Early pregnancy vitamin D status is associated with blood pressure in children: an Odense Child Cohort study

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ABSTRACT

Background: Blood pressure in childhood tracks into later life. Vitamin D status in adults is associated with blood pressure, but the impact of vitamin D status in pregnancy and childhood on blood pressure still needs investigation.

Objective: We investigated whether fetal rather than current vitamin D status is associated with blood pressure in children.

Methods: In a prospective observational study within the population-based Odense Child Cohort (OCC), we examined serum 25-hydroxyvitamin D_{2+3} [s-25(OH)D] in early and late pregnancy, cord blood, and at 5 y age, and the associations with systolic and diastolic blood pressure (SBP/DBP) in the 5-y-old children (n = 1,677). Multiple regression models were adjusted for maternal country of origin, parity, smoking during pregnancy, 5-y height, and weight. Two-stage mixed effect modeling was performed, integrating all s-25(OH)D data from pregnancy and cord blood.

Results: The median (IQR) s-25(OH)D in early pregnancy, late pregnancy, the umbilical cord, and at 5 y was 65.5 (50.7–78.5), 78.5 (60.3– 95.8), 45.4 (31.1– 60.7), and 71.9 (54.6– 86.5) nmol/L, respectively. The mean ±SD 5-y SBP/DBP was 101.0/63.8 (7.1/5.9) mmHg. In adjusted analyses, a 10 nmol/L increase of s-25(OH)D in early pregnancy associated with a 0.3/0.2 mmHg lower SBP/DBP at 5 y ($P < 0.05$). Optimal s-25(OH)D (>75 nmol/L) in early pregnancy was associated with lower 5-y SBP and DBP, β (95% CI) −1.45 (−2.6, −0.3), and −0.97 (−1.9, −0.1), compared with reference s-25(OH)D (50-74.9 nmol/L). Two-stage analysis combining early pregnancy, late pregnancy, and cord s-25(OH)D data showed an inverse association with 5-y SBP and DBP for boys ($P < 0.025$) with significant sex-difference for DBP ($P_{interaction} = 0.004$). No associations were found between s-25(OH)D and 5-y BP above the 90th percentile.

Conclusion: Early pregnancy s-25(OH)D concentrations, especially >75 nmol/L, were inversely associated with 5-y blood pressure in the offspring. A novel identified protective effect of optimal vitamin D levels in early pregnancy on offspring BP is suggested. *Am J Clin Nutr* 2022;116:470–481.

Keywords: vitamin D status, 25(OH)D, pregnancy, fetal programming, children, blood pressure, cardio-metabolic health, cohort

Introduction

High blood pressure (BP) is the most important modifiable risk factor for cardiovascular events and overall disease burden in adults (1). Much interest has been given to vitamin D supplementation as a potential prevention measure against high BP or hypertension. Recent systematic reviews with meta-analysis of randomized controlled trials (RCTs) do not, however, support an effect of supplementation with vitamin D alone (2, 3) or calcium and vitamin D combined (4), on systolic BP (SBP) or diastolic BP (DBP). One exception was seen for individuals with pre-existing cardiovascular disease, who had a 1.31 mmHg reduced DBP after vitamin D supplementation (5).

On the other hand, baseline s-25-hydroxyvitamin D [s-25(OH)D] was inversely associated with risk of hypertension in recent meta-analyses of observational studies (3, 6), and

Supported by the AP Møller foundation of medical research (jr.nr. 18-L0294) and Beckett-Fonden (jr.nr. 18-2-1818). Both applications done by JNP. These funds had no influence on the design, implementation, analysis, or interpretation of the study.

Supplementary Figures 1 and 2 and Supplementary Tables 1–8 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.

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Abbreviations used: BP, blood pressure; DBP, diastolic blood pressure; lowess, locally weighted scatterplot smoothing; OCC, Odense Child Cohort; RCT, randomized controlled trials; SBP, systolic blood pressure; s-25(OH)D, S-25-hydroxyvitamin D.

Received December 2, 2021. Accepted for publication April 27, 2022.

First published online May 3, 2022; doi: https://doi.org/10.1093/ajcn/nqac118.

a Mendelian randomization study provided evidence for a protective effect of higher vitamin D status on SBP, DBP, and hypertension (7). Several biological mechanisms have been proposed for a protective effect of vitamin D on hypertension, which has been supported by animal studies (8).

Elevated BP in children is a strong predictor of hypertension later in life (9, 10). Although no effect of vitamin D supplementation on BP was seen in a meta-analysis of RCTs in children and adolescents (11), higher vitamin D status is associated with lower BP in children in several observational studies (12–16). Furthermore, an association between vitamin D status [s-25(OH)D] in pregnancy or cord blood and offspring BP has been suggested in some (17–21), but not all studies (22, 23).

Increased BP and hypertension in adulthood may already be determined during the fetal period (24, 25). In humans, nephrogenesis begins in week 5 of pregnancy and impaired nephrogenesis results in reduced nephron numbers, which together with altered renin-angiotensin-aldosterone activity, glucocorticoid excess, altered tubular handling of sodium ions, and inappropriate activation of the endothelin system may lead to subsequent higher BP.

Vitamin D deficiency in pregnancy affects nephrons, glomeruli, renin, and endothelial relaxation, and increases SBP and DBP in animal studies (26–29). A specific vulnerable time window for hypovitaminosis D in the human fetus is not known, but early pregnancy may be the most vulnerable period for the impact of malnutrition on nephrogenesis in this period (30).

Hypovitaminosis D, defined as s-25(OH)D <50 nmol/L, is still very common in pregnant women especially at northern latitudes (31, 32), as also seen in our previous studies from the Odense Child Cohort (OCC) in Denmark, despite recommendations of vitamin D supplementation of 10 μg/d during pregnancy (33, 34). Previous association studies have not had the chance to investigate s-25(OH)D associations from several time points in early life in relation to BP.

In the present study, we aimed to investigate whether s-25(OH)D concentrations in early and late pregnancy, in cord blood, and at 5 y of age were associated with BP in 5-y-old children, hypothesizing early pregnancy to be the most vulnerable exposure time.

Subjects and methods

Design and study population

The study was a part of the OCC, an ongoing population-based prospective, observational mother–child cohort from early pregnancy onward. Newly pregnant women with residence in Odense, Denmark, were invited to participate between 1 January 2010 and 31 December 2012. The cohort included 2,875 pregnant women. A detailed description of the OCC has been given elsewhere (35).

In the present study, exclusion criteria were miscarriage, stillbirth, migration from the study region, and chronic diseases with risk of hypo- or hypertension (e.g., major congenital heart disease or chronic renal insufficiency). Furthermore, only singletons with information on BP at the age of 5 y and s-25(OH)D determined at either one, some, or all the time points: early and late pregnancy, in cord blood, and at 5 y, were included (**Figure 1**).

To best reflect a general population, mothers with preeclampsia ($n = 114$) or gestational hypertension ($n = 67$) were not excluded. Likewise, we included 64 preterm infants (GA median: 35 wk 5 d; range: 27 wk 1 d to 36 wk 6 d) and 14 term neonates with low birth weight (mean: 2,334 g; range: 1,800–2,495 g).

Vitamin D status

The vitamin D status was based on s-25(OH) D concentrations, considered to be the best marker of vitamin D status (36), and analyzed using gold standard HPLC-MS, calibrated against National Institute of Standards and Technology standard 972 as previously described in detail (33). S-25(OH)D was given as the sum of s-25(OH) D_2 and s-25(OH) D_3.

Blood samples were drawn during early pregnancy, median (IQR) gestational age 12.1 (10–15) wk; late pregnancy, 29 (28–30) wk, from the umbilical cord; and at child age 5.0 (5.0–5.1) y.

Blood pressure measurements

At the child's 5-y visit, SBP and DBP were measured with Welch Allyn vital signs on the left arm twice with cuffs of appropriate sizes and with the child in a sitting position and the arm resting down the side, with a 1-min rest before the measurement (37). All measures were performed by trained professionals.

Covariates

Information about covariates was obtained through medical records, self-reported data, questionnaires, and physical examination of the children performed by OCC staff, blinded for s-25(OH)D, at 3 and 18 mo, and 3 and 5 y. The Municipality of Odense provided information about the mothers' birth country and parental ethnicity (Danish/other Western or non-Western country of origin). Data on parity, maternal prepregnancy BMI, and smoking during pregnancy were retrieved from the journal report at the first antenatal visit. Maternal BP in the first, second, and third trimester of pregnancy was obtained as previously reported (38). Through questionnaires answered during pregnancy and 3 mo after birth, information was obtained about gestational weight gain, use of vitamin D supplement during pregnancy (<10 mg/daily or ≥10 mg/daily), maternal skin type on modified Fitzpatrick's Scale (I to VI) (39), sun exposure during pregnancy (never/rarely, sometimes, often, or most of the time), and parental education level (high school or less, high school 1–3 or ≥4 y). Parental-reported information about child vitamin D supplementation (μg/d) and duration of exclusive breastfeeding (wk) were collected in a later questionnaire, ∼18 mo after birth. Information about child skin type on the Fitzpatrick's scale was drawn from questionnaires completed by parents when their child was 3 y old.

The children's skin types were merged into 3 groups: I/II, III, and IV/V/VI, due to few participants in group I, V, and VI.

Information about the children, including sex and gestational age at birth (in days), was collected from medical files. Maternal

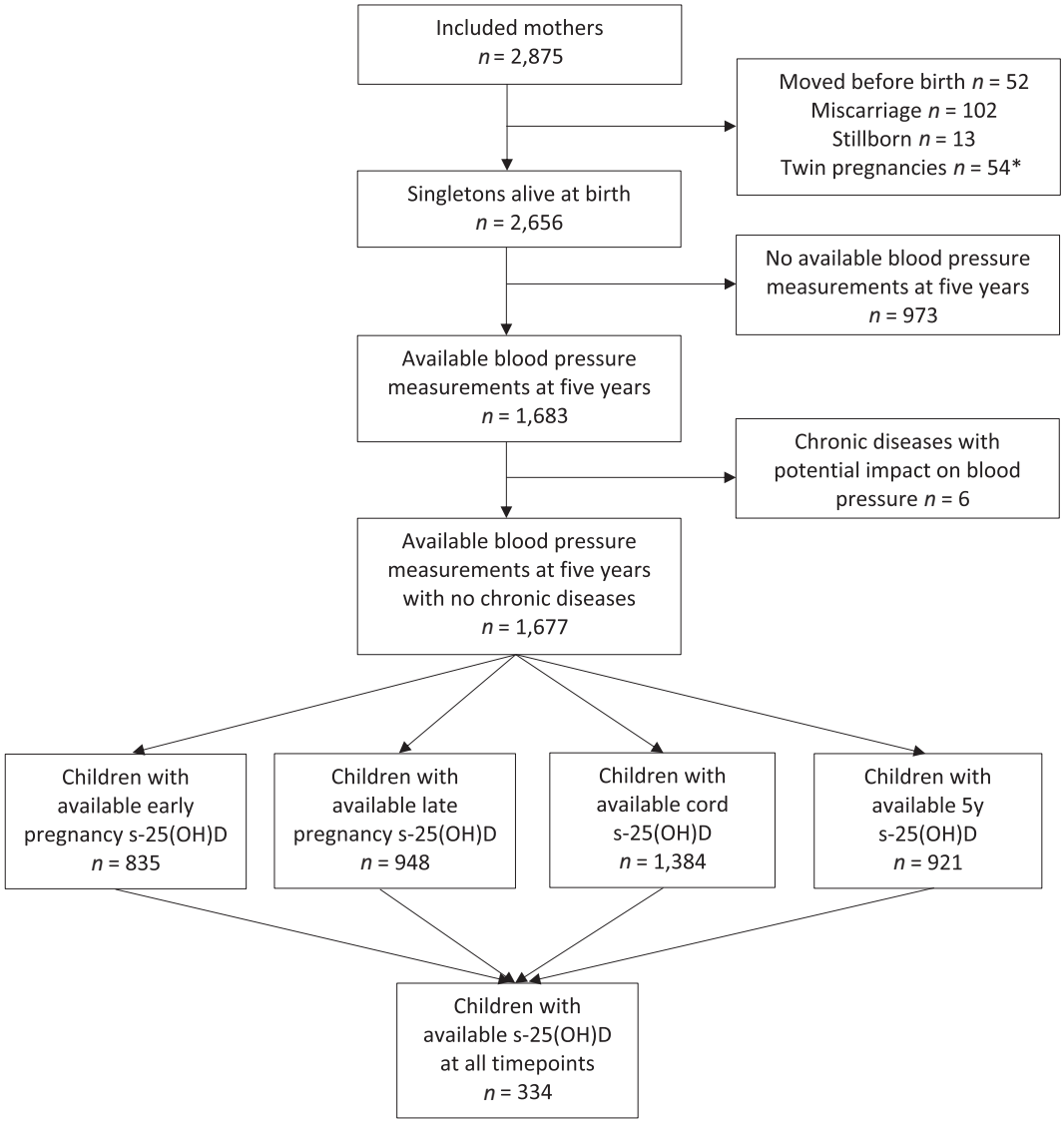

FIGURE 1 Participant inclusion flowchart. ∗Some participants were excluded due to >1 criterion. s-25(OH)D, serum 25-hydroxyvitamin D_2+D_3.

age was calculated at the time of birth. The time of blood sampling was categorized as high or low vitamin D season (May–October or November–April). At the 5-y examination, child height (to the nearest centimeter) was measured with a stadiometer and child weight (to the nearest 0.1 kg) without or with minimal clothing was measured by trained staff professionals at OCC on a digital weight scale.

Statistical analysis

Numerical data were presented as mean ± SD or median and IQR, where appropriate. BP was used as a continuous variable and was also dichotomized at the $\geq 90^{th}$ compared with the $<90^{th}$ percentile of our own data set. S-25(OH)D was used as a continuous variable and categorized according to quartiles and the routine cutoffs <25, 25–49.9, 50–74.9, and ≥75 nmol/L using the 1^{st} quartile and 50–74.9 nmol/L as references. Differences between participant characteristics in quartiles of early pregnancy s-25(OH)D were examined using an ANOVA or Kruskal–Wallis test for continuous variables and chi-square test for categorical variables. A Kruskal–Wallis test was also used to evaluate sex differences in s-25(OH)D.

Density plots with kernel distribution for s-25(OH)D at each time point and locally weighted scatterplot smoothing (lowess) for SBP/DBP compared with s-25(OH)D split by sex were performed for visual inspection. Univariate and multiple linear regression analyses were applied to test the associations between the measures of s-25(OH)D at the 4 different time points and 5-y BP. Moreover, the association of the s-25(OH)D samples at the 4 time points with BP $\geq 90^{th}$ percentile for the cohort was examined using multiple logistic regression models. The association between early pregnancy s-25(OH)D and 5-y SBP was chosen as the primary association and did not change throughout the course of the research.

Missing covariate data were handled by exclusion of the participants with missing data from the adjusted analysis.

Analyses were performed in the whole group as well as stratified by sex. Potential effect modification of sex on the association between vitamin D status and BP was examined by including an interaction term in the final adjusted models.

A two-stage model was applied to utilize all available s-25(OH)D data from early pregnancy and late pregnancy and cord blood in the analysis of a combined association to 5-y BP. The first stage applied a mixed effects linear regression adjusting for time point and with residual variance stratified by time point to determine each child individual overall level of s-25(OH)D as a random intercept. In a second stage, this determined level was applied as exposure in a linear regression with BP at 5 y as outcome adjusted for covariates. To consider the combined uncertainty in both steps, CIs and *P* values were determined by bootstrapping with 1,000 repetitions.

Analyses were conducted using Stata 15.0 software (StataCorp).

Model assumptions were checked by visual inspection of the distribution of the studentized residuals in a normal quantile-quantile plot. Furthermore, logistic regression models were tested by Pearson's goodness-of-fit test.

Two-sided *P* values <0.05 were considered statistically significant. No corrections for multiple testing were applied in the main analyses, as significant associations in the primary analysis (early pregnancy s-25(OH)D and 5-y BP) were supported by several similar findings. As a sensitivity analysis, however, we applied the Bonferroni adjusted *P* value <0.025 to correct for two outcomes (SBP and DBP).

Our study was a priori powered to detect a difference in SBP of 0.33 mmHg and DBP 0.27 mmHg for every 10 nmol/L difference in s-25(OH)D given $n = 800$, alfa = 0.05, beta = 0.20, early pregnancy s-25(OH)D ±SD 21.53 nmol/L, SBP ±SD = 7.10 mmHg, and DBP ±SD 5.81 mmHg.

Differences between participants and nonparticipants were assessed using Student's t-test or Mann-Whitney for continuous Gaussian or non-Gaussian data, respectively, and chi-square tests were applied for categorical variables. Nonparticipants were defined as included in OCC, but not participating in this study due to the exclusion criteria.

Analysis not prespecified were considered exploratory.

Ethics

The study was approved by the Regional Scientific Ethical Committee of Southern Denmark (no. S-20090130) and the Danish Data protection Board (application no. 13/14088). All women willing to participate gave informed written consent at enrollment. The study was carried out in accordance with the Helsinki Declaration II and reported according to STROBE guidelines for observational studies (40).

Results

Study population, exposure, and outcome

The present study included 1,677 mother-child pairs with data on 5-y BP and s-25(OH)D at any of the 4 time points. In early pregnancy, late pregnancy, cord blood, and at 5-y, hypovitaminosis D [s-25(OH)D <50 nmol/L] was found in 24.0%, 15.6%, 58.5%, and 19.7%, respectively. The medians [IQR] of s-25(OH)D at these time periods were 65.5 (50.7; 78.5), 78.5 (60.3; 95.8), 45.4 (31.1; 60.7) and 71.9 (54.6; 86.5) nmol/L, respectively. No sex difference in s-25(OH)D concentrations was found in pregnancy or cord samples, **Supplementary Figure 1**. At 5 y, boys had higher s-25(OH)D than girls, 74.2 (56.0; 88.1) nmol/L compared with 70.0 (53.4; 84.6) nmol/L, $P = 0.04$.

Compared with participants in this study, nonparticipant mothers within OCC were younger, darker skinned, and more likely to smoke during pregnancy and be of non-Western ethnicity. Nonparticipant children were more likely to be born earlier, have lower birthweight, not to be the first child, have darker skin, and be exclusively breastfeed for a shorter period (**Supplementary Table 1**).

Participant characteristics according to quartiles of early pregnancy s-25(OH)D are presented in **Table 1.** Mothers with s-25(OH)D in the 1st quartile (Q1; <50.7 nmol/L) had higher prepregnancy BMI, higher parity, less vitamin D supplementation during pregnancy, were more often of non-Western ethnicity, and were more likely to smoke during pregnancy compared with mothers with s-25(OH)D in higher quartiles. Early pregnancy blood sample season in May-October and lighter skin type of the child were significantly associated with higher quartiles of early pregnancy s-25(OH)D.

The mean ±SD of 5-y SBP/DBP was 101.0/63.8 (7.1/5.9) mmHg with no sex differences; boys 101.2/63.6 (7.1/5.7), girls 100.8/64.0 (7.2/6.0). Lowess smoothing plots for the unadjusted s-25(OH)D associations to 5-y SBP/DBP are given in **Supplementary Figure 2**.

Early pregnancy s-25(OH)D associations to blood pressure at 5 y

Early pregnancy s-25(OH)D showed inverse associations with 5-y SBP and DBP in the total cohort for all models, whether 25(OH)D was used as continuous or categorized by clinical cutoffs or quartiles (**Tables 2–4** and **Supplementary Tables 2–4**). Optimal s-25(OH)D (≥75 nmol/L) associated with 1.45 mmHg lower SBP ($P = 0.01$) and 0.97 mmHg lower DBP ($P = 0.04$) compared with reference s-25(OH)D (50-74.9 nmol/L). No associations were found between early pregnancy s-25(OH)D and offspring risk of increased BP (BP >90th percentile, **Supplementary Table 5**).

Applying Bonferroni correction for two outcomes, significant associations remained between continuous s-25(OH)D and SBP in the total cohort, and between s-25(OH)D >75 nmol/L and SBP in the total cohort and in girls ($P < 0.025$ for all). Tests for sex differences were not statistically significant (SBP; $P = 0.445$, DBP $P = 0.857$).

Late pregnancy and cord s-25(OH)D associations to blood pressure at 5 y

In the adjusted analysis, late pregnancy s-25(OH)D <25 nmol/L associated inversely with DBP in boys. Test for sex differences were not statistically significant (SBP; $P = 0.163$, DBP; $P = 0.056$). No other associations were found between late pregnancy s-25(OH)D and 5-y BP.

In cord blood, s-25(OH)D <50 nmol/L compared with reference (50-74.9 nmol/L) nmol/L associated to higher DBP

TABLE 1 Selected population characteristics by quartiles of early pregnancy s-25(OH)D[1]

		All quartiles of s-25(OH)D in early pregnancy, nmol/L					
	n	≥50.7	<50.7	50.7–65.5	>65.6 to 78.5	>78.5	*P* value
Maternal characteristics							
Age, y	835	30.3 (± 4.4)	30.7 (± 4.6)	30.6 (± 4.3)	30.1 (± 4.4)	29.8 (± 4.5)	0.125
Pregestational BMI	835	23.6 [21.5; 26.2]	24.5 [22.2; 27.5]	23.7 [21.7; 25.9]	23.4 [21.4; 26.0]	22.8 [21.2; 25.5]	<0.001
Smoking[2], *n* (%)	835	36 (4.3)	15 (7.2)	6 (2.9)	4 (1.9)	11 (5.3)	0.035
Alcohol consumption[2], *n* (%)	626	47 (7.5)	12 (8.3)	12 (7.6)	11 (6.9)	12 (7.3)	0.974
Education level	823						0.531
Low, *n* (%)		233 (28.3)	57 (27.8)	50 (24.3)	64 (31.2)	62 (30.0)	
Intermediate, *n* (%)		409 (49.7)	107 (52.2)	102 (49.5)	98 (47.8)	102 (49.3)	
High, *n* (%)		181 (22.0)	41 (20.0)	54 (26.2)	43 (21.0)	43 (20.8)	
Ethnicity	835						<0.001
Danish/Western, *n* (%)		807 (96.7)	192 (91.9)	206 (98.6)	201 (96.2)	208 (100.0)	
Non-Western country, *n* (%)		28 (3.4)	17 (8.1)	3 (1.4)	8 (3.8)	0 (0.0)	
Maternal skin type (Fitzpatrick)	632						0.328
I/II, *n* (%)		122 (19.3)	33 (22.5)	24 (15.2)	27 (16.8)	38 (22.9)	
III, *n* (%)		387 (61.2)	88 (59.9)	93 (58.9)	107 (66.5)	99 (59.7)	
IV, *n* (%)		117 (18.5)	25 (17.0)	38 (24.1)	26 (16.2)	28 (16.9)	
V/VI, *n* (%)		6 (1.0)	1 (0.7)	3 (1.9)	1 (0.6)	1 (0.6)	
Parity	835						<0.001
1, *n* (%)		473 (56.7)	88 (42.1)	129 (61.7)	125 (59.8)	131 (56.7)	
≥2, *n* (%)		362 (43.4)	121 (57.9)	80 (38.3)	84 (40.2)	77 (37.0)	
Vitamin D tablets[3], *n* (%)	522	461 (88.3)	92 (83.6)	111 (84.7)	127 (90.1)	131 (93.6)	0.043
Sun exposure[2]	634						0.455
Never/rarely, *n* (%)		10 (1.6)	1 (0.7)	4 (2.5)	3 (1.9)	2 (1.2)	
Sometimes, *n* (%)		135 (21.3)	37 (25.2)	30 (18.9)	40 (24.7)	28 (16.9)	
Often, *n* (%)		386 (60.9)	83 (56.5)	104 (65.4)	92 (56.8)	107 (64.5)	
Most of the time, *n* (%)		103 (16.3)	26 (17.7)	21 (13.2)	27 (16.7)	29 (17.5)	
Child characteristics							
Skin type (Fitzpatrick)	688						0.012
I/II, *n* (%)		361 (52.5)	84 (45.9)	94 (55.6)	98 (55.1)	85 (53.8)	
III, *n* (%)		303 (44.0)	85 (46.5)	74 (43.8)	75 (42.1)	69 (43.7)	
IV/V/VI, *n* (%)		24 (3.5)	14 (7.7)	1 (0.6)	5 (2.8)	4 (2.5)	
Age in y at examination	834	5.01 [5.0; 5.1]	5.01 [5.0; 5.0]	5.02 [5.0; 5.1]	5.02 [5.0; 5.1]	5.01 [5.0; 5.1]	0.031
Early pregnancy blood sample, May–Oct, *n* (%)	835	396 (47.4)	74 (36.6)	101 (46.3)	108 (49.1)	113 (58.0)	<0.001
Height at 5 y,cm	834	112.3 [109.2; 115.1]	112.5 [109.7; 114.9]	112.4 [109.1; 115.3]	111.8 [108.8; 115.2]	112.5 [109.3; 115.2]	0.681
Weight at 5 y, kg	819	19.1 [17.7; 20.6]	19.4 [18.2; 20.6]	18.9 [17.9; 20.5]	18.7 [17.4; 20.4]	19.1 [17.7; 20.8]	0.072
BMI at 5 y	819	15.2 [14.5; 15.9]	15.4 [14.7; 16.0]	15.1 [14.5; 15.8]	15.1 [14.4; 15.8]	15.1 [14.5; 15.9]	0.046
SPB at 5 y,mm Hg	835	100.9 (±7.3)	101.5 (±7.3)	101.4 (±7.9)	100.4 (±6.8)	101.4 (±7.1)	0.223
DBP at 5 y, mm Hg	835	63.6 (±5.8)	64.0 (±5.7)	63.9 (±5.5)	63.6 (±5.8)	63.1 (±6.1)	0.360
GA at birth, d	835	282 [275; 288]	282 [276; 287]	281 [274; 288]	281 [275; 287]	282 [275; 288]	0.850
Boys, *n* (%)	835	440 (52.7)	109 (52.2)	99 (47.4)	112 (53.6)	120 (57.7)	0.208
Vaginal birth, *n* (%)	835	684 (81.9)	166 (79.4)	173 (82.8)	170 (81.3)	175 (84.1)	0.633
Duration of exclusive breastfeeding,wk	743	8 [0; 17]	8 [0; 16]	10 [0; 18]	12 [0; 17]	8 [0; 16]	0.185
Paternal characteristics							
BMI	493	25.0 [23.0; 27.4]	25.3 [23.5; 28.3]	24.8 [23.0; 26.8]	25.3 [22.9; 27.4]	24.7 [22. 8;26.6]	0.349

[1]Values are presented as numbers [*n* or *n* (%)], mean ± SD, or median [IQR]. Sun exposure, education, and skin type were analyzed as categorical variables with reference to no sun exposure, low education, and Fitzpatrick I/II skin type. ANOVA or Kruskal–Wallis test used for continuous variables and chi-square test for categorical variables. DBP, diastolic blood pressure; GA, gestational age; SBP, systolic blood pressure; s-25(OH)D, serum 25-hydroxyvitamin D.

[2]During pregnancy.

[3]Vitamin D supplementation > 10 μg/d during pregnancy.

TABLE 2 Adjusted multiple linear regression of associations between 5-y SBP/DBP and continuous s-25(OH)D in pregnancy and cord blood[1]

	Association with s-25(OH)D concentration								
	Early pregnancy[2]			Late pregnancy[2]			Cord blood		
	n	*β* (95% CI)	*P* value	*n*	*β* (95% CI)	*P* value	*n*	*β* (95% CI)	*P* value
All									
SBP	819	−0.03 (−0.05, −0.01)	0.015	927	−0.01 (−0.02, 0.01)	0.486	1351	−0.00 (−0.02, 0.01)	0.686
DBP	819	−0.02 (−0.04, −0.00)	0.048	927	−0.00 (−0.02, 0.01)	0.894	1351	−0.00 (−0.02, 0.01)	0.568
Girls									
SBP	389	−0.04 (−0.08, −0.00)	0.044	443	0.01 (−0.02, 0.03)	0.602	638	0.01 (−0.02, 0.04)	0.460
DBP	389	−0.01 (−0.04, 0.02)	0.398	443	0.01 (−0.01, 0.03)	0.186	638	0.01 (−0.01, 0.03)	0.379
Boys									
SBP	430	−0.02 (−0.05, 0.01)	0.166	484	−0.02 (−0.04, 0.00)	0.097	713	−0.01 (−0.04, 0.01)	0.249
DBP	430	−0.02 (−0.05, 0.00)	0.083	484	−0.02 (−0.04, 0.00)	0.124	713	−0.02 (−0.04, 0.00)	0.084
Interaction, girls vs. boys									
SBP			0.445			0.163			0.905
DBP			0.857			0.056			0.892

[1] Values are results of multiple linear regression. All models adjusted for maternal ethnicity, smoking during pregnancy, height at 5 y, weight at 5 y, and parity. DBP, diastolic blood pressure; GA, gestational age; SBP, systolic blood pressure; vs., versus; s-25(OH)D, serum 25-hydroxyvitamin D.

[2] Early pregnancy, GA <140 d; late pregnancy, GA ≥140 d.

($P < 0.05$) in the total cohort. For boys, SBP were higher for cord s-25(OH)D <25 nmol/L compared with reference and DBP associated inversely with cord s-25(OH)D in test for trend and for <50 nmol/L compared with reference ($P < 0.05$ for all). However, the sex differences were not statistically significant (SBP; $P = 0.210$, DBP $P = 0.067$). No associations were found between cord s-25(OH)D and 5-y BP ≥90th percentile. No associations were observed in girls.

Two-stage analysis of overall association

The two-stage analysis combining early pregnancy, late pregnancy, and cord s-25(OH)D data showed an inverse association with both 5-y SBP and DBP for boys ($P < 0.025$), but not for girls or the total cohort (**Table 5**). Test for sex differences were statistically significant for DBP ($P = 0.004$), but not for SBP ($P = 0.092$).

Other analyses

No consistent associations were detected between 5-y s-25(OH)D and 5-y SBP/DBP (**Supplementary Tables 5–8**). In sensitivity analyses, quartiles defined for girls and boys separately did not change our results for any of the associations studied (data not shown).

Likewise, our primary association remained unchanged when *1*) excluding children born preterm, *2*) excluding mothers with preeclampsia or gestational hypertension, or *3*) adding maternal 1st trimester BP, or mean of 1st, 2nd, and 3rd trimester BP, as a covariate (data not shown).

Discussion

In our population-based cohort study, higher s-25(OH)D in early pregnancy was associated with lower child blood pressure at 5 y age. Split by routine cutoffs, s-25(OH)D >75 nmol/L associated with lower SBP and DBP. No associations with SBP or DBP >90th percentile or sex-specific associations were detected. For boys, inverse associations with blood pressure were found in the 2-stage model for overall pregnancy and cord vitamin D exposure.

Determinants of BP in childhood may include maternal factors already from early pregnancy. In a previous study, we identified positive associations between maternal first, second, and third trimester BP and offspring BP up to 5 y of age (38). In a large-scale genetic meta-analysis, BP in adults was linked to regions of active chromatin in fetal heart, muscle, kidney, and adrenal gland and lung tissues, suggesting a link between fetal development and later BP regulation (24).

Vitamin D plays an important role in the fetal development in many organs. In animal studies, vitamin D receptor gene deletion leads to activating of the renin-angiotensin system, hypertension, and target-organ damage (41) and similar effects are shown for 1α-hydroxylase gene knock out (42). Vitamin D deficiency during pregnancy increases the number of nephrons and glomeruli, but delay maturity of glomeruli in offspring (26, 27), and parental vitamin D depletion in rats leads to increased SBP and DBP with hypermethylation of the promotor region of the *Panx1* and impaired endothelial relaxation (28). Conversely,

TABLE 3 Adjusted associations between 5-y SBP/DBP and quartiles of s-25(OH)D in pregnancy and cord blood[1]

	Association with s-25(OH)D concentration								
	Early pregnancy			Late pregnancy			Cord blood		
All participants	*n*	β (95% CI)	*P* value	*n*	β (95% CI)	*P* value	*n*	β (95% CI)	*P* value
SBP	819			927			1,351		
Q1	203	Reference		229	Reference		321	Reference	
Q2	207	0.08 (−1.3, 1.5)	0.913	232	0.34 (−0.9, 1.6)	0.606	346	−0.49 (−1.6, 0.6)	0.365
Q3	205	−0.82 (−2.2, 0.6)	0.248	234	−0.05 (−1.3, 1.2)	0.943	342	−0.43 (−1.5, 0.6)	0.432
Q4	204	−1.22 (−2.6, 0.2)	0.090	232	−0.30 (−1.6, 1.0)	0.650	342	−0.28 (−1.4, 0.8)	0.604
Trend	819	−0.46 (−0.9, −0.0)	0.040	927	−0.13(−0.5, 0.3)	0.532	1351	−0.07 (−0.4, 0.3)	0.674
DBP	819			927			1,351		
Q1	203	Reference		229	Reference		321	Reference	
Q2	207	0.08 (−1.0, 1.2)	0.888	232	0.06 (−1.0, 1.1)	0.908	346	−0.26 (−1.2, 0.6)	0.564
Q3	205	−0.19 (−1.3, 0.9)	0.741	234	0.41 (−0.7, 1.5)	0.452	342	−0.30 (−1.2, 0.6)	0.517
Q4	204	−0.90 (−2.0, 0.2)	0.120	232	−0.24 (−1.3, 0.8)	0.660	342	−0.40 (−1.3, 0.5)	0.376
Trend	819	−0.30 (−0.7, 0.1)	0.097	927	−0.04 (−0.4, 0.3)	0.822	1,351	−0.12 (−0.4, 0.2)	0.393
Girls[2]									
SBP	389			443			638		
Q1	96	Reference		115	Reference		148	Reference	
Q2	110	−0.21 (−2.2, 1.8)	0.836	111	0.75 (−1.1, 2.6)	0.428	152	−0.44 (−2.0, 1.2)	0.595
Q3	95	−0.69 (−2.8, 1.4)	0.518	100	0.31 (−1.6, 2.2)	0.751	166	−0.22 (−1.8, 1.4)	0.782
Q4	88	−1.70 (−3.9, 0.5)	0.123	117	0.41 (−1.5, 2.3)	0.664	172	0.04 (−1.5, 1.7)	0.960
Trend	389	−0.56 (−1.2, 0.1)	0.104	443	0.08 (−0.5, 0.7)	0.790	638	0.04 (−0.5, 0.5)	0.863
DBP	389			443			638		
Q1	96	Reference		115	Reference		148	Reference	
Q2	110	−0.22 (−1.9,1.4)	0.796	111	0.42 (−1.1, 2.0)	0.596	152	−0.19 (−1.5, 1.2)	0.778
Q3	95	−0.47 (−2.2, 1.2)	0.584	100	1.35 (−0.3, 3.0)	0.099	166	−0.19 (−1.5, 1.1)	0.773
Q4	88	−0.32 (−2.1, 1.4)	0.723	117	0.64 (−0.9, 2.2)	0.420	172	0.20 (−1.1, 1.5)	0.765
Trend	389	−0.12 (−0.7, 0.4)	0.659	443	0.27 (−0.2, 0.8)	0.285	638	0.07 (−0.3, 0.5)	0.748
Boys[2]									
SBP	430			484			713		
Q1	107	Reference		114	Reference		173	Reference	
Q2	97	0.50 (−1.5, 2.5)	0.614	121	−0.09 (−1.8, 1.7)	0.922	194	−0.57 (−2.0, 0.9)	0.439
Q3	110	−0.86 (−2.8, 1.1)	0.382	134	−0.51 (−2.2, 1.2)	0.563	176	−0.56 (−2.0, 0.9)	0.450
Q4	116	−0.79 (−2.7, 1.1)	0.411	115	−1.08 (−2.9, 0.7)	0.239	170	−0.51 (−2.0, 1.0)	0.499
Trend	430	−0.38 (−1.0, 0.2)	0.217	484	−0.37 (−0.9, 0.2)	0.203	713	−0.15 (−0.6, 0.3)	0.529
DBP	430			484			713		
Q1	107	Reference		114	Reference		173	Reference	
Q2	97	0.44 (−1.1, 2.0)	0.583	121	−0.36 (−1.8, 1.1)	0.626	194	−0.34 (−1.5, 0.8)	0.570
Q3	110	0.11 (−1.4, 1.7)	0.889	134	−0.36 (−1.8, 1.1)	0.615	176	−0.38 (−1.6, 0.8)	0.537
Q4	116	−1.21 (−2.7, 0.3)	0.117	115	−1.10 (−2.6, 0.4)	0.146	170	−1.00 (−2.2, 0.2)	0.109
Trend	430	−0.42 (−0.9, 0.1)	0.086	484	−0.33 (−0.8, 0.1)	0.170	713	−0.30 (−0.7, 0.1)	0.123

[1]Values are results of multiple linear regression. All models adjusted for maternal ethnicity, smoking during pregnancy, height at 5 y, weight at 5 y, and parity. s-25(OH)D quartiles: early pregnancy: Q1, <50.7; Q2, 50.7–65.5; Q3, 65.6–78.5; and Q4, ≥78.5 nmol/L; late pregnancy: Q1, <60.3; Q2, 60.3–78.5; Q3, 78.6–95.8; and Q4, ≥95.8 nmol/L. DBP, diastolic blood pressure; GA, gestational age; Q, quartile; SBP, systolic blood pressure; vs., versus; s-25(OH)D, serum 25-hydroxyvitamin D.

[2]No interactions based on participant sex were found in any of the associations.

TABLE 4 Adjusted associations between 5-y SBP/DBP and clinical cutoffs for s-25(OH)D in pregnancy and cord blood[1]

	Association with s-25(OH)D concentration								
s-25(OH)D, nmol/L	Early pregnancy			Late pregnancy			Cord blood		
All participants	*n*	β (95% CI)	*P* value	*n*	β (95% CI)	*P* value	*n*	β (95% CI)	*P* value
SBP	819			927			1,351		
<25	17	1.08 (−2.4, 4.5)	0.538	13	1.03 (−2.8, 4.9)	0.603	216	1.04 (−0.1, 2.2)	0.077
25–49.9	177	−0.39 (−1.7, 0.9)	0.552	129	−0.42 (−1.9, 1.0)	0.571	571	0.60 (−0.3, 1.5)	0.182
0–49.9	194	−0.26 (−1.5, 1.0)	0.681	142	−0.29 (−1.7, 1.1)	0.686	423	0.71 (−0.1, 1.5)	0.090
50–74.9	358	Reference		266	Reference		141	Reference	
≥75	267	−1.45 (−2.6, −0.3)	0.011	519	−0.45 (−1.5, 0.6)	0.389	80	0.85 (−0.5, 2.2)	0.210
Trend[2]	819	−0.65 (−01.3, −0.0)	0.043	927	−0.18 (−0.8, 0.4)	0.552	1,351	−0.22 (−0.7, 0.2)	0.305
DBP	819			927			1,351		
<25	17	−0.72 (−3.5, 2.1)	0.611	13	0.82 (−2.4, 4.0)	0.616	216	0.70 (−0.3, 1.7)	0.152
25–49.9	177	−0.11 (−1.2, 0.9)	0.836	129	−0.52 (−1.7, 0.7)	0.405	571	0.77 (0.0, 1.5)	0.039
0–49.9	194	−0.16 (−1.2, 0.9)	0.752	142	−0.39 (−1.6, 0.8)	0.511	423	0.75 (0.1, 1.4)	0.032
50–74.9	358	Reference		266	Reference		141	Reference	
≥75	267	−0.97 (−1.9, −0.1)	0.037	519	−0.14 (−1.0, 0.7)	0.750	80	0.63 (−0.5, 1.7)	0.262
Trend[2]	819	−0.39 (−0.9, 0.1)	0.135	927	0.04 (−0.4, 0.5)	0.871	1,351	−0.21 (−0.6, 0.1)	0.241
Girls									
SBP	389			443			638		
<25	6	0.35 (−5.5, 6.2)	0.908	7	−0.81 (−6.2, 4.6)	0.768	95	0.11 (−1.6, 1.8)	0.905
25–49.9	87	−0.45 (−2.3, 1.4)	0.639	60	−0.86 (−3.0, 1.3)	0.433	257	0.92 (−0.4, 2.2)	0.157
0–49.9	93	−0.40 (−2.2, 1.4)	0.671	67	−0.86 (−2.9, 1.2)	0.418	352	0.71 (−0.5, 1.9)	0.245
50–74.9	183	Reference		136	Reference		214	Reference	
≥75	113	−2.25 (−3.9, −0.5)	0.010	240	−0.08 (−1.6, 1.4)	0.922	72	1.29 (−0.6, 3.2)	0.175
Trend[2]	389	−0.95 (−1.9, 0.0)	0.056	443	0.28 (−0.6, 1.2)	0.533	638	0.07 (−0.6, 0.7)	0.826
DBP	389			443			638		
<25	6	−1.56 (−6.4, 3.2)	0.522	7	−2.58 (−7.0, 1.9)	0.258	95	0.03 (−1.4, 1.5)	0.971
25–49.9	87	0.08 (−01.5, 1.6)	0.917	60	−0.70 (−02.5, 1.1)	0.444	257	0.71 (−0.4, 1.8)	0.192
0–49.9	93	−0.03 (−1.5, 1.5)	0.972	67	−0.89 (−2.6, 0.8)	0.309	352	0.54 (−0.5, 1.5)	0.296
50–74.9	183	Reference		136	Reference		214	Reference	
≥75	113	−0.72 (−2.1, 0.7)	0.308	240	0.59 (−0.7, 1.8)	0.355	72	1.06 (−0.5, 2.6)	0.185
Trend[2]	389	−0.30 (−1.1, 0.5)	0.459	443	0.71 (−0.0, 1.4)	0.053	638	0.08 (−0.4, 0.6)	0.756
Boys									
SBP	430			484			713		
<25	11	1.18 (−3.1, 5.5)	0.591	6	4.47 (1.2, 10.1)	0.120	121	1.66 (0.1, 3.2)	0.037
25–49.9	90	−0.46 (−2.3, 1.4)	0.621	69	−0.12 (−2.1, 1.9)	0.903	314	0.22 (−1.0, 1.4)	0.723
0–49.9	101	−0.29 (−2.0, 1.5)	0.748	75	0.23 (01.7, 2.2)	0.817	435	0.62 (−0.5, 1.8)	0.291
50–74.9	175	Reference		130	Reference		209	Reference	
≥75	154	−0.95 (−2.5, 0.6)	0.218	279	−0.87 (−2.3, 0.5)	0.228	69	0.40 (−1.5, 2.3)	0.679
Trend[2]	430	−0.41 (−1.2, 0.4)	0.333	484	−0.67 (−1.5, 0.1)	0.102	713	−0.45 (−1.0, 0.1)	0.137

(*Continued*)

TABLE 4 (*Continued*)

s-25(OH)D, nmol/L	Association with s-25(OH)D concentration								
	Early pregnancy			Late pregnancy			Cord blood		
All participants	*n*	*β* (95% CI)	*P* value	*n*	*β* (95% CI)	*P* value	*n*	*β* (95% CI)	*P* value
DBP	430			484			713		
<25	11	−0.31 (−3.8, 3.1)	0.859	6	5.53 (0.9, 10.2)	0.020	121	1.29 (−0.0, 2.6)	0.051
25–49.9	90	−0.39 (−1.9, 1.1)	0.603	69	−0.32 (−2.0, 1.3)	0.698	314	0.85 (−0.2, 1.9)	0.100
0–49.9	101	−0.38 (−1.8, 1.0)	0.598	75	0.13 (−1.5, 1.7)	0.879	435	0.97 (0.0, 1.9)	0.046
50–74.9	175	Reference		130	Reference		209	Reference	
≥75	154	−1.15 (−2.4, 0.1)	0.063	279	−0.70 (−1.9, 0.5)	0.240	69	0.17 (−1.4, 1.7)	0.836
Trend[2]	430	−0.42 (−1.1, 0.3)	0.219	484	−0.55 (−1.2, 0.1)	0.102	713	−0.51 (−1.0, −0.0)	0.043
Interaction, girls vs. boys									
SBP	819		0.776	927		0.200	1,351		0.081
DBP	819		0.697	927		0.012	1,351		0.426

[1]Values are results of multiple linear regression. All models adjusted for maternal ethnicity, smoking during pregnancy, height at 5 y, weight at 5 y, and parity. s-25(OH)D concentration quartiles: cord blood: Q1, <31.1; Q2, 31.1–45; Q3, 45.5–60.7, Q4, ≥60.7 nmol/L; early pregnancy: Q1, <50.7; Q2, 50.7–65.5; Q3, 65.6–78.5; Q4, ≥78.5 nmol/L; late pregnancy: Q1, <60.3; Q2, 60.3–78.5; Q3, 78.6–95.8; Q4, ≥95.8 nmol/L. DBP, diastolic blood pressure; Q, quartile; SBP, systolic blood pressure; vs., versus; s-25(OH)D, serum 25-hydroxyvitamin D.

[2]The test for trend is done for <25 nmol/L, 25–49.9 nmol/L, 50–74.9 nmol/L and ≥75 nmol/L.

calcitriol [1,25$(OH)_2D_3$] lowers renin expression through actions on the renin gene promoter (29).

No large RCTs have addressed the possible effect of vitamin D supplementation in pregnancy on offspring BP. However, in a small RCT (n = 52), BP was similar in the 12- to 16-mo-old offspring between groups with vitamin D supplementation or placebo in pregnancy (43).

Inverse associations between pregnancy or cord s-25(OH)D and offspring BP have been found in some (17–21), but not all (22, 23) observational studies. Of note, the large observational Dutch study by Miliku et al. (22), which did not find associations between s-25(OH)D in mid-gestation pregnancy and 6y BP in the offspring, adjusted for multivitamin supplementation and calcium intake in pregnancy, unlike our and other studies. As vitamin D supplementation is a major determinant for s-25(OH)D concentrations in pregnancy [Table 1 and previously shown (34)], adjusting for multivitamin supplementation may have masked a true association in the Dutch study.

We had the opportunity to explore 3 exposure times in early life and identified early pregnancy as the exposure time with most significant associations. In late pregnancy and cord blood, weaker associations were still present for boys and the 2-stage model for the combined exposure of early pregnancy, late pregnancy, and cord 25(OH)D were highly significant in boys, in keeping with the findings of males being more susceptible to developmental insults in early life with regard to cardiovascular health (44, 45).

Large-scale twin studies would be optimal to further address this sex difference.

We identified an inverse association between optimal vitamin D status in early pregnancy (s-25(OH)D ≥75 nmol/L) and SBP and DBP in the 5-y-old offspring, whereas vitamin D deficiency (<25 nmol/L) was not associated with SBP or DBP. This may suggest a beneficial role of optimal vitamin D status in early pregnancy on offspring BP. In former studies, only low vitamin D status in pregnancy (20), or the continuous full scale of s-25(OH)D (17–19, 21), showed associations with offspring BP.

Our mean s-25(OH)D concentrations were relatively high in early and late pregnancy compared with most other (46, 47), but not all, studies (48). A generally high vitamin D status in a cohort may lead to failure to detect an association between low vitamin D status and higher offspring BP, especially in late pregnancy where s-25(OH)D reach the highest concentrations, compatible with an increasing adherence to vitamin D supplementation recommendations during pregnancy in our cohort (34, 49). On the other hand, the failure to detect associations between optimal vitamin D status and lower BP in late pregnancy or cord suggests a time window of a protective effect of optimal vitamin D status on offspring BP confined to early pregnancy.

The lack of association between 5-y s-25(OH)D and BP is in keeping with null effect of vitamin D supplementation in childhood on BP in RCTs (11). However, our cohort was not suitable for studying associations of very low s-25(OH)D concentrations, nor at 5 y.

We noted that the mean SBP/DBP of 101/64 in our cohort was high compared with the consensus guideline BP pediatric reference (50), but only slightly higher than the mean SBP/DBP of 100/63 at 3 y of age (21). These high values can partly be ascribed to the oscillometric method used in OCC, partly to a mean 5-y height in OCC comparable with the 75th percentile height in the consensus reference population (data not shown).

TABLE 5 Two-stage analysis, associations between 5-y SBP/DBP and vitamin D (early pregnancy, late pregnancy, and cord blood)[1]

	Association with 5-y SBP/DBP and vitamin D											
				Girls				Boys				
	n	β (95% CI)	*P* value	*n*	β (95% CI)	*P* value	*n*	β (95% CI)	*P* value	$P_{interaction}$ girls vs. boys
SBP	1351	−0.02 (−0.04, 0.00)	0.099	638	0.00 (−0.03, 0.04)	0.861	713	−0.04 (−0.07, −0.01)	0.021	0.092
DBP	1351	−0.02 (−0.04, 0.00)	0.100	638	0.01 (−0.02, 0.05)	0.393	713	−0.04 (−0.07, −0.02)	0.001	0.004

[1] Values are results of 2-stage analysis (multiple regression) adjusted for maternal ethnicity, smoking during pregnancy, height at 5 y, weight at 5 y, and parity. DBP, diastolic blood pressure; SBP, systolic blood pressure; vs., versus; s-25(OH)D, serum 25-hydroxyvitamin D.

These differences were not believed to bias the associations studied.

Strengths and limitations

Strengths of this study included the use of a large population-based birth cohort, the longitudinal s-25(OH)D sampling, the use of s-25(OH)D measured by gold standard method instead of questionnaire data on vitamin D supplementation, and child examination performed by trained staff blinded for s-25(OH)D. Limitations of the study included the observational nature of our study with the use of self-reported data in covariates and the potential for chance findings and residual confounding. Moreover, eligible pregnant women who did not participate in the OCC at all were more likely to have higher parity, to smoke during pregnancy, be of non-Western ethnicity, and have children with darker skin in a previously reported selection bias analysis (35).

In conclusion, early pregnancy s-25(OH)D was inversely associated to measures of SBP and DBP at 5 y with a novel identified inverse association between optimal vitamin D status [s-25(OH)D >75 nmol/L] and BP at 5 y. Mixed effect models for pregnancy and cord s-25(OH)D identified an inverse association in the male offspring only.

Our findings may encourage women to obtain optimal vitamin D status already before or within early pregnancy. Although the associations led to only small differences in SBP and DBP and no associations to BP >90th percentile, the results may have clinical importance given the strong evidence for higher BP tracking from childhood into adulthood (9, 51) with association to clinical hypertension (9, 52, 53) and metabolic syndrome (53).

In the policy making of public health recommendations on vitamin D supplementation in pregnancy, the potential small beneficial effect on offspring BP must, however, be balanced against the risk of vitamin D toxicity. Longer follow-ups into adolescence and adulthood and high-evidence data from well-designed RCTs should address the question of vitamin D supplementation earliest possible in pregnancy with respect to offspring BP along with other outcomes.

We acknowledge the research staff at the Hans Christian Andersen children's Hospital for their careful examinations of the study participants. We are grateful to the OCC participants for their use of time and engagement in the cohort.

The authors' responsibilities were as follows – JNP, CD, HTC: designed the study; JNP, AB, MSA: collected the data; JNP, SM, CD: analyzed data; JNP, CD, LBA, SM, HTC: wrote the paper; HTC: had primary responsibility for final content; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, code book, and analytic code will not be made available as they contain personal information on the participants.

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