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ORIGINAL ARTICLE

The effect of pregnancy vitamin D supplementation on offspring bone mineral density in childhood: a systematic review and meta-analysis

Rebecca J. Moon[1,2] · Harry D. Green[1] · Stefania D'Angelo[1] · Keith M. Godfrey[1,3] · Justin H. Davies[2,4] · Elizabeth M. Curtis[1] · Cyrus Cooper[1,3,5] · Nicholas C. Harvey[1,3]

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Abstract

Summary Systematic review and meta-analysis of the effect of moderate- to high-dose vitamin D supplementation in pregnancy on offspring bone mineralisation found a positive effect of vitamin D supplementation on offspring bone mineral density (BMD) at age 4–6 years, with a smaller effect on bone mineral content.

Purpose A systematic review and meta-analysis was performed to assess the effect of pregnancy vitamin D supplementation on offspring bone mineral density (BMD) in childhood.

Methods A literature search was conducted for published RCTs of antenatal vitamin D supplementation with assessment of offspring BMD or bone mineral content (BMC) by dual-energy X-ray absorptiometry (DXA) using MEDLINE and EMBASE up to 13th July 2022. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool. Study findings were grouped in two age groups of offspring assessment: neonatal period and early childhood (3–6 years). Random-effects meta-analysis of the effect on BMC/BMD at 3–6 years was performed using RevMan 5.4.1, yielding standardised mean difference (SMD) (95% CI).

Results Five RCTs were identified with offspring assessment of BMD or BMC; 3250 women were randomised within these studies. Risk of bias was low in 2 studies and "of concern" in 3. Supplementation regimes and the control used (3 studies used placebo and 2 used 400 IU/day cholecalciferol) varied, but in all studies the intervention increased maternal 25-hydroxvitamin D status compared to the control group. Two trials assessing BMD in the neonatal period (total $n = 690$) found no difference between groups, but meta-analysis was not performed as one trial represented 96.4% of those studied at this age. Three trials assessed offspring whole-body-less-head BMD at age 4–6 years. BMD was higher in children born to mothers supplemented with vitamin D [0.16 SD (95% confidence interval 0.05, 0.27), $n = 1358$] with a smaller effect on BMC [0.07 SD (95% CI − 0.04, 0.19), $n = 1351$].

Conclusions There are few RCTs published to address this question, and these are inconsistent in methodology and findings. However, meta-analysis of three trials suggests moderate- to high-dose vitamin D supplementation in pregnancy might increase offspring BMD in early childhood, but further trials are required to confirm this finding. (Prospero CRD42021288682; no funding received).

Keywords BMD · Epidemiology · Osteoporosis · Pregnancy · RCT · Vitamin D

✉ Rebecca J. Moon
rm@mrc.soton.ac.uk

[1] MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK

[2] Paediatric Endocrinology, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[3] NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

[4] Faculty of Medicine, University of Southampton, Southampton, UK

[5] National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, University of Oxford, Oxford, UK

Introduction

Vitamin D supplementation in pregnancy has been shown to reduce the risk of symptomatic neonatal hypocalcaemia, but there is also much interest in other potential benefits of this gestational intervention for obstetric and offspring health [1]. Given the importance of vitamin D repletion for skeletal health, a role for in utero vitamin D exposure in offspring skeletal development has been suggested. Some observational mother–offspring cohort studies have shown positive associations between maternal serum 25-hydroxy-vitamin D [25(OH)D] status in pregnancy and offspring bone mineral density (BMD) in the neonatal period [2, 3], childhood [4–6] and through to peak bone mass [7]; however, these findings are not consistent across all cohorts [8, 9]. Several randomised controlled trials (RCT) assessing the effect of antenatal vitamin D supplementation on offspring BMD have been undertaken. We therefore performed a systematic review and meta-analysis to describe the current available literature and facilitate the best estimate of the association between antenatal vitamin D supplementation and offspring BMD.

Methods

The study protocol was registered in PROSPERO (www.crd.york.ac.uk/PROSPERO) on 2nd November 2021 (CRD42021288682), and the review and meta-analysis were undertaken in accordance with guidelines from PRISMA [10]. A literature search was undertaken to identify RCTs of vitamin D supplementation in pregnant women with offspring assessment of BMD or bone mineral content (BMC). The intervention studied was vitamin D during pregnancy either as cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2). All vitamin D supplementation regimes were included, including daily, weekly and single high-dose supplementation. Trials of vitamin D and calcium co-supplementation were excluded unless all treatment groups received the same calcium supplementation. Food fortification studies were also excluded. Studies in which the vitamin D supplementation continued according to maternal randomisation group in the offspring postnatally or in which there was secondary postnatal randomisation of the infant to vitamin D supplementation were also excluded as pre- and post-natal supplementation could have differing effects. We included studies with control groups using placebo, no treatment and low-dose ($\leq$400 IU/day) vitamin D. Low-dose vitamin D was included as a potential control group as this is currently standard care for pregnancy in many developed countries [11]. The study outcomes considered were dual-energy x-ray absorptiometry (DXA) assessment of BMD or BMC in the offspring. Assessment of BMD by other methods including single photon absorptiometry (SPA), radiographic density and quantitative ultrasonography (QUS) was not included, as these techniques are not reliable for assessment of bone mineralisation in this age group [12].

Search strategy and study selection

The literature search was initially conducted on 30th November 2021 and subsequently updated on 13th July 2022. MEDLINE and EMBASE was searched from conception via OvidSP using the search terms ("vitamin D" OR cholecalciferol OR colecalciferol OR ergocalciferol).af AND (Pregnan* OR Antenat* OR Gestation*).af AND (bone).af. Two authors (RJM and HDG) independently screened the titles and abstracts to identify full texts for review, and assessed these for inclusion. Disagreements were resolved through discussion. The reference lists of relevant reviews were additionally scanned for any additional applicable studies. We included only full reports that had been published in peer-reviewed journals. Conference abstracts without full publication of data were therefore excluded. Data for maternal 25(OH)D status and offspring BMD and BMC were extracted independently by two authors (RJM and HDG) and disagreements resolved by discussion. Results were tabulated into an excel spreadsheet for synthesis.

Risk of bias

Two authors (RJM and HDG) independently assessed risk of bias using the Risk of Bias 2.0 tool (www.riskofbias.info) [13].

Data analysis

All 25(OH)D data was converted to measurements in nanomoles/l using a conversion factor of 2.5 from nanograms/litre.

Data for bone outcomes were extracted from the papers as mean, standard deviation (SD) or standard error and number of participants (*n*) and entered into RevMan5.4. Where SD was not available, this was calculated using SE and *n* using the calculator within RevMan5.4. for further analysis. Forest plots were used as graphical representation of the results of the meta-analysis and showed standardised mean (SD) for neonatal whole-body BMD and BMC and childhood whole-body-less-head (WBLH) BMD and BMC. WBLH data were used as this is the recommended site for assessment of BMD in childhood due to the large contribution of the skull which responds to stimuli differently to the remainder of the skeleton

[14, 15]. As the data were derived from randomised controlled trials, random allocation of potential confounders could be assumed, so only unadjusted data were included in the meta-analysis. One study included follow-up of the offspring at both 3 and 6 years of age [16], and therefore the meta-analysis was performed twice using each set of data. For studies that included multiple arms of vitamin D supplementation at different doses, the findings for all doses were combined into a single group to include in the meta-analysis [17, 18]. The heterogeneity of the studies included in the meta-analysis was assessed using the I^2, chi-squared test and Tau^2. Random-effects meta-analysis was used due to differences in study methodology and standardised mean difference is reported to account for the difference in age at follow-up.

Results

The literature search revealed 2338 records after deduplication. After title and abstract screening, nine reports were eligible for full review [16, 19–26]. Three reports were subsequently excluded: one study assessed offspring BMD by SPA and included supplementation with an unknown amount of calcium in addition to vitamin D [26], one assessed only bone turnover markers and not BMC/BMD [25] and the third re-analysed the data included in another publication with stratification by postnatal vitamin D status [21]. Finally, the search identified 5 RCTs; one reported bone outcomes at two ages in separate reports; thus, there were 6 published reports for data extraction [16, 19, 20, 22–24] (Fig. 1).

Study characteristics

The characteristics of the included studies are presented in Table 1. The protocols for 4 of the studies had been reviewed by an research ethics review board [16, 19, 20, 23, 24]; the study of Sahoo et al. did not report ethical review but had been registered in a clinical trials registry [22]. Two trials reported assessment of offspring BMD in the neonatal period [20, 23], one in infancy [22] and three in early childhood (ages 3–6 years) [16, 19, 24]. No trials assessed the effect

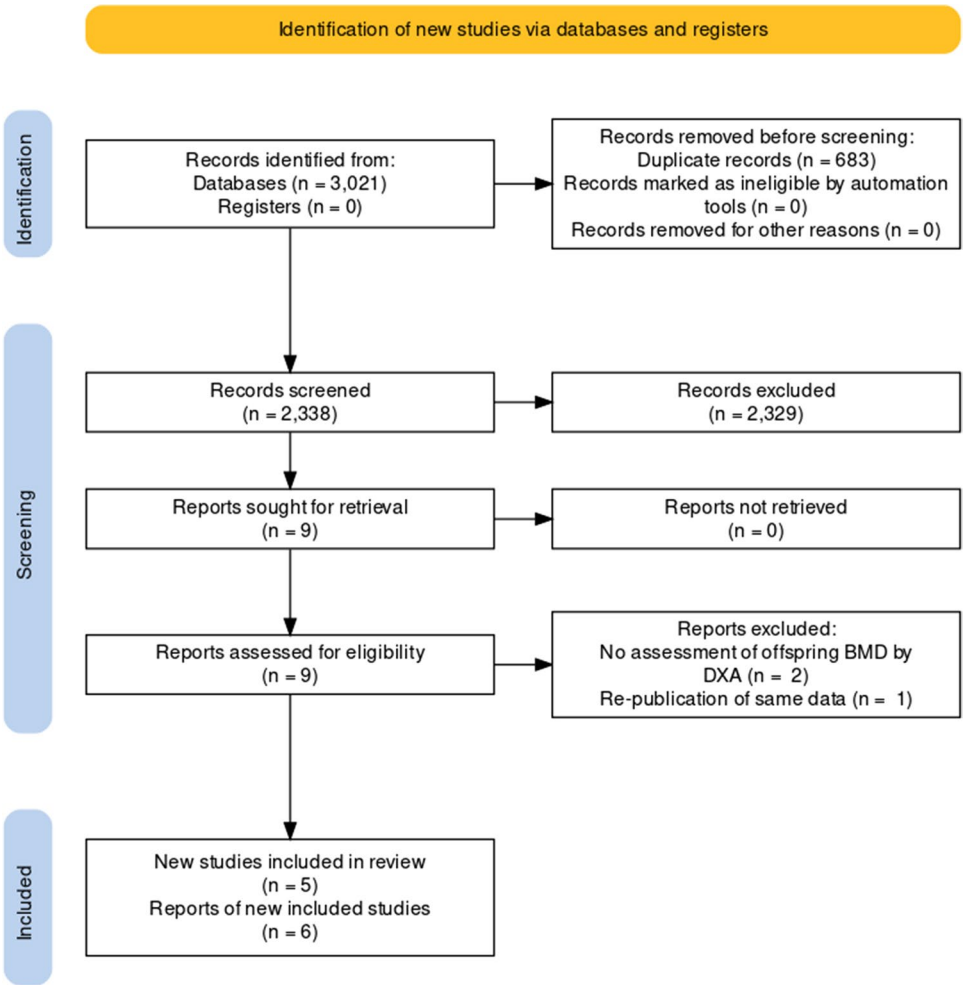

Fig. 1 Flow chart of systematic review

Table 1 Characteristics of studies included in the systematic review

Study	Cooper 2016 / Curtis 2022	Vaziri 2016	Sahoo 2017	Brustad 2020	O'Callaghan 2022
	MAVIDOS			$COPSAC_{2010}$	BONUSKids
Geographic region	UK	Iran	India	Denmark	Bangladesh
Number of women randomised	1134	153	300	623	1040
Intervention(s) [number randomised]	1000 IU/day oral cholecalciferol	2000 IU/day oral cholecalciferol	Group 1: 60,000 IU oral cholecalciferol every 4 weeks [*N* = 100] Group 2: 60,000 IU oral cholecalciferol every 8 weeks [*N* = 100]	2400 IU/day oral cholecalciferol	Group 1: 4200 IU/week oral cholecalciferol Group 2: 16,800 IU/week oral cholecalciferol Group 3: 28,000 IU/week oral cholecalciferol
Control group [number randomised]	Placebo	Placebo	400 IU/day cholecalciferol [*N* = 100]	400 IU/day cholecalciferol	Placebo
Gestation at intervention	IMP commenced at 14–17-week gestation and continued until delivery	IMP commenced at 26–28-week gestation and continued until delivery	IMP commenced at 14–20-week gestation until delivery	IMP commenced at 24-week gestation and continued until 1 week post-delivery	IMP commenced at 17–24-week gestation and continued until delivery
Other supplementation allowed/offered	Participants could self-supplement with up to 400 IU/day vitamin D	"Prescribed supplementation outside the study's protocol" Using other supplements: Vit D: 74.2% Control: 86.2%	Excluded if received vitamin D supplementation in the 3 months prior to randomisation All women received 1 g elemental calcium daily	All participants encouraged to continue taking 400 IU/day vitamin D	All participants received iron-folic acid and 500 mg/day calcium carbonate
Blinding	Double-blind	Double-blind	Double-blind	Double-blind	Double-blind
Maternal 25(OH) D at baseline (nmol/l)	Only women with baseline 25(OH) D 25–100 nmol/l eligible to participate *At randomisation (mean (SD))* Vit D: 46.7 (17.7) Control: 45.9 (17.0) *At baseline (median (IQR)* Vit D: 45.0 (33.9–57.4) Control: 45.1 (33.9–56.4)	*At randomisation (ng/ml[b], mean (SD))* Vit D: 29.1 (14.0) Control: 31.8 (20.9)	*At recruitment (Median (IQR))* Vit D group 1: 30.3 (16.5–41.0) Vit D group 2: 24.3 (11.5–34.0) Control: 28.5 (16.0–54.5)	*At randomisation (mean (SD))* Vit D: 76.6 (25) Control: 76.4 (25)	*At enrolment (mean (SD))* Vit D group 1: 27.5 (14.0) Vit D group 2: 28.8 (13.4) Vit D group 3: 26.0 (12.6) Control: 26.8 (14.5)
Maternal 25(OH) D following intervention (nmol/l)	*34-week gestation (mean (SD))* Vit D: 68.2 (21.9 Control: 43.4 (22.4) *34-week gestation (median, IQR)* Vit D: 67.4 (56.2–80.3) Control: 42.4 (23.3–56.4)	*At birth (ng/ml, mean (SD))* Vit D: 45.1 (24.0) Control: 30.1 (14.6)	*At term (mean (SD))* Vit D group 1: 59.8 (22.9) Vit D group 2: 47.3 (15.3) Control: 24.5 (17.3)	*At 1 week post-partum (mean (SD)* Vit D: 106.3 (36) Control: 73.1 (32)	*At delivery (mean (SD))* Vit D group 1: 70.2 (19.6) Vit D group 2: 97.9 (23.3) Vit D group 3: 112.2 (26.7) Control: 21.2 (11.0)
Method of 25(OH) D analysis	Diasorin RIA	Chemiluminescence immunoassay	Diasorin RIA	Not reported	LC MS/MS
Compliance with IMP	Not reported	Excluded from analysis if consumed < 8 weeks of vitamin D supplementation	Number of 60,000 IU cholecalciferol sachets consumed (mean SD): Vit D group 1: 4.7 (1.5) Vit D group 2: 2.6 ± (0.7)	Not reported	Only offspring of women with ≥ 80% compliance with IMP invited to the offspring follow-up % Compliance (mean (SD) Vit D group 1: 99.4 (2.0) Vit D group 2: 99.5 (1.9) Vit D group 3 99.4 (2.4) Control: 99.3 (1.9)

Table 1 (continued)

Study	Cooper 2016	Curtis 2022	Vaziri 2016	Sahoo 2017	Brustad 2020		O'Callaghan 2022
	MAVIDOS				$COPSAC_{2010}$		BONUSKids
Age at offspring follow-up	Days (mean (SD)) Vit D: 8 (7) Control: 7 (6)	Years (median (IQR) Vit D: 4.1 (4.0–4.2) Control: 4.1 (4.0–4.2)	Days (mean (SD)) Vit D: 21.69 (8.84) Control: 24.50 (11.28) $p=0.18$	Months (median (IQR)) Vit D group 1: 14 (13–15) Vit D group 2: 14 (13–15) Control: 16 (15–16) Significantly different between groups $p<0.001$	Years (mean (SD)) Vit D: 3.3 (0.2) Control: 3.3 (0.1)	Years (mean (SD)) Vit D: 6.2 (0.2) Control: 6.2 (0.2)	"4 years" Mean age at follow-up for each group not reported
Number of offspring with DXA (% of original randomised women)	665 (58.6)	452 (39.9) Only children born in one of three research centres ($n=723$) invited to follow-up at 4y	25 (16.3)	52 (17.3) Only infants who were born in the research centre invited to participate in this follow-up ($n=160$)	199 (31.9)	383 (61.5)	481 (46.3)
Region of interest of DXA	Whole body	Whole-body-less-head	Whole body	Whole body	Whole-body-less-head	Whole-body-less-head	Whole-body-less-head
Effect on BMD (g/cm^2), mean (SD) unless stated	Vit D: 0.203 (0.022) Control: 0.203 (0.019) $p=0.96$	Vit D: 0.477 (0.036) Control: 0.470 (0.037) $p=0.048$	Vit D: 0.194 (0.044) Control: 0.192 (0.034) $p=0.54$	Vit D group 1: 0.295 (0.041) Vit D group 2: 0.287 (0.023) Control: 0.335 (0.033) $p=0.001$	Vit D: 0.44 (0.03) Control: 105 0.44 (0.03) $p=0.14$ adjusted for age, sex, height and weight (unadjusted p values not provided)	Vit D: 0.56 (0.05) Control: 0.55 (0.04) $p=0.15$ adjusted for age, sex, height and weight (unadjusted p values not provided)	Vit D group 1: 0.436 (0.035) Vit D group 2: 0.444 (0.046) Vit D group 3: 0.439 (0.047) Control: 0.438 (0.039)
Effect on BMC (g), mean (SD) unless stated	Vit D: 61.6 (11.7) Control: 60.5 (11.1) $p=0.21$	Vit D: 361.2 (44.1) Control: 356.7 (43.6)	Vit D: 80.97 (17.97) Control: 81.16 (24.02) $p=0.94$	Vit D group 1: 213.1 (46.2) Vit D group 2: 202.9 (29.9) Control: 250.8 (42.5) $p=0.006$	Vit D: 293.8 (44.3) Control: 288.8 (41.7) $p=0.05$ adjusted for age, sex, height and weight (unadjusted p values not provided)	Vit D: 532.3 (86.6) Control: 523.9 (82.4) $p=0.03$ adjusted for age, sex, height and weight (unadjusted p values not provided)	Vit D group 1: 273.3 (44.9) Vit D group 2: 279.8 (58.6) Vit D group 3: 276.1 (59.8) Control: 276.2 (48.5)

of pregnancy vitamin D supplementation on offspring BMD after the age of 6 years. The number of offspring with BMD assessed by DXA in each trial varied between 25 and 665. The RCTs were conducted in both high- [16, 19, 20] and low-/middle-income countries [22–24]. All the RCTs were conducted in a double-blind manner and used oral cholecalciferol as the investigational medicinal product (IMP); daily supplementation (doses 1000–2400 IU/day) was assessed in three trials [19–21, 23], weekly supplementation in one study [24] and four- or eight-weekly supplementation in one study [22]. Overall, the doses used were equivalent to between 600 and 4000 IU/day. Three RCTs used placebo as the control group [19, 20, 23, 24] and two trials compared to a control group receiving 400 IU/day cholecalciferol [21, 22]. The MAVIDOS and $COPSAC_{2010}$ studies allowed women to continue self-supplementation with up to 400 IU/day cholecalciferol, and Vaziri et al. allowed women to continue to take prescribed supplements; thus, the exact supplemental vitamin D intake of both the control and intervention groups in these studies is unknown. Nonetheless, in all the studies, maternal 25(OH)D status in late pregnancy or at delivery was higher in the cholecalciferol group(s) than the control group for the study (Table 1). The gestation at which the vitamin D supplementation was commenced varied markedly between 11- and 28-week gestation. All studies continued supplementation until delivery. O'Callaghan et al. additionally included a group randomised to both pre- and post-natal supplementation with 28,000 IU/week. This group was excluded from consideration in this systematic review and meta-analysis.

Risk of bias

Two trials (MAVIDOS and $COPSAC_{2010}$) were graded as having low risk of bias [16, 19, 20] (Table 2). The studies by O'Callaghan et al., Sahoo et al. and Vaziri et al. were all deemed "of concern" which reflected the lack of a prespecified analysis plan [22–24].

The findings of the study by Sahoo et al. were however considered uninterpretable due to a significant difference in age of follow-up of the children in the three randomisation groups (detailed in Table 2), and therefore these data were not included in subsequent review and meta-analysis.

Effect of maternal vitamin D supplementation on offspring whole body BMD or BMC in the neonatal period

Two studies assessed offspring whole body BMD in the neonatal period. The UK-based MAVIDOS trial of 1000 IU/day cholecalciferol vs placebo assessed whole-body DXA in 338 neonates born to mothers randomised to cholecalciferol and 327 born to placebo-group mothers [20]. There

Table 2 Assessment of risk of bias

Author, year	Study name	Intervention (cholecalciferol regimen)	Comparator	Outcome	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Cooper 2016	MAVIDOS	1000 IU/day	Placebo	Neonatal BMD	+	+	+	+	+	+
Vaziri 2016		2000 IU/day	Placebo	Neonatal BMD	+	+	+	+	!	!
Sahoo 2017		60,000 IU every 4 or 8 weeks	400 IU/day cholecalciferol	BMD in infancy	+	+	+	+	!	!
Brustad 2020	$COPSAC_{2010}$	2800 IU/day	400 IU/day cholecalciferol	BMD at 3 and 6 years	+	+	+	+	+	+
O'Callaghan 2022	BONUSKids	4000, 16,000 or 28,000 IU/week	Placebo	BMD at 4 years	+	+	+	+	!	!
Curtis 2022	MAVIDOS	1000 IU/day	Placebo	BMD at 4 years	+	+	+	+	+	+

+ low risk, ! some concerns,—high risk

was no difference in whole-body BMD or BMC between the two groups, although, in a pre-planned secondary analysis, there was evidence of a positive effect of the intervention amongst winter deliveries. Vaziri et al. conducted a trial of 2000 IU/day cholecalciferol vs. placebo in India. This study was deemed "of concern" for risk of bias and had only a small number of participants with DXA assessment ($n=25$) and very low rates of DXA follow-up (16.3%). No difference in offspring whole-body BMD in the late neonatal period [23] was identified. As the data from MAVIDOS represented 96.4% of the total number of neonates studied, meta-analysis of data from these two studies was not performed.

Effect of maternal vitamin D supplementation on offspring whole body BMD in early childhood

Three studies assessed offspring WBLH BMD at ages 3–6 years [16, 19, 24]. In the $COPSAC_{2010}$ study performed in Denmark, offspring DXA assessment was undertaken at both 3 and 6 years of age [16]; in MAVIDOS and the BONUSKids study in Bangladesh, offspring DXA was at 4 years of age [19, 24], although the exact age at DXA and comparison of age between randomisation groups in BONUSKids is not reported. In both the MAVIDOS trial (placebo vs 1000 IU/day vitamin D) and $COPSAC_{2010}$ (400 IU/day vs 2400 IU/day), vitamin D supplementation resulted in higher offspring WBLH BMD at ages 4 and 6 years, respectively [16, 19]. This effect was not observed in $COPSAC_{2010}$ at age 3 years in a smaller subset of children ($n=94$ vit D/105 control compared with $n=187$ vit D/196 control at 6 years of age). In contrast in the BonusKIDS trial in Bangladesh, which used weekly cholecalciferol supplementation with either 4200 IU, 16,800 IU or 28,000 IU compared with placebo, no effect of cholecalciferol on offspring WBLH BMD or BMC at age 4 years was identified [24].

Meta-analysis of these data, including 802 children born to mothers randomised to vitamin D and 556 children born to the control-groups, showed a significant effect of maternal vitamin D supplementation on offspring BMD when the data from $COPSAC_{2010}$ at age 6 years were included (SMD 0.16, 95% CI 0.05, 0.27, Fig. 2A). This was consistent but attenuated when the smaller data set at age 3 years was substituted for the 6-year data, including 720 vitamin D group children and 454 control-group children (SMD 0.11, 95% CI − 0.02, 0.23, Fig. 2B). There was a similar direction of effect for WBLH BMC, but the 95% confidence interval just bounded zero (Fig. 3A and 3B).

Data for whole body BMD and BMC and head BMD and BMC were also reported in $COPSAC_{2010}$ and BONUSKids, but not in MAVIDOS. Similarly to the findings for WBLH, positive effects of supplementation were observed in $COPSAC_{2010}$ at age 6 years (whole body BMD mean difference 0.009 g/cm^2 (95% CI 0.001–0.017), BMC mean difference 13.9 g (95% CI 3.2–24.7); head BMD mean difference 0.033 g/cm^2 (95% CI 0.010–0.057), BMC mean difference 6.1 g (95% CI 0.4–11.7)), but no effect for any of the cholecalciferol doses used compared to placebo in BONUSKids.

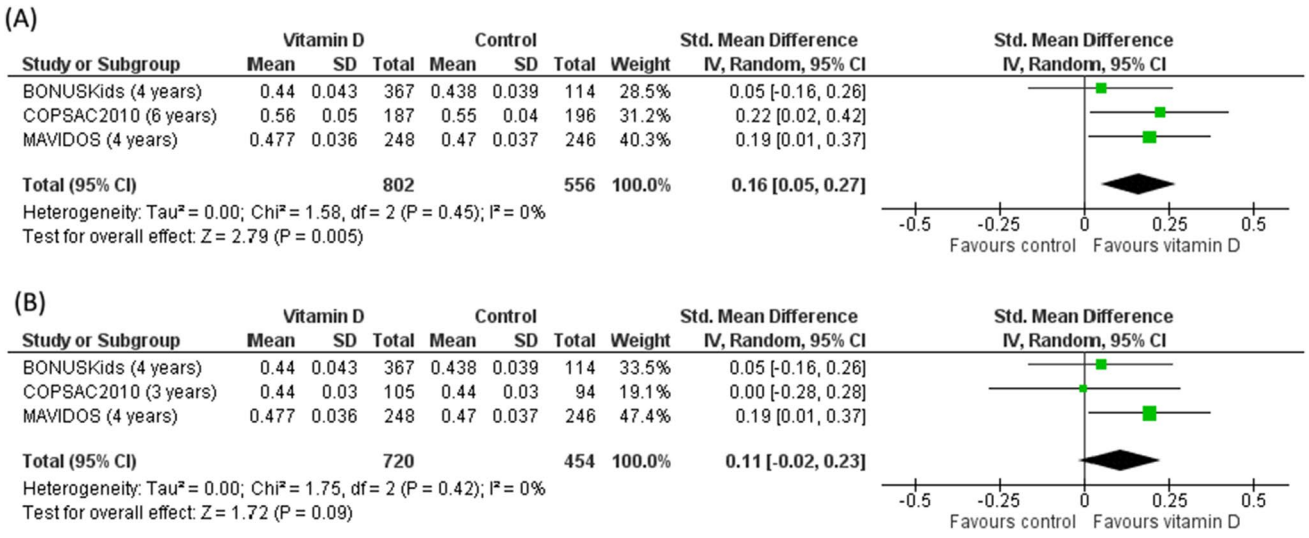

Fig. 2 Meta-analysis of the effect of maternal antenatal vitamin D supplementation on offspring whole-body-less-head bone mineral density. **A** Using the $COPSAC_{2010}$ data collected at 6 years of age and **B** using the $COPSAC_{2010}$ data collected at 3 years of age

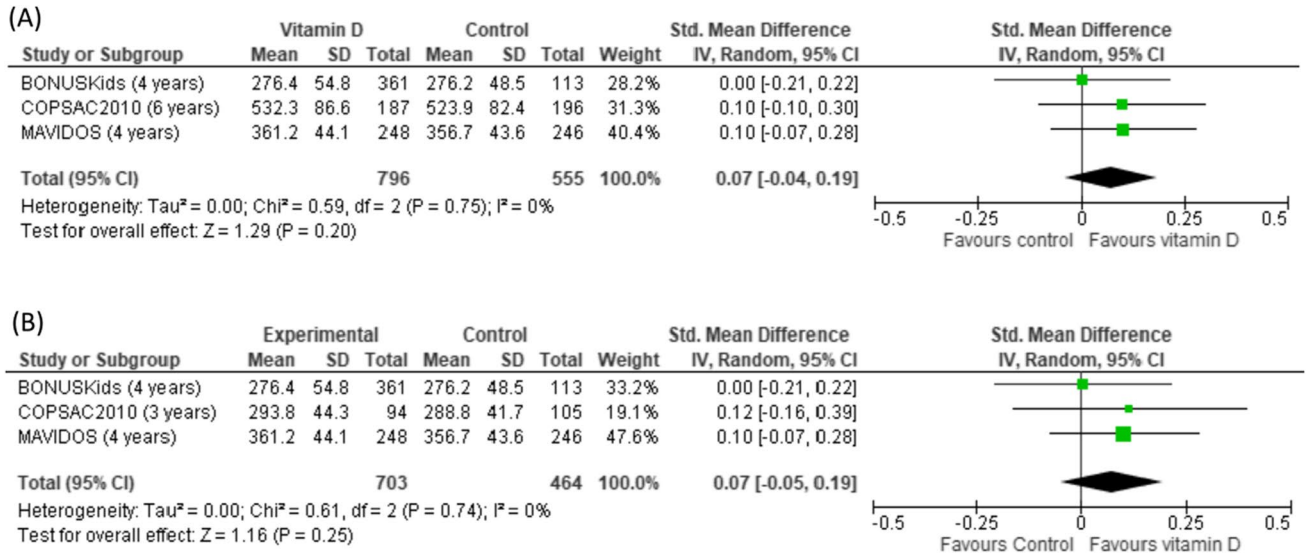

Fig. 3 Meta-analysis of the effect of maternal antenatal vitamin D supplementation on offspring whole-body-less-head bone mineral content. **A** Using the $COPSAC_{2010}$ data collected at 6 years of age and **B** using the $COPSAC_{2010}$ data collected at 3 years of age

Discussion

Summary of main findings

There are few randomised controlled trials that have assessed the effect of pregnancy vitamin D supplementation on offspring bone mineral density, and the existing trials vary markedly in terms of the population studied and supplementation protocols used. There were only two published RCTs of the effect of pregnancy vitamin D supplementation on offspring whole body bone outcomes in the neonatal period of which one trial included only a very small number of participants. Neither study reported an effect of the intervention on offspring BMD, but meta-analysis was not undertaken due to the majority of the data being from one of the two studies. In contrast, meta-analysis of RCTs reporting offspring BMD in early childhood (ages 4–6 years) suggests that moderate- to high-dose vitamin D supplementation during pregnancy might increase offspring WBLH BMD, with a similar direction of effect for WBLH BMC. However, caution should be taken in the interpretation of this due to the differences in study population and trial design, although the two studies most similar in population (MAVIDOS and COPSAC2010) reported similar outcomes in childhood.

The differing findings for the neonatal period and early childhood may reflect statistical power, with fewer data available in the neonatal period than at age 3–4 years and 4–6 years. Similarly, this is likely to reflect the difference in the findings of the meta-analysis in early childhood when the two follow-up ages of $COPSAC_{2010}$ was used. It is however possible that an evolving effect is responsible for this difference, as seen in the MAVIDOS trial, in which no significant effect on neonatal BMD was observed [20], yet at 4 years, a difference in BMD between the two randomisation groups was present [19]. Prenatal vitamin D supplementation increases breast milk vitamin D content [27], and is one potential mechanism for a stronger effect size beyond the neonatal period. Changing associations between maternal 25(OH)D status in late pregnancy and offspring adiposity have also been documented in a birth cohort study, with a positive association with fat mass at birth, no association at age 4 years and a negative association at age 6 years [28]. Associations of pregnancy 25(OH)D status with epigenetic markers [29] and differences in DNA methylation in response to supplementation [30] have been reported. Maternal 25(OH)D status in pregnancy has also been associated with metabolomic profiles in the offspring [31] in an observational study but has not yet been explored in an RCT. These may represent mechanisms by which in utero vitamin D exposure has a long-lasting and evolving effect on postnatal health outcomes.

Quality of evidence

Currently, there are only five reported RCTs of vitamin D supplementation in pregnancy to assess offspring BMD as an outcome, despite there being many trials that have assessed other outcomes, such as birth anthropometry, neonatal calcium status [32] and maternal health in pregnancy [33]. Due to the limited number of studies, we are unable to assess publication bias. Assessment of BMD was the primary trial outcome in only the MAVIDOS study [20, 34]. Risk of bias was considered "of concern" in three studies due to a lack of a pre-specified analysis plan, but this may reflect BMD being a secondary outcome. Overall, these studies all had high attrition, with follow-up between 16.3 and 61.5% (although typically higher in the studies

considered low risk of concern for bias), often leading to differences in participants and non-participants where these data are reported. This high attrition is in part due to the technical challenges of obtaining DXA scans without movement artefact in the age groups studied, with substantially more children attending follow-up visits than DXA data available. For example, only 199 technically acceptable DXA scans were obtained from 517 children attending the follow-up visit at age 3 in $COPSAC_{2010}$. Information on factors that may additionally affect BMD in the offspring for example current vitamin D status, physical activity and vitamin D supplement use was typically lacking. Unless allocation to pregnancy vitamin D supplementation is also influencing these outcomes (which would not be expected) and thus could represent a mechanistic pathway between pregnancy vitamin D supplementation and offspring bone mineralisation, random distribution of these factors between study arms would be expected. It is, however, not possible to completely rule out an imbalance in relevant covariates during follow-up as a result of chance. Application of the GRADE rating for evidence quality would rate the evidence for the effect of maternal vitamin D supplementation on offspring BMD as low due to the inconsistency between the reported studies and inability to assess publication bias, but currently the best possible estimate of the effect based on the available evidence is as shown in Fig. 2.

Potential bias in the review process

The authors of this systematic review and meta-analysis also authored the MAVIDOS study. However, this review was performed using pre-specified inclusion criteria. Additionally, given the authors' familiarity with the literature on this topic and completion of a previous comprehensive systematic review of antenatal vitamin D supplementation [35], there is high certainty that all RCTs of maternal vitamin D supplementation in pregnancy assessing this outcome have been identified.

Comparison to other reviews

A previous systematic review from the current research group conducted in 2013 identified only one intervention study assessing offspring BMD as an outcome of antenatal vitamin D supplementation [35, 36], but that study has not been included in this systematic review as offspring bone mineralisation was assessed by SPA and the women randomised to vitamin D also received an unknown quantity of calcium supplementation (which was not received by the control group) [36]. All the RCTs identified in this updated systematic review were published since 2016.

O'Callaghan and the BONUSKids research team also performed meta-analysis of the MAVIDOS, $COPSAC_{2010}$ and BONUSKids study findings although this was not done as part of a formal systematic review. No effect of pregnancy vitamin D supplementation on offspring WBLH BMD or BMC at ages 3–4 years was found in that meta-analysis [24]. However, only the data from the mother–offspring pairs randomised to 28,000 IU/week combined with the group randomised to 28,000 IU/week pre- and post-natal supplementation in the BONUSKids study was included. Care should be taken in using data from this pre-/post-natal supplementation arm, as differing effects of in utero and post-natal vitamin D exposure may occur [1]. Furthermore, although all the RCTs included in our meta-analysis used different doses of cholecalciferol, an increase in maternal 25(OH)D for each dose used was observed in all 5 studies in this systematic review; as a result, inclusion of the data from both the 4000 IU/week and 16,000 IU/week supplementation groups in BONUSKids in the meta-analysis is appropriate.

Implications for clinical practice and ongoing research

An overall effect of pregnancy vitamin D supplementation on offspring early childhood BMD is suggested by this meta-analysis and supports the use of higher dose vitamin D supplementation during pregnancy than is currently recommended in many developed countries [37–40]. However, the studies included differed markedly in terms of the population studied, baseline and achieved 25(OH)D status, the timing of vitamin D commencement and supplementation regimes used and therefore extrapolation of these findings should be undertaken with care. Offspring assessment of BMD should be considered in other existing RCTs of antenatal vitamin D supplementation. Increasing the available data for meta-analysis would enable stratification by population factors and cholecalciferol doses and dosing regimens and enable further understanding on whether achieved 25(OH)D, change in 25(OH)D or dose of supplementation used are important. For example, the positive effects of antenatal vitamin D supplementation on childhood BMD were observed in the two studies conducted in high-income countries on women predominantly of White ethnicity using daily supplementation [16, 19], whereas this effect was not found in the study conducted in Bangladesh using weekly supplementation [24]. This could be a chance finding in only a small number of studies, but differing response to vitamin D supplementation by ethnicity and other lifestyle factors has been reported [41]. This may in part reflect genetic clustering and distribution of single nucleotide polymorphisms in the vitamin D pathway [42], which have been associated with the response to vitamin D supplementation in pregnancy [43–45]. Thus, care should be taken in the translation of clinical trial findings to differing populations, and further studies in diverse populations and using multiple dosing arms to establish optimal dosing regimens would enable greater understanding.

Furthermore, ongoing follow-up of the children included in these RCTs is important to demonstrate a sustained effect of this intervention through to peak bone mass and a longer-term benefit on skeletal health.

Conclusions

Although the currently available data is limited, vitamin D supplementation during pregnancy using doses higher than currently recommended in many guidelines may have a beneficial effect of offspring bone mineral density in early childhood. Further data are required in diverse population groups either through BMD assessment in offspring born into existing RCTs or in newly established trials to confirm that this effect is consistent across all populations. Long-term follow-up of these offspring to confirm persistence of this effect should also be undertaken.

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Declarations

Consents and ethics approval This systematic review and meta-analysis contains no original data and thus issues of ethics, informed consent and patient confidentiality do not apply.

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