Original Article

Association between maternal vitamin D status during pregnancy and offspring cognitive function during childhood and adolescence

Sargoor R Veena PhD[1], Ghattu V Krishnaveni PhD[1], Krishnamachari Srinivasan MD[2], Kotrangada P Thajna MSc[1], Bhavya G Hegde MSc[1], Catharine R Gale PhD[3,4], Caroline HD Fall DM[3]

[1]*Epidemiology Research Unit, CSI Holdsworth Memorial Hospital, Mysore, South India*
[2]*St. John's Research Institute, St. John's National Academy of Health Sciences, Bangalore, India*
[3]*MRC Lifecourse Epidemiology Unit, Southampton General Hospital, Southampton, UK*
[4]*Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, Edinburgh, UK*

Background and Objectives: Animal studies have demonstrated poor cognitive outcomes in offspring in relation to maternal vitamin D deficiency before and/or during pregnancy. Human studies linking maternal vitamin D status during pregnancy with offspring cognitive function are limited. We aimed to test the hypothesis that lower maternal vitamin D status during pregnancy is associated with poor offspring cognitive ability in an Indian population. **Methods and Study Design:** Cognitive function was assessed in children from the Mysore Parthenon birth cohort during childhood (age 9-10 years; n=468) and adolescence (age 13-14 years; n=472) using 3 core tests from the Kaufman Assessment Battery for children and additional tests measuring learning, long-term retrieval/storage, short-term memory, reasoning, verbal fluency, visuo-spatial ability, and attention and concentration. Maternal serum 25-hydroxyvitamin D concentration was measured at 30±2 weeks of gestation. **Results:** During pregnancy 320 (68%) women had 'vitamin D deficiency' (serum 25-hydroxyvitamin D concentration <50 nmol/L). Girls scored better than boys in tests of short-term memory, reasoning, verbal fluency, and attention (p<0.05 for all). Maternal vitamin D status (low as well as across the entire range) was unrelated to offspring cognitive function at both ages, either unadjusted or after adjustment for the child's current age, sex, maternal age, parity, season at the time of blood sampling, gestational age, the child's birth and current size, socio-economic status, parents' education, maternal intelligence and home environment. **Conclusions:** In this population, despite a high prevalence of vitamin D deficiency during pregnancy, there was no evidence of an association between maternal vitamin D status and offspring cognitive function.

Key Words: maternal vitamin D, pregnancy, cognitive function, children, India

INTRODUCTION

Vitamin D is an important micronutrient essential for bone growth and regulation of calcium homeostasis.[1] Apart from its vital role in skeletal growth, vitamin D has a number of biological actions fundamental to neurodevelopment and function, including a signalling role in cell differentiation and synaptic formation,[2] gene expression,[2] regulation of the metabolism of neurotrophic and neurotoxic factors[3] and a protective role during brain inflammation.[4] The main source of vitamin D is sunlight; it is also obtained from a few foods such as oily fish and fortified margarines.[5] Vitamin D deficiency is a public health problem across the globe.[6] Despite abundant sunshine, there is a high prevalence of vitamin D deficiency in Indians, including pregnant women.[7,8] The vitamin D supply to the growing fetus depends on maternal vitamin D status.[9] Therefore maternal vitamin D deficiency during pregnancy might lead to adverse health outcomes in the offspring.[10] Some studies have observed fetal growth restriction,[11] reduced bone size and bone mineral content[12] and recurrent wheeze[13] in the offspring of mothers with vitamin D deficiency.

Interest in the relationship of maternal vitamin D status during pregnancy to offspring cognitive function is recent, and literature is limited. Animal studies have demonstrated poor learning and memory, and alterations in attention, in association with vitamin D deficiency before conception and/or during pregnancy.[14,15] In humans, only five studies, all from developed populations, have examined

Corresponding Author: Dr Sargoor R Veena, Epidemiology Research Unit, CSI Holdsworth Memorial Hospital, P.O. Box 38, Mandi Mohalla, Mysore 570021, India.
Tel: 0091-821-2521651; Fax: 0091-821-2565607
Email: veenasr@gmail.com
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the relationship between maternal vitamin D status and offspring cognitive function.[16-20] The findings are inconsistent. Two studies, one in Spain and another in Australia, observed poor cognitive outcomes in children of deficient mothers.[16,17] A study in the UK and another in Denmark found no association.[18,19] The fifth study in the USA, observed an association in young children that was no longer evident when the children were older.[20]

In the Mysore Parthenon Study in south India, we have measured maternal serum 25-hydroxyvitamin D concentration in pregnancy using stored serum samples; more than 60% of the women had vitamin D deficiency at 30±2 weeks gestation.[21] Cognitive function in the offspring was assessed during childhood and adolescence. Using these data, we aimed to test the hypothesis that lower maternal vitamin D status and/or vitamin D deficiency were associated with poorer offspring cognitive ability, independent of socio-demographic factors.

MATERIALS AND METHODS

Study population

The Mysore Parthenon birth cohort was initiated in 1997-1998.[22] Eight hundred and thirty women booking consecutively into the antenatal clinic at the Holdsworth Memorial Hospital (HMH), Mysore, India and satisfying the eligibility criteria (no history of diabetes before pregnancy, planning to deliver at HMH, and having a singleton pregnancy of <32 weeks gestation) participated in the study. Six hundred and seventy four women (81% of the participants) delivered their babies at HMH. Excluding 7 stillborn babies, and 4 with major congenital anomalies, detailed newborn anthropometry was performed on 663 normal live born babies according to a standard protocol, within 72 hours of birth, as reported previously.[23] Excluding 25 children who died, and 8 with major medical problems, 630 healthy children were followed up with repeat anthropometry, annually till the age of 5 years and every 6 months thereafter.

Maternal25-hydroxyvitamin D concentration

Maternal serum 25-hydroxyvitamin D concentration was measured in stored samples (frozen at –80^{o}C), using radioimmunoassay (IDS Immunodiagnostics Ltd, Boldon, Tyne and Wear, UK) standardized against Nichols and Incstar methodology. Each assay complied with international DEQAS (vitamin D external quality assurance scheme) requirements.[24] Intra- and inter-assay coefficients of variations were 8.8% and 10.8%, respectively. Low vitamin D status was defined as concentrations <50 nmol/L.[8,25] Of 663 mothers who delivered at HMH, adequate samples were available for 568 mothers (86%).

Vitamin D and calcium supplementation

General practitioners and obstetricians routinely prescribe multivitamin supplements to pregnant women. Data on supplement use was collected at recruitment (<32 weeks of gestation) but not subsequently, and therefore no information is available on their use when blood samples were collected or at term.

Study sample for cognitive function assessment

Children were invited for assessment of their cognitive function during childhood (age 9-10 years) and adolescence (age 13-14 years). Of the 630 children, 88 were excluded (61 unwilling, 17 moved away from Mysore and 10 untraceable), resulting in 542 (86%) who underwent cognitive testing during childhood. During adolescence, 85 were excluded (51 unwilling, 22 moved away and 12 untraceable), resulting in 545 (86%) who participated in cognitive function assessment. Among the participants, 74 children and 73 adolescents were excluded because maternal 25-hydroxyvitamin D concentrations were unavailable. The current analysis is restricted to 468 children (228 boys and 240 girls) and 472 adolescents (226 boys and 246 girls) (Figure 1).

Tests of cognitive function

These comprised a series of neuropsychological tests applicable for use in school aged children and related to specific cognitive domains (memory, attention, fluid reasoning) consistent with the Carroll model.[26] They included three core tests from the Kaufman Assessment Battery for Children[27] and additional tests[28-31] that underwent extensive adaptation to the local cultural context and validation.[32,33] The tests (Table 1) covered the domains of learning, long-term memory and retrieval ability (Atlantis), short-term memory (Word order), reasoning ability (Pattern reasoning), language production (Verbal fluency), visuo-spatial ability (Kohs' block design) and visuo-motor processing speed and coordination, attention and concentration (coding-Wechsler Intelligence Scale for Children-III). The tests were administered in a single session of 60 to 90 minutes in a quiet room by one of 2 trained masters' level child psychologists (unaware of maternal vitamin D status) in the local Kannada language.

Covariates and confounders

We considered the following as important covariates and potential confounding variables: 'Parental factors' included maternal age, season at the time of blood sampling, parity, maternal and paternal educational attainment (completed years), current socio-economic status (SES), assessed using the Standard of Living Index,[34] maternal intelligence assessed using the Revised Bhatia's Short battery of Performance Tests of Intelligence for Adults[35] and home environment assessed using The Home Observation for Measurement of the Environment Inventory-Early Adolescent version.[36] We considered season at the time of blood sampling (summer, March–June; rainy season, July–October; and winter, November-February) because exposure to sunlight tends to vary in these 3 seasons. None of the mothers had ever smoked or consumed alcohol. 'Infant factors' included the child's sex, gestational age at birth, newborn weight and head circumference, and the child's weight, length and head circumference at age 2 years. 'Child factors' included the current age, body mass index (BMI) and head circumference. The research ethics committee of the HMH approved the study and informed verbal consent was obtained from parents and children.

Statistical methods

Variables with skewed distributions were transformed appropriately. Maternal 25-hydroxyvitamin D concentra-

tions were log transformed; Fisher Yates transformation and square root transformation was used for Kohs block design and pattern reasoning scores respectively during childhood. To facilitate interpretation of regression models cognitive tests scores and maternal 25-hydroxyvitamin D concentrations were z-standardized. Comparisons of

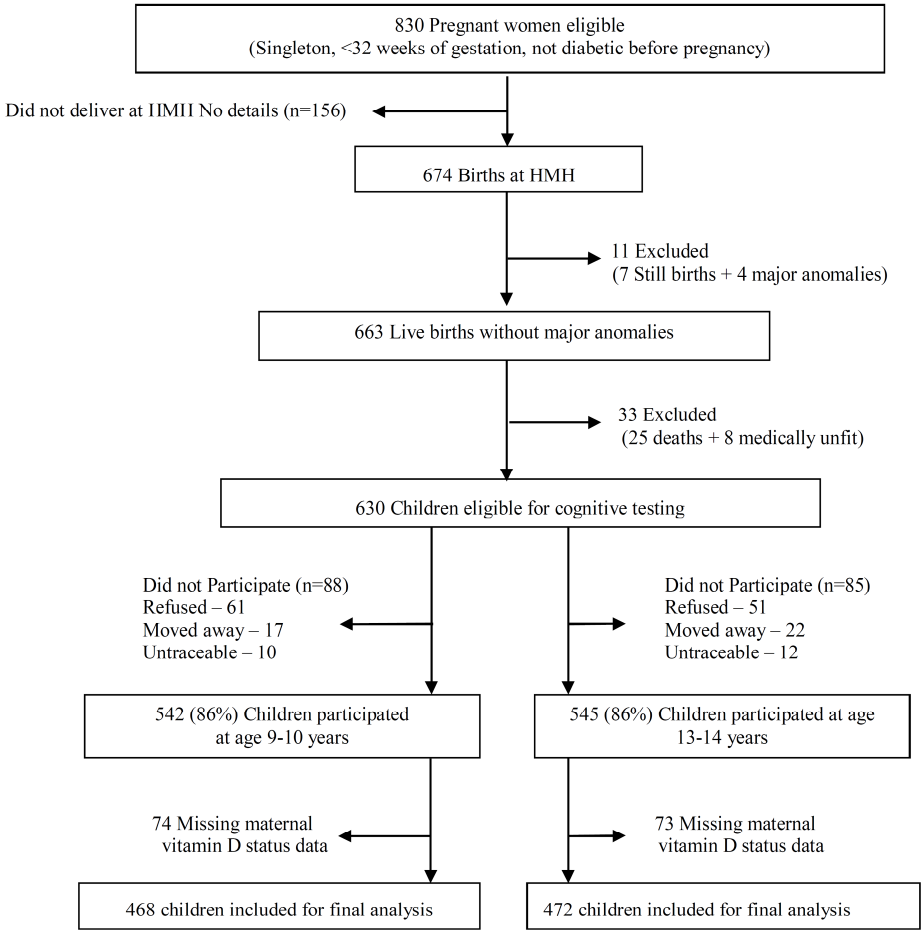

Figure 1. Flow chart of the study participants.

Table 1. Description of the cognitive tests used in the study

Tests from KABC-II[†]		
Name of the test	Description	Cognitive abilities
Atlantis	The child is taught nonsense names for fish, plants and shells and is asked to point to the named object among an array of pictures	Learning ability/long-term storage and retrieval, associative memory
Word order	The child points to a series of silhouettes of common objects in the same order as mentioned by the examiner; an interference task (color naming) is added between the stimulus and the response for the more difficult items	Memory span, short term memory, working memory
Pattern Reasoning	The child completes a pattern by selecting the correct image from a set of 4 to 6 options shown; most stimuli are abstract, geometric shapes and the difficulty of the task increases as the test progresses.	Reasoning abilities such as induction and deduction and fluid reasoning
Additional tests		
Verbal fluency	The child is asked to name as many first names as possible in 1 minute.	Broad retrieval ability; speed and flexibility of verbal thought process; neuropsychological test of language production
Kohs block Design	A psychometric test in which the child arranges groups of 4, 9, or 16 multi-colored blocks to copy picture designs presented on test cards.	Visuo-spatial problem solving, visual perception and organization
Coding-WISC-III[‡]	The child has to substitute specific symbols for numbers presented in boxes, and complete as many items as possible in 2 minutes.	Visual-motor processing speed and coordination, short term memory, visual perception, visual scanning, cognitive flexibility, attention

[†]Kaufman assessment battery for children-2nd edition.[27]
[‡]Wechsler Intelligence Scale for Children-3rd edition.[31]

means and percentages between groups were made using *t* tests and chi-square tests, where appropriate. Associations of covariates and confounders with maternal 25-hydroxyvitamin D concentrations (exposure) and cognitive scores (outcomes) were initially examined using multiple linear regression adjusting for sex and current age. Associations of maternal 25-hydroxyvitamin D concentrations (as a binary variable (deficient compared to normal concentrations) and as a continuous variable) with cognitive scores were then examined using multiple linear regression analyses adjusting for covariates/confounders (the child's sex, and current age, season at the time of blood sampling, gestational age at birth, newborn weight and head circumference, maternal age, parity, parents' SES, education, maternal intelligence, home environment, and the child's BMI and head circumference at the time of outcome assessment) that were significantly associated with either 25-hydroxyvitamin D concentrations or cognitive outcomes. Data for maternal intelligence and home environment were missing for ~7% and ~37% of the children, respectively. In order to maintain the sample size and to reduce bias we imputed maternal intelligence and home environment data by replacing each of these original variables with two newly constructed variables: a) a binary variable which took the value 0 if the original variable had a known value and 1 if it was missing; b) the mean value of the original variable when it was missing. The imputed variables were used in the regression analyses. Interaction terms were used to test for differences in the associations between exposure and sex in relation to cognitive scores. After ensuring that there was no interaction between exposure and sex in predicting cognitive ability, the sexes were pooled in all analyses, with adjustment for sex. Quadratic terms were used to examine for non-linear effects. Stata (version10.0, Stata Corporation, Texas, USA) was used for all analyses.

RESULTS

Characteristics of the study sample are summarized in Table 2. During pregnancy 68% of women had low 25-hydroxyvitamin D concentrations. Maternal education and SES were higher among non-participants compared with participants ($p<0.05$ for both); there were no differences in maternal 25-hydroxyvitamin D concentrations or the prevalence of low concentrations, maternal age, parity and the children's birth size between participants and non-participants (data not shown).

Girls scored better than boys in tests of short-term memory, reasoning, verbal fluency, and attention and concentration at both time points ($p<0.05$ for all) (Table 2). Boys were heavier, and had larger head circumference at birth and at age 2 years (also taller at age 2 years) and higher home environment score compared with girls; girls had longer gestational age than boys ($p<0.05$ for all; Table 2). One percent of mothers were illiterate, approximately 35% had only received primary school education; 50% had completed secondary school education, and 14% were graduates or postgraduates and/or professionals. Corresponding figures for fathers were 3%, 34%, 39% and 24%, respectively.

As already reported,[21] 25-hydroxy vitamin D concentrations were higher among mothers whose blood sample was collected during winter compared with those whose samples were collected during the rainy ($p<0.010$) or summer season ($p<0.001$) (Table 2). Approximately 70% of women were recruited at <24 weeks gestation and 30% were recruited between 24-32 weeks. At recruitment, 131 (28%) women reported taking supplements containing calcium and vitamin D-3. Of these, 66 (50%) were recruited at <24 weeks gestation and 65 (50%) between 24-32 weeks gestation. There were no associations of supplement use at recruitment with 25-hydroxyvitamin D concentrations at 30±2 weeks of gestation. This was true among women recruited early (<24 weeks of gestation) and those recruited later (24-32 weeks).

Associations of maternal 25-hydroxy vitamin D concentrations and cognitive outcomes with covariates and confounders

There were no associations of maternal age or parity, or the child's size at birth, at age 2 years and at the time of outcome assessment, SES, parental education, maternal intelligence and home environment with maternal 25-hydroxyvitamin D concentrations (Table 3). Cognitive scores tended to be lower in children of mothers of higher parity and to increase with increasing maternal age and children's birth size. The children's weight, length and head circumference at age 2 years, current BMI and head circumference, parental educational level, SES, maternal intelligence and home environment were strongly positively related to most of the cognitive outcomes (Table 3).

Associations of maternal 25-hydroxyvitamin D concentrations with offspring cognition

Maternal vitamin D status (both deficiency versus non-deficiency, and the continuous variable) was unrelated to offspring cognitive performance in childhood (Table 4). The findings were similar during adolescence, but there was a positive association between 25-hydroxyvitamin D concentrations and verbal fluency which became stronger and significant after adjusting for season and covariates and confounders (Table 5). The findings were similar in boys and girls.

DISCUSSION

To our knowledge, this is the first study in a developing country to examine associations between maternal 25-hydroxyvitamin D concentrations during pregnancy and cognitive performance in their children. We found a high prevalence of maternal vitamin D deficiency (68%) and a significant seasonal variation in 25-hydroxyvitamin D concentrations. There were no associations between maternal 25-hydroxyvitamin D concentrations and offspring cognitive ability during childhood and adolescence.

Strengths of the study were a large sample of children and a battery of cognitive function tests specifically adapted for, and validated in, a South Indian population. The cognitive tests that we used in our study are typical tests applicable for school aged children and relevant to everyday life. These tests assess the day-to-day problem solving abilities which are more likely to be associated with academic performance and behavioural outcome of an individual. Furthermore, data on a range of important confounding factors were recorded. Missing data on ma-

Table 2. General characteristics of the study participants

Variable	Participants during childhood			Participants during adolescence		
	Boys (n=228)	Girls (n=240)	All (n=468)	Boys (n=226)	Girls (n=246)	All (n=472)
Maternal characteristics in pregnancy						
Age (years)	24.0±4.3	23.8±4.3	23.9±4.3	23.9±4.3	23.8±4.3	23.8±4.3
Parity (n (%))						
0	113 (49.5)	124 (51.7)	237 (50.6)	114 (50.4)	123 (50.0)	237 (50.2)
1	76 (33.3)	78 (32.5)	154 (32.9)	74 (32.7)	78 (32.5)	158 (33.5)
≥2	39 (17.1)	38 (15.8)	77 (16.4)	38 (16.8)	38 (15.8)	77 (16.3)
Serum 25-hydroxyvitamin D concentration (nmol/L)	38.0 (23.0, 54.0)	40.6 (23.9, 62.1)	38.9 (23.5, 58.3)	37.5 (23.0, 54.0)	39.0 (23.8, 60.0)	38.1 (23.5, 56.8)
Low 25-hydroxyvitamin D concentration, <50nmol/L (n (%))	154 (67.5)	159 (66.3)	313 (66.9)	154 (68.1)	166 (67.5)	320 (67.8)
25-hydroxyvitamin D concentration according to season at the time of blood sampling (nmol/L)						
Summer (March-June)	31.0 (22.0, 46.0)	29.0 (21.0, 44.5)	30.0 (21.5, 45.0)	30.0 (20.8, 44.8)	28.0 (20.9, 42.5)	29.0 (20.9, 43.0)
Rainy (July-October)	36.6 (18.7, 52.0)	42.5 (23.0, 71.0)	39.1 (21.9, 62.0)	36.0 (18.7, 52.0)	42.0 (22.8, 71.0)	38.9 (21.6, 62.0)
Winter (November-February)	51.5 (28.0, 78.0)	49.3 (31.2, 87.0)	50.8 (31.0, 79.0)	50.0 (32.8, 77.4)	47.0 (31.0, 79.0)	47.2 (31.1, 77.7)
Children's characteristics						
Tests of cognitive function (score)						
Learning, long-term retrieval/storage	67.8±18.3	68.4±16.6	68.1±17.4	80.1±14.5	79.8±14.7	80.0±14.6
Short-term memory	16.2±2.6	16.9±2.5	16.5±2.6	18.6±3.6	19.5±4.0	19.0±3.8
Reasoning	9.0 (4.0, 13.0)	11.0 (6.0, 14.0)	10.0 (5.0, 14.0)	14.8±6.5	16.4±6.7	15.7±6.7
Verbal fluency	14.8±4.2	17.6±5.3	16.2±5.0	19.6±4.6	22.9±6.2	21.3±5.7
Visuo-spatial ability	76.8 (63.4, 87.8)	77.0 (63.7, 89.2)	76.9 (63.7, 88.5)	85.5±26.2	82.3±25.4	83.8±25.8
Attention and concentration	30.3±7.8	35.2±8.0	32.8±8.3	44.5±9.7	50.9±11.2	47.8±11.0
At birth						
Gestational age (weeks)	39.2 ±1.4	39.5±1.2	39.4±1.3	39.2±1.4	39.5 ±1.1	39.4 ±1.3
Birth weight (kg)	2.96±0.424	2.87±0.425	2.92±0.426	2.95±0.423	2.87±0.417	2.90±0.422
Head circumference (cm)	34.2±1.3	33.6±1.2	33.9±1.3	34.2±1.3	33.6±1.3	33.9±1.3
At age 2 years						
Weight (kg)	10.8±1.2	10.2±1.3	10.5±1.2	10.8±1.2	10.2±1.2	10.5±1.2
Length (cm)	84.5±3.2	82.9±3.2	83.7±3.3	84.5±3.2	82.8±3.2	83.6±3.3
Head circumference (cm)	46.8±1.4	45.8±1.3	46.3±1.4	46.9±1.3	45.8±1.3	46.3±1.4
At the time of testing						
Age (years)	9.7±0.3	9.7±0.3	9.7±0.3	13.5±0.1	13.5±0.1	13.5±0.1
BMI (kg/m^2)	14.6±1.7	14.7±2.0	14.6±1.9	17.0±2.7	18.4±3.4	17.8±3.2
Head circumference (cm)	50.8±1.4	50.5±1.5	50.7±1.4	51.5±1.4	51.3±1.4	51.4±1.4
Parents socio-economic status						
Standard of living index (score)	36.6±7.7	36.7±8.6	36.7±8.2	38.9±7.3	36.7±7.3	38.8±7.3
Maternal education (n (%))						
<10 completed years	88 (38.8)	75 (31.2)	163 (34.9)	84 (37.2)	72 (29.3)	156 (33.1)
-10 completed years	69 (30.4)	79 (32.9)	148 (31.7)	70 (31.0)	87 (35.4)	157 (33.3)
>10 completed years	70 (30.8)	86 (35.8)	156 (33.4)	72 (31.9)	87 (35.4)	159 (33.7)

Values are mean ± SD or medians (inter quartile range) unless otherwise stated.

Table 2. General characteristics of the study participants (cont.)

Variable	Participants during childhood			Participants during adolescence		
	Boys (n=228)	Girls (n=240)	All (n=468)	Boys (n=226)	Girls (n=246)	All (n=472)
Paternal education (n (%))						
<10 completed years	90 (39.7)	80 (33.3)	170 (36.4)	79 (35.0)	69 (28.1)	148 (31.4)
-10 completed years	80 (35.2)	103 (42.9)	183 (39.2)	58 (25.7)	51 (20.7)	109 (23.1)
>10 completed years	57 (25.1)	57 (23.8)	114 (24.4)	89 (39.4)	126 (51.2)	215 (45.6)
Maternal intelligence (score)	85.9±16.4	85.7±17.2	85.8±16.8	85.5±16.2	85.7±17.3	85.8±16.8
Home environment (score)	45.1±5.7	43.5±7.0	44.2±6.4	45.0±5.7	43.5±7.0	44.3±6.5

Values are mean ± SD or medians (inter quartile range) unless otherwise stated.

Table 3. Associations of covariates or confounders with cognitive outcomes and maternal 25-hydroxyvitamin D concentrations[†]

Covariates/confounders	β (95% CI)						
	Learning, long-term retrieval	Short-term memory	Reasoning ability	Verbal fluency	Visuo-spatial ability	Attention and concentration	Maternal 25-hydroxy vitamin D concentrations
Maternal age (years)	0.26 (-0.11, 0.63)	0.06 (0.004, 0.11)*	0.03 (0.01, 0.06)**	0.01 (-0.09, 0.12)	0.04 (0.02, 0.06)***	0.17 (0.01, 0.33)*	0.01 (-0.004, 0.02)
Maternal parity (0, 1 and ≥2)	-2.56 (-4.41, -0.71)**	-0.35 (-0.62, -0.07)*	-0.15 (-0.27, -0.04)**	-0.36 (-0.87, 0.15)	0.04 (-0.14, 0.07)	-0.01 (-0.83, 0.81)	0.06 (-0.01, 0.13)
Birthweight (kg)	3.09 (-0.66, 6.84)	0.23 (-0.33, 0.78)	0.16 (-0.07, 0.39)	-0.19 (-1.22, 0.84)	0.30 (0.09, 0.51)**	1.30 (-0.35, 2.95)	-0.08 (-0.23, 0.07)
Head circumference at birth (cm)	1.86 (0.62, 3.11)**	0.16 (-0.03, 0.34)	0.05 (-0.02, 0.13)	0.04 (-0.31, 0.38)	0.09 (0.02, 0.16)*	0.26 (-0.29, 0.82)	-0.008 (-0.06, 0.04)
Weight at age 2 years (kg)	2.31 (0.99, 3.64)**	0.40 (0.20, 0.59)***	0.14 (0.07, 0.23)***	0.31 (-0.06, 0.67)	0.11 (0.04, 0.19)**	1.02 (0.45, 1.59)***	-0.001 (-0.05, 0.05)
Length at age 2 years (cm)	1.02 (0.52, 1.52)***	0.15 (0.08, 0.23)***	0.07 (0.04, 0.10)***	0.15 (0.01, 0.29)*	0.06 (0.03, 0.09)***	0.43 (0.21, 0.65)***	-0.003 (-0.02, 0.02)
Head circumference at age 2 years (cm)	2.53 (1.35, 3.71)***	0.33 (0.16, 0.51)***	0.15 (0.08, 0.22)***	0.43 (0.10, 0.76)*	0.11 (0.04, 0.18)**	0.81 (0.29, 1.32)**	-0.006 (-0.05, 0.04)
Child's current BMI (kg/m^2)	1.58 (0.74, 2.43)***	0.18 (0.05, 0.30)**	0.09 (0.04, 0.14)***	0.31 (0.07, 0.54)**	0.04 (-0.01, 0.09)	0.75 (0.38, 1.12)***	0.004 (-0.03, 0.04)
Child's current head circumference (cm)	2.37 (1.28, 3.46)***	0.38 (0.22, 0.53)***	0.15 (0.09, 0.22)***	0.41 (0.10, 0.71)**	0.11 (0.05, 0.18)***	1.08 (0.60, 1.56)***	-0.008 (-0.05, 0.04)
Standard of living index (score)	0.42 (0.23, 0.61)***	0.07 (0.04, 0.10)***	0.03 (0.02, 0.05)***	0.10 (0.05, 0.16)***	0.03 (0.02, 0.04)***	0.19 (0.10, 0.27)***	-0.004 (-0.01, 0.003)
Maternal education (completed years)	1.06 (0.61, 1.51)***	0.22 (0.15, 0.28)***	0.09 (0.06, 0.11)***	0.25 (0.13, 0.37)***	0.09 (0.06, 0.11)***	0.44 (0.25, 0.64)***	-0.005 (-0.02, 0.01)
Paternal education (completed years)	0.78 (0.43, 1.12)***	0.12 (0.07, 0.17)***	0.07 (0.04, 0.09)***	0.17 (0.08, 0.27)**	0.06 (0.04, 0.08)***	0.35 (0.19, 0.50)***	0.008 (-0.006, 0.02)
Maternal intelligence (score)	0.21 (0.12, 0.31)***	0.03 (0.02, 0.04)***	0.02 (0.01, 0.02)***	0.02 (-0.01, 0.05)	0.01 (0.005, 0.02)***	0.05 (0.01, 0.09)*	-0.0008 (-0.005, 0.003)
Home environment (score)	0.58 (0.27, 0.89)***	0.08 (0.03, 0.12)***	0.06 (0.04, 0.08)***	0.18 (0.10, 0.27)***	0.04 (0.02, 0.06)***	0.36 (0.22, 0.49)***	-0.004 (-0.02, 0.01)

[†]Data presented for the participants during childhood. βis the effect size of the cognitive scores and maternal 25-hydroxy vitamin D concentrations per unit change in covariates/confounders, derived using multiple linear regression adjusted for the child's sex and current age, and using all variables as continuous.
*p<0.05; **p<0.01; ***p<0.001; p values derived by multiple linear regression adjusted for the child's sex and current age.

Table 4. Associations of maternal 25-hydroxyvitamin D concentrations in pregnancy with offspring cognitive performance during childhood

		Cognitive function tests					
Maternal vitamin D concentrations	N	Learning, long-term retrieval	Short-term memory	Reasoning ability	Verbal fluency	Visuo-spatial ability	Attention and concentration
Vitamin D status ,							
Score							
Normal (>50 nmol/L)	155	68.7±17.8	16.5±2.5	10.0 (4.0, 15.0)	16.4±5.4	77.5 (63.0, 89.3)	33.2±9.1
Low (<50 nmol/L)	313	67.8±17.3	16.5±2.6	10.0 (5.0, 13.0)	16.1±4.8	76.9 (63.7, 88.4)	32.7±7.8
p[†]		0.6	0.9	0.7	0.6	0.9	0.5
β (95% CI)[‡]							
Model 1	468	-0.03 (-0.23, 0.17)	0.04 (-0.15, 0.24)	-0.005 (-0.20, 0.19)	-0.01 (-0.20, 0.18)	-0.001 (-0.19, 0.19)	0.03 (-0.16, 0.21)
Model 2	468	0.01 (-0.20, 0.21)	0.05 (-0.16, 0.25)	0.003 (-0.20, 0.20)	-0.02 (-0.22, 0.18)	0.03 (-0.16, 0.23)	0.002 (-0.19, 0.19)
Model 3	465	-0.04 (-0.24, 0.15)	0.01 (-0.19, 0.21)	-0.04 (-0.23, 0.16)	-0.04 (-0.25, 0.16)	0.02 (-0.18, 0.21)	0.04 (-0.15, 0.22)
Vitamin D quartiles							
Score							
<23.5 nmol/L	121	68.3±16.7	16.5±2.6	10.0 (6.0, 13.0)	15.6±4.3	77.6 (63.7, 87.8)	32.7±7.9
23.6 – 38.9 nmol/L	113	67.7±17.2	16.3±2.4	10.0 (4.0,14.0)	16.3±5.1	75.0 (63.1, 89.2)	32.0±8.1
39.0 – 57.0 nmol/L	116	68.9±17.4	16.8±2.9	11.0 (7.0,14.0)	16.3±4.9	76.8 (66.3, 88.2)	33.4±7.7
>57.0 nmol/L	118	67.4±18.7	16.5±2.4	10.0 (4.0,14.0)	16.6±5.6	77.5 (62.0, 90.2)	33.3±9.3
p for trend[§]		0.7	0.9	0.2	0.6	0.9	0.7
β (95% CI)[¶]							
Model 1	468	-0.02 (-0.11, 0.07)	-0.01 (-0.10, 0.09)	-0.06 (-0.15, 0.04)	0.02 (-0.07, 0.12)	0.008 (-0.08, 0.10)	-0.02 (-0.11, 0.07)
Model 2	468	-0.03 (-0.13, 0.06)	-0.01 (-0.11, 0.09)	-0.06 (-0.16, 0.03)	0.03 (-0.07, 0.12)	-0.006 (-0.10, 0.09)	-0.01 (-0.10, 0.08)
Model 3	465	-0.01 (-0.11, 0.08)	0.005 (-0.09, 0.10)	-0.05 (-0.14, 0.04)	0.04 (-0.05, 0.14)	0.002 (-0.09, 0.09)	-0.02 (-0.11, 0.07)

Values are mean±SD or medians (inter quartile range) unless otherwise stated.

[†] *p* value for the difference in cognitive test scores between children of mothers with normal and low 25-hydroxyvitamin D concentrations derived using *t* test.

[‡] β (SD) is the difference in cognitive test score between children of mothers with normal and low 25-hydroxyvitamin D concentrations.

[§] *p* for trend adjusted for the child's sex and current age derived by multiple linear regression using 25-hydroxyvitamin D concentrations as a continuous variable.

[¶] β is the effect size (SD) of the cognitive test score per SD change in 25-hydroxyvitamin D concentrations (used as a continuous variable) derived by multiple linear regression.

Model 1: adjusted for the child's sex and current age.

Model 2: Model 1 + season at the time of blood sampling.

Model 3: Model 2 + gestational age, the child's birth weight, head circumference at birth, weight, length and head circumference at age 2 years, current BMI and head circumference, maternal age, parity, standard of living index, maternal and paternal education, maternal intelligence (imputed) and home environment (imputed).

Table 5. Associations of maternal 25-hydroxyvitamin D concentrations in pregnancy with offspring cognitive performance during adolescence

Maternal vitamin D concentrations	N	Cognitive function tests					
		Learning, long-term retrieval	Short-term memory	Reasoning ability	Verbal fluency	Visuo-spatial ability	Attention and concentration
Vitamin D status							
Score							
Normal (>50 nmol/L)	152	80.3±15.7	19.1±4.0	16.4±7.0	21.7±5.8	85.5±25.3	48.6±12.1
Low (<50 nmol/L)	320	79.9±14.0	19.0±3.7	15.3±6.4	21.1±5.7	83.0±26.1	47.5±10.4
p[†]		0.7	0.8	0.1	0.3	0.3	0.3
β (95% CI)[‡]							
Model 1	472	-0.02 (-0.21, 0.18)	-0.01 (-0.21, 0.18)	-0.14 (-0.34, 0.05)	-0.09 (-0.29, 0.10)	-0.08 (-0.28, 0.11)	-0.07 (-0.25, 0.12)
Model 2	472	0.06 (-0.14, 0.27)	0.02 (-0.18, 0.22)	-0.07 (-0.28, 0.13)	-0.14 (-0.33, 0.06)	-0.08 (-0.28, 0.12)	-0.11 (-0.30, 0.08)
Model 3	472	0.04 (-0.17, 0.24)	0.01 (-0.20, 0.21)	-0.10 (-0.28, 0.10)	-0.12 (-0.32, 0.08)	-0.08 (-0.28, 0.12)	-0.07 (-0.26, 0.12)
Vitamin D quartiles							
Score							
<23.5 nmol/L	123	80.9±13.4	19.2±3.7	15.4±6.4	20.7±5.3	82.3±26.1	47.7±10.6
23.6–38.9 nmol/L	118	79.0±13.7	18.7±3.7	14.8±6.6	20.8±6.1	83.6±26.1	46.5±11.0
39.0–57.0 nmol/L	116	80.0±15.0	19.0±3.8	16.2±6.6	22.1±5.7	83.5±25.3	48.9±10.6
>57.0 nmol/L	115	79.8±16.2	19.1±4.1	16.3±7.1	21.8±5.8	86.0±26.0	48.3±11.8
p for trend[§]		0.7	0.7	0.7	0.08	0.6	0.9
β (95% CI)[‡]							
Model 1	472	-0.02 (-0.11, 0.08)	-0.02 (-0.11, 0.07)	0.02 (-0.07, 0.11)	0.08 (-0.01, 0.17)	0.03 (-0.07, 0.12)	0.003 (-0.08, 0.09)
Model 2	472	-0.05 (-0.15, 0.04)	-0.04 (-0.13, 0.06)	-0.01 (-0.11, 0.08)	0.10 (0.01, 0.19)[*]	0.02 (-0.07, 0.12)	0.02 (-0.07, 0.11)
Model 3	472	-0.02 (-0.11, 0.08)	-0.02 (-0.12, 0.07)	0.01 (-0.08, 0.10)	0.10 (0.01, 0.20)[*]	0.03 (-0.07, 0.12)	0.02 (-0.07, 0.11)

Values are mean ± SD unless otherwise stated

[†] *p* value for the difference in cognitive test scores between children of mothers with normal and low 25-hydroxyvitamin D concentrations derived using t test

[‡] β (SD) is the difference in cognitive test score between children of mothers with normal and low 25-hydroxyvitamin D concentrations

[§] *p* for trend adjusted for the child's sex and current age derived by multiple linear regression using 25-hydroxyvitamin D concentrations as a continuous variable

[¶] β is the effect size (SD) of the cognitive test score per SD change in 25-hydroxyvitamin D concentrations (used as a continuous variable) derived by multiple linear regression

Model 1: adjusted for the child's sex and current age

Model 2: Model 1 + season at the time of blood sampling

Model 3: Model 2 + gestational age, the child's birth weight, head circumference at birth, weight, length and head circumference at age 2 years current BMI and head circumference, maternal age, parity, standard of living index, maternal and paternal education, maternal intelligence (imputed) and home environment (imputed)

[*] $p<0.05$; *p* values derived by multiple linear regression

ternal 25-hydroxyvitamin D concentrations in ~14% of the participants was a limitation. However, birth size, socio-demographic factors and cognitive scores were similar among those who did and did not have this data and therefore the risk of bias is low. Other important limitations were lack of information on maternal diet, sunlight exposure, and use of vitamin D supplements at the time of blood sampling and the child's vitamin D status.

The high prevalence of maternal vitamin D deficiency in our study is consistent with findings in other Indian[7,8,37-39] and western populations.[17,18,20] South Asians, both in their country of origin and after migration to Europe or the USA, have lower vitamin D concentrations than white Caucasians,[8,40] probably because of skin pigmentation, dress code (especially in women) and low dietary vitamin D intake. Another possible reason may be differences in vitamin D metabolism in Asian Indians; *in vitro* studies have shown that tissue fibroblasts have increased 25-hydroxy-24-hydroxylase activity, leading to increased catabolism of activated vitamin D and therefore an increased risk of developing vitamin D deficiency.[41]

We found no significant associations between intake of vitamin supplements and 25-hydroxyvitamin D concentrations. This is possibly due to a lack of complete information on supplement intake, as the study was not originally designed to examine maternal vitamin D status and supplement use was recorded only at the time of recruitment. Among women recruited between 24 and 32 week gestation, very few were taking supplements. Women who took supplements in early pregnancy might have stopped taking them by 30 week and women not taking supplements at recruitment may have been prescribed them later in pregnancy. However, despite the common practice of obstetricians prescribing calcium and vitamin D during the second trimester of pregnancy, many women had low 25-hydroxyvitamin D concentrations.

The finding of seasonal variation in 25-hydroxyvitamin D concentrations in our study is probably related to sunlight exposure. As reported earlier, although data on sunlight exposure was not available, 25-hydroxyvitamin D concentrations were lowest during the cloudy rainy season, and the summer season when people avoid the hot sun, and highest in the winter season when the weather is cooler and people go out in the sun.[21] Seasonal variations in 25-hydroxyvitamin D concentrations and correlations with sunlight exposure have been reported in other Indian[8] and Asian populations.[42] Low 25-hydroxyvitamin D concentrations during winter have been reported among western populations.[40,43]

In our study, neither maternal vitamin D status (low versus normal) nor the range of 25-hydroxyvitamin D concentrations at 30±2 weeks of gestation was associated with cognitive performance in the children at either time point. Consistent with our findings, a study with a very small sample (n=178) in the UK found no associations between maternal vitamin D status at 32 weeks of gestation and offspring IQ assessed using Wechsler Abbreviated Scale of Intelligence at age 9 years.[18] Similarly, a study in Denmark (n=850) found no association of maternal 25-hydroxyvitamin D concentrations at 30 weeks of gestation with children's scholastic achievement at age 15-16 years.[19] A large study in the USA (n=3,896) assessed maternal 25-hydroxyvitamin D concentrations at ≤26 weeks gestation and children's global infant development at age 8 months using the Bayley Scales of Mental and Motor Development, IQ at age 4 and 7 years using the Stanford-Binet Intelligence Scale and the Wechsler Intelligence Scale for Children respectively, and a student achievement test at 7 years.[20] Findings were mostly *null* except for a small positive association with offspring IQ (0.10 score points per 5nmol/L increase in maternal 25-hydroxyvitamin D concentration) at age 7 years. In contrast to our findings, a study in Spain (n=1,800) found a positive association between maternal 25-hydroxyvitamin D concentrations at 12-23 weeks of gestation and offspring mental and psychomotor development scores (0.8-0.9 score points (~0.06 SD) per 25 nmol/L increase) assessed using the Bayley Scales of Infant Development at age 11-23 months.[16] It also found higher mental and psychomotor development scores (2-3 score points (0.1-0.2 SD)) in children of mothers with normal vitamin D status (>75 nmol/L) compared with children of deficient (<50 nmol/L) mothers. A study in Australia (n=~500) observed a two-fold increase in language impairment (assessed using the Peabody Picture Vocabulary Test-Revised) in 5 and 10 years old children of mothers with vitamin D deficiency (<46 nmol/L) at 18 weeks of gestation compared with children of mothers with normal vitamin D status (>70 nmol/L).[17] Comparison of our study with these studies is difficult due to differing ages of children and test batteries used, but it is notable that the two positive studies measured maternal vitamin D status during the second trimester of pregnancy, while the others (including ours) measured it in the third trimester. It is possible that there is a critical period for neurodevelopment in mid-pregnancy, when vitamin D is required. The lack of association in our study may reflect adaptation of the Indian population to low sunlight exposure and/or low dietary intakes across centuries of cultural dress codes for women and vegetarian diets. Alternatively, the positive associations between maternal vitamin D status and offspring cognitive function in two developed populations[16,17] could have been due to confounding rather than a biological effect of vitamin D; these studies did not adjust for maternal intelligence or home stimulation and care.

In conclusion, in this Indian population, despite a wide variation in maternal vitamin D concentrations and a high prevalence of low maternal 25-hydroxyvitamin D concentrations, maternal vitamin D status was unrelated to the children's cognitive function. Our findings add to a very small literature on this topic; randomized controlled trials of vitamin D supplementation in pregnancy would be valuable in clarifying the importance of maternal vitamin D status for offspring cognitive function.

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AUTHOR DISCLOSURES

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