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A compromised maternal vitamin D status is associated with congenital heart defects in offspring

M.P.H. Koster[a,1], L. van Duijn[a,1], Y.H.M. Krul-Poel[b], J.S. Laven[c], W.A. Helbing[d], S. Simsek[b], R.P.M. Steegers-Theunissen[a,e,*]

[a] Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine, Erasmus MC, University Medical Centre, PO Box 2040, 3000CA Rotterdam, The Netherlands
[b] Department of Internal Medicine, Medical Centre Alkmaar, PO Box 501, 1800AM Alkmaar, The Netherlands
[c] Department of Obstetrics and Gynaecology, Division of Reproductive Medicine, Erasmus MC, University Medical Centre, PO Box 2040, 3000CA Rotterdam, The Netherlands
[d] Department of Pediatrics, Division of Cardiology, Erasmus MC, University Medical Centre, PO Box 2040, 3000CA Rotterdam, The Netherlands
[e] Department of Pediatrics, Division of Neonatology, Erasmus MC, University Medical Centre, PO Box 2040, 3000CA Rotterdam, The Netherlands

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ABSTRACT

Background: Interactions between genetic and environmental factors, including modifiable maternal nutrition and lifestyle, play a significant role in the pathogenesis of most congenital heart defects (CHD). The aim of this study was to investigate associations between periconceptional maternal vitamin D status and the prevalence of CHD in offspring.

Methods: A case-control study was performed in 345 mothers of a child with CHD and 432 mothers of a child without CHD from four tertiary hospitals in the Netherlands between 2003 and 2005. Approximately 15 months after pregnancy mothers filled out questionnaires regarding general characteristics and periconceptional lifestyle. Maternal blood was obtained to determine serum 25-hydroxyvitamin D and lipid concentrations. The 25-hydroxyvitamin D concentration was stratified into a deficient < 50 nmol/l, moderate 50–75 nmol/l and adequate > 75 nmol/l status. Logistic regression was performed to study associations between vitamin D status and CHD risk, adjusted for maternal age, body mass index, ethnicity, smoking and total cholesterol concentration.

Results: Case mothers less often had an adequate vitamin D status compared with controls (27% vs. 38%; $p = 0.002$). The use of multivitamin supplements, ethnicity, season and body mass index were associated with vitamin D concentrations. A moderate (odds ratio 1.58, [95%CI 1.08, 2.32]) and deficient (odds ratio 2.15, [95%CI 1.44–3.19]) vitamin D status were associated with CHD in offspring.

Conclusion: A compromised maternal vitamin D status is associated with an approximately two-fold increased prevalence of CHD in offspring. Therefore, improvement of the periconceptional maternal vitamin D status is recommended.

1. Introduction

Congenital heart defects (CHD) are the most common congenital malformations. The birth prevalence rate of CHD is 9.1 per 1000 live births worldwide and accounts for almost one-third of congenital malformation-related infant deaths [1]. Only 15% of CHD can be attributed to a known cause, such as genetic factors (trisomies, 22q11 deletion), maternal diabetes mellitus, medication, poor nutrition and obesity [2]. It is assumed that interactions between genetic and environmental factors including modifiable maternal nutrition and lifestyle play a significant role in the pathogenesis of most CHD [3].

Previously, it has been reported that maternal multivitamin supplement use in early pregnancy is associated with a reduced risk of CHD in the offspring [4]. This is supported by the estimated 70% reduction of CHD risk in mothers with a strong adherence to a one carbon dietary pattern characterized by fish and seafood [5]. Conversely, a deranged maternal lipid profile, a high dietary intake of saturated fats, vitamin A or vitamin E are associated with CHD in offspring [6–9].

* Corresponding author at: Departments of Obstetrics and Gynaecology and Pediatrics, Division of Neonatology, Erasmus MC, University Medical Centre, PO Box 2040, 3000CA Rotterdam, The Netherlands.
E-mail addresses: m.p.h.koster@erasmusmc.nl (M.P.H. Koster), l.vanduijn.1@erasmumc.nl (L. van Duijn), y.krul@vumc.nl (Y.H.M. Krul-Poel), j.laven@erasmusmc.nl (J.S. Laven), w.a.helbing@erasmusmc.nl (W.A. Helbing), s.simsek@nwz.nl (S. Simsek), r.steegers@erasmusmc.nl (R.P.M. Steegers-Theunissen).
[1] Both authors contributed equally.

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Other studies have shown that calcium supplement use in early pregnancy has a protective effect for CHD [10,11]. Calcium homeostasis is maintained by parathyroid hormone and vitamin D. 25-hydroxyvitamin D (25(OH)D), like vitamin A and E, is a fat-soluble vitamin and present in oil-rich fish. It is a vitamin synthesized in the skin under the influence of solar ultraviolet B radiation and involved in skeletal health [12]. Recent in vitro and animal studies have shown that active 1,25-dihydroxyvitamin D and its receptor are also involved in heart development [13,14].

Although many studies have been performed focusing on the associations between maternal vitamin D status and pregnancy complications, e.g. gestational diabetes [15], none have yet assessed associations with CHD in offspring. We hypothesize that the maternal vitamin D status is inversely associated with the prevalence of CHD, modified by the maternal lipid status. Here we investigated this association in a population-based case-control family study in the Netherlands.

2. Methods

2.1. Study population

The Heart Defects, Vascular status, Genetic factors and Nutritional factors (HAVEN)-study is a case-control family (parents and offspring) study designed to investigate the role of genetics and nutrients in the pathogenesis and prevention of CHD [16]. Children with CHD and their parents (cases) were recruited from four University Medical Centers in the Netherlands. Children without any congenital malformations and their parents (controls) were randomly recruited from public child health centers that regularly monitor growth and development of all children < 4 years in the Netherlands. All participants were included and studied at the Department of Obstetrics and Gynecology of the Erasmus MC, University Medical Centre Rotterdam between June 2003 and December 2005.

Fig. 1 shows a flowchart of the HAVEN-study population. A total of 360 case-children were diagnosed by a pediatric cardiologist based on EUROCAT classification, with tetralogy of Fallot (n = 46), transposition of the great arteries (n = 57), atrial-ventricular septal defect (n = 35), perimembranous ventricular septal defect (n = 101), coarctation of the aorta (n = 36), aortic valve stenosis (n = 7), pulmonary valve stenosis (n = 51), hypoplastic left heart syndrome (n = 15) or other CHD (n = 12). CHD phenotype selection was based on studies demonstrating associations between use of folate, hyperhomocysteinemia and CHD [16–18]. Controls were children without any congenital malformation at approximately 15 months of age as retrieved from questionnaires and verified by medical records and who were unrelated to the case families.

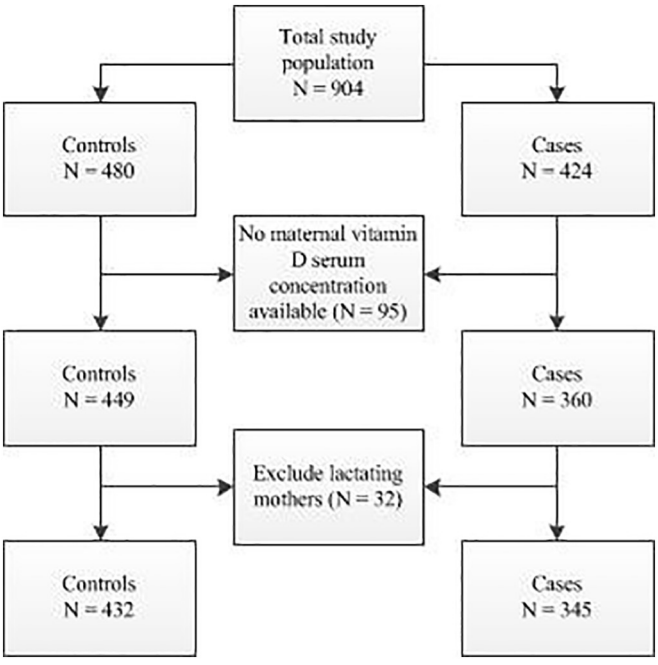

Fig. 1. Flowchart describing the exclusion criteria for the HAVEN-study population.

Children and their parents in both the case and the control group were invited to the Erasmus MC between the ages of 11 and 18 months to collect questionnaire data and blood of both parents and children. This post-pregnancy clinic visit was chosen as study moment to reduce misclassification of undiagnosed CHD or other congenital malformations in the control group [19]. Several studies have demonstrated that dietary habits and metabolism are fairly stable and hardly change over time, except during illnesses, episodes of dieting, pregnancy and breast feeding [20–23]. Information on current maternal dietary habits at the time of study was therefore used as a proxy for those habits during the periconception period, defined as the 14 weeks prior to conception until 10 weeks thereafter [24]. For this particular study, lactating mothers at the time of blood sampling were excluded for analysis (n = 32), which resulted in a dataset of 345 case and 432 control families.

The study protocol was approved by the Central Committee of Research in Humans in The Hague, the Netherlands, and by the Medical Ethics Committees of all participating hospitals (CCMO07.1052/MA/PA3.0200, approved 27 March 2003; MEC212.508/2002/91, approved 16 April 2002). Written informed consent was obtained from all individual participants included in the study.

2.2. Data collection

Standardized anthropometric measurements were carried out including maternal height with 0.1 cm accuracy and weight with 0.1 kg accuracy (anthropometric rod and weighing scale; SECA, Hamburg, Germany). Questionnaires included information on general characteristics as well as current and periconceptional lifestyle behaviors. Extracted data included maternal age, ethnicity, educational level, smoking, use of alcohol, folic acid and multivitamin supplements, family history of CHD and gestational age and weight.

The time after the index-pregnancy is defined as months after the delivery of the child. Ethnicity was categorized as Western (both parents born in a country in North America, Oceania or Europe, Turkey excluded) or Non-Western (one of the parents born in Turkey or a country in Africa, Asia or South America). Educational level was categorized according to the definition of Statistics Netherlands in low (primary/lower vocational/intermediate secondary), intermediate (higher secondary, intermediate vocational) or high (higher vocational/university). Smoking and alcohol was defined as any consumption in the questioned period. Use of folic acid and multivitamin supplements was defined as the daily intake of supplements. If multivitamin supplements contained folic acid, the use of folic acid as well as multivitamin supplements were recoded. Family history of CHD was classified as first, second or third degree family members with CHD. The presence of any other congenital anomalies differentiated between isolated CHD and complex CHD.

2.3. Blood sampling and biochemistry

Venous blood samples were drawn at the visit 15 months after pregnancy. After blood sampling, a serum separator tube was kept at room temperature and an ethylenediamine tetraacetic acid (EDTA) tube was put on ice. Within 1 h after collection, both tubes were centrifuged at 4000g for 10 min at 4 °C and separated. Until measurement, all sera and plasma were stored at − 80 °C. Analysis of lipid profile, i.e. total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides and apolipoprotein B, was performed within six months after blood sampling and has been

Table 1
Baseline characteristics of mothers of children with (cases) and without (controls) congenital heart defects.

Characteristic	Cases (*n* = 345)			Controls (*n* = 432)			
	%	Median	Interquartile range	%	Median	Interquartile range	*P*-value
Maternal factors							
Age, years		31.5	28.3–34.8		31.2	27.6–33.8	0.054
Time after index pregnancy, months		16	15.0–18.0		15	14.0–17.0	0.035
Body mass index, kg/m^2		24.6	22.1–28.0		24.2	22.0–27.3	0.174
Educational level							0.077
Low	26.7			21.5			
Intermediate	42.3			50.0			
High	31.0			28.0			
Ethnicity							0.272
Western	88.1			85.4			
Non-western	11.9			14.6			
25(OH)D serum, nmol/l		57.8	41.6–78.7		65.8	40.5–86.6	0.020
Total cholesterol, mmol/l[a]		4.80	4.30–5.50		4.60	4.20–5.35	0.024
HDL-cholesterol, mmol/l[a]		1.46	1.22–1.75		1.45	1.23–1.71	0.735
LDL-cholesterol, mmol/l[a]		2.86	2.36–3.45		2.73	2.30–3.22	0.020
Triglycerides, mmol/l[a]		0.91	0.67–1.22		0.90	0.68–1.22	0.735
Apolipoprotein B, mg/dl[b]		84.1	72.3–94.7		78.8	68.8–91.4	0.006
Periconceptional factors							
Nullipara	49.8			44.3			0.206
Alcohol	38.3			33.3			0.346
Smoking	19.7			21.8			0.485
Folic Acid	63.2			64.4			0.737
Multivitamin	34.2			28.5			0.076
Diabetes mellitus	1.2			1.2			0.998
Season of blood collection							0.204
Winter	23.8			27.3			
Spring	27.0			30.1			
Summer	22.6			17.1			
Autumn	31.6			20.8			
Offspring							
Birthweight, grams		3305	2880–3652		3500	3200–3880	< 0.001
Gestational age, days		277	267–284		280	272–287	< 0.001
Family history of CHD	8.7			5.6			0.087
Prematurity, < 37 weeks	14.5			6.3			< 0.001

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; CHD, congenital heart defect.
[a] Missing *n* = 52.
[b] Missing *n* = 137.

described in detail previously [6]. Approximately 10 years after blood sampling serum 25-hydroxyvitamin D (25(OH)D) concentrations were measured anonymously as the most reliable marker of the vitamin D status with a half-life of three weeks [25]. After hexane liquid-liquid extraction, 25(OH)D was measured by liquid chromatography-mass spectrometry using an Acquity ULPC-MSMS system (Waters, Milford, MA, USA). The inter-assay coefficients of variation for vitamin D were 9.3% at 16.0 nmol/l and 10.2% at 80.3 nmol/l.

2.4. Statistical analysis

Medians and interquartile ranges (IQR) were calculated for continuous variables and compared using Mann-Whitney-*U* test. Dichotomous and categorical data were presented as number and percentages of subjects in cases and controls and compared using Chi-square tests.

So far there is no clear recommendation of the optimal 25(OH)D serum concentration in the general population nor (pre)pregnant women. One guideline recommends an optimal serum 25(OH)D concentration of 50 nmol/l, yet another suggests a concentration of 75 nmol/l (to convert to ng/l figures have to be divided by 2.496) [12,26]. Therefore, 25(OH)D concentrations were stratified into a deficient (< 50 nmol/l), moderate (50–75 nmol/l) and adequate (> 75 nmol/l) status. The associations between maternal vitamin D status and CHD in offspring were estimated by odds ratios (OR) and 95% confidence intervals (CI) in a logistic regression model using the adequate group as reference category. Crude OR was adjusted for potential confounders based on literature, i.e., maternal age, body mass index (BMI), smoking, ethnicity and lipids. In case of missing data, logistic regression was not performed. To assess the most appropriate determinant(s) of the lipid profile for adjustment, correlations between the lipids were assessed and checked for collinearity by Spearman rank correlation coefficients.

Subgroup analyses were performed for isolated and complex CHD as well as for the three most prevalent CHD phenotypes in our study group (transposition of the great arteries, perimembranous ventricular septal defect, and pulmonary valve stenosis). Due to the retrospective study design, the use of multivitamins and season may differ between the study moment and the periconception period. For a more accurate reflection of vitamin D levels in the periconception period, post-hoc analyses were performed in subgroups with the same season and/or maternal use of multivitamin supplements during the periconception period and the moment of blood sampling, since these exposures can influence maternal vitamin D serum concentrations. Significance for trend across the categories was analyzed by using Chi-square tests. *P*-values < 0.05 were considered statistically significant. All analyses were performed using SPPS-software package version 21.0 (SPSS Inc., Chicago, IL, USA).

3. Results

General characteristics of case (*n* = 345) and control (*n* = 432) mothers and children are presented in Table 1. The serum 25(OH)D concentration at the study moment was significantly lower in case

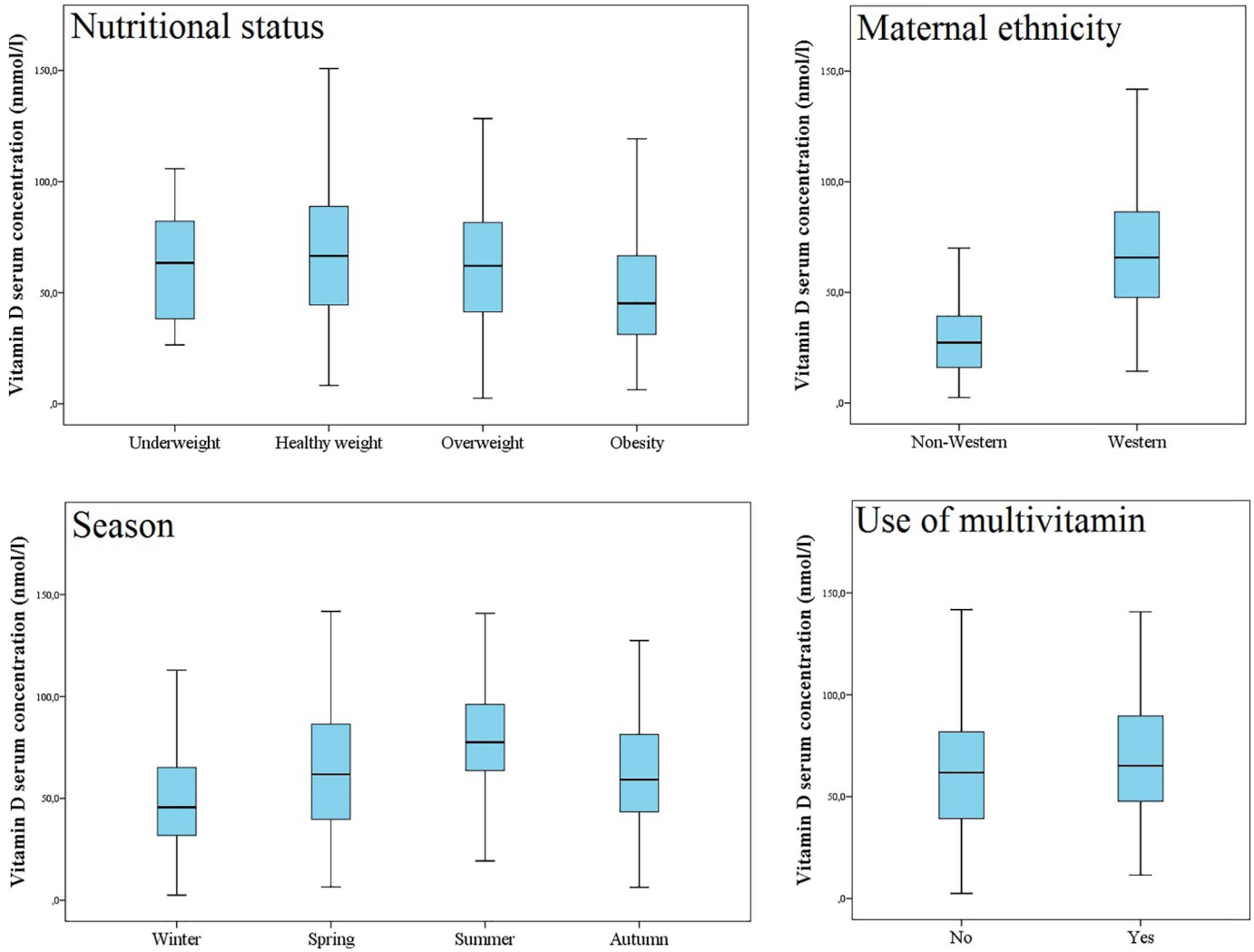

Fig. 2. Distributions of the maternal 25(OH)D serum concentration (nmol/l) stratified for a) BMI ($P < 0.001$), b) mothers of Western and Non-Western origin ($P < 0.001$), c) mothers who did and did not use multivitamins at the time of blood sampling ($P = 0.018$) and d) season at the time of blood sampling ($P < 0.001$).

mothers compared to controls (57.8 versus 65.8 nmol/l, $P = 0.020$). Maternal characteristics and periconceptional lifestyle were comparable between the groups. The time interval since the delivery of the index-pregnancy and study moment revealed a one month difference (cases 16 [IQR 15–18] months and controls 15 [IQR 14–17] months). Case children had a lower birthweight and were more often born before 37 weeks gestational age.

Inverse associations were shown between maternal serum 25(OH)D concentrations and BMI, non-Western ethnicity, season of blood sampling and no use of multivitamin supplements (Fig. 2).

Only 94 (27%) case and 163 (38%) control mothers had an adequate vitamin D status ($P = 0.002$). There were no subjects who had a toxic serum 25(OH)D concentration above 200 nmol/l. Spearman rank correlation demonstrated significant correlations between all determinants of the maternal lipid profile, except for the correlation between HDL-cholesterol and apolipoprotein B (Supplemental Table 1). Since all maternal lipids were significantly correlated with total cholesterol, the latter determinant was used for adjustment.

A deficient vitamin D status (adjusted OR 1.82, [95%CI 1.25, 2.66]) and a moderate vitamin D status (adjusted OR 1.58, [95%CI 1.11, 2.26]) were significantly associated with CHD in the offspring after adjusting for maternal age, BMI, ethnicity and periconceptional smoking (Table 2). The additional adjustment for the maternal lipid profile resulted in stronger associations. Table 2 also shows the results of the post-hoc analyses performed only in cases and controls in which the maternal use of multivitamins and season were equal during the periconception period and at the moment of blood sampling. In these women the ORs were comparable and for seasonality revealed to be higher.

When case children were stratified into isolated and complex CHD, only isolated CHD showed a significant association with maternal vitamin D status (deficient: adjusted OR 1.99, [95%CI 1.32, 3.00]; moderate: adjusted OR 1.51 [95%CI 1.02, 2.23]). Additional maternal lipid profile adjustment altered this association (deficient: adjusted OR 2.24, [95%CI 1.46, 3.45]; moderate: adjusted OR 1.44, [95%CI 0.95, 2.19]) (Table 3). Logistic regression analyses for the phenotypes transposition of the great arteries, perimembranous ventricular septal defect, and pulmonary valve stenosis separately also showed associations with maternal vitamin D status, however only the association with perimembranous ventricular septal defect was statistically significant (adjusted OR 1.90, [95%CI 1.04, 3.47]) (Table 4).

4. Discussion

The aim of this study was to investigate associations between periconceptional maternal vitamin D status and CHD in offspring. Serum 25(OH)D concentrations as marker of vitamin D status were associated with maternal BMI, the use of multivitamin supplements, ethnicity and season of blood sampling. Our results demonstrate that a deficient or moderate maternal vitamin D status is associated with CHD

Table 2
Associations between maternal vitamin D status and congenital heart defects in the offspring, when multivitamin supplement use, season or both were equal in the periconception period and at blood sampling.

	25(OH)D, serum (nmol/l)	Cases/controls	Crude		Adjusted model 1[a]		Adjusted model 2[b]	
			OR	95% CI	OR	95% CI	OR	95% CI
All		*n* = 345/432						
	Deficient (0–50)	130/138	1.63	1.15, 2.32	1.82	1.25, 2.66	2.15	1.44, 3.19
	Moderate (50–75)	121/131	1.60	1.12, 2.28	1.58	1.11, 2.26	1.58	1.08, 2.32
	Adequate (> 75)	94/163	1.00	Reference	1.00	Reference	1.00	Reference
	P-trend		0.006		0.002		< 0.001	
Season		*n* = 176/237						
	Deficient (0–50)	78/80	2.07	1.28, 3.34	2.33	1.39, 3.92	2.59	1.57, 4.60
	Moderate (50–75)	56/68	1.75	1.05, 2.91	1.67	0.99, 2.81	1.84	1.08, 3.13
	Adequate (> 75)	42/89	1.00	Reference	1.00	Reference	1.00	Reference
	P-trend		0.004		0.001		< 0.001	
Multivitamin		*n* = 242/314						
	Deficient (0–50)	94/106	1.56	1.03, 2.35	1.78	1.13, 2.81	2.13	1.32, 3.45
	Moderate (50–75)	82/92	1.57	1.03, 2.39	1.57	1.03, 2.41	1.65	1.04, 2.60
	Adequate (> 75)	66/116	1.00	Reference	1.00	Reference	1.00	Reference
	P-trend		0.038		0.011		0.002	
Both		*n* = 125/163						
	Deficient (0–50)	60/59	2.03	1.15, 3.59	2.47	1.32, 4.62	2.81	1.47, 5.36
	Moderate (50–75)	35/44	1.59	0.85, 2.97	1.55	0.82, 2.91	1.67	0.87, 3.21
	Adequate (> 75)	30/60	1.00	Reference	1.00	Reference	1.00	Reference
	P-trend		0.015		0.005		0.002	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio; 95%CI, 95% confidence interval.
[a] Adjusted for maternal age, body mass index, ethnicity and smoking.
[b] Adjusted for maternal age, body mass index, ethnicity, smoking and maternal total cholesterol.

Table 3
Associations between maternal vitamin D status and congenital heart defects (CHD) in the offspring, stratified into isolated and non-isolated CHD.

	25(OH)D, serum (nmol/l)	Cases/controls	Crude		Adjusted model 1[a]		Adjusted model 2[b]	
			OR	95% CI	OR	95% CI	OR	95% CI
Isolated		*n* = 264/432						
	Deficient (0–50)	106/138	1.76	1.21, 2.57	1.99	1.32, 3.00	2.24	1.46, 3.45
	Moderate (50–75)	87/131	1.53	1.03, 2.25	1.51	1.02, 2.23	1.44	0.95, 2.19
	Adequate (> 75)	71/163	1.00	Reference	1.00	Reference	1.00	Reference
	P-trend		0.003		0.001		0.001	
Complex		*n* = 81/432						
	Deficient (0–50)	24/138	1.23	0.67, 2.28	1.32	0.68, 2.58	1.80	0.88, 3.68
	Moderate (50–75)	34/131	1.84	1.03, 3.28	1.78	0.99, 3.18	2.03	1.07, 3.88
	Adequate (> 75)	23/163	1.00	Reference	1.00	Reference	1.00	Reference
	P-trend		0.481		0.335		0.09	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio; 95%CI, 95% confidence interval.
[a] Adjusted for maternal age, body mass index, ethnicity and smoking.
[b] Adjusted for maternal age, body mass index, ethnicity, smoking and maternal total cholesterol.

in the offspring, after adjusting for maternal age, BMI, ethnicity, smoking and lipids. Post-hoc analyses of women at the same season and with similar use of multivitamins during the periconception period and at study moment showed comparable associations.

This is the first study that assessed associations between maternal vitamin D status and CHD in offspring. An advantage of our study is its large sample size, allowing for well-powered comparisons between CHD and controls. However, the small numbers of specific CHD phenotypes limit the validity of the effect sizes of their individual associations with maternal vitamin D status. Moreover, due to the heterogeneity of CHD phenotypes, we only demonstrated associations between maternal vitamin D status and the three most common CHD phenotypes in our study population.

Due to the low birth prevalence rate of CHD, a prospective periconception cohort study to demonstrate a causal relationship between maternal vitamin D status and CHD in offspring was not feasible. Therefore, we conducted a case-control study with a standardized study moment of 15–16 months after delivery, which is equivalent to approximately two years after the periconception period of the index-pregnancy and reduces potential confounding due to seasonality. Although women may have altered their diet and lifestyle because of their pregnancy, previous research has shown that this moment accurately represents the metabolic, nutritional and hormonal status in the periconception period [20–23]. To eliminate any residual discrepancies of seasonality or maternal use of multivitamins at the two time points that may have distorted the associations, we also performed the post-hoc analyses in women in which these effect modifiers are equal for both time points. Moreover, there is a slight possibility of reverse causation bias when mothers of a child with CHD have altered their lifestyle due to this lifechanging event compared with mothers of healthy children.

Despite the small difference of only one month, CHD cases were included significantly later after delivery compared with controls. However, the correlation between maternal vitamin D concentration and time after delivery was not statistically significant (data not shown). Moreover, this difference is minimized in post-hoc analyses for equal season of conception and blood sampling.

Although 25(OH)D is stable over time and multiple freeze-thaw cycles, theoretically long-time storage of serum samples at − 80 °C may have impacted the measurement of 25(OH)D. However, because of the

Table 4
Associations between maternal vitamin D status and congenital heart defects (CHD) in the offspring for the three most common CHD phenotypes in the study population.

	25(OH)D, serum (nmol/l)	Cases/controls	Crude		Adjusted model 1[a]		Adjusted model 2[b]	
			OR	95% CI	OR	95% CI	OR	95% CI
TGA		*n* = 54/432						
	Deficient (0–50)	21/138	1.18	0.62, 2.25	1.78	0.90, 3.52	1.84	0.89, 3.79
	Moderate (50–75)	12/131	0.71	0.34, 1.50	0.74	0.35, 1.57	0.77	0.35, 1.69
	Adequate (> 75)	21/163	1.00	Reference	1.00	Reference	1.00	Reference
	P-trend		0.633		0.131		0.138	
pVSD		*n* = 97/432						
	Deficient (0–50)	36/138	1.64	0.94, 2.84	1.90	1.04, 3.47	2.42	1.28, 4.57
	Moderate (50–75)	35/131	1.68	0.96, 2.92	1.66	0.94, 2.92	1.68	0.90, 3.11
	Adequate (> 75)	26/163	1.00	Reference	1.00	Reference	1.00	Reference
	P-trend		0.085		0.033		0.006	
Pulm. valve stenosis		*n* = 49/432						
	Deficient (0–50)	21/138	2.26	1.05, 4.84	2.09	0.90, 4.84	1.84	0.78, 4.38
	Moderate (50–75)	17/131	1.92	0.87, 4.25	1.87	0.94, 4.15	1.18	0.49, 2.83
	Adequate (> 75)	11/163	1.00	Reference	1.00	Reference	1.00	Reference
	P-trend		0.039		0.082		0.168	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio; 95%CI, 95% confidence interval; TGA, transposition of the great arteries; pVSD, perimembranous ventricular septum defect.

[a] Adjusted for maternal age, body mass index, ethnicity and smoking.

[b] Adjusted for maternal age, body mass index, ethnicity, smoking and maternal total cholesterol.

random blood sampling, storage and measurements of 25(OHD) in cases and controls it is not very likely that this has affected our results [27,28].

Several studies have investigated the associations between maternal intake of vitamins and other micronutrients and CHD in offspring, including our studies conducted in the HAVEN-study [7–9,29–32]. In our study population, there were no statistically significant correlations between maternal vitamin 25(OH)D concentrations, vitamin E intake and homocysteine plasma concentrations (data not shown). This suggests that low vitamin D concentration is an independent risk factor for CHD.

A slightly elevated concentration of some nutrients can have a teratogenic effect, vitamin D and others seem beneficial in embryonal cardiac development. It is plausible that vitamin D interacts with many other genetic and environmental factors in the complex pathogenesis of CHD. Vitamin D affects cell processes through the binding of its active form 1,25-dihydroxyvitamin D to the vitamin D receptor. This vitamin D receptor belongs to the nuclear receptor family and is involved in gene regulation [33]. Vitamin D receptors are present in almost all cells and, once activated, have an effect in many (patho)physiological processes. A precise regulation of involved genes is extremely important during embryogenesis and cardiogenesis in particular which takes place between week 2 and 7 of pregnancy [34]. Recent studies have demonstrated that components of the vitamin D pathway are involved in cardiogenesis [13,14]. Interestingly, the 1,25-dihydroxyvitamin D concentration increases by 100–200% during the first trimester, suggesting an increased need during this early pregnancy period [35]. When the 25(OH)D concentration is inadequate, the conversion into active 1,25-dihydroxyvitamin D might be decreased, resulting in a low vitamin D status and alterations of gene regulation. This is supported by the increasing evidence that vitamin D deficiency is involved in the development of cardiovascular and other common diseases [36]. However, it should be noted that the complex alterations of the vitamin D metabolism during fetal-placental development are still under investigation.

Vitamin D deficiency is a worldwide problem in people of all ages [37]. However, the exact cut-off value for vitamin D deficiency is still under debate. The Institute of Medicine suggests a concentration of 50 nmol/l or higher to meet the needs of 97.5% of the population [26]. On the other hand, the Endocrine Society recommends a 25(OH)D concentration above 75 nmol/l based on optimal bone mineral density [12]. We show already an elevated risk for CHD in the offspring of maternal 25(OH)D concentrations below 75 nmol/l, thereby supporting the recommendation of The Endocrine Society [12]. Despite the reported associations between vitamin D deficiency and increased risks of preeclampsia, cesarean section due to prolonged labor and other pregnancy complications, a specific threshold for (pre)pregnant women is lacking [38,39].

Only a few women in our study population had an adequate vitamin D status of above 75 nmol/l, which is in line with studies among pregnant women from different geographical locations [40]. To increase the vitamin D status more emphasis should be given to more but safe sunlight exposure, a higher dietary intake of fish and seafood, and the use of a low dose vitamin D supplement [5]. The Endocrine Society suggests that pregnant and lactating women require at least 600 IU/day of vitamin D and recognizes that in order to maintain a serum concentration > 75 nmol/l, 1500–2000 IU/day of vitamin D may be needed [12]. The Royal College of Obstetricians and Gynecologists guideline for vitamin D during pregnancy recommends three categories for vitamin D supplementation: 400 IU/day of vitamin D for all pregnant women, 800–1000 IU/day for high-risk women and 2000 IU/week as treatment for deficient women [41]. High-risk women are those with increased skin pigmentation, reduced sunlight exposure and obesity. This is in line with our study demonstrating inverse associations between BMI, non-Western ethnicity and vitamin D status.

5. Conclusion

In conclusion, we have demonstrated that a moderate to severely compromised maternal vitamin D status is associated with CHD in the offspring. The first weeks of pregnancy, when pregnancy is often not yet recognized, are crucial for cardiogenesis, which emerges the need of an adequate maternal vitamin D status already in the preconception period. However, evidence concerning adequate and safe intakes of dietary and synthetic vitamin D for this target group are lacking thereby emphasizing the need for research to establish recommendations. Future studies should therefore focus on the benefits and safety of strong adherence to a vitamin D rich diet or the use of vitamin D supplements.

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Conflict of interest

None to declare.

Contributor statement

LD and MPHK were responsible for the first draft of the manuscript, statistical analysis, interpretation of data and for the revisions of the manuscript. SS and JSL provided the vitamin D measurements and contributed to the revision of the manuscript. YHMK-P was responsible for the laboratory determinations of vitamin D and contributed to revisions of the manuscript. RPMS-T initiated the study, interpreted the data, supervised all aspects and revised all versions of the manuscript.

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