjusted for school of attendance and presence versus absence of exercise-induced bronchoconstrictionn at baseline.
†Deseasonalised values.
‡Median value 466 mg/day.
25(OH)D, 25-hydroxyvitamin D.

placebo. Of 450 randomised substudy participants, 391 (86.9%) attended the substudy follow-up visit at 3 years postrandomisation and contributed data to analyses presented here. Mean serum 25(OH)D_3 concentration at 3-year follow-up was higher in participants randomised to vitamin D versus placebo (97.6 vs 58.8 nmol/L, respectively: mean difference 39.9 nmol/L, 95% CI 36.1 to 43.6).

Outcomes

Allocation to vitamin D versus placebo did not influence grip strength or long jump distance, either overall or within subgroups defined by male versus female sex, baseline 25(OH)D concentration or calcium intake (table 2). No effect of allocation to vitamin D versus placebo was seen for mean VO_{2peak}, either overall or by subgroup (table 3). Similarly, no effect of allocation was seen on the proportion of participants with EIB, either overall or by subgroup (table 4).

DISCUSSION

We present findings of the first RCT investigating the effects of vitamin D supplementation on muscle strength and cardiorespiratory fitness to be conducted in Africa—and the first RCT conducted anywhere to test whether vitamin D supplementation influences the risk of EIB. Weekly oral administration of 10 000 IU vitamin D_3 was effective in elevating circulating 25(OH)D concentrations; however, this was not associated with any statistically significant differences in any other outcome investigated. Our null findings for grip strength, long jump distance and VO_{2peak} are in keeping with those from a similarly designed phase 3 RCT conducted in Mongolia, where the effects of a 3-year course of 14 000 IU vitamin D/week were investigated.[31 35–37]

Our study has several strengths. Weekly vitamin D supplementation allowed direct observation of capsule administration during term time, and this was reflected in the significant interarm difference in serum 25(OH)D concentrations observed at 3-year follow-up. 25(OH)D concentrations were measured using the gold-standard methodology (LC-MS/MS) in a laboratory that participated in a rigorous external quality assessment scheme (DEQAS). Low rates of loss to follow-up maximised our power to detect effects of the intervention, and we assessed a comprehensive range of outcomes relating to muscle strength, cardiorespiratory fitness and respiratory function.

Our study also has some limitations. Fewer than 6% of children had baseline 25(OH)D concentrations <50 nmol/L, limiting generalisability of our findings to settings where vitamin D deficiency is more common. Additionally, we draw attention to that fact that our findings relate specifically to the effects of weekly vitamin D supplementation. Daily administration of vitamin D has been reported to be more beneficial for prevention of acute respiratory infections than weekly administration,[38] and the possibility that this may also be the case for musculoskeletal and cardiorespiratory outcomes cannot be excluded. Further trials comparing the effects of daily versus weekly supplementation would be needed to resolve this question definitively. We also acknowledge that the parameters investigated in the current study were secondary outcomes (although prespecified ones), and that multiple tests for statistical significance were performed; we would not, therefore, have been able to rule out type I error as an explanation for statistically significant findings, had these arisen. In the absence of validated equations to estimate VO_{2peak} from shuttle run performance in South African children, we used equations developed for East Asian children, in order to maximise comparability of our findings with those of a similarly designed RCT conducted in Mongolia.[31] While we acknowledge that this may have introduced a degree of imprecision, randomisation will very likely

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2024-002019 on 26 September 2024. Downloaded from http://bmjopensem.bmj.com/ on October 7, 2024 at Imperial College London Library. Protected by copyright.

have distributed this equally between intervention versus control arms, minimising any risk of bias.

In conclusion, we report that a weekly oral dose of 10 000 IU vitamin D_3, administered to South African children for 3 years, was effective in elevating serum 25(OH)D concentrations but did not influence grip strength, long jump distance, VO_{2peak} or risk of EIB. Taken together with null results from a similarly designed phase 3 RCT conducted in Ulaanbaatar, Mongolia,[31] our study does not suggest a role for weekly oral vitamin D supplementation to enhance muscle strength or exercise capacity in schoolchildren in whom rickets have been excluded.

Author affiliations
[1]Desmond Tutu HIV Centre, Institute of Infectious Diseases & Molecular Medicine, University of Cape Town, Observatory, South Africa
[2]Department of Medicine, University of Cape Town, Observatory, South Africa
[3]Health through Physical Activity, Lifestyle and Sport Research Centre (HPALS), Division of Physiological Sciences, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
[4]SAMRC/Wits Developmental Pathways for Health Research Unit, Department of Paediatrics, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[5]School of Sport and Health Sciences, University of Brighton, Eastbourne, UK
[6]Wolfson Institute of Population Health, Faculty of Medicine and Dentistry, Queen Mary University of London, London, UK
[7]Blizard Institute, Faculty of Medicine and Dentistry, Queen Mary University of London, London, UK
[8]Riverland Academy of Clinical Excellence, Riverland Mallee Coorong Local Health Network, South Australia Health, South Australia, Australia
[9]Norwich Medical School, University of East Anglia, Norwich, UK
[10]Departments of Laboratory Medicine, Clinical Biochemistry and Departments of Diabetes and Endocrinology, Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich, UK
[11]MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK
[12]NIHR Southampton Biomedical Research Centre, University of Southampton, and University Hospital Southampton NHS Foundation Trust, Southampton, UK
[13]Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Observatory, South Africa
[14]The Francis Crick Institute, London, UK
[15]Imperial College London, London, UK

Acknowledgements We thank all the children who participated in the trial and their parents/guardians; members of the Independent Data Monitoring Committee (Professor Guy Thwaites, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam (Chair); Professor John Pettifor, University of the Witwatersrand, Johannesburg, South Africa and Prof Sarah Walker, MRC Clinical Trials Unit, London, UK) and members of the Trial Steering Committee (Professor Beate Kampmann, London School of Hygiene and Tropical Medicine, London, UK (Chair); Professor Ashraf Coovadia, University of the Witwatersrand, Johannesburg, South Africa; Dr Karen Jennings, City Health, Cape Town, South Africa; Dr Robin Dyers, Western Cape Government, Cape Town, South Africa and Dr Guy de Bruyn, Sanofi Pasteur, Swiftwater, Pennsylvania, USA).

Contributors ARM conceived the study. KM, LM, SH, CC, NCH, RJW and ARM contributed to study design and protocol development. KM led on trial implementation, with support from LM, JS, DAJ, AEM and ARM. JCYT performed and supervised the conduct of biochemical assays. NW and ARM drafted the statistical analysis plan. DAJ, KM, JS and NW managed data. NW, KM and DAJ accessed, verified and analysed the data underlying the study. NW and DAJ analysed data. ARM and DAJ wrote the first draft of the trial report. All authors made substantive comments thereon and approved the final version for submission. ARM is the guarantor.

Funding This research was funded by the UK Medical Research Council (refs MR/R023050/1 and MR/M026639/1, both awarded to ARM). RJW was supported by Wellcome (104803, 203135). He also received support from the Francis Crick Institute which is funded by Cancer Research UK (FC2112), the UK Medical Research Council (FC2112) and Wellcome (FC2112). NCH and CC are supported by the UK Medical Research Council (MC_PC_21003; MC_PC_21001). RJW is also supported in part by the NIHR Biomedical Research Centre of Imperial College NHS Trust.

Competing interests ARM declares receipt of funding in the last 36 months to support vitamin D research from the following companies who manufacture or sell vitamin D supplements: 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 Ltd and Abiogen Pharma; receipt of consultancy fees from DSM Nutritional Products and Qiagen; receipt of a speaker fee from the Linus Pauling Institute; participation on Data and Safety Monitoring Boards for the VITALITY trial (Vitamin D for Adolescents with HIV to reduce musculoskeletal morbidity and immunopathology, Pan African Clinical Trials Registry ref PACTR202000989766029) and the Trial of Vitamin D and Zinc Supplementation for Improving Treatment Outcomes Among COVID-19 Patients in India (ClinicalTrials.gov ref NCT04641195) and unpaid work as a Programme Committee member for the Vitamin D Workshop.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (Ref: 796/2015) and the London School of Hygiene and Tropical Medicine Observational/Interventions Research Ethics Committee (Ref: 7450-2). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available on reasonable request. Anonymised data are available from corresponding authors on reasonable request, subject to terms of IRB and regulatory approval.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/.

ORCID iD
Adrian R Martineau http://orcid.org/0000-0001-5387-1721

REFERENCES

1 Smith JJ, Eather N, Morgan PJ, *et al*. The health benefits of muscular fitness for children and adolescents: a systematic review and meta-analysis. *Sports Med* 2014;44:1209–23.
2 García-Hermoso A, Ramírez-Campillo R, Izquierdo M. Is Muscular Fitness Associated with Future Health Benefits in Children and Adolescents? A Systematic Review and Meta-Analysis of Longitudinal Studies. *Sports Med* 2019;49:1079–94.
3 Raghuveer G, Hartz J, Lubans DR, *et al*. Cardiorespiratory Fitness in Youth: An Important Marker of Health: A Scientific Statement From the American Heart Association. *Circulation* 2020;142:e101–18.
4 García-Hermoso A, Ramírez-Vélez R, García-Alonso Y, *et al*. Association of Cardiorespiratory Fitness Levels During Youth With Health Risk Later in Life: A Systematic Review and Meta-analysis. *JAMA Pediatr* 2020;174:952–60.
5 Ceglia L. Vitamin D and its role in skeletal muscle. *Curr Opin Clin Nutr Metab Care* 2009;12:628–33.
6 Lykkedegn S, Sorensen GL, Beck-Nielsen SS, *et al*. The impact of vitamin D on fetal and neonatal lung maturation. A systematic review. *Am J Physiol Lung Cell Mol Physiol* 2015;308:L587–602.

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2024-002019 on 26 September 2024. Downloaded from http://bmjopensem.bmj.com/ on October 7, 2024 at Imperial College London Library. Protected by copyright.

7 Hunter L, Ferguson R, McDevitt H. Vitamin D deficiency cardiomyopathy in Scotland: a retrospective review of the last decade. *Arch Dis Child* 2020;105:853–6.
8 Roth DE, Abrams SA, Aloia J, *et al*. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. *Ann N Y Acad Sci* 2018;1430:44–79.
9 Voortman T, van den Hooven EH, Heijboer AC, *et al*. Vitamin D deficiency in school-age children is associated with sociodemographic and lifestyle factors. *J Nutr* 2015;145:791–8.
10 Middelkoop K, Walker N, Stewart J, *et al*. Prevalence and Determinants of Vitamin D Deficiency in 1825 Cape Town Primary Schoolchildren: A Cross-Sectional Study. *Nutrients* 2022;14:1263.
11 Bater J, Bromage S, Jambal T, *et al*. Prevalence and Determinants of Vitamin D Deficiency in 9595 Mongolian Schoolchildren: A Cross-Sectional Study. *Nutrients* 2021;13:4175.
12 Bjarnadottir A, Kristjansdottir AG, Hrafnkelsson H, *et al*. Insufficient autumn vitamin D intake and low vitamin D status in 7-year-old Icelandic children. *Public Health Nutr* 2015;18:208–17.
13 Valtueña J, Gracia-Marco L, Huybrechts I, *et al*. Cardiorespiratory fitness in males, and upper limbs muscular strength in females, are positively related with 25-hydroxyvitamin D plasma concentrations in European adolescents: the HELENA study. *QJM* 2013;106:809–21.
14 Chinellato I, Piazza M, Sandri M, *et al*. Serum vitamin D levels and exercise-induced bronchoconstriction in children with asthma. *Eur Respir J* 2011;37:1366–70.
15 Beaudart C, Buckinx F, Rabenda V, *et al*. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 2014;99:4336–45.
16 Bezrati I, Ben Fradj MK, Hammami R, *et al*. A single mega dose of vitamin D_3 improves selected physical variables in vitamin D-deficient young amateur soccer players: a randomized controlled trial. *Appl Physiol Nutr Metab* 2020;45:478–85.
17 Ward KA, Das G, Roberts SA, *et al*. A randomized, controlled trial of vitamin D supplementation upon musculoskeletal health in postmenarchal females. *J Clin Endocrinol Metab* 2010;95:4643–51.
18 Thams L, Hvid LG, Stounbjerg NG, *et al*. Vitamin D supplementation and increased dairy protein intake do not affect muscle strength or physical function in healthy 6-8-year-old children: the D-pro randomized trial. *Eur J Nutr* 2022;61:3613–23.
19 Mortensen C, Mølgaard C, Hauger H, *et al*. Winter vitamin D_3 supplementation does not increase muscle strength, but modulates the IGF-axis in young children. *Eur J Nutr* 2019;58:1183–92.
20 Wright CS, Laing EM, Pollock NK, *et al*. Serum 25-Hydroxyvitamin D and Intact Parathyroid Hormone Influence Muscle Outcomes in Children and Adolescents. *J Bone Miner Res* 2018;33:1940–7.
21 Dubnov-Raz G, Livne N, Raz R, *et al*. Vitamin D Supplementation and Physical Performance in Adolescent Swimmers. *Int J Sport Nutr Exerc Metab* 2015;25:317–25.
22 El-Hajj Fuleihan G, Nabulsi M, Tamim H, *et al*. Effect of vitamin D replacement on musculoskeletal parameters in school children: a randomized controlled trial. *J Clin Endocrinol Metab* 2006;91:405–12.
23 Middelkoop K, Stewart J, Walker N, *et al*. Vitamin D supplementation to prevent tuberculosis infection in South African schoolchildren: multicenter phase 3 double-blind randomized placebo-controlled trial (ViDiKids). *Int J Infect Dis* 2023;134:63–70.
24 Middelkoop K, Micklesfield LK, Walker N, *et al*. Influence of vitamin D supplementation on bone mineral content, bone turnover markers, and fracture risk in South African schoolchildren: multicenter double-blind randomized placebo-controlled trial (ViDiKids). *J Bone Miner Res* 2024;39:211–21.
25 Middelkoop K, Micklesfield L, Stewart J, *et al*. Influence of vitamin D supplementation on growth, body composition, pubertal development and spirometry in South African schoolchildren: a randomised controlled trial (ViDiKids). *BMJ Paediatr Open* 2024;8:e002495.
26 España-Romero V, Artero EG, Santaliestra-Pasias AM, *et al*. Hand span influences optimal grip span in boys and girls aged 6 to 12 years. *J Hand Surg Am* 2008;33:378–84.
27 Castro-Piñero J, Ortega FB, Artero EG, *et al*. Assessing muscular strength in youth: usefulness of standing long jump as a general index of muscular fitness. *J Strength Cond Res* 2010;24:1810–7.
28 Trajković N, Rančić D, Ilić T, *et al*. Measuring handgrip strength in school children: inter-instrument reliability between Takei and Jamar. *Sci Rep* 2024;14:1074.
29 Fernandez-Santos JR, Ruiz JR, Cohen DD, *et al*. Reliability and Validity of Tests to Assess Lower-Body Muscular Power in Children. *J Strength Cond Res* 2015;29:2277–85.
30 Graham BL, Steenbruggen I, Miller MR, *et al*. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med* 2019;200:e70–88.
31 Ganmaa D, Hemmings S, Jolliffe DA, *et al*. Influence of vitamin D supplementation on muscle strength and exercise capacity in Mongolian schoolchildren: secondary outcomes from a randomised controlled trial. *BMJ Sports Exerc Med* 2024.
32 Parsons JP, Hallstrand TS, Mastronarde JG, *et al*. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 2013;187:1016–27.
33 Matsuzaka A, Takahashi Y, Yamazoe M, *et al*. Validity of the Multistage 20-M Shuttle-Run Test for Japanese Children, Adolescents, and Adults. *Pediatr Exerc Sci* 2004;16:113–25.
34 Ganmaa D, Khudyakov P, Buyanjargal U, *et al*. Prevalence and Determinants of QuantiFERON-Diagnosed Tuberculosis Infection in 9810 Mongolian Schoolchildren. *Clin Infect Dis* 2019;69:813–9.
35 Ganmaa D, Uyanga B, Zhou X, *et al*. Vitamin D Supplements for Prevention of Tuberculosis Infection and Disease. *N Engl J Med* 2020;383:359–68.
36 Ganmaa D, Bromage S, Khudyakov P, *et al*. 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. *JAMA Pediatr* 2023;177:32–41.
37 Ganmaa D, Khudyakov P, Buyanjargal U, *et al*. Vitamin D supplements for fracture prevention in schoolchildren in Mongolia: analysis of secondary outcomes from a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2024;12:29–38.
38 Jolliffe DA, Camargo CA, Sluyter JD, *et al*. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. *Lancet Diabetes Endocrinol* 2021;9:276–92.

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2024-002019 on 26 September 2024. Downloaded from http://bmjopensem.bmj.com/ on October 7, 2024 at Imperial College London Library. Protected by copyright.