Prenatal high-dose vitamin D supplementation and offspring bone mineral content and density at age 13 years: a secondary analysis of a randomised clinical trial

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Summary

Background We previously demonstrated effect of maternal high-dose vitamin D supplementation on offspring bone health in preschool-age children. However, it is unknown whether this effect is long-lasting.

Methods We investigated the effect of 2800 (high-dose) vs. 400 (placebo + standard-dose) IU/day of gestational vitamin D supplementation on the prespecified secondary outcomes (bone mineral content and density (BMC and BMD)) at age 13 years and longitudinally (age 3, 6 and 13 years) in a double-blinded, randomized clinical trial (RCT) (NCT00856947) of 584 children in $COPSAC_{2010}$. In addition, we investigated the risk of radiologically verified fractures age 0–13 years in a post hoc analysis.

Findings In 416 children (71%) with a DXA scan at age 13 years, there were no differences in a linear regression model in total body BMC (6.7 (−28.3:41.6), p = 0.71) or total body BMD (−0.003 (−0.017:0.011), p = 0.68) among children in the high-dose (n = 212) vs. standard-dose vitamin D group (n = 204). In sensitivity analyses stratified by sex, birth season or maternal pre-interventional vitamin D levels there were no differences between the intervention groups. A mixed effects model of DXA scans from age 3, 6 and 13 years combined also showed no effects and there was no effect on fracture risk until age 13 years in a Cox (time to first) or Quasi-Poisson (incidence) regression model.

Interpretation This 13-year follow-up of a prespecified secondary outcome of the $COPSAC_{2010}$ vitamin D RCT did not show any lasting effect on offspring bone mineral content until age 13 years.

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Keywords: Vitamin D; Bone; Fracture; Childhood; RCT

Introduction

Low maternal levels of 25-hydroxyvitamin D (25(OH)D) in pregnancy have been associated with impaired bone mineral content in the offspring.[1,2] Further, maternal supplementation with high-dose vitamin D has been shown to have a beneficial effect on offspring bone mineral status in the first years of life in preschool-age children in the only two large conducted randomized clinical trials (RCTs) investigating this; our Copenhagen Prospective Studies on Asthma in Childhood 2010 ($COPSAC_{2010}$)[3] and the Maternal Vitamin D Osteoporosis Study (MAVIDOS)[4] vitamin D trials. In addition, we demonstrated even larger effects from the supplementation if children had high levels of 25(OH)D during the first year of life including a reduced risk of radiologically verified fractures in our $COPSAC_{2010}$ RCT.[5] Since early bone mineral content is considered to influence bone health in adulthood, these observed effects could have clinical implications on fracture and osteoporosis risk later in life through an increased peak

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Research in context

Evidence before this study

We searched the MEDLINE database using PubMed from the database inception until April, 2026, to identify all relevant publications, including systematic reviews, meta-analyses and randomized clinical trials (RCTs) investigating the influence of maternal gestational high-dose vitamin D intervention and the effect on bone mineralization and fracture risk in offspring. We used the keywords: *"vitamin D"*, *"RCT"*, *"bone mineral content"*, *"bone health"*, *"offspring bone mineral density"*, *"vitamin D supplementation"*, *"fractures"* and *"randomized controlled trial"*. Further, the reference lists of relevant articles were scrutinized for all applicable publications.

We identified two large RCTs investigating the relationship between high-dose vitamin D during pregnancy with bone mineralization outcomes as predefined outcomes. One of them was the MAVIDOS study, which showed a positive effect on age 6–7 years offspring bone mineral density (BMD) from 1000 IU/day vs. placebo. The other was our own RCT in $COPSAC_{2010}$, where we previously demonstrated a positive effect from 2800 IU/day vs. 400 IU/day of vitamin D in pregnancy on both whole-body BMD and bone mineral content (BMC) until age 6 years.

Added value of this study

This 13-year follow-up of a predefined outcome in our high-dose vitamin D double-blinded RCT showed that there was no lasting effect of pregnancy supplementation with vitamin D on child bone mineralization and fracture risk as suggested in current literature. These findings suggest that the previously hypothesized effect on reducing osteoporosis risk in adulthood by increasing peak bone mass from pregnancy vitamin D supplementation is not supported.

Implications of all the available evidence

Our study indicates that while high-dose vitamin D supplementation during pregnancy may have short-term benefits for offspring bone mineralization, these effects do not appear to persist into adolescence. This challenges the notion that maternal supplementation alone can meaningfully influence long-term skeletal health or fracture risk in offspring.

bone mass achieved in early adulthood.[6,7] Inverse associations between bone mineral content and risk of both childhood and adulthood fractures[8,9] have previously been reported, which is most likely due to a tracking phenomenon already beginning in utero.[6] The biological mechanisms are already well established as vitamin D is a crucial nutrient for the uptake and homeostasis of calcium and phosphate, which are the main components forming the hydroxyapatite complexes i.e., bone mineral.[10,11] This follow-up study of the $COPSAC_{2010}$ vitamin D RCT investigates potential long-lasting effects of prenatal supplementation with high-dose (2800 IU/day) vs. standard-dose (400 IU/day) vitamin D on bone mineral content and fracture risk until age 13 years and is uniquely positioned to answer whether the previously reported effect in preschool-age children is a lasting phenomenon as this is the only RCT with a follow-up until 13 years on this outcome. In addition, we investigate the combined effects of prenatal supplementation and early measurements of child 25-hydroxyvitamin D (25OHD) levels measured at age 6 months.

Methods

Study population

The Danish population-based $COPSAC_{2010}$ cohort enrolled 623 mother-child pairs in pregnancy week 24 with deep clinical phenotyping of the children from birth until 13 years. The cohort, baseline characteristics and the enrollment procedure have previously been described in detail.[3] The original trial protocol and statistical analysis plan are available in Supplement 1.

Ethics approval

The trial was registered on clinicaltrials.gov (NCT00856947), approved by the Danish Ethics Committee (H-B-2008-093) and the Danish Data Protection Agency (2015-41-3696), adhering to the Declaration of Helsinki and CONSORT guidelines were followed. Both parents gave written informed consent before enrollment.

The $COPSAC_{2010}$ pregnancy vitamin D RCT

Mothers were randomized in a 1:1 setting to receive high-dose (2400 + standard-dose of 400 IU/day) vs. placebo (+standard-dose of 400 IU/day) of vitamin D_3 (cholecalciferol) from pregnancy week 24 until 1 week after birth. Both groups were recommended to follow the daily recommended standard-dose intake advised by the Danish Health Authority i.e., 400 IU/day making it a dose-comparison study of 2800 IU/day vs. 400 IU/day. Serum 25OHD levels were measured at randomization in pregnancy week 24 for mothers using isotope dilution liquid chromatography-tandem mass spectrometry[12,13] and in childhood at age 6 months using the DiaSorin LIAISON 25-OH Vitamin D Total Assay.[14] The study was unblinded at age 3 years.

Dual-energy X-ray absorptiometry scans at age 13 years

Dual-energy X-ray absorptiometry (DXA) scans were performed at age 13 years with a Lunar iDXA densitometer (GE Healthcare, United States) with Lunar iDXA enCORE software (v. 17) and Horizon A, (Hologic Inc., United States), with Hologic APEX (v. 5.6.1.4)

for bone mineral analyses and the children were scanned for approximately 3 min in one movement. This method was chosen for its low radiation dose and short scan time as recommended in young participants. All scans were validated by two independent experienced specialists (PMG and CHN) unknowing of the allocation to the intervention groups. Measures of whole-body bone mineral density (BMD (g/cm^2)) and bone mineral content (BMC (g)) were performed. These outcomes were predefined secondary outcomes of the RCT.[3]

Longitudinal assessment of fractures until age 13 years

Fractures were longitudinally diagnosed from birth until age 13 years by parental interviews and children's medical record checks as previously described in detail.[5] All fractures were radiologically verified by physicians and included larger long bones i.e., clavicle, radius, ulna, tibia, fibula, femur and humerus and excluded fissures i.e., minor cracks.

Statistical analysis

The prespecified analysis of the effect of prenatal vitamin D intervention on BMC and BMD outcomes were analyzed using multivariable linear regression models adjusted for age, sex, height and weight as these factors have been proposed to influence DXA results in children in an intention-to-treat analysis.[15] In addition, we adjusted for the concomitant pregnancy omega 3 fish oil trial[16] and type of DXA scanner (Hologic or Lunar iDXA). In a sensitivity analysis, we further adjusted for individual Tanner Stages from parental questionnaires to account for puberty.[17] A combined analysis including BMC and BMD results from previously conducted DXA scans (Lunar iDXA, GE Healthcare) at age 3 and 6 years were analyzed using a random intercept mixed-effects model combining all three timepoints including the current 13-year DXA scans.

In sensitivity analyses, we stratified by scanner type, birth season, maternal baseline 25(OH)D levels, sex and a concomitant fish oil trial.[16] We added child 6 months 25(OH)D levels (sufficient (≥75 nmol/l) vs. insufficient (<75 nmol/l) in a combined variable with the intervention creating a high–high group (VitaminD & Sufficient) vs. a low–low group (Placebo & Insufficient) as previously described in an exploratory post-hoc analysis.[5] A post-hoc analyses of risk of fractures were conducted using a Cox proportional hazards regression model to assess time to first fracture diagnosis and a Quasi-Poisson regression model to account for repeated measurements in each child. Only children with full follow-up until age 13 years were included in the analyses. Statistical analyses were performed with R (4.4.1). p-values below 0.05 were considered statistically significant.

Role of the funding source

The funding agencies did not have any role in design, data collection, data analysis, interpretation or writing of the report.

Results

We randomized 623 pregnant women from March 4, 2009, to November 17, 2010, living in Greater Copenhagen area. 43 children were withdrawn before birth, leaving 584 children available for analysis. We previously reported no differences in baseline characteristics between the vitamin D vs. standard-dose group and showed increased maternal 25(OH)D levels at the end of supplementation period verifying adherence and effect of the intervention,[18] which is also showed for the characteristics for the children with DXA data at age 13 years (eTable 1). Further, there were no differences in baseline characteristics among children with available vs. no available DXA data at age 13 years (eTable 2). An overview of the flow of participants is illustrated in Fig. 1 where it is illustrated that 212 (71%) children of 297 randomized to high-dose vitamin D and 204 (71%) and 287 randomized to standard-dose had DXA scans performed at age 13 years.

Bone mineral content and density age 13 years

At age 13 years, 416 children (71%) had a whole-body DXA scan with 219 (53%) boys and 197 (47%) girls. Comparing children in the high-dose vitamin D (n = 212) vs. standard-dose (n = 204) group, there were no differences in the overall population on any of the bone mineral outcomes i.e., total body less head BMC and BMD or total body BMC and BMD (Table 1) and with no proportional increases (Fig. 2). All analyses were adjusted for age, sex, height, weight, scanner type and fish oil intervention, similar to our previously conducted study.[3] In sex stratified analyses, there were also no differences in bone outcomes between intervention groups (Table 1), and when stratified by maternal week 24 pre-interventional 25(OH)D levels or the mothers' allocation to the fish oil RCT, we did not see any differences between intervention groups either (Table 2). There were no interactions between these variables and the vitamin D intervention as well (all $p_{interactions} > 0.05$). Additionally, when adjusting for Tanner Stages reflecting puberty the results were unchanged. When analyzing the effect in stratified analysis for each scanner type there were no effect on total body BMC (33.5 (–10.5:77.4), p = 0.14) or total body BMD (0.013 (–0.004:0.030), p = 0.14) for the Hologic scans (n = 250) or total body BMC (–26.9 (–80.2:26.3), p = 0.32) or total body BMD (–0.019 (–0.042:0.005, p = 0.11)) for Lunar iDXA scans (n = 166).

We previously demonstrated for age 3 and 6 years DXA scans that the largest vitamin D effects were on

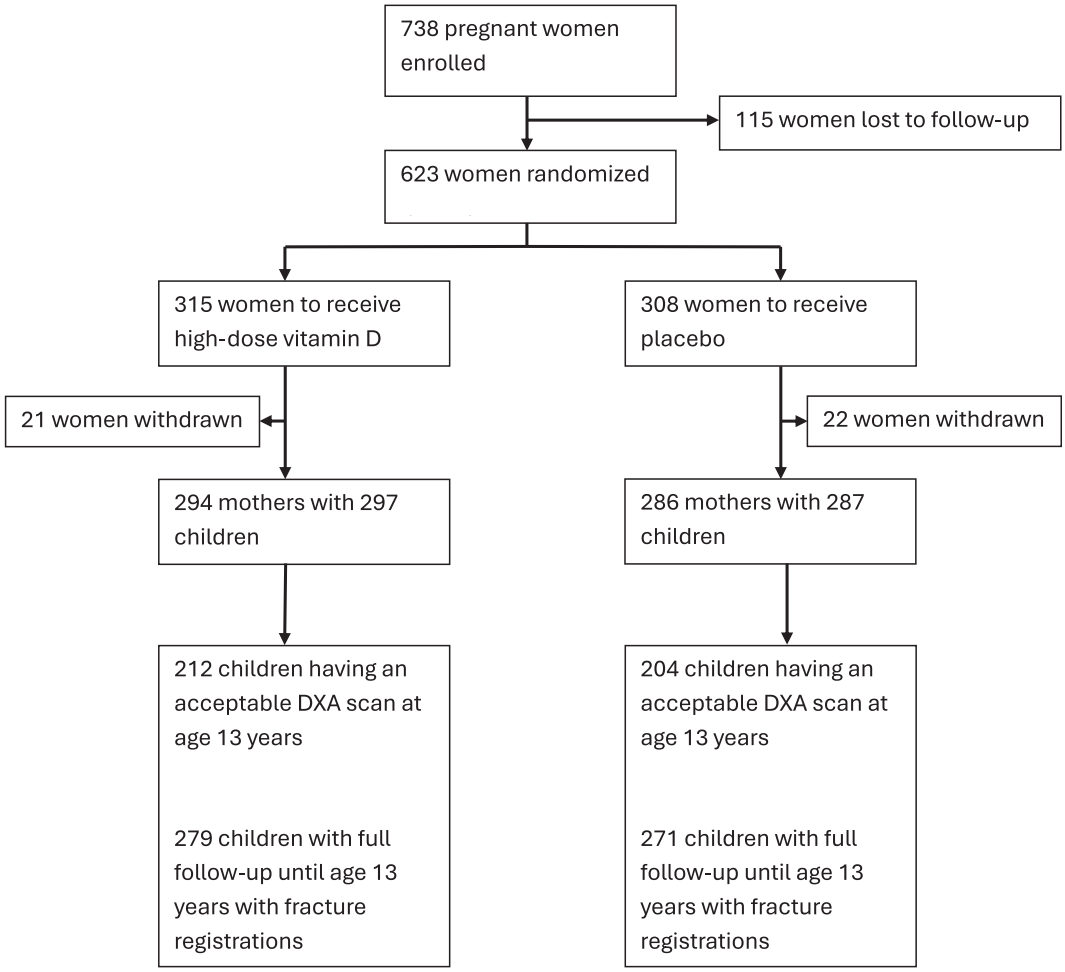

Fig. 1: Flowchart of the participants in the vitamin D RCT.

bone mineral in children born during dark months i.e., winter season or during a low 25OHD level season (November 8 to May 7) based on maternal 25OHD levels,[3] but in stratified analyses there were no effect among these children as well for the 13 year DXA outcomes (eTable 3). Additionally, there were no differences in any of the regular birth seasons i.e., winter, spring, fall or summer as demonstrated in Fig. 3.

In an exploratory post-hoc analysis, we included information on child 25(OH)D levels at age 6 months as we previously demonstrated a combined effect between the vitamin D intervention and 25(OH)D levels. Children whose mothers received high-dose vitamin D intervention and had sufficient (≥75 nmol/l) 25(OH)D levels at age 6 months (VitaminD&Sufficient) vs. children whose mothers received placebo (standard-dose) and had insufficient (<75 nmol/l) 25(OH)D levels (Placebo&Insufficient) did not have any differences in bone mineral outcomes at age 13 years (eTable 4) in contrast to our previous findings for the age 3 and 6 years DXA outcomes.[5] However, we found that among the children receiving the vitamin D intervention and being sufficient vs. being insufficient at 6 months, had overall higher bone mineral outcomes (eTable 4) and there was evidence of interaction between the intervention and 6 months child vitamin D status: total body BMC $p_{interaction}$ = 0.002 and total body BMD $p_{interaction}$ = 0.07.

Longitudinal bone mineral content and density until age 13 years

As we previously demonstrated effect of prenatal high-dose vitamin D intervention of bone mineral outcomes at age 3 and 6 years,[3,5] we analyzed the longitudinal effects in a random-intercept mixed-effects model combining age 3, 6 and 13 years (n = 976). There were no differences in either total body BMC or BMD values: adjusted estimate (95% CI): 3.79 (–20.3; 27.9), p = 0.76 and 0.001 (–0.009; 0.010), p = 0.91. There was also no interaction between intervention and DXA age for total

Measurement	Overall population (n = 416)				Boys (n = 219)		Girls (n = 197)	
	High-dose vitamin D, mean (SD) (n = 212)	Standard-dose, mean (SD) (n = 204)	Adjusted estimate[a], mean difference (95% CI)	p-value	Adjusted estimate[b], mean difference (95% CI)	p-value	Adjusted estimate[b], mean difference (95% CI)	p-value
Total body BMC (g)	1868.7 (356.5)	1890.6 (385.5)	6.7 (−28.3:41.6)	0.71	11.6 (−36.4:59.6)	0.64	−7.8 (−58.5:43.0)	0.76
Total body BMD (g/cm^2)	0.97 (0.10)	0.98 (0.10)	−0.003 (−0.017:0.011)	0.68	−0.002 (−0.020:0.017)	0.85	−0.007 (−0.03:0.015)	0.51
Total body less head BMC (g)	1481.9 (319.8)	1505.5 (345.4)	0.21 (−29.5:30.0)	0.99	4.9 (−38.5:48.2)	0.83	−9.3 (−49.9:31.3)	0.65
Total body less head BMD (g/cm^2)	0.87 (0.09)	0.88 (0.10)	−0.006 (−0.019:0.008)	0.40	−0.003 (−0.022:0.016)	0.74	−0.010 (−0.029:0.01)	0.32

Prenatal high-dose vitamin D vsstandard-dose. [a]Adjusted for age, sex, height, weight, scanner type and fish oil supplementation. [b]Adjusted for age, height, weight, scanner type and fish oil supplementation.

Table 1: **DXA scan results at age 13 years in the COPSAC$_{2010}$ cohort.**

body BMD ($p_{interaction}$ = 0.21) or total body BMC ($p_{interaction}$ = 0.48).

Longitudinal fracture risk until age 13 years

Among the 550 children (94%) with full follow-up until age 13 years, 114 fractures were registered (vitamin D vs. standard-dose; 53 vs. 61) among 99 children having at least one fracture during this period. There was no effect of prenatal high-dose vitamin D vs. standard-dose in a time to first fracture analysis; hazard ratio (HR) (95% CI): 0.85 (0.57–1.25), p = 0.40 (Fig. 4) or incidence analysis; incidence rate ratio (IRR): 0.84 (0.57–1.24),

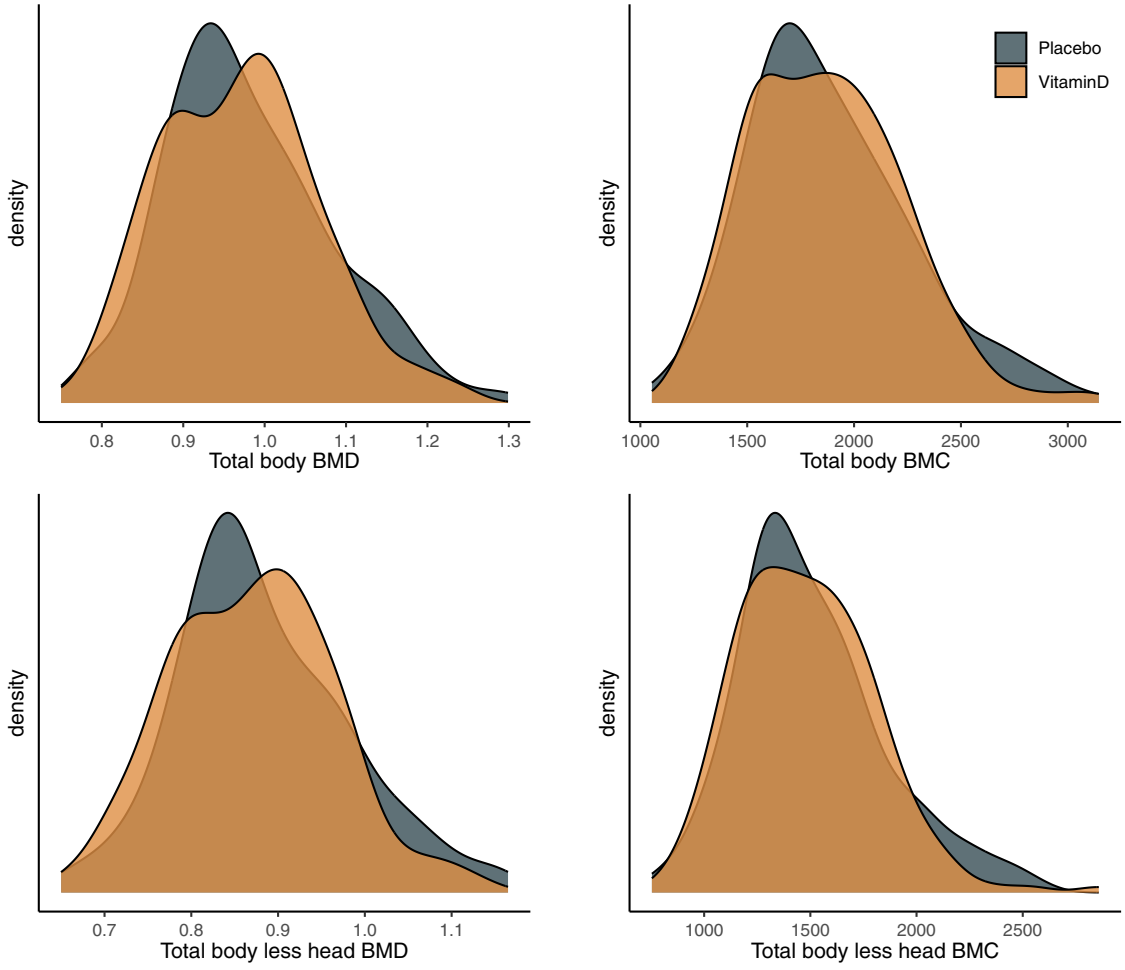

Fig. 2: Density plots of total body and total body less head bone mineral density (BMD) (g/cm^2) and bone mineral content (BMC) (g) of the 13-year DXA scans of children in the COPSAC$_{2010}$. Prenatal high-dose vitamin D vs. placebo (+standard-dose of vitamin D) group.

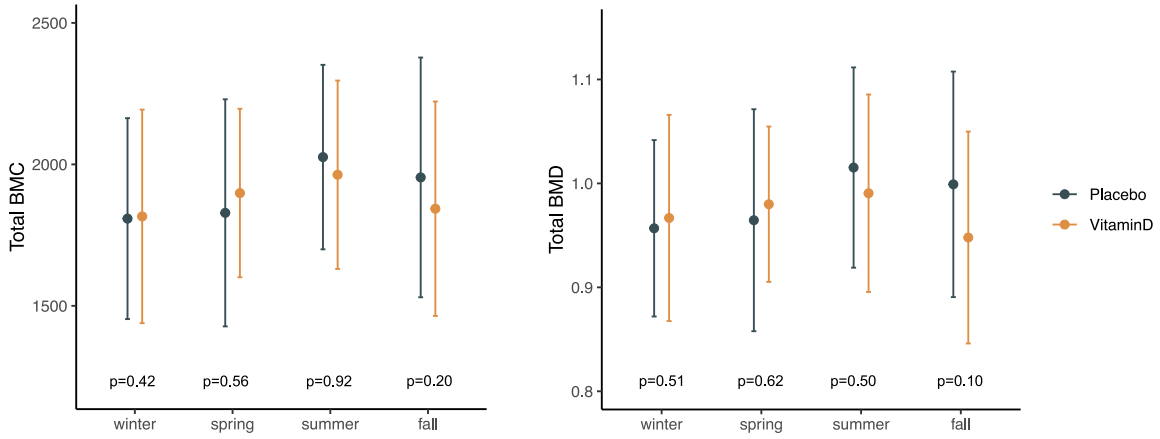

Fig. 3: Effect of high-dose vitamin D vs. placebo (+standard-dose of vitamin D) stratified by birth seasons for age 13-year DXA outcomes. Adjusted for age, sex, height, weight, scanner type and fish oil intervention and p-values from linear regression models.

p = 0.39. Adjusting for sex, season of birth, maternal pre-interventional 25(OH)D levels and the fish oil RCT did not change the results and there were no interactions between these factors and the vitamin D intervention (eTable 4). Analyzing the period between age 6–13 years there was also no effect of the supplementation.

VitaminD&Sufficient children (n = 167) had no reduced risk of time to first fracture (HR: 0.64 (0.36–1.16), p = 0.14) or a lower incidence age 0–13 years (IRR: 0.61 (0.35–1.08), p = 0.09) compared with children being in the Placebo&Insufficient group (n = 92) (eFig. 1). There was also no reduced risk comparing VitaminD&Sufficient vs. Standard-dose&-Sufficient (HR: 0.78 (0.46–1.33), p = 0.37) and comparing VitaminD&Sufficient vs. VitaminD&Insufficient (0.70 (0.39–1.25), p = 0.23) and no interaction between supplementation and child 6 months levels ($p_{interaction}$ = 0.61).

Finally, we found a borderline inverse association between number of fractures age 0–13 years and total body BMC values at age 13 years from DXA scans in a linear regression model adjusted for vitamin D and fish oil interventions, scanner type, age, sex, height and weight; adjusted estimate: (–36.9 (–73.9:0.18) p = 0.051). There was no association between number of fractures age 0–13 years and total body BMD values at age 13 years (–0.009 (–0.024:0.006), p = 0.23). Finally, when excluding children having a fracture between age 0–13 years, there was no effect of the vitamin D supplementation on bone outcomes at age 13 years when analyzing the subgroup of children not having a fracture (n = 339).

Discussion

In this Danish pregnancy vitamin D RCT of 623 women, we showed that prenatal supplementation with high-dose vitamin D of 2800 IU/day vs. standard-dose of 400 IU/day from pregnancy week 24 until 1 week after birth had no effect on bone mineral outcomes at age 13 years, which is in contrast to our previous findings with beneficial bone mineral effects at age 3 and 6 years, respectively. In addition, there was no

Measurement	Stratified by maternal pre-interventional 25(OH)D status				Stratified by maternal fish oil supplementation			
	Mothers being vitamin D sufficient (25OHD ≥ 75 nmol) (n = 218)		Mothers being vitamin D insufficient (25OHD <75 nmol/l) (n = 196)		Mothers receiving fish oil intervention (n = 205)		Mothers not receiving fish oil intervention (olive oil) (n = 211)	
	Adjusted estimate, mean difference (95% CI)	p-value	Adjusted estimate, mean difference (95% CI)	p-value	Adjusted estimate, mean difference (95% CI)	p-value	Adjusted estimate, mean difference (95% CI)	p-value
Total body BMC (g)	23.1 (–24.1:70.2)	0.34	–19.4 (–73.1:34.3)	0.48	7.7 (–45.7:61.0)	0.78	3.2 (–34.1:49.5)	0.89
Total body BMD (g/cm^2)	–0.003 (-0.02:0.016)	0.76	–0.005 (–0.027:0.017)	0.65	–0.01 (–0.030:0.011)	0.37	0.003 (–0.017:0.023)	0.76
Total body less head BMC (g)	14.2 (–25.8:54.2)	0.49	–24.3 (–69.8:21.3)	0.29	9.5 (–35.0:54.0)	0.67	–11.0 (–51.4:29.5)	0.59
Total body less head BMD (g/cm^2)	–0.006 (–0.024:0.012)	0.53	–0.008 (–0.029:0.012)	0.43	–0.008 (–0.027:0.011)	0.43	–0.004 (–0.023:0.015)	0.67

Prenatal high-dose vs. standard-dose vitamin D. Adjusted for age, sex, height, weight and scanner type. Also adjusted for fish oil supplementation.

Table 2: **DXA scan results at age 13 years stratified by maternal pre-interventional 25(OH)D levels and fish oil intervention.**

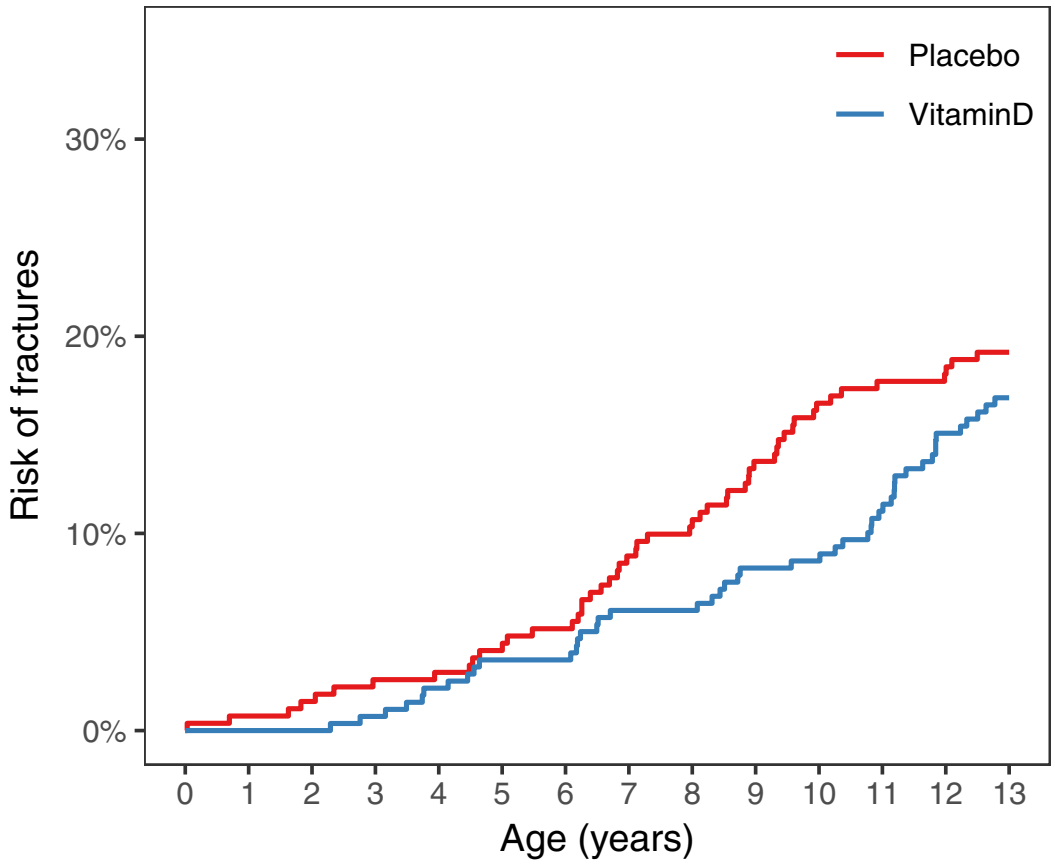

Fig. 4: Kaplan Meier curve illustrating the time to first fracture event between age 0–13 years in the COPSAC$_{2010}$ vitamin D RCT. Prenatal high-dose vitamin D vs. placebo (+standard-dose of vitamin D) group.

effect of the intervention on risk of developing fractures from birth until age 13 years in the offspring and no effects when combining with early serum vitamin D levels measured at age 6 months in the children.

The primary strength of the study is the randomized, double-blinded, placebo-controlled design with a predefined endpoint in BMC and BMD mitigating the risk of potential confounding in combination with a thorough longitudinal 13-year follow-up from birth and onwards with a 94% clinical follow-up of the children where we believe that the few children not having a follow-up are considered random and would not have a substantial impact on the general findings. In addition, we had a high follow-up rate of the children until age 13 years. The cohort is a population-based cohort aiming at representing the Danish background population, which may allow for generalization of our findings in a Danish context. The main limitation of our study is the relatively few fractures in the post hoc analysis and that we were potentially underpowered for showing effects on bone health in general as the study was powered for persistent wheeze/asthma. Another limitation is the number of DXA scans with 29% of the children not having a DXA scan performed at age 13 years. Another limitation is the exploratory post-hoc analysis of fractures introducing risk of potential bias and the fact that fracture risk among children is also correlated with physical activity and subsequent accidents not accounted for, however, our findings point towards an inverse association between number of fractures and BMC values at 13 years. Finally, the interpretation of bone density during adolescence particularly around time of peak height velocity can be challenging as areal BMD may decrease despite normal growth.

This is the first RCT to investigate long-term effects of prenatal high-dose vitamin D supplementation on offspring bone health. Previous observational studies have linked low measured maternal 25(OH)D levels with impaired offspring bone mineral until school age in 198 children recruited in the United Kingdom (UK)[1] and among 341 children until age 20 years, i.e., around peak bone mass, in the Australian Raine cohort assessed by DXA scans.[2] On the contrary, another UK study of the ALSPAC cohort did not show this

association among 3960 mothers with measurements of 25(OH)D in pregnancy and DXA scans performed at age 10 years.[19] These findings emphasized the need for RCTs eliminating the risk of potential confounding such as lifestyle related factors that may influence the relationship. To our knowledge, only one other previous RCT has been conducted investigating the effect of daily supplementation of high-dose vitamin D during pregnancy on offspring bone mineral content, but with a reported follow-up only until age 6 years and with a lower supplementation dose of 1000 IU/day, although, they still showed effect resulting in higher offspring BMD and BMC values among children whose mothers received supplementation compared with placebo.[20] However, they did not report on the potential effect on fracture risk reduction, hence, we are the first study to investigate this in combination with a long-term DXA scan follow-up until age 13 years.

We investigated both the prenatal intervention effects alone and in combination with early vitamin D measurements in the children, as both prenatal and early postnatal life seem to be crucial for optimal bone health in childhood, which is supposed to track throughout life.[7] A mathematical analysis has predicted that a 10% increase in peak bone mass around age 20 years could delay the osteoporosis risk later in adulthood by 13 years also pointing at peak bone mass as the most important factor for prevention of osteoporosis compared with age at menopause and non-menopausal bone loss,[9] which is supported by views from the National Osteoporosis Foundation.[21] This emphasizes the importance of interventions early in life trying to reduce later disease risk. Interestingly, we showed that among children receiving the high-dose vitamin D supplementation in pregnancy, those who also had sufficient levels at 6 months had overall higher bone mineral content and found evidence of interaction between the supplementation and vitamin D status suggesting early life vitamin D levels to be of importance for the intervention effect.

We and others previously suggested that optimizing vitamin D supplies in early life could be a safe and cost-effective approach against bone loss and risk of developing osteoporosis later in life.[5,22] However, our findings from this 13-year follow-up study are suggesting that the early effects of vitamin D on bone health as we previously observed is a transient phenomenon with no lasting effects into adolescence and ultimately adulthood. The MAVIDOS results have not yet been published later than for age 6–7 years,[23] showing effects from prenatal vitamin D supplementation similar to our results at age 6 years,[3] hence, it will be interesting to follow their trial to see whether the vitamin D effects attenuate similar to our study.

In sensitivity analyses, we investigated the potential targeted supplementation effect among specific groups of children as both we and the MAVIDOS RCT reported largest effects in children born during months with least sun exposure i.e., children in higher risk of having lower vitamin D levels at birth.[20] Similarly, we hypothesized that there might be sex-specific effects or specific effects in children from mothers having the lowest vitamin D levels before intervention. However, our study did not support such hypotheses. Neither did our findings point towards any effect modification from these factors.

In conclusion, our findings from this 13-year follow-up study of a pregnancy RCT with high-dose vitamin D intervention of 2800 IU/day vs. standard-dose of 400 IU/day did not show any effect from intervention on offspring bone mineral outcomes or fracture risk. This is the first pregnancy high-dose vitamin D RCT reporting on DXA scans after school-age with a 13-year follow-up adding valuable evidence to existing literature on this subject. In contrast to our previous findings that demonstrated effects on both age 3- and 6-years bone mineral status and a trend towards a longitudinally lower risk of fractures, these findings indicate a transient beneficial effect only observed in younger children with the effect not reaching into adolescence. The proposed hypothesis that prenatal vitamin D has the potential to change later peak bone mass around age 20 years and ultimately osteoporosis risk remains an important area of investigation for future research, although, our 13-year findings from this RCT do not support such a hypothesis.

Contributors

NB has written the first draft of the manuscript, performed all the statistical analyses and responsible for the decision to submit the manuscript. NB, PMG and CH have accessed and verified the data. Conceptualization: NB, BC; Data curation: NB, PMG, CH, TS, NV, SKJ, RV, KA; formal analysis: NB; funding acquisition: NB; Investigation; NB; Methodology: NB and BC; Project administration: NB; Supervision: NB, KB and BC; Visualisation: NB; Writing - original draft: NB; writing – review and editing: NB, TS, NV, SKJ, RV, KA, PMG, CH, KB and BC.

Data sharing statement

Data are available upon request to the corresponding author.

Declaration of interests

None.

Acknowledgements

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All authors declare no conflict of interest.

Ethics: The study was approved by the Danish Ethics Committee (H-B-2008-093) and the Danish Data Protection Agency (2015-41-3696). Both parents gave informed consent before enrollment.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2026.101870.

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