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Maternal Plasma 25-Hydroxyvitamin D during Gestation Is Positively Associated with Neurocognitive Development in Offspring at Age 4–6 Years

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ABSTRACT

Background: Vitamin D is critical to embryonic neuronal differentiation and other developmental processes that may affect future neurocognitive function. However, observational studies have found inconsistent associations between gestational vitamin D and neurocognitive outcomes.

Objectives: We examined the association of gestational 25-hydroxyvitamin D [25(OH)D] with children's IQ at 4–6 y, and explored whether associations differed by race.

Methods: This study used data from the CANDLE (Conditions Affecting Neurocognitive Development and Learning in Early Childhood) cohort. Between 2006 and 2011, CANDLE recruited 1503 women in their second trimester of healthy singleton pregnancies. Inclusion criteria for this analysis were gestation of ≥34 wk and availability of 25(OH)D and IQ data. Associations between second-trimester 25(OH)D plasma concentration and Stanford-Binet IQ scores in offspring at 4–6 y were examined using multivariable linear regression; interaction terms were used to explore possible effect modification by race.

Results: Mean ± SD 25(OH)D concentration among 1019 eligible dyads was 21.6 ± 8.4 ng/mL, measured at a mean ± SD gestational age of 23.0 ± 3.0 wk. Vitamin D deficiency [25(OH)D < 20 ng/mL] was observed in 45.6%. Maternal 25(OH)D differed by race with a mean ± SD of 19.8 ± 7.2 ng/mL in Blacks sand 25.9 ± 9.3 ng/mL in Whites ($P < 0.001$). In adjusted models a 10-ng/mL increase in 25(OH)D was associated with a 1.17-point higher Full Scale IQ (95% CI: 0.27, 2.06 points), a 1.17-point higher Verbal IQ (95% CI: 0.19, 2.15 points), and a 1.03-point higher Nonverbal IQ (95% CI: 0.10, 1.95 points). We observed no evidence of effect modification by race.

Conclusions: Second-trimester maternal 25(OH)D was positively associated with IQ at 4–6 y, suggesting that gestational vitamin D status may be an important predictor of neurocognitive development. These findings may help inform prenatal nutrition recommendations and may be especially relevant for Black and other dark-skinned women at high risk of vitamin D deficiency. *J Nutr* 2021;151:132–139.

Keywords: vitamin D, 25-hydroxyvitamin D, neurodevelopment, IQ, prenatal nutrition

Introduction

Vitamin D deficiency is a worldwide problem affecting the general public and women of childbearing age (1, 2), especially among those with darker skin (3). Observational studies have linked low perinatal and prenatal vitamin D to developmental brain disorders including schizophrenia and autism (4–6), and some (7–9) but not all (10–13) cohort studies have found positive associations between gestational vitamin D and childhood IQ. During gestation vitamin D influences the expression of genes that regulate the production, migration, and differentiation of neuronal structures, setting the foundation for many aspects of future neurocognitive development (14–16).

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The vitamin D receptor (VDR) is expressed in the mammalian brain as early as 12 d into gestation (17) and VDRs are found throughout brain matter (18). Maternal vitamin D is transported through the placenta (19), and by binding to VDR in the fetal brain, it exerts transcriptional control over many genes related to structural brain development (20). Vitamin D influences embryonic neuronal differentiation (21, 22), regulates neurotransmitter concentrations (23–25), and plays a role in regulating neuronal calcium, reactive oxygen species, and neurotrophic factors (26). Therefore, gestational vitamin D status may have important implications for neurocognitive development in offspring.

Cutaneous synthesis is a major source of vitamin D for many individuals, because the modern diet has few rich sources of vitamin D. Cutaneous synthesis is reduced in Blacks and others with pigmented skin due to the absorption of UV radiation by melanin (3), making these populations especially vulnerable to deficiency. Vitamin D deficiency in the general population is defined by the Institute of Medicine (IOM) as 25-hydroxyvitamin D [25(OH)D] concentrations <20 ng/mL, and is based on bone health (27). Desirable concentrations in pregnant women have yet to be established and may differ from those in the general public (28). Nationally representative data from 2001–2006 indicated that 13% of White pregnant women in the United States had 25(OH)D concentrations <20 ng/mL compared with 80% of pregnant Black women (2). Thus, the potential consequences of gestational vitamin D deficiency may disproportionately affect children of Black women.

We previously reported that maternal 25(OH)D status during pregnancy was associated with receptive language in offspring at age 2 y in a majority Black cohort, the CANDLE (Conditions Affecting Neurocognitive Development and Learning in Early Childhood) study (29). Whether or not this association persists beyond age 2 y in this population with high vulnerability to vitamin D deficiency has not yet been explored. The aim of this study was to examine the hypothesis that maternal 25(OH)D during pregnancy is associated with neurocognitive development through 4–6 y of age.

Methods

Study design and population

The CANDLE study, which has been described in detail previously (30), was designed to examine biological and environmental influences on early childhood neurocognitive development. CANDLE is a prospective pregnancy cohort study in Shelby County, Tennessee, that recruited pregnant women between December 2006 and July 2011. Women were eligible for participation if they were between 16 and 28 weeks of gestation, had a singleton low-risk pregnancy, resided in Shelby County, and planned to deliver at one of the 5 participating health care settings in the county. The CANDLE study conducted 2 clinic visits during pregnancy, 1 at labor and delivery, annual visits after birth, frequent phone visits, and 2 home visits during early childhood.

Mother–child dyads in the CANDLE study were excluded from this analysis if mothers delivered earlier than 34 weeks of gestation ($n = 34$), if data were unavailable for second-trimester 25(OH)D plasma concentration ($n = 26$), or if children did not have complete and valid IQ testing at the age 4–6 y visit ($n = 448$).

Maternal measures

At baseline clinic visits conducted during the second trimester, research staff collected maternal demographic information. Women self-reported their race and ethnicity, household income, educational attainment, and marital status. Self-reported health insurance status was collapsed to a binary variable, coded as either public (Medicare, Medicaid, or TennCare) or private/other (employer, union, private, military, or other source). Women also reported whether they had used alcohol or tobacco during this pregnancy and responses were coded as binary. Prepregnancy BMI was calculated from women's self-reported weight and height (in kg/m^2). Research staff administered the Block 2005 FFQ, a validated 111-item questionnaire used to estimate usual dietary intake over the preceding 3 mo (31). FFQ data were used to estimate diet quality using the Healthy Eating Index (HEI) 2010, a measure with a maximum score of 100 that assesses conformance with US dietary guidance (32). Maternal IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (33).

Venous blood was collected from mothers during baseline visits at 16–28 weeks of gestation. Blood samples were transported on ice, centrifuged at 4°C, divided into aliquots, and frozen at −20°C within 6 h of collection. Plasma concentrations of 25(OH)D, the most reliable marker of vitamin D status (34), were measured using a commercial enzymatic immunoassay kit (Immunodiagnostic Systems) according to the manufacturer's instructions. Assays were performed at the University of Tennessee Health Science Center in a laboratory that participates in the College of American Pathology Quality Assessment Program for 25(OH)D assays. National Institute of Standards and Technology SRM972 Vitamin D was used for quality assurance of 25(OH)D. The minimum detection range of the assay was 2 ng/mL. The interassay variability was <6% for the laboratory assay controls, and precision was within 1 SD of the mean vitamin D concentration.

Child IQ assessment

Child IQ was measured at the age 4–6 y study visit using the Stanford-Binet Intelligence Scales, Fifth Edition (SB5) (35). The SB5 was normed and standardized using a diverse sample of 4800 individuals in the United States (36, 37) and has been extensively tested for reliability and validity (38, 39). The SB5 is composed of 10 subtests, 5 of which are verbal and 5 nonverbal. The 5 verbal subtests yield a Verbal IQ (VIQ) and the 5 nonverbal subtests yield a Nonverbal IQ (NVIQ). The VIQ and NVIQ are then combined to yield a composite score, Full Scale IQ (FSIQ), with a mean of 100 and an SD of 15. FSIQ was examined as the primary outcome in this study; VIQ and NVIQ were examined as secondary outcomes.

Data analysis

All data analysis was conducted using SAS version 9.4 (SAS Institute). Descriptive statistics were calculated to characterize the study sample overall and by vitamin D status defined using the IOM deficiency cutoff of 20 ng/mL (27).

Associations of maternal vitamin D status with IQ outcomes were examined through multivariable linear regression with robust SEs using maximum likelihood type robust estimates as introduced by Huber (40). All model covariates were chosen a priori based on existing evidence with no reliance on statistical significance. Minimally adjusted models included the child's sex and age (continuous) at the time of the age 4–6 y assessment as covariates. The fully adjusted models also included the following suspected confounders and precision variables: HEI 2010 score (41, 42) (continuous), insurance status (43,

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Supplemental Table 1 is 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: BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; FSIQ, full scale IQ; HEI, Healthy Eating Index; IOM, Institute of Medicine; NVIQ, nonverbal IQ; SB5, Stanford-Binet Intelligence Scales, Fifth Edition; VDR, vitamin D receptor; VIQ, verbal IQ; 25(OH)D, 25-hydroxyvitamin D.

44) (public, private/other), maternal IQ (43, 45) (continuous), maternal education (44, 45) (less than high school, high school diploma, technical school, college degree, graduate or professional degree), maternal age (46) (continuous), marital status (44, 45) (cohabitation, single), prepregnancy BMI (47, 48) (continuous), tobacco use during pregnancy (49, 50) (yes, no), alcohol use during pregnancy (51, 52) (yes, no), race (53–55) (Black, White, other/multiple races), mother's parity (45) (continuous), and annual household income adjusted for the number of children and adults supported by the income (43, 44, 56) (continuous). Because of differences in vitamin D metabolism between Blacks and Whites (57, 58) we examined the possibility of effect modification by race using additional models that included an interaction term between race and 25(OH)D concentration. These interaction models excluded the small portion of women who identified as multiple/other races (6.5%) in order to specifically examine the implications of differing vitamin D metabolism between Black and White women.

Complete data for the covariates used in the fully adjusted regression models were available for 88% of the eligible sample. Missingness of each covariate was <1% except for HEI score, which was missing among 11% of eligible participants. Covariate data were assumed to be missing at random, and were multiply imputed by fully conditional specification, a validated method ideal for imputation in large epidemiologic data sets consisting of variables on differing scales and with complex relations (59). The discriminant function was used to impute variables with binary or nominal responses, whereas the regression method was used for continuous variables. Imputed data sets ($n = 10$) were used to conduct regression analyses and data were pooled to generate inferential statistics.

Supplemental analyses were conducted to examine potential nonlinearity in dose-response between 25(OH)D concentration and IQ. We explored the association of vitamin D status as a binary variable [25(OH)D < 20 ng/mL compared with ≥20 ng/mL] with IQ scores in our fully adjusted regression models. In addition, to allow a more flexible fit to the data, we created fully adjusted regression models applying a natural cubic spline effect to the 25(OH)D variable.

Results

Participant characteristics

Mean age of mothers at the time of enrollment was 26 y and most (63.2%) identified as Black (**Table 1**). Over half (59.3%) were insured through Medicaid or Medicare and 32% had earned a college degree or above at the time of enrollment. Approximately two-thirds (67.1%) had an adjusted annual income of <$22,000. Mean ± SD age of children at the time of IQ assessment was 4.4 ± 0.6 y (minimum: 3.8 y; 5th percentile: 4.0 y; 95th percentile: 5.4 y; maximum: 8.0 y). Participants who were enrolled in CANDLE but excluded from this analysis were generally similar in sociodemographic characteristics to those included in the analysis (**Supplemental Table 1**).

Mean ± SD maternal 25(OH)D was 21.6 ± 8.4 ng/mL and nearly half (45.6%) of participants had 25(OH)D concentrations < 20 ng/mL. Compared with women with lower 25(OH)D, those with concentrations ≥20 ng/mL were more likely to experience socioeconomic advantages including higher educational attainment, greater income, and higher diet quality. Mean ± SD 25(OH)D concentration was higher in White women (25.9 ± 9.3 ng/mL) than in Black women (19.8 ± 7.2 ng/mL) ($P < 0.001$).

Modeling of gestational 25(OH)D and IQ scores

In multivariable linear regression models adjusted for child sex and age, plasma 25(OH)D was significantly and positively associated with FSIQ, VIQ, and NVIQ (**Figure 1**). After additional adjustment for socioeconomic and demographic factors, a 10-ng/mL increase in 25(OH)D was associated with a 1.17-point (95% CI: 0.27, 2.06 points) greater FSIQ, 1.17-point (95% CI: 0.19, 2.15 points) greater VIQ, and 1.03-point (95% CI: 0.10, 1.95 points) greater NVIQ. Interaction terms used to examine potential effect modification by race were nonsignificant (*P*-interaction: FSIQ: 0.22; VIQ: 0.42; NVIQ: 0.12) (**Table 2**).

When we examined vitamin D as a binary variable in fully adjusted models, having 25(OH)D concentrations ≥20 ng/mL was associated with a 2.23-point (95% CI: 0.76, 3.70 points) greater FSIQ, 1.65-point (95% CI: 0.04, 3.25 points) greater VIQ, and 2.61-point (95% CI: 1.10, 4.12 points) greater NVIQ than predicted for those with 25(OH)D deficiency (<20 ng/mL). A natural cubic spline used to visualize the bivariate association of 25(OH)D with FSIQ suggested no marked departures from linearity through 25(OH)D concentrations of ~40 ng/mL, a range that encompassed the observed 25(OH)D values of 992 (97%) of the 1019 mothers (**Figure 2**). In fully adjusted regression models, the natural cubic spline effect added to the 25(OH)D variable (knots at 22.0, 37.5, and 52.9 ng/mL) did not meaningfully improve model fit. Residual plots from models both with and without spline effects exhibited homoscedasticity without detectable outliers or patterns.

Discussion

We observed that maternal 25(OH)D during pregnancy is positively associated with children's FSIQ, VIQ, and NVIQ at age 4–6 y. We previously reported that maternal 25(OH)D was positively associated with receptive language development at 2 y in CANDLE, as assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) (29). This analysis suggests that an association between gestational 25(OH)D and neurocognitive development may persist through age 4–6 y. Associations between 25(OH)D concentrations and offspring IQ were similar between races. Because of the high risk of vitamin D deficiency in Black women due to skin melanin content, the implications of these findings may be especially relevant to this population.

The observed effect size of 1.17-point greater FSIQ per 10-ng/mL 25(OH)D may translate meaningfully to other positive future outcomes. It has been estimated that for each IQ point decrement, males experience a 1.93% decrease in lifetime earnings and females experience a 3.23% decrease (60). In addition, a meta-analysis revealed that a 1-SD advantage in cognitive test scores was associated with a 24% lower risk of death during 17–69 y of follow-up (61).

Our findings are consistent with results from several other prospective cohorts around the world. In rural Vietnam, infants born to mothers with 25(OH)D < 15 ng/mL had significantly lower BSID-III developmental language scores at 6 mo of age than those born to mothers with sufficient 25(OH)D (defined as ≥30 ng/mL) (9). Gestational 25(OH)D was also associated with greater BSID-III mental and psychomotor development scores at 14 mo in a Spanish cohort (8). Similarly, among Caucasian women in an Australian cohort gestational 25(OH)D was inversely associated with language impairment at ages 5 and 10 y (7). In 2 other predominantly Caucasian cohorts from Australia and Denmark, neonatal and cord blood 25(OH)D concentrations, which correlate with maternal 25(OH)D (62, 63), were positively associated with language development at 18 mo and 4 y (64), and with IQ at 19 y (65).

TABLE 1 Characteristics of the study population, overall and with stratification by plasma 25(OH)D status[1]

		Second-trimester maternal 25(OH)D status	
	Overall	<20 ng/mL	≥20 ng/mL
n	1019	465	554
Maternal age, y	26.4 ± 5.6	25.4 ± 5.4	27.3 ± 5.6
Maternal race			
Black	644 (63.2)	348 (74.8)	296 (53.4)
White	309 (30.3)	77 (16.6)	232 (41.9)
Other or multiple races	66 (6.5)	40 (8.6)	26 (4.7)
Maternal education[2]			
Less than high school diploma	119 (11.7)	81 (17.5)	38 (6.9)
High school diploma or GED	477 (46.9)	238 (51.2)	239 (43.1)
Technical school	96 (9.4)	48 (10.3)	48 (8.7)
College degree	206 (20.2)	63 (13.6)	143 (25.8)
Graduate/professional degree	120 (11.8)	34 (7.3)	86 (15.5)
Maternal IQ[2,3]			
<85	278 (27.6)	174 (37.9)	104 (18.9)
85 to <100	327 (32.4)	160 (34.9)	167 (30.4)
100 to <115	270 (26.8)	89 (19.4)	181 (32.9)
≥115	134 (13.3)	36 (7.8)	98 (17.8)
Prepregnancy BMI status[2,4]			
Underweight	48 (4.7)	23 (5.0)	25 (4.5)
Normal weight	384 (37.8)	147 (31.8)	237 (42.8)
Overweight	245 (24.1)	117 (25.3)	128 (23.1)
Obese	339 (33.4)	175 (37.9)	164 (29.6)
Maternal marital status[2]			
Cohabitation	570 (55.9)	212 (45.6)	358 (64.6)
Single	448 (44.0)	252 (54.2)	196 (35.4)
Health insurance status			
Public	604 (59.3)	340 (73.1)	264 (47.7)
Private/other	415 (40.7)	125 (26.9)	290 (52.4)
Adjusted household income,[2] $			
<10k	438 (43.1)	273 (59.1)	165 (29.8)
10k to <16k	136 (13.4)	57 (12.3)	79 (14.3)
16k to <22k	108 (10.6)	38 (8.2)	70 (12.6)
22k to <40k	188 (18.5)	59 (12.8)	129 (23.3)
≥40k	146 (14.4)	35 (7.6)	111 (20.0)
Prenatal alcohol use (yes)[2]	88 (8.6)	30 (6.5)	58 (10.5)
Prenatal tobacco use (yes)[2]	93 (9.1)	48 (10.3)	45 (8.1)
Maternal 25(OH)D, ng/mL	21.6 ± 8.4	14.4 ± 3.1	27.6 ± 6.4
Maternal 25(OH)D status			
<20 ng/mL	465 (45.6)	465 (100)	—
20 to <30 ng/mL	413 (40.5)	—	413 (74.6)
≥30 ng/mL	141 (13.8)	—	141 (25.5)
Maternal HEI 2010 score[2]	60.2 ± 11.3	57.7 ± 11.1	62.0 ± 11.1
Child age at assessment, y	4.4 ± 0.6	4.5 ± 0.6	4.3 ± 0.5
Child sex			
Male	504 (49.5)	226 (48.6)	278 (50.2)
Female	515 (50.5)	239 (51.4)	276 (49.8)
Child IQ[3]			
Full Scale IQ	100.0 ± 14.9	96.0 ± 14.5	103.3 ± 14.5
Verbal IQ	99.3 ± 15.2	95.5 ± 14.8	102.4 ± 14.8
Nonverbal IQ	101.1 ± 14.7	97.3 ± 14.3	104.3 ± 14.4

[1] Values are mean ± SDs or *n* (%). HEI, Healthy Eating Index; 25(OH)D, 25-hydroxyvitamin D.
[2] Maternal education, marital status, alcohol use, and tobacco use were missing for 1 participant each; prepregnancy BMI (in kg/m^2) and adjusted household income were missing for 3 participants each; maternal IQ was missing for 10 participants; HEI score was missing for 112 participants; percentages were calculated after excluding missing cases from the denominator.
[3] Maternal IQ was assessed using the Wechsler Abbreviated Scale of Intelligence; child IQ was assessed using the Stanford-Binet Intelligence Scales, Fifth Edition.
[4] BMI status was classified using CDC guidelines: BMI < 18.5 was considered underweight; BMI ≥ 18.5 and <25 was considered normal weight; BMI ≥ 25 and <30 was considered overweight; BMI ≥ 30 was considered obese.

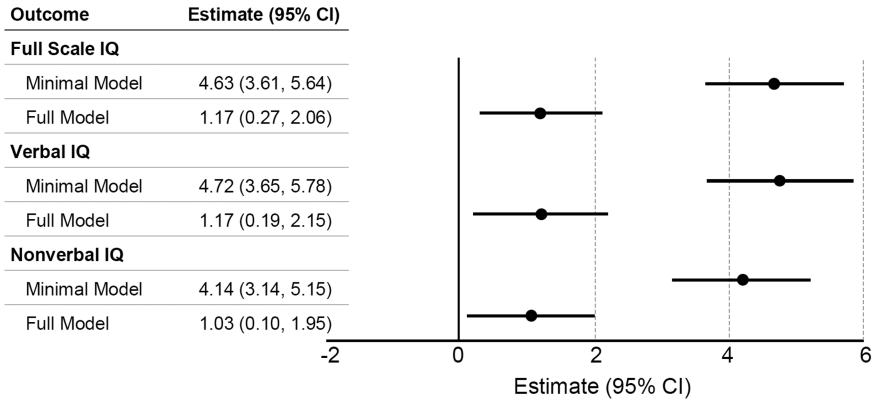

FIGURE 1 Estimated difference in offspring Stanford-Binet Intelligence Scales, Fifth Edition IQ per 10-ng/mL increase in maternal plasma 25-hydroxyvitamin D. The minimal model adjusted for child sex (male, female) and child age at year 4 assessment (continuous). The full model adjusted for the covariates in the minimal model plus prepregnancy BMI (continuous), race (Black, White, other/multiple races), mother's IQ (continuous), mother's education (less than high school, high school diploma, technical school, college degree, graduate/professional degree), marital status (cohabitation, single), previous pregnancies to term (continuous), health insurance (public, private/other), alcohol use (yes, no), tobacco use (yes, no), mother's age at baseline (continuous), Healthy Eating Index 2010 score (continuous), and income (continuous).

Results of other studies, however, have not fully confirmed an association. In a cohort in Greece, maternal vitamin D was not associated with cognitive function at age 4 y, but was negatively associated with behavioral difficulties, hyperactivity/inattention, and externalizing behavior (66). Another cohort in England found that gestational vitamin D was not significantly associated with IQ at age 8 y, but was positively associated with motor and social development in children <4 y old (67). Other observational studies detected no association between gestational 25(OH)D and children's neurodevelopmental outcomes (10–13, 68, 69).

Differences in findings between studies may be related to several factors including differences in the vitamin D status of participants. Nearly half of the mothers in CANDLE were classified as deficient in 25(OH)D (<20 ng/mL), which is likely related to the predominance of Black participants. In contrast, several studies that did not detect significant associations were comprised of populations in which deficiency was relatively uncommon (67, 69) or not observed at all (10). In addition, whereas we separately examined 25(OH)D as a continuous and a binary variable, others have considered vitamin D only as a categorical exposure (12, 66, 67, 70). Our categorical

TABLE 2 Estimated regression coefficients (95% CIs) for association of maternal plasma 25(OH)D concentration and IQ at 4–6 y with interaction of race and 25(OH)D[1]

	Outcome		
Model term	Full Scale IQ	Verbal IQ	Nonverbal IQ
Maternal 25(OH)D (ng/mL) × race (Black)[2]	0.11 (−0.07, 0.29)	0.08 (−0.12, 0.28)	0.15 (−0.04, 0.33)
Maternal 25(OH)D, ng/mL	0.06 (−0.07, 0.20)	0.08 (−0.07, 0.23)	0.03 (−0.11, 0.17)
Maternal race, Black	−6.22 (−11.09, −1.37)	−5.74 (−11.04, −0.44)	−6.11 (−11.14, −1.09)
Maternal age, y	0.23 (0.04, 0.43)	0.15 (−0.07, 0.36)	0.24 (0.04, 0.44)
Maternal education			
Less than high school diploma	−2.18 (−6.30, 1.94)	−2.82 (−7.32, 1.67)	−1.93 (−6.19, 2.32)
High school diploma or GED	−0.33 (−3.52, 2.86)	−2.00 (−5.49, 1.48)	0.75 (−2.55, 4.05)
Technical school	1.80 (−1.80, 5.39)	−0.17 (−4.09, 3.75)	2.60 (−1.11, 6.31)
College degree	0.71 (−1.98, 3.41)	−0.90 (−3.84, 2.04)	2.03 (−0.76, 4.82)
Graduate/professional degree	—	—	—
Maternal IQ	0.19 (0.12, 0.26)	0.18 (0.10, 0.26)	0.18 (0.11, 0.25)
Prepregnancy BMI, kg/m^2	−0.09 (−0.19, 0.00)	−0.09 (−0.19, 0.01)	−0.09 (−0.18, 0.01)
Maternal marital status (single)	−0.39 (−2.16, 1.37)	0.18 (−1.75, 2.11)	−1.04 (−2.87, 0.79)
Health insurance (public)	−0.51 (−2.68, 1.65)	−0.64 (−3.01, 1.72)	−0.41 (−2.65, 1.83)
Adjusted household income (in thousands of dollars)	0.04 (0.00, 0.12)	0.07 (0.00, 0.10)	0.02 (−0.10, 0.10)
Prenatal alcohol use (no)	−2.07 (−4.63, 0.47)	−2.21 (−4.99, 0.57)	−1.56 (−4.20, 1.07)
Prenatal tobacco use (no)	2.65 (0.07, 5.23)	2.95 (0.13, 5.76)	2.46 (−0.21, 5.13)
Parity	−1.59 (−2.30, −0.87)	−1.47 (−2.26, −0.69)	−1.50 (−2.25, −0.76)
Maternal HEI 2010 score	0.07 (−0.01, 0.14)	0.07 (−0.01, 0.16)	0.05 (−0.03, 0.14)
Child age at assessment, y	−1.06 (−2.42, 0.30)	−0.96 (−2.45, 0.53)	−0.94 (−2.35, 0.47)
Child sex (male)	−3.69 (−5.10, −2.28)	−4.55 (−6.09, −3.01)	−2.86 (−4.32, −1.41)
Intercept	84.80 (71.65, 97.95)	86.47 (72.13, 100.82)	85.07 (71.46, 98.68)

[1] Interaction models were created using data from participants identified as either White or Black (n = 953). HEI, Healthy Eating Index; 25(OH)D, 25-hydroxyvitamin D.
[2] Interaction coefficients represent the estimated difference in the slope of the relation between 25(OH)D (ng/mL) and IQ predicted for Blacks compared with Whites.

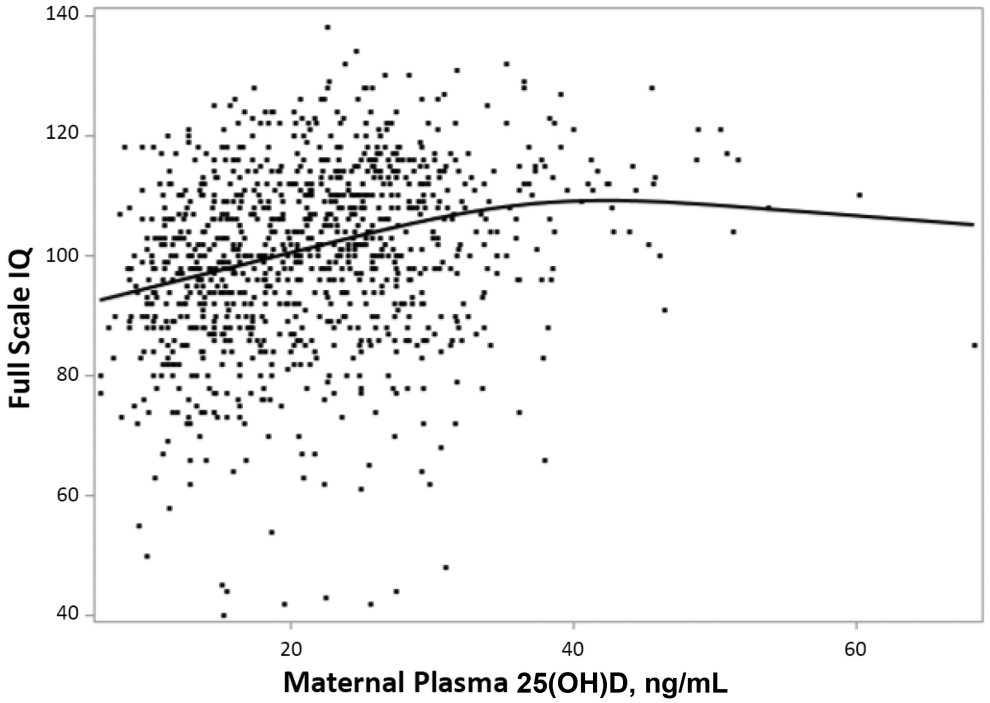

FIGURE 2 Natural cubic spline regression of maternal plasma 25(OH)D concentration and offspring Full Scale IQ. 25(OH)D, 25-hydroxyvitamin D.

and continuous modeling approaches both revealed positive associations between 25(OH)D and IQ. However, it is possible that use of certain categorization schemas may obscure a true relationship, particularly in cohorts with little variation in vitamin D concentrations or those with few cases of vitamin D deficiency.

Findings from observational studies may also differ because of the timing of vitamin D assessment during pregnancy. This study and multiple others have found that first- (66, 71) or second-trimester (7, 8, 29) maternal vitamin D was significantly and positively associated with neurocognitive outcomes, but only 1 (64) of several studies (4, 10, 64, 68) that examined vitamin D at delivery found a significant relationship. These observations may suggest that a critical window exists early in gestation, yet experimental data from animals have suggested a critical window in late pregnancy (72). Further study is needed to clarify these potential critical periods.

Animal studies support the biological plausibility of our findings, demonstrating that gestational vitamin D deficiency can alter brain morphology in offspring (73, 74) and disrupt normal regulation of the cell cycle and apoptosis in the developing brain (75). Experimental studies also indicate that vitamin D deficiency may impair the synthesis of neurotrophic factors and reduce the expression of neurotrophic receptors (73, 76, 77). Deficiency may affect genes related to speech and language development (74) and lead to disturbed brain function in adult offspring (72, 78). Localization studies in humans have shown that 1α-hydroxylase, the enzyme responsible for formation of active vitamin D, is present throughout the cytoplasm of neurons and glial cells (79), suggesting that the human brain metabolizes vitamin D locally and that vitamin D may have similar roles in the human brain to those observed in animal studies.

Our findings highlight the importance of assessing 25(OH)D status in pregnant women and addressing deficiencies. This study and others (80) have called attention to the high prevalence of vitamin D deficiency among Black women, which is thought to be largely related to reduced cutaneous synthesis of 25(OH)D (81). Vitamin D supplementation may be indicated for women who have poor dietary intake of vitamin D and/or reduced cutaneous synthesis related to skin pigmentation, geographic setting, or lifestyle factors affecting sun exposure. Popular prenatal supplements, which typically contain 400–600 IU vitamin D, are likely insufficient to correct 25(OH)D deficiencies. Randomized controlled trials have suggested that daily supplementation of 800 (82) to 1000 IU (83) may be needed for repletion in pregnancy, and that doses as high as 4000 IU may be ideal in cases of severe deficiency (84). Importantly, there is currently no established consensus regarding optimal 25(OH)D concentrations during pregnancy, and additional research in diverse populations is needed to develop guidelines, which may need to be population-specific, for treating deficiency during pregnancy.

Primary strengths of this study include its large size and racial diversity. CANDLE includes large numbers of White and Black mothers, which allowed for the exploration of potential effect modification by race. Mothers in this study all resided in 1 county, which reduced potential confounding by geographic variation in sunlight exposure, a critical factor in cutaneous vitamin D synthesis. This study also has limitations. This study did not examine genetic makeup, but future studies should consider several known single-nucleotide polymorphisms in vitamin D pathway genes (85) that may modify an association between gestational vitamin D and cognitive outcomes.

In conclusion, gestational vitamin D concentrations were positively associated with IQ at age 4–6 y, suggesting that vitamin D plays an important role in programming neurocognitive development. Vitamin D status may therefore be an important modifiable factor during pregnancy that can be optimized through appropriate nutritional recommendations and guidance. Vitamin D deficiency was especially prevalent

among Black women in this cohort, suggesting a heightened need for screening and nutritional intervention in this vulnerable population. Future studies examining vitamin D status throughout pregnancy should be conducted to elucidate potential critical windows during gestation.

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