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Original Research Article

Gestational vitamin D concentration and child cognitive development: a longitudinal cohort study in the Environmental influences on Child Health Outcomes Program

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ABSTRACT

Background: Low vitamin D concentrations are common—especially among those with darker pigmented skin—and are frequently observed during pregnancy. Given its important role in brain development, inadequate gestational vitamin D may impair child cognitive development.

Objectives: We aimed to evaluate associations of gestational vitamin D concentrations with childhood cognitive scores, explore whether this relationship differs by self-reported race, and examine sensitive exposure windows within pregnancy.

Methods: This prospective cohort study included 912 mother–child dyads (37.3% Black, 52.3% White) from the Environmental influences on Child Health Outcomes program. 25-hydroxyvitamin D [25(OH)D] concentrations were measured in prenatal or cord blood collected between 4 and 42 wk gestation (median: 23 wk). Children's cognition was assessed at ages 7–12 y using the NIH Toolbox Cognition Battery. Relationships of 25(OH)D and cognitive scores were examined using mixed-effects linear models adjusted for confounders. Potential sensitive periods were explored by estimating population 25(OH)D patterns across gestation for varying levels of the cognitive outcomes.

Results: Mean gestational 25(OH)D was 23.8 ng/mL (SD: 10.0 ng/mL). Each 10-ng/mL increase was associated with greater overall (β: 1.11; 95% CI: 0.08, 2.14) and fluid cognition scores (β: 1.21; 95% CI: 0.07, 2.34), but not crystallized cognition. Although these associations were not significantly modified by self-reported race, associations appeared stronger in children of Black mothers (β: 2.99; 95% CI: 0.82, 5.16) than those in non-Black mothers (β: 0.43; 95% CI: −0.93, 1.78) for fluid cognition. Early pregnancy may be a critical exposure period, evidenced by the greatest divergence in the pattern of 25(OH)D during this period between the mothers of children in the 90th and those in the 10th percentiles of cognitive outcomes.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; COI, Child Opportunity Index; ECHO, Environmental influences on Child Health Outcomes; LLOD, lower limit of detection; NIHTB-CB, National Institutes of Health Toolbox Cognition Battery; VDAART, Vitamin D Antenatal Asthma Reduction Trial; VDR, vitamin D receptor.

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Conclusions: Gestational 25(OH)D concentrations were positively associated with cognitive scores, especially in children of Black mothers. Given higher deficiency risk among Black women, vitamin D repletion before or in early pregnancy may be an important strategy for reducing racial disparities in child neurodevelopment.

Keywords: vitamin D, childhood cognitive development, prenatal nutrition, racial health disparities, fluid cognition

Introduction

Vitamin D deficiency is one of the most common nutrient deficiencies worldwide [1,2]. Defined as serum 25-hydroxyvitamin D [25(OH)D] concentration of <20 ng/mL [3,4], vitamin D deficiency affects one-third of pregnant women in the United States [5]. Vitamin D deficiency is even more prevalent among certain groups of United States pregnant women, including 80% of Black women and 46% of those with incomes below the federal poverty level [5]. Low gestational vitamin D concentrations may harm childhood cognitive development [6], leading to lower academic achievement throughout adolescence [7].

The vitamin D receptor (VDR) and the enzyme required to produce the active form of vitamin D are both found in neuronal and glial cells in the human brain [8]. By binding to VDR in the fetal brain, vitamin D exerts transcriptional control over many genes influencing structural brain development, embryonic neuronal differentiation, neurotransmitter concentrations, and neurotrophic factors [9,10]. Experimental evidence from animal studies also indicates that gestational vitamin D deficiency can alter brain morphology in offspring [11] and disrupt normal regulation of the cell cycle and apoptosis in the developing brain [12,13]. Vitamin D deficiency in both early [14,15] and late [16] gestation has been linked to cognitive problems, highlighting its role throughout pregnancy, yet it remains unclear whether a certain critical window for its impact exists.

Epidemiological studies have identified positive associations of prenatal 25(OH)D with cognition in the first 2 y of life [14,17–20] and with IQ at 4–7 y [15,21,22]. However, other studies have observed no associations with IQ at age 7 [23] or 9 y [24] or with cognitive function measured at 9–10 or 13–14 y [25]. It is possible that effects of prenatal vitamin D are obscured by other influences on cognition (e.g., environmental enrichment and parent–child interactions) that accumulate throughout childhood. However, true associations could also have gone undetected in some studies due to small sample size [24], homogeneous and predominantly White populations [23,24], or 25(OH)D assessment conducted only in late pregnancy [23–25].

Additional studies, particularly those assessing cognition in older children and diverse populations, are needed to clarify the importance of this modifiable factor for childhood neurodevelopment. Therefore, this study explored associations of gestational 25(OH)D with crystallized, fluid, and overall cognition in children aged 7–12 y in the Environmental influences on Child Health Outcomes (ECHO) program. Because melanin inhibits vitamin D synthesis [26] and because preliminary evidence suggests differing relationships of 25(OH)D with skeletal [27] and nonskeletal [28,29] outcomes between Black and non-Black individuals, we also examined whether this relationship differs by self-reported race. Finally, we aimed to identify critical gestational periods where vitamin D status may most significantly impact future cognitive outcomes in offspring.

Methods

ECHO cohort

ECHO is a longitudinal cohort study consisting of 69 pediatric cohort sites aimed at exploring the effects of early exposures on child health [30]. The study protocol was approved by the cohort-specific and/or the central ECHO institutional review board. Written informed consent or parent's/guardian's permission was obtained along with child assent as appropriate. This report follows the STROBE-nut reporting guidelines for cohort studies [31].

Study population

This study included biological mother–child pairs from 5 ECHO cohort sites from across the United States Northeast, Midwest, South, and West: Archive for Research in Child Health [32], the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) cohort [33], the Healthy Start study [34], the Safe Passage Study [35], and the Vitamin D Antenatal Asthma Reduction Trial (VDAART) [36] (Supplemental Table 1). Inclusion criteria for this study were singleton births; available gestational 25(OH)D data; and National Institutes of Health Toolbox Cognition Battery (NIHTB-CB) [37] data from children aged 7–12 y. For families with >1 child enrolled in the ECHO cohort site ($n = 21$ families), 1 sibling was randomly selected to be included in this study (Figure 1).

Assessment of 25(OH)D concentrations

Concentrations of 25(OH)D were measured in maternal plasma or serum collected during pregnancy or in cord blood serum collected at delivery. Prenatal and cord blood 25(OH)D concentrations are highly correlated, with a recent meta-analysis of 6212 mother–infant dyads reporting a pooled correlation coefficient of 0.72 (95% CI: 0.64, 0.79) [38]. In addition to a strong correlation, many studies report similar mean 25(OH)D concentrations between maternal and cord blood samples, within 1.5 ng/mL [39–43]. Although this high level of agreement has not been observed across all studies [21,44,45], the strong correlations and comparable concentrations observed in many studies led us to include all eligible dyads with 25(OH)D measured in either prenatal (n = 648) or cord blood (n = 264) in our primary analyses. The timing of specimen collection (Supplemental Table 1) and 25(OH)D assessment methods (Supplemental Table 2) varied between sites. Pregnancy dates ranged from 2006 to 2015 (Supplemental Table 2). When multiple 25(OH)D measurements were available within 1 pregnancy, the earliest observation was selected, as preliminary data suggest a critical window for the impact of 25(OH)D on brain development may occur in early pregnancy [46]. Notably, data from CANDLE have indicated relative stability of 25(OH)D concentrations across pregnancy, yet heterogeneous patterns are seen across individuals [47]. Gestational 25(OH)D analysis results that were below the lower limit of detection (LLOD) were set to LLOD/$\sqrt{2}$ [48]. LLOD substitutions were applied to 25(OH)D_2 and 25(OH)D_3 analytes

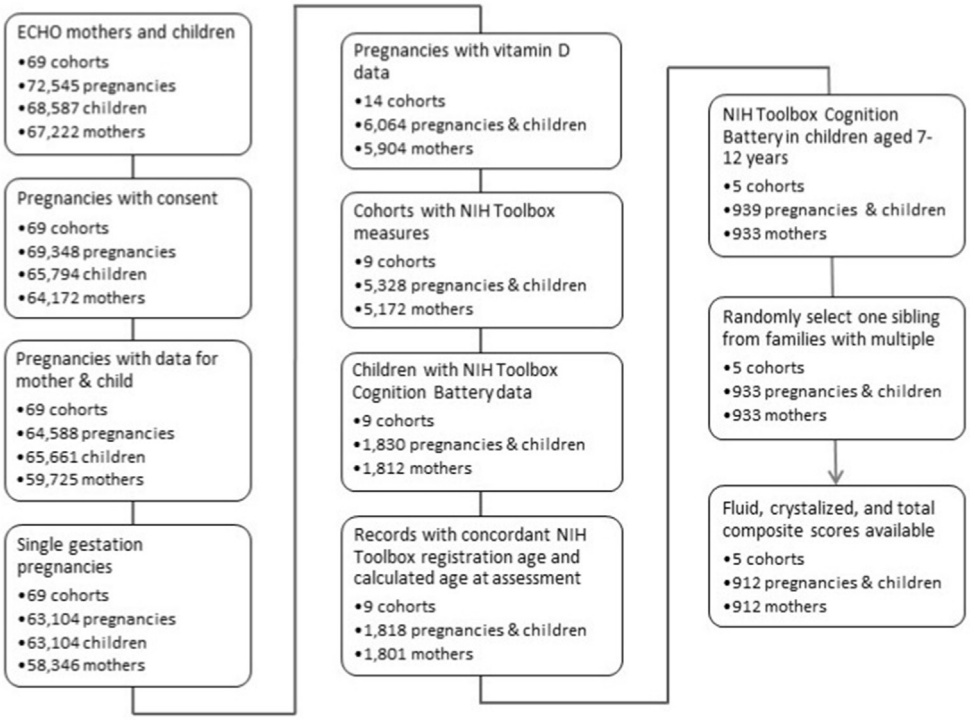

FIGURE 1. Flowchart of participant inclusion. ECHO, Environmental influences on Child Health Outcomes.

separately before adding them to obtain the total gestational 25(OH)D metric used in analysis.

Child cognition

Cognition was measured using the NIHTB-CB [49]. Component scores were used to create composite scores for crystallized, fluid, and overall cognition [50,51]. Crystallized intelligence refers to cognitive abilities that depend on experience and learning. Crystallized subscales emphasize verbal ability. Fluid intelligence involves novel problem solving and quick thinking, believed to be more biologically based and less dependent on learning or social resources. NIHTB-CB fluid intelligence tasks assess working memory, cognitive flexibility, inhibitory control and attention, and processing speed [52]. We used age-standardized scores for our analysis. Specifically, the NIHTB-CB converts raw scores for each test to age-standardized ones based on a nationally representative sample of children drawn from diverse United States locations, encompassing varied race and ethnicity groups and a range of family education and income levels [52]. Consistent with other psychometric measures of cognition, these NIHTB-CB scores are standardized to a mean of 100 and SD of 15 [50].

Covariates

Model covariates were identified using a directed acyclic graph (Supplemental Figure 1). Maternal ethnicity was defined as Hispanic or non-Hispanic, and self-reported maternal race was categorized as shown in Table 1. Race was included in this analysis for descriptive purposes, as a model covariate, and as a possible effect modifier. Race is a political and social construct that often serves as a proxy measure of socioeconomic [53] and environmental [54] disparities that can impact cognitive development and test performance. Additionally, self-reported race is strongly associated with vitamin D status. In a recent study of 71,685 United States children and adults, self-reported Black race was a stronger predictor of vitamin D deficiency than any other sociodemographic (i.e., age, sex, education, and family income), lifestyle-related (i.e., physical activity level, sun-protective behaviors, smoking, milk consumption, or BMI), or seasonal factors in a mutually adjusted model [2]. This association is primarily attributed to darker skin pigmentation, which is experimentally shown to reduce UVB-induced vitamin D synthesis [55]. In the absence of skin pigmentation data available to us in this study, we considered self-reported race as a correlate of vitamin D photoproduction due to associations of race and skin pigmentation [56,57], recognizing there exists wide variability in skin tone within racial groups and multiple factors influencing 25(OH)D concentrations. As described earlier, self-reported race was also explored as a potential effect modifier based on previous studies showing differing relationships of 25(OH)D with skeletal [27] and nonskeletal [28,29] outcomes between self-reported Black and non-Black individuals.

Maternal education was self-reported and categorized as shown in Table 1. Parity (continuous) was based on medical record abstraction or maternal report at the time of the index pregnancy. Children's sex at birth was defined as male, female, or ambiguous. Other covariates included child age at outcome assessment and Child Opportunity Index (COI) 2.0. The COI 2.0 incorporates 29 neighborhood conditions spanning 3 domains (education, health and environment, and social and economic) [58]. Using ArcGIS geospatial software (Esri), we geocoded the most recent residential address before or at the time of the NIHTB-CB assessment and assigned a census tract location to each child using 2010 United States census tract boundaries. We linked this to census tract-level COI 2.0 at year 2015 because NIHTB-CB assessment occurred in 2018–2023. Consistent with previous literature [58,59], we categorized COI percentiles into 5 categories: very low (<20th percentile), low (20th to <40th percentile), moderate (40th to <60th percentile),

TABLE 1
Characteristics of the study population, overall, and with stratification by gestational vitamin D status, presented as *n* (%) or mean (SD).

Characteristic	Vitamin D status		Overall ($N = 912$)
	<20 ng/mL ($n = 348$)	≥20 ng/mL ($n = 564$)	
Maternal age at delivery (y)			
Mean (SD)	26.8 (5.49)	28.8 (5.52)	28.0 (5.59)
Median (minimum, maximum)	26.5 (16.9, 41.1)	28.8 (16.4, 44.1)	27.8 (16.4, 44.1)
Cohort			
ARCH	12 (3.4)	40 (7.1)	52 (5.7)
CANDLE	159 (45.7)	217 (38.5)	376 (41.2)
Healthy Start	49 (14.1)	134 (23.8)	183 (20.1)
PASS	46 (13.2)	101 (17.9)	147 (16.1)
VDAART	82 (23.6)	72 (12.8)	154 (16.9)
Maternal race			
American Indian or Alaska Native	12 (3.4)	9 (1.6)	21 (2.3)
Asian	<5[1]	<12	12 (1.3)
Black	198 (56.9)	142 (25.2)	340 (37.3)
Multiple race	22 (6.3)	25 (4.4)	47 (5.2)
White	108 (31.0)	369 (65.4)	477 (52.3)
Other race	<10	<10	10 (1.1)
Missing	1 (0.3)	4 (0.7)	5 (0.5)
Maternal ethnicity			
Non-Hispanic	307 (88.2)	503 (89.2)	810 (88.8)
Hispanic	40 (11.5)	60 (10.6)	100 (11.0)
Missing	1 (0.3)	1 (0.2)	2 (0.2)
Maternal education			
High school degree and equivalent or less	106 (30.5)	82 (14.5)	188 (20.6)
Some college, no degree; Associate degree (AA, AS); trade school	133 (38.2)	148 (26.2)	281 (30.8)
Bachelor degree (BA, BS)	54 (15.5)	168 (29.8)	222 (24.3)
Graduate or professional degree	52 (14.9)	163 (28.9)	215 (23.6)
Missing	3 (0.9)	3 (0.5)	6 (0.7)
Prepregnancy BMI status			
Underweight (BMI < 18.5)	9 (2.6)	20 (3.5)	29 (3.2)
Normal ($18.5 \leq$ BMI < 25)	86 (24.7)	214 (37.9)	300 (32.9)
Overweight ($25 \leq$ BMI < 30)	58 (16.7)	125 (22.2)	183 (20.1)
Obese (BMI ≥ 30)	111 (31.9)	129 (22.9)	240 (26.3)
Missing	84 (24.1)	76 (13.5)	160 (17.5)
Prenatal alcohol use			
No	274 (78.7)	409 (72.5)	683 (74.9)
Yes	62 (17.8)	115 (20.4)	177 (19.4)
Missing	12 (3.4)	40 (7.1)	52 (5.7)
Prenatal nicotine use			
No	300 (86.2)	489 (86.7)	789 (86.5)
Yes	36 (10.3)	35 (6.2)	71 (7.8)
Missing	12 (3.4)	40 (7.1)	52 (5.7)
Parity			
Nulliparous	132 (37.9)	283 (50.2)	415 (45.5)
1 previous birth	116 (33.3)	168 (29.8)	284 (31.1)
2+ previous births	100 (28.7)	113 (20.0)	213 (23.4)
Gestational age at birth (wk)			
Mean (SD)	38.7 (1.67)	38.9 (1.60)	38.9 (1.63)
Median (minimum, maximum)	39.0 (31.0, 42.0)	39.0 (26.0, 42.0)	39.0 (26.0, 42.0)
Gestational 25(OH)D (ng/mL)			
Mean (SD)	14.3 (3.78)	29.6 (8.02)	23.8 (10.0)
Median (minimum, maximum)	14.9 (5.50, 19.9)	27.4 (20.0, 65.3)	23.0 (5.50, 65.3)
Gestational age at 25(OH)D assessment (wk)			
Mean (SD)	24.0 (9.77)	25.5 (10.2)	24.9 (10.0)
Median (minimum, maximum)	22.0 (4.00, 42.0)	23.0 (4.00, 42.0)	23.0 (4.00, 42.0)
Child age at assessment (y)			
Mean (SD)	10.6 (1.39)	10.0 (1.41)	10.3 (1.42)
Median (minimum, maximum)	11.3 (7.65, 12.0)	10.3 (7.61, 12.0)	10.7 (7.61, 12.0)
Child Opportunity Index			
Very low	157 (45.1)	112 (19.9)	269 (29.5)
Low	52 (14.9)	66 (11.7)	118 (12.9)
Moderate	45 (12.9)	82 (14.5)	127 (13.9)
High	38 (10.9)	107 (19.0)	145 (15.9)
Very high	49 (14.1)	193 (34.2)	242 (26.5)
Missing	7 (2.0)	4 (0.7)	11 (1.2)

(*continued on next page*)

TABLE 1 (*continued*)

Characteristic	Vitamin D status		Overall ($N = 912$)
	<20 ng/mL ($n = 348$)	≥20 ng/mL ($n = 564$)	
Child sex			
Male	152 (43.7)	297 (52.7)	449 (49.2)
Female	196 (56.3)	267 (47.3)	463 (50.8)
Overall cognition composite score			
Mean (SD)	87.1 (16.7)	95.8 (16.2)	92.5 (17.0)
Median (minimum, maximum)	86.5 (48.0, 132)	96.0 (42.0, 147)	92.0 (42.0, 147)
Crystallized cognition composite score			
Mean (SD)	91.8 (15.3)	100 (16.0)	96.9 (16.2)
Median (minimum, maximum)	90.0 (57.0, 149)	99.0 (57.0, 160)	95.0 (57.0, 160)
Fluid cognition composite score			
Mean (SD)	87.1 (17.2)	93.5 (16.7)	91.1 (17.2)
Median (minimum, maximum)	87.0 (42.0, 136)	93.0 (46.0, 151)	91.0 (42.0, 151)

Abbreviations: ARCH, Archive for Research on Child Health; CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; PASS, Safe Passage Study; VDAART, Vitamin D Antenatal Asthma Reduction Trial.

[1] It is an Environmental Influences on Child Health Outcomes requirement that table cells that report data from fewer than 5 participants must be suppressed to protect participant confidentiality.

high (60th to <80th percentile), or very high (≥80th percentile) opportunity. Additional covariates included prepregnancy BMI and prenatal use of nicotine or alcohol. Prepregnancy BMI (continuous) was defined using measured or self-reported height and weight. Prenatal substance use was ascertained through self-report or medical record abstraction. Nicotine exposure was defined as cigarette smoking, use of Electronic Nicotine Delivery Devices (e-cigarettes, vapes, and vape pens), and other forms of tobacco (chewing tobacco/snuff, nicotine patch, nicotine gum/lozenges, cigar, pipe, hookah, Bidi/Beedi). Alcohol use (yes/no) included consumption of any type of alcohol. Neither prenatal nor childhood vitamin D supplementation was included as a covariate. Maternal supplementation lies upstream of the primary exposure, prenatal 25(OH)D (Supplemental Figure 1), and childhood supplementation is not a strong precision variable given null [60] or mixed [15] evidence for the association of childhood 25(OH)D concentration with cognitive outcomes.

Statistical analysis

Analyses were performed using R statistical software, version 4.2.2 [61]. We computed frequencies and percentages of sociodemographic characteristics and other variables of interest in the full study population and by vitamin D status. We constructed linear mixed-effects models (R package "lme4") to estimate associations of 10-ng/mL increments in 25(OH)D (equal to 1 SD in this sample) with continuous NIHTB-CB scores. As noted earlier, when multiple 25(OH)D measurements were available for a pregnancy, we used the earliest value, resulting in 1 observation per dyad in the main models. Linearity and normality assumptions were assessed by graphical presentation of exposure and outcome variables and model residuals. Random intercepts for cohorts were specified in models to account for within-cohort correlation. Among several factors that may differ between cohorts, this approach helps account for differences in 25(OH)D assessment methods.

Linear mixed-effects models with random intercept for cohort were minimally adjusted for children's sex and age at NIHTB-CB assessment. Fully adjusted models additionally included maternal race and ethnicity, maternal education, parity (continuous), and categorical COI. Effect modification by maternal race was assessed by adding a term for the interaction of 25(OH)D and race (categorized as Black or non-Black). Black was defined as Black race or multiple races with Black race identified.

Missingness of most covariates was low, with <2% missing data for all covariates included in the main models (Table 1). Imputation was performed for missing covariate data using multiple imputation by chained equations ("mice" R package) [62]. All variables included in the analytical models plus additional variables that were informative of missingness were included in the imputation model. Cohort site membership was included as a clustering variable. Results were pooled after 50 imputed data sets with 5 iterations. Regression estimates from imputed data sets were pooled using Rubin's rules with the *mice::pool()* function.

Several sensitivity analyses were conducted to determine the robustness of results. First, because 25(OH)D concentrations in prenatal and cord blood samples may not be fully comparable [21,44,45], a sensitivity analysis was conducted after removing cord blood 25(OH)D measurements. Second, we assessed whether observed associations between 25(OH)D and child cognition scores varied after the removal of individual cohort sites. Additional sensitivity analyses further adjusted for prenatal use of nicotine and prenatal alcohol use in the linear mixed models. Sensitivity analyses were also carried out to adjust for prepregnancy BMI, a factor associated with child cognitive development in numerous studies [63]. Notably, the mechanisms underlying this association are uncertain, with ongoing debate about whether it may be explained by an increased prevalence of vitamin D deficiency in individuals with prepregnancy obesity [64], social confounding [65], or physiological mechanisms such as increased inflammation [66]. Finally, we conducted a post-hoc analysis to examine relationships of 25(OH)D with cognitive outcomes in dyads stratified by 25(OH)D status (<20 and ≥20 ng/mL). Additional ad hoc analyses included the investigation of NIHTB-CB subtests and associations with prenatal 25(OH)D concentration.

To supplement findings from the main regression models, we conducted exploratory analyses to identify outcome-dependent exposure patterns—using adapted code from Sánchez et al. [67]—and potential critical gestational periods where vitamin D status may most significantly impact child cognition. The selected method (identified as method 4) [67] does not require a priori knowledge of a pattern of exposure and allows for the aggregation of participant data collected at 1 or more gestational time points. For this analysis, we incorporated

all repeated 25(OH)D measures over pregnancy (or at delivery) for each pregnant individual that were available. Linear models were fit with child age at outcome assessment, child sex, maternal race, maternal ethnicity, maternal education, and parity as independent variables for each NIHTB-CB outcome and for each of the 50 imputed data sets. Model results were pooled using Rubin's rules, and residuals were extracted and combined with a longitudinal dataset of 25(OH)D measures. A second model was fit with NIHTB-CB residuals, completed gestational weeks, gestational weeks^2, NIHTB-CB residuals* gestational weeks, and NIHTB-CB residuals* gestational weeks^2 as predictors; cohort site and participant as random intercepts; and 25(OH)D concentration as the outcome. Results were considered statistically significant if the global F-test P value was <0.05 for the inclusion of predictors for NIHTB-CB residuals and residuals-by-gestational week interactions. Using the population exposure pattern model, we predicted 25(OH)D concentrations for each participant at each specimen collection time point and plotted the predicted values for children in the 90th and 10th percentiles of NIHTB-CB residuals for visualization.

Results

Participant characteristics and vitamin D status

The study included 912 biological mother–child pairs from 5 ECHO sites (Figure 1). The mean serum or plasma 25(OH)D concentration was 23.8 ng/mL (SD: 10.0 ng/mL), measured in samples collected at 4–42 wk of gestation (Table 1). Approximately 38% were characterized as vitamin D deficient. Mean maternal age at delivery was 28.0 (SD: 5.59) years. Approximately half of the population self-identified as White, and self-identified Black individuals were disproportionally classified as having vitamin D deficiency (56.9% Black women compared with 31.0% White women). Some factors that appeared to be associated with 25(OH)D deficiency included lower maternal education, prepregnancy obesity, and prenatal nicotine use.

Associations of gestational 25(OH)D and childhood cognition

In age-adjusted and sex-adjusted models, gestational 25(OH)D concentration was significantly and positively associated with overall, fluid, and crystallized cognition (Table 2). In fully adjusted models, a 10-ng/mL increase in 25(OH)D was associated with a 1.11-point greater overall cognition score (95% CI: 0.08, 2.14) and a 1.21-point greater fluid cognition score (95% CI: 0.07, 2.34). The association with crystallized cognition was no longer significant (β: 0.65; 95% CI: −0.33, 1.63) (Table 2, Figure 2).

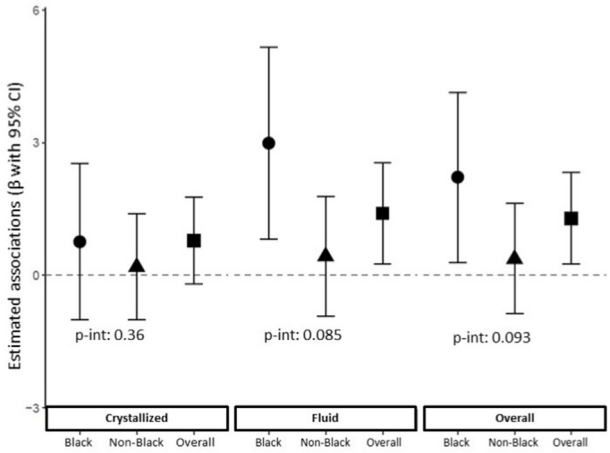

FIGURE 2. Relationships between gestational 25(OH)D and crystallized, fluid, and overall cognition in children at ages 7–12 [estimates for expected change in outcome per 10-ng/mL increase in 25(OH)D] shown for the full study sample (n = 912) and stratified by self-identified Black (n = 372) or non-Black maternal race (n = 535); models adjusted for child sex (male, female), child age at assessment (continuous), maternal race (for nonstratified models), maternal ethnicity, mother's education (high school diploma or less, some college or AA, Bachelors or higher), parity (continuous), mother's age (continuous), and Child Opportunity Index 2.0 (categorical).

Effect modification by maternal race

When examining effect modification by race, interaction terms were non-significant (Figure 2, Supplemental Table 3). However, stratum-specific estimates were larger and significant only for children of Black mothers compared to non-Black mothers. For example, a 10 ng/mL increase in 25(OH)D was associated with 2.99 (95% CI: 0.82, 5.16) points higher fluid cognition in children of Black mothers and 0.43 (95% CI: −0.93, 1.78) points higher in children of non-Black mothers. Using a post-hoc analysis we explored whether these findings may be related to differing prevalence of deficiency. We speculated that beneficial associations may be most observable in the context of deficiency, which was more prevalent among Black mothers than other races. In stratified models, we observed that associations of 25(OH)D with fluid cognition persisted among the 564 dyads with 25(OH)D ≥20 ng/mL (β: 1.92; 95% CI: 0.24, 3.61), but not among the smaller subset (n = 348) with 25(OH)D deficiency (β: 0.33; 95% CI: −4.29, 4.95) (Supplemental Table 4).

Sensitivity analyses

Associations of gestational 25(OH)D with overall and fluid cognition remained significant after further adjustment for prenatal nicotine

TABLE 2
Relationships between gestational 25(OH)D and overall, fluid, and crystallized cognition in children at ages 7–12 y.

Outcome	N	Unadjusted	Minimally adjusted[2]	Fully adjusted[3]
		β (95% CI)[1]	β (95% CI)	β (95% CI)
Overall cognition	912	4.65 (3.59, 5.72)	4.52 (3.46, 5.59)	1.11 (0.08, 2.14)
Fluid cognition	912	3.65 (2.56, 4.75)	3.55 (2.45, 4.65)	1.21 (0.07, 2.34)
Crystallized cognition	912	4.09 (3.07, 5.12)	3.97 (2.94, 5.00)	0.65 (−0.33, 1.63)

[1] β Estimates represent expected change in cognitive score per 10-ng/mL increase in serum or plasma 25(OH)D concentration.
[2] Minimal model adjusted for child sex (male, female) and child age at assessment (continuous).
[3] Full model adjusted for covariates in minimal model plus maternal race, maternal ethnicity, mother's education (high school diploma or less, some college or AA, Bachelors or higher), parity (continuous), mother's age (continuous), and Child Opportunity Index 2.0 (categorical).

and alcohol use (Supplemental Table 5). After adjusting for prepregnancy BMI, we did not observe significant associations (Supplemental Table 5). Importantly, this analysis excluded all 154 participants from the VDAART site due to unavailable prepregnancy BMI data. The exclusion of these participants not only reduced statistical power but also notably modified the composition of the study sample, as VDAART had the greatest proportion of 25(OH)D measurements <20 ng/mL (53.2%) and the earliest mean gestational age at 25(OH)D assessment. Thus, this sensitivity analysis primarily reflects later 25(OH)D measurements in participants with higher vitamin D status, where relationships may be less pronounced. In another sensitivity analysis excluding dyads with 25(OH)D ascertained in cord blood, we observed similar associations to the main analysis (Supplemental Table 6). After the sequential omission of any single cohort, general conclusions did not change, although statistical significance was reduced in some cases, as discussed earlier with the omission of VDAART, or with the omission of the largest cohort site, CANDLE (n = 376) (Supplemental Figure 2). We observed no significant associations with NIHTB-CB subtests (Supplemental Table 7).

Population exposure patterns of 25(OH)D

There were 523 biological mothers with ≥2 gestational 25(OH)D specimen collection time points, and 118 with 3 specimen collection time points. Mean gestational ages at the first, second, and third collections were 24.9, 36.9, and 38.8 wk, respectively. Mean gestational 25(OH)D concentrations were lowest at the first (23.7 ng/mL), slightly increased at the second (26.48 ng/mL), and highest at the third collection (37.6 ng/mL). There were significant changes in 25(OH)D exposure patterns across gestation for children with higher fluid cognition scores, adjusted for 25(OH)D patterns over time unrelated to the outcome (H_0: $\beta_{\text{Fluid residuals}} = \beta_{\text{Fluid residuals* GA}} = \beta_{\text{Fluid residuals* GA}^2} = 0$; $P = 0.029$). Exposure patterns over pregnancy for children with higher overall and crystallized NIHTB-CB scores were not significantly different (H_0: $\beta_{\text{Overall residuals}} = \beta_{\text{Overall residuals* GA}} = \beta^2_{\text{Overall residuals* GA}} = 0$; $P = 0.078$; H_0: $\beta_{\text{Crystallized residuals}} = \beta_{\text{Crystallized residuals* GA}} = \beta^2_{\text{Crystallized residuals* GA}} = 0$; $P = 0.714$, respectively).

Figure 3 suggests greater differences in predicted 25(OH)D earlier in pregnancy for the 90th compared with 10th percentiles of covariate-adjusted overall and fluid cognition, as shown by the separation between the trend lines in earlier gestational weeks. However, the CIs overlap between the 2 groups' predicted 25(OH)D values throughout most of pregnancy for all 3 cognition outcomes.

Discussion

In this diverse cohort, higher gestational 25(OH)D concentrations were associated with greater fluid and overall cognitive scores in children. These findings could have meaningful population-level impacts as higher NIH Toolbox composite scores have been linked to better reported school performance and health status in children [52]. The magnitudes of the associations observed in this study are comparable to previously reported associations of maternal tobacco use during pregnancy [68] and maternal social disadvantage factors—such as educational attainment less than a high school diploma or receipt of government-provided nutrition assistance [69]—with fluid cognition measured using the NIHTB-CB in late childhood or early adolescence. Although not significantly different between self-reported races, associations appeared stronger in children of Black mothers. Results also suggested that early pregnancy may be a sensitive period in which optimal vitamin D status is particularly important for childhood neurodevelopment. Overall, this study indicates that vitamin D status may be a modifiable target to support child cognitive development. Interventions prior to or earlier in pregnancy, and those focused on Black women and others at high risk of deficiency, may have the greatest impact.

Our findings are consistent with data from other cohorts linking higher 25(OH)D concentrations in cord blood [70], prenatal blood [14,17–20,22,71], or both [15,21] to greater language development [14,17,19,71] and cognitive scores [14,15,18,20–22,70] throughout childhood. However, the existing literature is not fully consistent as multiple studies have detected no associations [23–25,72–74]. Null findings in some previous studies could be related in part to modest sample sizes [24,25,72,74] or the evaluation of 25(OH)D status only in late pregnancy or at delivery [24,25,72,73]. Further, our study suggests that some abilities may be more vulnerable than others, with associations observed among fluid cognitive tasks but not crystallized tasks. This is consistent with the notion that fluid reasoning abilities are particularly vulnerable to insult during gestation because they are programmed during this period [52]. The potential adverse impacts of vitamin D deficiencies on crystallized abilities, in contrast, may be attenuated by educational and environmental enrichment. The nature of the skills assessed and sample demographics could account for some of the variability observed in earlier research.

This study suggested that early pregnancy may be an important period to optimize vitamin D status to promote cognitive development. This finding may have important implications for prenatal nutritional counseling. Among pregnant individuals in the United States, 33% have 25(OH)D concentrations of <20 ng/mL and 28% do not consume any supplemental vitamin D [5]. A large multinational study showed that even among women who were actively planning to become pregnant, >48% had 25(OH)D concentrations of <20 ng/mL [75]. Few studies have directly evaluated potential critical periods of exposure, yet some studies with repeated 25(OH)D assessments provide insights. For example, Voltas et al. [14] linked severe vitamin D deficiency (defined as 25(OH)D <12 ng/mL) in the first trimester, but not in the third trimester, with lower cognitive scores at 40 d postpartum. Similarly, Cantio et al. [15] observed that vitamin D deficiency in early pregnancy, but not in late pregnancy, was associated with lower IQ in boys at 7 y [15].

An early critical window is biologically plausible due to the complex processes of brain development, including neurogenesis and differentiation, which begin in early gestation [76]. In rodents, VDR emerges in the fetal brain during early development, 1 d after the closure of the neural tube [6]. In these early developmental stages, VDR is widely distributed in rat brain including in the cerebellum, midbrain, diencephalon, cortex, and basal ganglia [77]. Additional research is needed to confirm the importance of early pregnancy vitamin D in order to better inform nutritional counseling for pregnant individuals and those who may become pregnant.

Similar to others [19,21,22], this study showed no significant effect modification by self-identified race. However, stratum-specific estimates suggested stronger associations among children of Black mothers. Our findings underscore the need to identify and address prenatal vitamin D deficiency, especially among Black women, as they may be at increased risk [78]. Additional research is warranted to investigate vitamin D requirements during pregnancy, recognizing that needs may be sensitive to differences in the concentrations, genotypes, and binding affinities of vitamin D–binding proteins [79]. Determining appropriate 25(OH)D targets and supplementation recommendations is

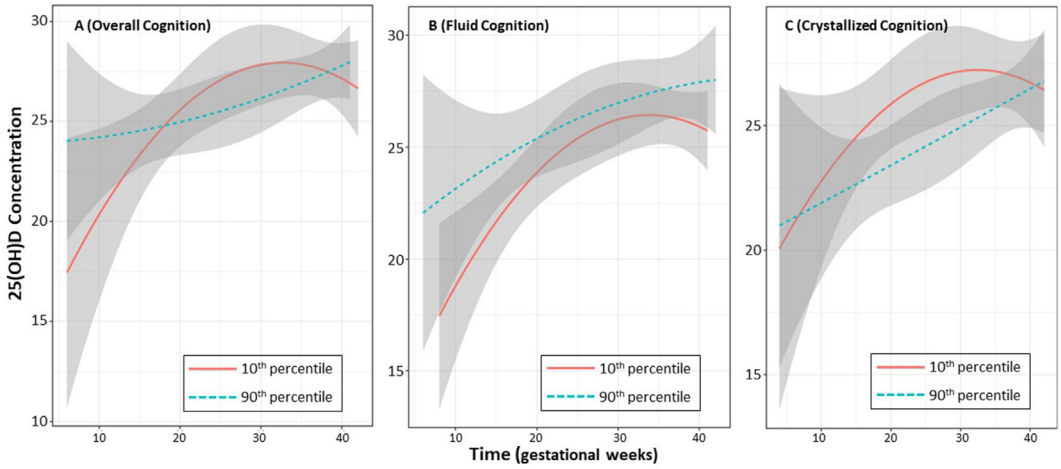

FIGURE 3. Predicted gestational 25(OH)D pattern across gestational period (weeks) for children in the 10th percentile (solid red) and 90th percentile (dashed blue) of covariate-adjusted overall (A), fluid (B), and crystallized (C) cognition with shaded 95% CIs (n = 912).

essential; although vitamin D toxicity is very rare [80], it is possible with excessive intake.

This study has numerous strengths including its geographic, socioeconomic, and racial diversity. The long-term follow-up allowed for investigation of distal impacts of prenatal nutritional status. Use of an innovative method [67] also enabled us to explore potential periods of vulnerability in pregnancy. One limitation is the use of 25(OH)D measurements from multiple laboratories and methods. However, each laboratory implemented strict quality control procedures and several participated in standardization programs. Mixed-effects models also accounted for cohort to reduce this potential limitation. Residual confounding may be present as we could not account for several individual-level sociodemographic factors such as income and marital status due to a large percentage of missing data. However, inclusion of maternal education and COI in our models helps address some of these factors at individual and neighborhood levels. We were also unable to adjust for certain postnatal factors, such as breastfeeding, childhood diet, and changes in family structure over time, which may influence child cognitive outcomes. Finally, this study used self-reported race categories—which include individuals with varied skin tones, and thus differing susceptibility to vitamin D deficiency [81]—as an imperfect proxy for skin pigmentation, potentially leading to nondifferential misclassification that could attenuate race-stratified associations. Within self-reported race categories, there is also substantial heterogeneity in sun-related behaviors and genetic variation affecting vitamin D metabolism [79].

In conclusion, greater gestational 25(OH)D concentrations were associated with higher fluid and overall cognition in children. Promoting vitamin D adequacy beginning in early pregnancy may enhance cognitive development in children. Given the high prevalence of vitamin D deficiency, especially among Black women, this may represent a modifiable factor for optimizing childhood neurodevelopmental outcomes. Future randomized controlled trials are needed to evaluate whether improving gestational vitamin D status can serve as an effective intervention target and to determine the optimal timing for such intervention.

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Author contributions

The authors' responsibilities were as follows – MMM, SS, BRC: conceived the study; MM, MP: performed data curation, methodology, formal analysis, software, and visualization; MM, MMM: wrote the original draft; SS: supervised the study; and all authors: contributed to interpretation of results, reviewed and edited the manuscript critically, and approved the final manuscript.

Conflicts of interest

The authors report no conflicts of interest.

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Data availability

Select deidentified data from the ECHO Program are available through NICHD's Data and Specimen Hub (DASH). Information on study data not available on DASH, such as some Indigenous datasets, can be found on the ECHO study DASH webpage.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2025.06.017.

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