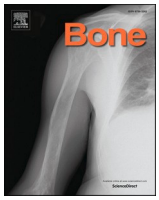
Bone 207 (2026) 117843

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone



Full Length Article

Vitamin D supplementation during pregnancy and offspring bone microarchitecture: A post hoc analysis of the MAVIDOS randomised controlled trial

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ARTICLE INFO

Keywords:
Bone microarchitecture
Bone mineral density
Cholecalciferol
High resolution peripheral quantitative computed tomography (HR-pQCT)
pregnancy

ABSTRACT

Background: Randomised trials have shown that pregnancy vitamin D supplementation results in greater offspring bone mineral density (BMD) in childhood. The effect of this intervention on bone microarchitecture, a further determinant of bone strength, and possible interactions with genetic variation in vitamin D metabolism, have not previously been investigated. We investigated these in a post hoc analysis of a randomised controlled trial.

Methods: MAVIDOS was a randomised placebo-controlled trial of 1000 IU/day cholecalciferol from 14 to 17 weeks' gestation until delivery. Offspring tibial bone microarchitecture was assessed at age 6–7 years using high resolution peripheral quantitative computed tomography (HR-pQCT; Stratec Xtreme CTII). Maternal and child genotype at four single nucleotide polymorphisms (SNPs) [rs12785878 (*DHCR7*), rs10741657 (*CYP2R1*), rs6013897 (*CYP24A1*), rs2282679 (*GC*)] was determined using serum samples.

Differences in bone microarchitecture by randomisation were assessed using linear regression, and additionally across clusters of bone microarchitecture phenotypes generated using cluster analysis approaches.

Results: 222 children (placebo $n = 110$, cholecalciferol $n = 112$) were included. No significant differences in cross-sectional area, cortical thickness or porosity, trabecular thickness or number, or volumetric BMD (total, cortical or trabecular) were found using linear regression, and there was no interaction with either maternal or offspring SNP genetic variants.

Three phenotypic bone clusters were generated. Differences in child anthropometry were evident across clusters, but the proportion of mothers randomised to cholecalciferol was similar across the clusters ($p = 1.0$).

Conclusion: In this subset of children born to mothers participating in a trial of vitamin D supplementation in pregnancy, no effect of the supplementation on tibial microarchitecture was observed.

1. Introduction

Randomised controlled trials have suggested that antenatal vitamin D supplementation results in greater offspring areal bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) [1–4]. In the MAVIDOS trial, we observed a 0.18 standard deviation (SD) greater whole-body-less-head (WBLH) BMD at 6–7 years in offspring born to mothers randomised to 1000 IU/day cholecalciferol from 14 to 17 weeks gestation until delivery, compared to placebo [1] with a similar effect size being observed in the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort ($COPSAC_{2010}$) albeit using a higher dose of vitamin D supplementation (2800 IU/day) and started later in

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https://doi.org/10.1016/j.bone.2026.117843
Received 20 November 2025; Received in revised form 23 February 2026; Accepted 4 March 2026
Available online 7 March 2026

pregnancy [2]. O'Callaghan et al. did not identify an effect of pregnancy vitamin D supplementation in women in Bangladesh on offspring BMD at 4 years of age [5]. Differences in study design, geographical location and age at follow-up of the published trials however limit dose-response assessments [3].

Low BMD is associated with increased fracture risk in both children and adults [6–9]. Whilst the existing intervention studies of vitamin D supplementation in pregnancy do not have sufficient power to demonstrate a positive effect on fracture risk in childhood (although a borderline lower incidence of fractures was observed in the $COPSAC_{2010}$ study [10]), if such an effect on BMD were maintained to peak bone mass, it would have a beneficial effect on long-term skeletal health and fracture risk [11].

Geometric and microarchitectural properties of bone are also associated with fracture risk. These can be assessed using high resolution peripheral quantitative computed tomography (HR-pQCT). Farr et al. demonstrated that children with a recent distal forearm fracture had bones with thinner cortices and reduced trabecular number compared to non-fracturing controls [12]. Similar findings have been demonstrated in adults [13,14].

Data from one observational cohort suggested that maternal 25-hydroxyvitamin D [25(OH)D] status during pregnancy is associated with offspring bone geometry. Viljakainen et al. found greater tibia cross-sectional area measured by (low resolution) peripheral quantitative computed tomography in offspring born to mothers with 25(OH)D above the median for the cohort (group mean 55 nmol/l) compared to below the median (group mean 36 nmol/l) in the neonatal period [15] and persisting at 14 months of age [16]. However, the effect of antenatal vitamin D supplementation on offspring microarchitecture using HR-pQCT or in an intervention trial has not been previously investigated.

Furthermore, the effect of pregnancy vitamin D supplementation on maternal and offspring serum 25(OH)D status may be modified by genetic variation. Common single nucleotide polymorphisms (SNP) in genes within the vitamin D metabolism pathway, including *DHCR7*, *CYP2R1*, and *GC* (encoding for 7-dehydrocholesterol reductase, vitamin D 25-hydroxylase and vitamin D-binding protein, respectively), have been associated with serum 25(OH)D levels in pregnant women and the response to vitamin D supplementation [17,18]. It remains unexplored, however, whether such genetic variation in the mother and/or offspring interacts with pregnancy vitamin D supplementation in determining offspring health outcomes, such as BMD or bone microarchitecture.

The aims of this study were therefore to (1) assess the effect of pregnancy vitamin D supplementation on offspring bone microarchitecture and volumetric BMD (vBMD) and (2) to explore whether common genetic variation in the form of SNPs in the vitamin D metabolism pathway of either the mother and/or offspring interacts with the effects of vitamin D supplementation on these outcomes.

2. Methods

MAVIDOS was a randomised double-blind placebo-controlled trial of 1000 IU/day cholecalciferol from 11 to 14 weeks gestation until delivery. The full study protocol has previously been published [19]. Briefly, inclusion criteria were adult females attending early pregnancy ultrasound screening at University Hospital Southampton NHS Foundation Trust, Oxford University Hospitals NHS Foundation Trust, or Sheffield Hospitals NHS Trust, with a singleton pregnancy less than 17 weeks gestation, and a baseline serum 25(OH)D measured on the local hospital platform of 25–100 nmol/l. Exclusion criteria included women with known metabolic bone disease, renal calculi, hyperparathyroidism, hypercalciuria, or recent cancer diagnosis, those with any fetal anomalies or taking medication that may affect fetal growth. All participants were allowed to continue taking vitamin D supplements up to 400 IU/day; women wanting to continue taking >400 IU/day vitamin D supplementation were excluded.

The participants were randomised in a 1:1 ratio to either oral cholecalciferol 1000 IU/day or placebo from 14 to 17 weeks gestation until delivery. Standard antenatal care by blinded healthcare professionals continued throughout the pregnancy.

Questionnaire assessments of health, lifestyle and nutrition and maternal anthropometry occurred at randomisation and again at 34 weeks gestation. Maternal venous blood samples (collected at randomisation and 34 weeks), and umbilical cord blood (collected at delivery) were stored at −80 °C and analysed by chemiluminescence immunoassay for 25(OH)D (Liaison automated platform, Diasorin).

2.1. Offspring follow-up

Children born to women recruited in Southampton were invited to take part in the offspring follow-up phases at birth, 1, 2, 4 and 6–7 years [1,4,20]. Duration of breast feeding was established during interviewer-led questionnaires at 1 and 2 years of age. This analysis focused on data collected at age 6–7 years.

2.1.1. 6–7 year follow-up

At age 6–7 years, milk intake, use of vitamin D supplementation, physical activity, and medical diagnoses were established by an interviewer-administered questionnaire. Standing height was measured using a portable stadiometer (Leicester height measurer, Seca Ltd., Birmingham, UK), to the nearest 0.1 cm. Weight was measured in light clothing using calibrated electronic scales (Seca Ltd., Birmingham, UK) to the nearest 0.1 kg. Height, weight and body mass index (BMI) z-scores for age and sex were calculated using British reference data [21,22].

Whole body and lumbar spine DXA scans were obtained using a Hologic Discovery instrument (Hologic Inc., Bedford, MA) in paediatric scan mode. Outcomes of interest were bone area (BA), bone mineral content (BMC), BMD, and bone mineral apparent density (BMAD) [23] for WBLH [24] and lumbar spine. Two researchers masked to treatment allocation reviewed the scans and those with substantial movement artefact affecting the whole body and/or both legs/both arms ($n = 82$) were excluded. In scans with movement artefact in one limb, the region of interest of the unaffected limb was transposed into the limb with movement artefact. The DXA instrument underwent daily calibration using a spine phantom. The experimental coefficient of variation for this instrument when a spine phantom was repeatedly scanned in the same position 16 times, in a single session with no repositioning, was 0.68%.

A sequential subset of the children in Southampton had tibial HR-pQCT (Stratec Xtreme CTII). Measurements were taken from the non-dominant distal tibia except if it had previously been fractured, in which case the dominant side was scanned. This allowed acquisition of a stack of parallel CT slices using a two-dimensional detector array. A total of 110 slices were obtained for each child which represented a volume of bone 9 mm in axial length with a nominal resolution (voxel size) of 82 μm. The scanned limb was immobilized during the examination in a carbon fibre cast. Antero-posterior 2D scout views were performed to define the anatomic reference line (tibial plafond) and the region of interest for scanning was the 8% site of the distal tibia. All scans were acquired by one of two trained technicians. Each scan image was assessed for motion artefact by a trained technician using a 5-point scale (1, excellent; 2, good; 3, acceptable; 4, poor; 5, unacceptable) [25]. Only images with quality grades 1 to 3 ($n = 222$) were included in the analysis. HR-pQCT variables assessed were total vBMD, cortical vBMD, trabecular vBMD, trabecular number, trabecular thickness, cortical thickness, cortical porosity and total cross-sectional area (CSA). The season in which the HR-pQCT scans were performed was reported following the UK Meteorological Office classification, as winter (December to February), spring (March to May), summer (June to August), and autumn (September to November).

2.2. Genotyping

Maternal and offspring genotyping was undertaken by LGC

Genomics (Hoddeston, UK) using KASP competitive allele-specific polymerase chain reaction. SNPs selected for analysis (rs12785878 (*DHCR7*), rs10741657 (*CYP2R1*), rs6013897 (*CYP24A1*), and rs2282679 (*GC*)) were based on the findings of a previous genome wide association study [26].

2.3. Statistical analysis

This analysis was limited to the subset of children for whom a useable HR-pQCT image (quality grade 1–3) was available. Only children aged between 6.0 and 8.1 years at the follow-up were include, a range selected to accommodate delays in attendance caused by the COVID-19 pandemic. Whilst the aim of this analysis was to assess the effect of pregnancy vitamin D supplementation on offspring bone microarchitecture assessed using HR-pQCT, comparison of DXA outcomes (BA, BMC, BMD and BMAD) in this subset was undertaken to establish consistency with the previously reported analysis of these outcomes in the full cohort . Between-group comparisons of maternal characteristics for children included versus not included in this analysis, and the effects of pregnancy vitamin D supplementation on bone outcomes were performed using *t*-tests, Mann-Whitney *U* tests and Chi-squared tests for normally distributed continuous, non-normally distributed continuous and categorical variables, respectively. Results are presented as mean (standard deviation (SD)), median (interquartile range (IQR)) and n (%), respectively.

HR-pQCT and DXA variables were subsequently standardised using a Fisher-Yates transformation to enable comparison of effect sizes between outcomes. Linear regression was used to assess the effect of pregnancy cholecalciferol on standardised HR-pQCT and DXA outcomes in adjusted models: Model 1 included the child's sex and age to improve the precision of the estimates, model 2 additionally included height and weight, based on literature showing that these factors may affect BMD and bone microarchitecture [9,27,28] and model 3 also included duration of breastfeeding, as this may be associated with increased bone mass [29] and was found to differ between the two groups. In a sensitivity analysis infants born preterm (gestational age < 37 weeks $n = 14$) were excluded from the analysis to include only those children that had full exposure to the study intervention. As previous observational work has suggested that the associations between maternal 25(OH)D status and offspring bone outcomes may differ by sex [30], we assessed for an interaction between maternal randomisation and offspring sex.

To further explore bone microarchitecture, and given that microarchitectural parameters may not be mutually independent, cluster analysis was used to identify clinical phenotypes of bone microarchitecture. To increase the precision of the cluster generation, HR-pQCT variables were adjusted for age and sex using linear regression before inclusion in the cluster models. Each HRpQCT parameter was regressed on age and sex, and individual values were then adjusted by removing the portion attributable to deviations in these covariates from their sample means. This produced values for each HRpQCT parameter that were standardised to the average age and sex of the cohort. Successful adjustment was confirmed by verifying that regressing the adjusted variables on age and sex yielded coefficients close to zero. K-means partitioning was then used to generate 3 clusters based on the following age- and sex-adjusted HRpQCT variables: total vBMD, cortical vBMD, trabecular vBMD, trabecular number, trabecular thickness, cortical thickness, cortical porosity and total CSA. The number of clusters selected ($n = 3$) was based on the distinctiveness of the clusters, according to the Calinski/Harabasz pseudo-F statistic, and on the potential for identifying interpretable clusters with contrasting phenotypes between clusters [31]. $\chi 2$ and one-way ANOVA were used to assess differences between clusters for demographic, anthropometric and HR-pQCT variables, and to assess the relative distribution of randomisation to the study intervention.

Statistical interactions between maternal/offspring SNP genotypes and randomisation group (placebo vs cholecalciferol), were assessed for each HR-pQCT variable using additive linear regression models [32]. For each HR-pQCT variable, models included randomisation group (placebo vs cholecalciferol), SNP genotype (entered as a categorical predictor), and a genotype×randomisation group interaction term, with adjustment for age at assessment and sex. Each SNP variant was analysed separately. Given the exploratory nature of these analyses and the large number of correlated tests, results were considered of interest if $p < 0.01$. All analyses were performed in Stata v18.0 (StataCorp, College Station, TX).

3. Results

3.1. Study participants

Of 1449 women who agreed to baseline blood screening for eligibility to take part in the study, 1134 were randomised to placebo ($n = 569$) or cholecalciferol ($n = 565$). 965 women remained in the study until delivery, of which 767 (79%) gave birth in Southampton (Fig. 1).

The 6–7 year follow up was attended by 494 children, of whom 311 (63%) had an HR-pQCT scan. Eighty-two scan images (26% of those with an HR-pQCT image) could not be included due to poor quality and a further 7 participants were not suitable for inclusion (Fig. 1). Thus, HR-pQCT data for 222 children (placebo $n = 110$ and cholecalciferol $n = 112$) were included (Fig. 1); those included were born to mothers who were, on average, older at randomisation, less likely to smoke, more likely to be of White ethnicity and more highly educated than those who were not included in this analysis (*Supplementary Table 1*).

Maternal age, parity, ethnicity, smoking, educational achievement and BMI were similar at randomisation between the two cholecalciferol and placebo groups (Table 1). Maternal 25(OH)D was similar at randomisation (Table 1), but as expected, was greater in late pregnancy in the women randomised to cholecalciferol (placebo: median 42 nmol/l (IQR 28, 57), cholecalciferol: median 69 nmol/l (IQR 56, 83), $p < 0.01$)).

The children in the placebo and cholecalciferol groups had similar age, height, weight and BMI z-scores for age and sex at the 6–7-year follow-up visit (Table 2). The children in the cholecalciferol group were, on average, breastfed for longer (placebo: median 3 months (IQR 0–7), cholecalciferol: median 6 months (IQR 1–12) $p = 0.004$). There was no difference in distribution of HR-pQCTs across the four seasons by randomisation group (Table 2).

3.2. HR-pQCT and DXA

Table 3 shows the HR-pQCT and DXA outcomes in their original units by randomisation group for this subset of children. Whilst there were no statistically significant differences between the two groups in bone microarchitecture, cortical vBMD appeared numerically greater in the children born to mothers randomised to cholecalciferol (placebo: 735 mg/cm^3 (IQR 716, 759), cholecalciferol: mean 745 mg/cm^3 (IQR 722, 744), $p = 0.07$).

In adjusted analysis, similarly there were no differences in bone microarchitecture or vBMD between the two groups (Table 4), although cortical vBMD remained numerically greater in the cholecalciferol group. Notably, a difference in WBLH BMD was observed between the two groups in fully adjusted analysis ($\beta = 0.15$ SD 95% CI [−0.01 to 0.30]). This was of similar magnitude to that observed in the analysis of the full cohort of children with DXA at age 6–7 years [1], with the effect on cortical vBMD being of similar effect size but not reaching statistical significance ($\beta = 0.19$ SD 95% CI [−0.08 to 0.46]). There was no significant interaction between offspring sex and maternal randomisation on the HR-pQCT outcomes.

In sensitivity analysis excluding 14 children born preterm, the findings were unchanged (*Supplementary Tables 2–3*).

3.2.1. Genotype-intervention interaction

The distribution of the SNPs in the cohort included in the analysis

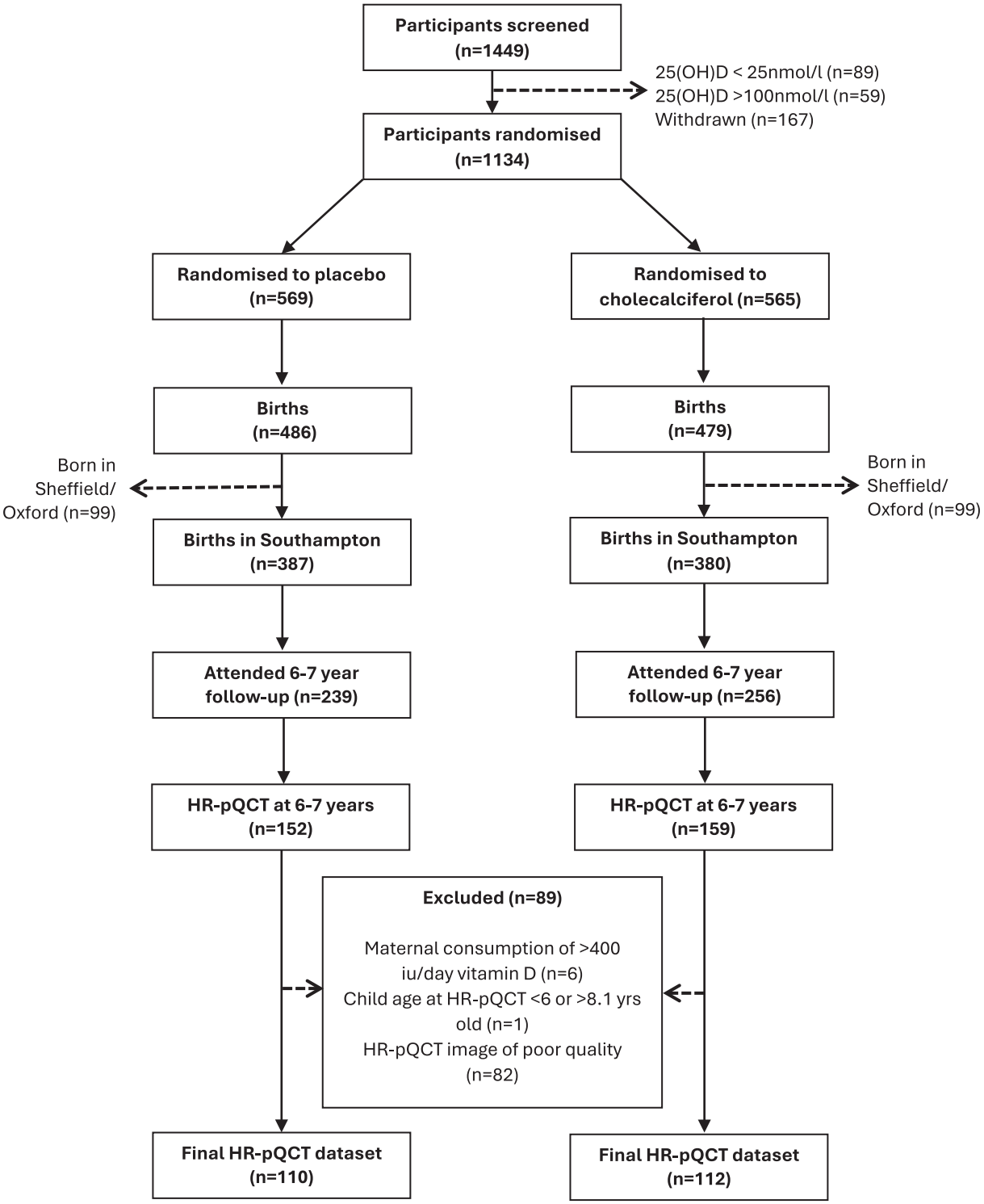

Fig. 1. Participant flow chart.

was similar between the two randomisation groups (*Supplementary Table 4)*. There was no evidence of any statistically significant interaction of intervention and genotype (in either the mother or offspring) on offspring HR-pQCT variables (data not shown, $p > 0.05$ for all). Stratified analyses by SNP genotype were therefore not performed.

3.3. HR-pQCT phenotypes by cluster analysis

Three bone microarchitecture phenotypes were generated using cluster analysis (Table 5). There were differences in anthropometry between the phenotypes, such that children in cluster 1 were the shortest and lightest for age and sex and had the lowest vBMD (cortical, trabecular and total). Children in cluster 2 were the tallest and heaviest for age and sex, with the largest bone CSA. Height and weight z-scores for cluster 3 were greater than those for cluster 1 but smaller than those for cluster 2. Children in cluster 3 also had the smallest bone CSA but greatest cortical thickness and highest vBMD (cortical, trabecular and total). Maternal randomisation to placebo or cholecalciferol did not vary

Table 1
Maternal characteristics at randomisation for the children who had HR-pQCT, by randomisation group.

Maternal characteristic	Placebo $n = 110$		Cholecalciferol $n = 112$		*P* value[a]
Age (years), mean (SD)	104	31 (5)	105	31 (5)	0.78
Nulliparous, n (%)	104	49 (47)	105	46 (44)	0.63
White ethnicity, n (%)	104	101 (97)	103	99 (96)	0.69
Smoking, n (%)	104	5 (5)	104	5 (5)	1.00
Weight (kg), median (IQR)	104	71 (65, 83)	105	68 (60, 80,)	0.07
BMI (kg/m^2), median (IQR)	104	26 (23,30)	105	25 (22, 29)	0.59
Strenuous exercise at least once per week, n (%)	94	14 (15)	93	19 (20)	0.49
Educational attainment at least A level, n (%)	103	84 (82)	105	91 (87)	0.45
Milk consumed (pints/day), median (IQR)	90	0.5 (0.3, 1.0)	92	0.5 (0.3, 1.0)	0.65
Serum 25(OH)D (nmol/l), median (IQR)	109	43 (32, 52)	112	45 (35, 55)	0.28

[a] *P* values were obtained from t-tests (normally distributed continuous variables), Mann-Whitney U (non-normally distributed continuous variables) or χ^2 (categorical variables).

Table 2
Characteristics of the offspring at 6–7 years, by randomisation group.

Baseline infant and child characteristic	Placebo n = 110		Cholecalciferol n = 112		P value[a]
Age (years), mean (SD)	110	7.0 (0.5)	112	7.0 (0.5)	0.71
Male sex, n (%)	110	60 (55)	112	58 (52)	0.68
Height (cm), mean (SD)	106	124.0 (5.7)	106	123.2 (5.8)	0.30
Height z-score (SD), mean (SD)	106	0.44 (0.93)	106	0.31 (0.96)	0.35
Weight (kg), median (IQR)	106	24.3 (21.9, 28.0)	106	23.7 (21.3, 26.6)	0.19
Weight z-score (SD), mean (SD)	106	0.41 (1.0)	106	0.20 (0.99)	0.13
BMI (kg/m^2), median (IQR)	106	15.8 (14.8, 17.0)	106	15.4 (14.8, 16.6)	0.29
BMI z-score (SD), mean (SD)	106	0.21 (1.08)	106	0.02 (0.98)	0.28
Age last breast fed[b] (months), median (IQR)	108	3 (0, 7)	108	6 (1,12)	0.004
Milk consumption (pints/day), median (IQR)	106	0.5 (0.4, 0.8)	107	0.5 (0.3, 0.7)	0.74
Use of vitamin D supplements, n (%)	102	37 (36)	98	44 (45)	0.21
Season of HR-pQCT scan, n (%)					
Autumn	110	29 (26)	112	33 (29)	0.62
Spring		19 (17)		25 (22)	
Summer		23 (21)		22 (20)	
Winter		39 (35)		32 (29)	

[a] P values were obtained from t-tests (normally distributed continuous variables), Mann-Whitney U (non-normally distributed continuous variables) or χ^2 (categorical variables)
[b] Established from questionnaires completed at 1 and 2 years of age.

between the clusters (Table 5).

4. Discussion

This study assessed the effect of 1000 IU/day pregnancy cholecalciferol supplementation compared to placebo on offspring tibia bone microarchitecture at age 6–7 years in follow-up of a randomised controlled trial. There was little statistical evidence of an effect of this intervention on HRpQCT outcomes, despite evidence of a positive effect on WBLH BMD assessed by DXA.

Table 3
HR-pQCT and DXA results for placebo and cholecalciferol groups at 6–7 years.

HR-pQCT	Placebo		Cholecalciferol		P value[a]
Total vBMD (mg/cm^3), median (IQR)	101	282 (257, 304),	106	280 (264, 304)	0.75
Cortical vBMD (mg/cm^3), median (IQR)	105	735 (716, 759)	104	745 (722, 774)	0.07
Trabecular vBMD (mg/cm^3), median (IQR)	101	168 (155, 189)	106	171 (156, 185)	0.99
Trabecular number (mm^{-1}), median (IQR)	101	2.0 (1.8, 2.1)	106	2.0 (1.8, 2.1)	0.47
Trabecular thickness (mm), mean (SD)	101	0.07(0.01)	106	0.07 (0.01)	0.68
Cortical thickness (mm), mean (SD)	105	1.0 (0.2)	104	1.0 (0.2)	0.89
Cortical porosity (%), mean (SD)	105	6.3 (1.9)	104	6.0 (1.8)	0.18
Total Cross-sectional Area (CSA) (mm^2), median (IQR)	101	331 (287, 377)	106	332 (292, 368)	0.79
DXA					
Whole-body-less-head (WBLH)					
BA (cm^2) mean (SD)	108	948 (61)	108	953 (73)	0.61
BMC (g), mean (SD)	109	565 (79)	110	566 (82)	0.95
BMD (g/cm^2), mean (SD)	108	0.59 (0.05)	108	0.59 (0.05)	0.78
BMAD (g/cm^3), mean (SD)	108	0.019 (0.001)	108	0.019 (0.001)	0.89
Lumbar spine (LS)					
BA (cm^2), mean (SD)	109	31 (4)	110	30 (4)	0.18
BMC (g), mean (SD)	108	20 (4)	109	20 (4)	0.48
BMD (g/cm^2), mean (SD)	108	0.65 (0.06)	109	0.66 (0.06)	0.54
BMAD (g/cm^3), mean (SD)	108	0.25 (0.03)	112	0.26 (0.03)	0.24

[a] P values were obtained from t-tests (normally distributed continuous variables) or Mann-Whitney U (non-normally distributed continuous variables)

In a previously reported follow-up of the MAVIDOS cohort at 6–7 years, we demonstrated evidence of a positive effect of pregnancy vitamin D supplementation on offspring WBLH BMD assessed by DXA . This finding was replicated in the subset of children included in this analysis. Similarly, in the COPSAC$_{2010}$ study, evidence of a positive effect on offspring WBLH BMD, assessed by DXA at age 6 following maternal supplementation with 2800 IU/day cholecalciferol from mid-pregnancy compared with 400 IU/day, was identified [10]. To date, no other randomised controlled trials have evaluated the effect of maternal vitamin D supplementation in pregnancy on offspring bone microarchitecture. In contrast to the findings of an observational study of maternal vitamin D status in pregnancy and offspring bone geometry assessed by pQCT [15,16], we did not identify an effect of pregnancy vitamin D supplementation on offspring bone CSA, nor other microarchitectural parameters. However, it is possible that this reflects the small sample size as HR-pQCT data was only available for a subset of the children. This was due to the introduction of this scan to the data collection protocol after the follow-up phase had begun, a technical issue with the HR-pQCT instrument during the follow-up phase, and a significant number with poor-quality images due to extreme sensitivity of the instrument to movement. Indeed, the effect size demonstrated by the beta coefficient for cortical vBMD was similar to WBLH BMD, albeit with larger confidence intervals. Interestingly, this finding is consistent with that of a study in children aged 10 to 12 years old ($n = 193$) that demonstrated the children with vitamin D deficiency (<25 nmol/l) had lower radial and tibial cortical vBMD measured by pQCT than those with vitamin D insufficiency (26–40 nmol/l) and sufficiency (>40 nmol/l) [33]. A study of adolescents in Hong Kong similarly found that serum 25 (OH)D was positively associated with cortical vBMD in girls, as well as

Table 4
Effect of 1000 IU/day cholecalciferol in pregnancy compared with placebo on HR-pQCT and DXA z-scores at age 6–8 years.

	Model 1 adjusted for age and sex			Model 2 adjusted for age, sex, weight and height			Model 3 adjusted for age, sex, weight, height and age when stopped breastfeeding		
	N	β (95% CI)	P value	N	β (95% CI)	P value	N	β (95% CI)	P value
HR-pQCT									
Total vBMD (SD)	207	0.06 (−0.21, 0.33)	0.67	198	0.03 (−0.24, 0.31)	0.82	195	0.03 (−0.25, 0.32)	0.81
Cortical vBMD (SD)	209	0.25 (−0.02, 0.51)	0.07	199	0.23 (−0.03, 0.49)	0.09	195	0.19 (−0.08, 0.46)	0.17
Trabecular vBMD (SD)	207	−0.01 (−0.28, 0.26)	0.93	198	−0.01 (−0.28, 0.27)	0.95	195	−0.04 (−0.32, 0.25)	0.79
Trabecular number (SD)	207	0.08 (−0.19, 0.35)	0.55	198	0.16 (−0.12, 0.44)	0.25	195	0.09 (−0.19, 0.38)	0.53
Trabecular thickness (SD)	207	−0.07 (−0.34, 0.19)	0.59	198	−0.14 (−0.41, 0.13)	0.30	195	−0.09 (−0.37, 0.19)	0.52
Cortical thickness (SD)	209	0.07 (−0.19, 0.34)	0.59	199	0.07 (−0.20, 0.35)	0.60	195	0.10 (−0.18, 0.38)	0.48
Cortical porosity (SD)	209	−0.15 (−0.41, 0.10)	0.24	199	−0.15 (−0.41, 0.11)	0.25	195	0.10 (−0.37, 0.17)	0.47
Total cross-sectional area (CSA) (SD)	207	0.05 (−0.20, 0.30)	0.71	198	0.12 (−0.09, 0.34)	0.26	195	0.09 (−0.14, 0.31)	0.45
Whole-body-less-head (WBLH) DXA									
BA (SD)	216	0.06 (−0.19, 0.31)	0.63	207	0.11 (−0.06, 0.29)	0.20	202	0.12 (−0.06, 0.30)	0.20
BMC (SD)	219	0.03 (−0.21, 0.28)	0.78	210	0.14 (−0.003, 0.28)	0.05	205	0.11 (−0.03, 0.26)	0.13
BMD (SD)	216	0.07 (−0.17, 0.32)	0.56	207	0.19 (0.04, 0.34)	0.01	202	0.15 (−0.01, 0.30)	0.06
BMAD (SD)	216	0.04 (−0.21, 0.29)	0.76	207	0.16 (−0.03, 0.34)	0.10	202	0.11 (−0.08, 0.30)	0.26

Table 5
Bone phenotypes generated by cluster analysis of HR-pQCT variables and characteristics of the children in each cluster.

Variable	Cluster 1 ($n = 58$)	Cluster 2 ($n = 69$)	Cluster 3 ($n = 67$)	P value[a]
Total vBMD (mg/cm^3), mean (SD)	256 (21)	270 (26)	319 (32)	<0.001
Cortical vBMD (mg/cm^3), mean (SD)	714(25)	743 (30)	767 (29)	<0.001
Trabecular vBMD (mg/cm^3), mean (SD)	162 (17)	174 (23)	175 (28)	0.004
Trabecular number (mm^{-1}), mean (SD)	2.0 (0.2)	2.0 (0.2)	1.9 (0.3)	0.03
Trabecular thickness (mm), mean (SD)	0.07 (0.01)	0.07 (0.01)	0.08 (0.01)	<0.001
Cortical thickness (mm), mean (SD)	0.9 (0.1)	0.9 (0.1)	1.2 (0.2)	<0.001
Cortical porosity (%), mean (SD)	6.9 (1.6)	5.6 (1.8)	6.1 (1.8)	<0.001
Total cross-sectional area (CSA) (mm^2), mean (SD)	322 (36)	384 (41)	287 (46)	<0.001
Male sex, n (%)	33 (57)	40 (58)	32 (48)	0.43
Age (years), mean (SD)	7.1 (0.5)	6.9 (0.4)	7.0 (0.4)	0.16
Height z-score (SD), mean (SD)	−0.1 (0.8)	1.0 (0.8)	0.2 (0.9)	<0.001
Weight z-score (SD), mean (SD)	−0.2 (0.7)	0.9 (0.8)	0.1 (1.0)	<0.001
BMI z-score (SD), mean (SD)	−0.3 (0.9)	0.5 (1.0)	−0.0 (1.0)	<0.001
Whole body total percentage fat (%)	28 (5)	29 (6)	29 (6)	0.20
Age last breast fed[b] (months), mean (SD)	5 (5)	6 (5)	5 (5)	0.09
Randomisation to cholecalciferol, n (%)	29 (50)	35 (51)	32 (51)	1.0

[a] P values were obtained from χ^2 (categorical variables) and one-way ANOVA (continuous variables).
[b] Established from questionnaires completed at 1 and 2 years of age.

cortical area, cortical thickness and total vBMD in both sexes [34].

We found no difference in the distribution of randomisation to placebo or cholecalciferol amongst the three bone phenotypes generated by cluster analysis. Differences in anthropometric measures of the children were however apparent between the bone phenotypes, highlighting the complex interactions between growth and adiposity on bone structure and BMD. Cross-sectional data has been used to demonstrate higher DXA-measured BMC and BMD in overweight and obese children, compared to healthy weight children [35], likely due to increased muscle mass and greater mechanical loading [36]. Lean mass, rather than fat mass, is a key contributor to increased bone strength and optimised bone microarchitecture (increased cortical area and thickness and trabecular density) [35], though at weight-bearing sites, like the tibia, excess fat may also contribute to loading effects [36]. Singhal et al. previously showed a positive association between tibia CSA and body weight in adolescent and young adult females [37]. Similarly, in our study, children in cluster 2 (the tallest and heaviest for age and sex) also had the largest total bone CSA. In contrast to our findings, Singhal et al. found that body weight was positively associated with vBMD (total and trabecular) and several studies have shown higher trabecular vBMD in overweight and obese children [38,39]. In our cohort, vBMD was highest in the group with more average height and weight for age and sex. Our cohort were prepubertal, and therefore the interplay between pubertal bone mineral acquisition, growth and body size and composition could account for these differences. Overall, the much larger effect of body size on bone microarchitecture may mask a potentially modest effect of pregnancy vitamin D. Similarly, other post-natal influences on bone development such as physical activity and diet could mask the effect of the intervention.

As we have previously demonstrated a SNP in each of *CYP2R1* (25 hydroxylase) and *GC* (vitamin D binding protein) were associated with the 25(OH)D response to 1000 IU/day cholecalciferol in pregnancy, we hypothesised that these SNPs may interact with the intervention in determining the bone outcomes, through an effect on maternal and/or umbilical cord 25(OH)D [17,18]. In this subset of participants, the distribution of the maternal genotypes was very similar to that of the larger trial dataset [18]. However, no significant interactions were identified, perhaps reflecting the wide variation in maternal 25(OH)D status across the cohort and overlap between the two treatment groups, and the modest sample size which may be insufficient to detect a significant effect. Future research could consider stratification by clusters of maternal genotypes associated with low and high responsiveness to vitamin D supplementation [41]. The small sample size with successful HR-pQCT imaging limited the use of multi-SNP approaches such as polygenic risk scores though exploration of this in larger datasets may have been potentially informative given that BMD is a highly polygenic trait.

These findings therefore would not support the use of personalised, genotype-directed vitamin D supplementation to optimise offspring bone health. The limited sample size and small number of biologically relevant variants meant that multi-SNP approaches such as polygenic risk scores could not be applied, though these may have been potentially informative given that BMD is a highly polygenic trait [42]. Whilst exploration in larger study cohorts would further the understanding of the mechanistic effects of pregnancy vitamin D supplementation on offspring BMD, the low cost and few identified risks of moderate-high dose vitamin D supplementation would likely not make such an

approach cost-effective in clinical care.

To our knowledge, this is the first randomised controlled trial of vitamin D supplementation in pregnancy to assess offspring bone microarchitecture measured by HR-pQCT. There are however a number of limitations to this study. HR-pQCT was only available for a subset of the children. Due to the inherent difficulty in ensuring paediatric subjects keep still and the exquisite sensitivity of the instrument to movement, 26% of images were not useable thus reducing the available sample size. Additionally, we only acquired HR-pQCT images of the tibia and therefore have only examined the effect of pregnancy vitamin D supplementation on bone microarchitecture of weight bearing bones. The children that had HR-pQCT were born to mothers that were more highly educated and less likely to smoke in early pregnancy and were breast-fed for longer. This may mean that they were more likely to exhibit other healthy lifestyle behaviours, potentially limiting the generalisability of the findings. Postnatal bone development is influenced by many factors, including diet, calcium intake [43–45] and vitamin D status [46–48], physical activity and body weight. Due to the randomisation and ongoing blinding of participants, we would not expect maternal allocation to cholecalciferol or placebo to alter these post-natal behaviours. Milk intake and use of vitamin D supplementation at age 6–7 years was similar between the two groups, but physical activity was not formally assessed. Detailed assessment of physical activity in future follow-up or studies could help to confirm this and potentially delineate mechanistic pathways between maternal vitamin D supplementation and offspring bone health outcomes.

Due to an ethical stipulation, participants were permitted to take vitamin D supplementation throughout the study, up to a maximum of 400 IU/day. Thus, the placebo group may have been taking 0–400 IU/day and the intervention group 1000–1400 IU/day. This is likely to bias towards a null effect, although notably, despite of this, a difference in maternal 25(OH)D in late pregnancy was observed between the randomisation groups, and in the larger cohort of offspring, an effect on WBLH BMD at 4 [4] and 6–7 years [1] was also detected. Maternal baseline characteristics (including serum 25(OH)D levels) were similar between the two groups included in this analysis. Future research may also wish to consider approaches to supplementation doses based on baseline 25(OH)D levels [49] to optimise clinical outcomes for all women and offspring given variability in the 25(OH)D achieved in late pregnancy [50] and/or higher dose vitamin D supplementation to determine if this may confer greater benefit to offspring bone health.

Most of the women who participated in the MAVIDOS trial were of White ethnicity, which reflected the local population at the time of study recruitment. However, bone microarchitecture and vitamin D status do differ between ethnic groups [51–55] so care should be taken in extrapolating the findings to the wider populations.

5. Conclusion

In this post hoc analysis of a subset of children born to mothers participating in a randomised placebo-controlled trial of 1000 IU/day cholecalciferol during pregnancy, no effect of the intervention on tibia bone microarchitecture or vBMD at 6–7 years was identified. This finding was unexpected given the previously reported differences in BMD assessed by DXA but could reflect the smaller sample size with HRpQCT. Although bone phenotype groups did not differ by randomisation, they showed distinct variations in height and weight, highlighting the marked effect of anthropometric parameters on bone microarchitecture in growing children, which may overshadow the smaller effects of other early life exposures. Larger randomised controlled trials are required to robustly evaluate the effects of pregnancy vitamin D supplementation on pre-pubertal child bone microarchitecture.

CRediT authorship contribution statement

Charlotte Maden: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Stefania D'Angelo:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Leo D. Westbury:** Writing – review & editing, Formal analysis. **Elizabeth M. Curtis:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Sarah R. Crozier:** Writing – review & editing, Methodology, Funding acquisition, Data curation. **Keith M. Godfrey:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Kate A. Ward:** Writing – review & editing, Methodology. **Cyrus Cooper:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Nicholas C. Harvey:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Rebecca J. Moon:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Funding

This work was supported by Versus Arthritis UK (17702), Medical Research Council (MRC) [MC_PC_21003; MC_PC_21001], Bupa Foundation, University of Southampton, University Hospital Southampton NHS Foundation Trust, National Institute for Health Research (NIHR) Southampton Biomedical Research Centre, and NIHR Biomedical Research Centre, University of Oxford. CM was supported by an NIHR Biomedical Research Centre Clinical fellowship. EMC was supported by a Wellcome Trust Clinical Research Fellowship. RJM and EMC are/were supported by NIHR Academic Clinical Lectureships. KMG is supported by the NIHR (NIHR Senior Investigator NF-SI-0515-10042) and Alzheimer's Research UK (ARUK-PG2022A-008). NCH is supported by UK MRC [MC_PC_21003; MC_PC_21001] and NIHR (as an NIHR Senior Investigator (NIHR305844), and through the NIHR Southampton Biomedical Research Centre (NIHR203319)). The work leading to these results was supported by the European Union's Seventh Framework Programme (FP7/2007-2013), projects EarlyNutrition and ODIN under grant agreement numbers 289346 and 613977. We are extremely grateful to Merck GmbH for the kind provision of the Vigantoletten supplement. Merck GmbH had no role in the trial execution, data collection, analysis or manuscript preparation. The original protocol incorporated suggestions from the Arthritis Research UK Clinical Trials Collaboration. The funders had no other role in the study, and the corresponding author had full access to all of the data and the final responsibility to submit for publication.

Declaration of competing interest

EMC has received travel bursaries or lecture fees from Eli Lilly, Pfizer, Thornton and Ross and UCB, unrelated to this work. KMG has received reimbursement for speaking at conferences sponsored by companies selling nutritional products and is part of an academic consortium that has received research funding from Bayer, Boehringer Ingelheim, Nestec, BenevolentAI Bio Ltd. and Danone, outside the submitted work. CC reports personal fees from ABBH, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier and Takeda, outside the submitted work. NCH reports personal fees, consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Theramex, Shire, Consilient Healthcare, Echolight, Kyowa Kirin and Internis Pharma, outside the submitted work. RJM has received travel bursaries from Kyowa Kirin unrelated to this work. CM, SD, LDW, SRC and KAW declare no conflicts of interest related to the submitted work.

Acknowledgements

We would like to thank the study participants, the MAVIDOS Study Group, and the staff of the MRC Lifecourse Epidemiology Centre, University of Southampton for their support with this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2026.117843.

Data availability

Data may be made available on reasonable request.

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