The Journal of Nutrition 153 (2023) 1502–1511

American Society for Nutrition
Excellence in Nutrition Research and Practice

JN THE JOURNAL OF NUTRITION

journal homepage: www.journals.elsevier.com/the-journal-of-nutrition

Nutritional Epidemiology

Greater Gestational Vitamin D Status is Associated with Reduced Childhood Behavioral Problems in the Environmental Influences on Child Health Outcomes Program

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A B S T R A C T

Background: Vitamin D deficiency is common in pregnancy. Vitamin D plays an important role in the developing brain, and deficiency may impair childhood behavioral development.

Objectives: This study examined the relationship between gestational 25(OH)D concentrations and childhood behavior in the Environmental influences on Child Health Outcomes (ECHO) Program.

Methods: Mother-child dyads from ECHO cohorts with data available on prenatal (first trimester through delivery) or cord blood 25(OH)D and childhood behavioral outcomes were included. Behavior was assessed using the Strengths and Difficulties Questionnaire or the Child Behavior Checklist, and data were harmonized using a crosswalk conversion. Linear mixed-effects models examined associations of 25(OH)D with total, internalizing, and externalizing problem scores while adjusting for important confounders, including age, sex, and socioeconomic and lifestyle factors. The effect modification by maternal race was also assessed.

Results: Early (1.5–5 y) and middle childhood (6–13 y) outcomes were examined in 1688 and 1480 dyads, respectively. Approximately 45% were vitamin D deficient [25(OH)D $<$ 20 ng/mL], with Black women overrepresented in this group. In fully adjusted models, 25(OH)D concentrations in prenatal or cord blood were negatively associated with externalizing behavior T-scores in middle childhood [−0.73 (95% CI: −1.36, −0.10) per 10 ng/mL increase in gestational 25(OH)D]. We found no evidence of effect modification by race. In a sensitivity analysis restricted to those with 25(OH)D assessed in prenatal maternal samples, 25(OH)D was negatively associated with externalizing and total behavioral problems in early childhood.

Abbreviations: CBCL, Child Behavior Checklist; ECHO, Environmental influences on Child Health Outcomes; IPTW, inverse probability of treatment weighting; SDQ, Strengths and Difficulties Questionnaire; VDR, vitamin D receptor.

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https://doi.org/10.1016/j.tjnut.2023.03.005
Received 13 November 2022; Received in revised form 2 March 2023; Accepted 7 March 2023; Available online 4 April 2023

Conclusions: This study confirmed a high prevalence of vitamin D deficiency in pregnancy, particularly among Black women, and revealed evidence of an association between lower gestational 25(OH)D and childhood behavioral problems. Associations were more apparent in analyses restricted to prenatal rather than cord blood samples. Interventions to correct vitamin D deficiency during pregnancy should be explored as a strategy to improve childhood behavioral outcomes.

Keywords: pregnancy, prenatal nutrition, vitamin D, 25-hydroxyvitamin D, behavioral problems, externalizing behaviors, internalizing behaviors

Introduction

Vitamin D deficiency, defined by the Endocrine Society as 25(OH)D concentrations <20 ng/mL [1], affects one in 3 pregnant women in the United States [2]. Because melanin pigment reduces endogenous vitamin D synthesis (by reducing the amount of ultraviolet radiation available to initiate synthesis) [3], ~80% of Black pregnant women compared with 13% of White pregnant women in the United States are deficient in vitamin D [2]. Low vitamin D concentrations during pregnancy may be associated with an increased risk for pregnancy complications and poor growth, immune dysfunction, and respiratory disease in children [4,5]. Recent epidemiological studies also link prenatal vitamin D deficiency with childhood behavioral problems [6,7]. These findings warrant additional investigation, as childhood behavioral problems are important predictors of other difficulties later in life, including substance use disorders, poor physical health, poorer academic performance, and psychiatric disorders [8–11].

Animal and experimental data support the role of gestational vitamin D in behavioral development. The vitamin D receptor (VDR) is expressed in the rodent brain as early as 12 d into gestation, when vitamin D may begin to influence proliferation and apoptosis in the developing brain [12]. Gestational vitamin D deficiency in rodents has been shown to reduce cortical thickness, decrease the number of synapses in the molecular layer of the hippocampus, and impair brain function in adult offspring [13,14]. These findings have not been fully translated to humans, yet the expression of VDR in the adult human brain is similar to that reported in rodents [15]. A limited number of studies have examined the associations between gestational vitamin D status and childhood behavioral outcomes such as socio-emotional development, hyperactivity, and internalizing and externalizing behaviors. Some results suggest positive associations of prenatal vitamin D status with behavioral outcomes [6,7], yet not all have observed significant relationships [16–19]. It is possible that some studies failed to detect significant associations due to small sample sizes [19], homogeneity of the study population [16,17], lack of participants with vitamin D deficiency [18], or differences in the timing of gestational vitamin D assessment.

The vitamin D status of pregnant individuals may be an important target for nutritional interventions to improve childhood health outcomes. Yet, existing findings on the association between gestational vitamin D status and childhood behavior are inconsistent. Furthermore, whether relationships between 25(OH)D and behavioral outcomes differ between races is unclear. Some studies indicate that the associations of low 25(OH)D concentrations with bone disease [20] and cardiovascular events [21] observed in White populations are attenuated in Black populations despite lower 25(OH)D, possibly related to differences in vitamin D metabolism. Racial differences in the association between gestational 25(OH)D and childhood behavior have also been reported in at least 1 study [7], yet the authors postulated that a small sample size may have contributed to this unanticipated finding. Thus, the possible effect modification by race should be evaluated in a large and diverse sample.

The objective of this study was to examine the relationship between gestational 25(OH)D concentrations with internalizing, externalizing, and total behavioral problem scores in early and middle childhood. We hypothesized that greater gestational 25(OH)D concentrations would be associated with reduced childhood behavioral problems and that this relationship would be similar across races. This analysis was conducted with a large and diverse sample of participants from the Environmental influences on Child Health Outcomes (ECHO) Program, a consortium of pediatric cohort studies collecting data under a common protocol since 2019 [22].

Methods

Study population

The ECHO program was established by the United States NIH and brought together 69 existing cohort studies across the country to facilitate research aiming to improve the health of children [23]. Mother-child dyads participating in ECHO were eligible for this study if they had data available for both the exposure and outcome of interest. The main exposure was serum or plasma concentration of 25(OH)D in prenatal or cord blood samples. Six out of the 7 cohorts with 25(OH)D data had data on the primary outcome: childhood behavioral problems assessed using the Child Behavior Checklist (CBCL) or the Strengths and Difficulties Questionnaire (SDQ). These cohorts included the Atlanta ECHO Cohort of Emory University [24], the Conditions Affecting Neurocognitive Development and Learning in Early childhood [25], the Healthy Start study [26], Project Viva [27], the Pittsburgh Girls Study [28], and the Vitamin D Antenatal Asthma Reduction Trial [29]. Of these cohorts, 4 collected outcome data during early childhood (1.5–5 y of age) and 5 collected outcome data in middle childhood (6–13 y of age), which were analyzed as separate endpoints in this study. Both early and middle childhood data were available in 3 of the cohorts. A detailed flowchart of participant inclusion is provided in Supplemental Figure 1.

Assessment of 25(OH)D concentrations

Concentrations of 25(OH)D were previously measured in maternal plasma or serum samples collected during pregnancy or in cord blood serum collected at delivery. Most cohorts measured 25(OH)D in maternal serum or plasma, and the dates of sample collection within the pregnancy varied between the cohorts (Supplemental Table 1). The Healthy Start study measured

25(OH)D concentrations in cord blood serum, reflecting late-term vitamin D exposure. Cord blood 25(OH)D concentrations have been shown in previous studies to be highly correlated with maternal serum samples, with correlation coefficients ranging from 0.58 to 0.91 across several studies [30–35]. Furthermore, these studies showed that cord blood 25(OH)D concentrations match maternal concentrations well, often ranging between 87% and 124% of maternal concentrations [31,32,34,36], likely depending largely on the timing of maternal measurements. In this analysis, when multiple measurements of 25(OH)D were available within one pregnancy, the earliest observation was used, as epidemiological data suggest a critical window for the impact of 25(OH)D on brain development likely occurs in early pregnancy [37]. Details on laboratory methods and quality control procedures used for 25(OH)D measurement by each cohort are described in Supplemental Table 2.

Assessment of behavioral outcomes

Child behavioral problems were reported by caregivers using the CBCL [38] or SDQ [39]. Scores were expressed as T-scores norm-referenced by gender and age group using data from the general pediatric population, standardized to a mean of 50 and SD of 10. The CBCL Preschool version for children aged 1.5–5 y comprises 99 closed items describing specific behaviors that can be rated on a 3-point scale (not true; somewhat or sometimes true; very true or often true), with increasing scores indicating increasing behavioral problems. For children aged 6–18 y, the CBCL School aged version consisting of 113 items is administered and scored similarly. All versions of the SDQ contain 25 items, each rated on a 3-point scale (not true; somewhat true; certainly true). Because the SDQ assesses similar constructs to the CBCL, we used a conversion method recently developed by Mansolf et al. [40] to convert SDQ scores in 3 domains (T-scores for internalizing, externalizing, and total problems) to their equivalent CBCL T score, allowing analysis of outcomes from both instruments to be conducted together in this study.

Assessment of covariates

Covariates were selected a priori based on the current literature. Self-reported maternal race and ethnicity were considered potential confounders due to their association with vitamin D deficiency [41] and evidence of the harmful impacts of experiences and perceptions of racial and ethnic discrimination on childhood behavior [42,43]. Other potential confounders included maternal age at delivery, child age at outcome assessment, child sex, maternal education, prepregnancy BMI, parity, prenatal use of tobacco, and prenatal alcohol use. Missing data of each covariate was between 0 and 4.3% among the total sample for both the early and middle childhood analyses (Table 1). The availability of these data within each cohort was more variable, but missing data were generally modest (Supplemental Tables 3 and 4). Missing covariates were imputed using multiple imputations by chained equations. Ten imputations with 5 iterations of each covariate were performed.

Statistical analysis

Descriptive statistics were used to summarize the mean and SD of 25(OH)D concentrations in the study sample and to evaluate the relationships between sociodemographic characteristics and vitamin D deficiency. Linear mixed-effects models (R package "lme4") were fitted to examine the associations of 25(OH)D concentrations with childhood total, internalizing, and externalizing problem T-scores. Separate models were constructed for early childhood and middle childhood outcomes. Random intercepts of the cohorts were included in the models to account for the within-cohort correlation. Among several factors that may differ between cohorts, this statistical approach helps account for differences in 25(OH)D assessment methods because each cohort used 1 laboratory and method, which was distinct from all other cohorts (Supplemental Table 2). Minimally adjusted models were controlled for maternal age and child sex and age during outcome assessment. Fully adjusted models included all covariates as described above. The linearity assumption was assessed by a graphical presentation of exposure and outcome variables and model residuals. The effect modification by maternal race was assessed by adding a term for the interaction of 25(OH)D concentration and race categorized as a binary variable (Black or non-Black).

A post hoc analysis using the inverse probability of treatment weighting (IPTW) was conducted to estimate risk difference in borderline or clinical CBCL scores depending on vitamin D status. IPTW methods enable causal inference in observational studies by weighting observations proportionately to the inverse of the probability of having a given exposure, thus balancing observed covariates between exposed and unexposed groups. Using IPTW, we estimated risk differences for 25(OH)D concentrations $\geq$20 ng/mL (the Institute of Medicine's threshold for sufficiency based on skeletal health outcomes [44]) and for $\geq$30 ng/mL (the higher threshold for sufficiency advised by the Endocrine Society based on skeletal and extraskeletal health outcomes [1]).

Sensitivity analyses were conducted to determine the robustness of the results. First, to evaluate the importance of exposure timing within pregnancy or delivery, we removed participants with cord blood 25(OH)D measurements. We also examined results after further restricting the study sample to dyads with 25(OH)D measurements in the second trimester, which has been suggested as a possible critical window of exposure [37]. To evaluate the harmonization of CBCL and SDQ scores, we constructed models with an additional term to represent the data collection instrument used. Finally, because of possible differences in 25(OH)D measurements or other data collection procedures between the cohorts, we repeated the main analysis leaving out one cohort at a time. All data analyses were performed in R software version 4.1.0.

The relationships between vitamin D and behavioral outcomes were analyzed using linear regression models, and the sign of the beta coefficients was used to interpret the direction of the relationship as either "negative" or "positive." It should be noted that these terms are used only to describe quantitative results and are not intended to imply a qualitative assessment.

Results

A total of 2195 unique mother-child dyads were included in this study; 1688 dyads in the analysis of early childhood outcomes, 1480 in middle childhood, and 973 contributed to both analyses. The mean age of mothers at delivery was 27.2 (SD: 5.48) and 28.8 (SD: 5.90) y in the early and middle

TABLE 1
Characteristics of the overall study population with stratification by gestational vitamin D status[1]

	Early childhood (1.5–5 y)			Middle childhood (6–13 y)		
	Overall	Gestational vitamin D status		Overall	Gestational vitamin D status	
		<20 ng/mL	≥20 ng/mL		<20 ng/mL	≥20 ng/mL
	n = 1688	*n* = 760	*n* = 928	*n* = 1480	*n* = 659	*n* = 821
Maternal age (y)	27.2 (5.48)	26.1 (5.22)	28.1 (5.54)	28.8 (5.90)	28.1 (6.18)	29.3 (5.62)
Cohort site						
Healthy Start	239 (14.2%)	86 (11.3%)	153 (16.5%)	170 (11.5%)	<55 (8.3%)	<120 (14.6%)
Atlanta ECHO Cohort	233 (13.8%)	120 (15.8%)	113 (12.2%)	10 (0.7%)	<5	<10 (1.2%)
Pittsburgh Girls Study	53 (3.1%)	38 (5.0%)	15 (1.6%)	—	—	—
CANDLE	1163 (68.9%)	516 (67.9%)	647 (69.7%)	961 (64.9%)	421 (63.9%)	540 (65.8%)
VDAART	—	—	—	59 (4.0%)	14 (2.1%)	45 (5.5%)
Project Viva	—	—	—	280 (18.9%)	166 (25.2%)	114 (13.9%)
Maternal race/ethnicity						
Non-Hispanic White	520 (30.8%)	125 (16.4%)	395 (42.6%)	653 (44.1%)	200 (30.3%)	453 (55.2%)
Non-Hispanic Black	1015 (60.1%)	546 (71.8%)	469 (50.5%)	648 (43.8%)	359 (54.5%)	289 (35.2%)
Non-Hispanic Other	79 (4.7%)	49 (6.4%)	30 (3.2%)	90 (6.1%)	57 (8.6%)	33 (4.0%)
Hispanic	74 (4.4%)	40 (5.3%)	34 (3.7%)	89 (6.0%)	43 (6.5%)	46 (5.6%)
Maternal education						
High school degree or lower	<490 (29.0%)	290 (38.2%)	<200 (21.6%)	<220 (14.9%)	134 (20.3%)	<90 (11.0%)
Some college or associate degree	510 (30.2%)	265 (34.9%)	245 (26.4%)	430 (29.1%)	226 (34.3%)	204 (24.8%)
Bachelor's degree or higher	691 (40.9%)	205 (27.0%)	486 (52.4%)	830 (56.1%)	299 (45.4%)	531 (64.7%)
Missing	<5	0 (0%)	<5	<5	0 (0%)	<5
Prepregnancy BMI status						
Underweight	66 (3.9%)	31 (4.1%)	35 (3.8%)	64 (4.3%)	29 (4.4%)	35 (4.3%)
Normal weight	658 (39.0%)	259 (34.1%)	399 (43.0%)	616 (41.6%)	247 (37.5%)	369 (44.9%)
Overweight	394 (23.3%)	167 (22.0%)	227 (24.5%)	353 (23.9%)	162 (24.6%)	191 (23.3%)
Obese	510 (30.2%)	261 (34.3%)	249 (26.8%)	384 (25.9%)	204 (31.0%)	180 (21.9%)
Missing	60 (3.6%)	42 (5.5%)	18 (1.9%)	63 (4.3%)	17 (2.6%)	46 (5.6%)
Prenatal alcohol use						
Yes	236 (14.0%)	84 (11.1%)	152 (16.4%)	<195 (13.2%)	<70 (10.6%)	125 (15.2%)
Missing	38 (2.3%)	26 (3.4%)	12 (1.3%)	<5	<5	0 (0%)
Prenatal tobacco use						
Yes	165 (9.8%)	86 (11.3%)	79 (8.5%)	100 (6.8%)	46 (7.0%)	54 (6.6%)
Missing	36 (2.1%)	26 (3.4%)	10 (1.1%)	7 (0.5%)	7 (1.1%)	0 (0%)
Parity						
Nulliparous	721 (42.7%)	282 (37.1%)	439 (47.3%)	689 (46.6%)	286 (43.4%)	403 (49.1%)
1 previous birth	520 (30.8%)	231 (30.4%)	289 (31.1%)	460 (31.1%)	202 (30.7%)	258 (31.4%)
2+ previous births	431 (25.5%)	238 (31.3%)	193 (20.8%)	331 (22.4%)	171 (25.9%)	160 (19.5%)
Missing	16 (0.9%)	9 (1.2%)	7 (0.8%)	0 (0%)	0 (0%)	0 (0%)
Gestational 25(OH)D (ng/mL)	21.6 (8.55)	14.1 (3.47)	27.7 (6.38)	21.8 (8.62)	14.4 (3.50)	27.8 (6.57)
Gestational 25(OH)D status						
<20 ng/dL	760 (45.0%)	760 (100%)	—	659 (44.5%)	659 (100%)	—
20 to <30 ng/dL	682 (40.4%)	—	682 (73.5%)	588 (39.7%)	—	588 (71.6%)
30+ ng/dL	246 (14.6%)	—	246 (26.5%)	233 (15.7%)	—	233 (28.4%)
Gestational period of 25(OH)D assessment[2]						
Trimester 1	228 (13.5%)	121 (15.9%)	107 (11.5%)	44 (3.0%)	<15 (2.3%)	<35 (4.3%)
Trimester 2	1043 (61.8%)	471 (62.0%)	572 (61.6%)	935 (63.2%)	409 (62.1%)	526 (64.1%)
Trimester 3	146 (8.6%)	72 (9.5%)	74 (8.0%)	319 (21.6%)	181 (27.5%)	138 (16.8%)
Delivery	241 (14.3%)	88 (11.6%)	153 (16.5%)	171 (11.6%)	55 (8.3%)	116 (14.1%)
Missing	30 (1.8%)	8 (1.1%)	22 (2.4%)	11 (0.7%)	<5	<10
Child age at assessment (y)	3.00 (0.81)	3.01 (0.80)	3.00 (0.82)	8.76 (1.18)	8.82 (1.22)	8.71 (1.14)
Child sex						
Male	869 (51.5%)	384 (50.5%)	485 (52.3%)	733 (49.5%)	322 (48.9%)	411 (50.1%)
Female	819 (48.5%)	376 (49.5%)	443 (47.7%)	747 (50.5%)	337 (51.1%)	410 (49.9%)
Child behavioral problem scores[3]						
Total problems	46.6 (10.6)	47.5 (11.2)	45.9 (10.1)	47.2 (11.0)	47.4 (11.2)	47.1 (10.9)
Externalizing	46.6 (10.1)	47.2 (10.3)	46.2 (9.92)	47.5 (10.2)	47.8 (10.4)	47.3 (9.93)
Internalizing	46.4 (10.6)	47.3 (11.0)	45.8 (10.1)	48.2 (10.1)	48.2 (10.2)	48.1 (10.0)

CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early childhood; ECHO, Environmental influences on Child Health Outcomes; VDAART, Vitamin D Antenatal Asthma Reduction Trial.

[1] Data presented as n (column %) or mean (SD). Counts <5 are masked (displayed as "<5") for the protection of participant privacy.

[2] Gestational age at vitamin D assessment was calculated using the child's date of birth, maternal gestational age at delivery, and cohort-provided specimen collection dates.

[3] Behavioral problem scores presented as T-scores standardized to mean = 50, SD = 10.

childhood analyses, respectively (Table 1). Mean 25(OH)D concentrations (assessed in maternal or cord blood) were similar in the younger and older childhood analyses, at 21.6 (SD: 8.55) and 21.8 (SD: 8.62) ng/mL, respectively. In both analyses, ~45% were deficient in vitamin D. Distributions of 25(OH)D concentrations across pregnancy trimesters and by specimen type (that is, maternal and cord blood) are shown in Supplemental Table 5 and Supplemental Figure 2. A large portion of mothers self-identified as non-Hispanic Black (60.1% and 43.8% in the younger and older analyses, respectively), and Black women were disproportionately classified as having vitamin D deficiency (71.8% and 54.5% in the younger and older analyses). Other factors that appeared to be associated with vitamin D deficiency included lower maternal educational attainment, prepregnancy obesity, prenatal tobacco use, and higher parity.

Fully adjusted models in the main analysis showed no significant association of 25(OH)D concentrations in prenatal or cord blood samples with behavioral scores in early childhood (Table 2). Similar results were observed in a sensitivity analysis restricted to dyads with 25(OH)D assessed in the second trimester (Supplemental Table 6). However, when restricted to dyads with 25(OH)D assessed in prenatal samples (that is, excluding cord blood measures), 25(OH)D was negatively associated with total and externalizing problem scores in early childhood. In this sensitivity analysis, a 10 ng/mL increase in prenatal 25(OH)D was associated with 0.75-point lower total problem T-scores (95% CI: −1.43, −0.07) and 0.65-point lower externalizing problems (95% CI: −1.29, 0.00).

In the analysis of middle childhood outcomes, prenatal or cord blood 25(OH)D concentrations were negatively associated with externalizing behaviors in both minimally and fully adjusted models (Table 2). After controlling for important confounders, a 10 ng/mL increase in 25(OH)D was associated with 0.73-point lower externalizing behavior T-scores (95% CI: −1.36, −0.10). This relationship appeared to be strengthened in sensitivity analyses restricted to dyads with prenatal 25(OH)D measurements (β: −0.93; 95% CI: −1.60, −0.26) or dyads with second trimester 25(OH)D (β: −1.02; 95% CI: −1.81, −0.24) (Supplemental Table 6).

We examined whether the relationships between gestational 25(OH)D and childhood behavioral outcomes differ between Black and non-Black mothers. Model terms representing the interaction of 25(OH)D concentration (in prenatal or cord blood samples) and Black race all had negative beta estimates, suggesting a relatively stronger protective effect of higher gestational 25(OH)D concentration against child behavioral problems for Black compared with non-Black mothers (Table 3). However, these terms were not statistically significant for any of the behavioral outcomes during early or middle childhood.

In a sensitivity analysis, we recreated full models with additional adjustments for the behavioral outcome instrument used (Supplemental Tables 7 and 8). The instrument used was a significant predictor of the outcomes in early but not middle childhood. The inclusion of this additional term in the models diminished the association of prenatal or cord blood 25(OH)D concentrations with externalizing problems in middle childhood that were observed in the main analysis (β: −0.61; 95% CI: −1.25, 0.04) (Supplemental Table 7). In another sensitivity analysis, the omission of any single cohort did not lead to significant changes in conclusions compared with the main analysis. As depicted in Supplemental Figure 3, CIs in this sensitivity analysis overlapped the point estimates generated in the main analyses.

In the post hoc IPTW analysis, we found that risk of behavioral problems was generally reduced with greater prenatal or cord blood 25(OH)D status, particularly for early childhood outcomes and at a higher exposure level of 30 ng/mL (Supplemental Table 9). For example, prenatal or cord blood 25(OH)D ≥ 30 ng/mL was associated with a −2% (95% CI: −7%, 3%) difference in risk for borderline or clinical CBCL scores during early childhood. However, the findings in this post hoc analysis did not reach statistical significance.

TABLE 2
Relationships between gestational vitamin D and behavioral problem T-scores in early and middle childhood in the ECHO program[1]

	Prenatal or cord blood 25(OH)D				Prenatal 25(OH)D	
	Minimally adjusted model[2]		Fully adjusted model[2]		Fully adjusted model[3]	
	β (95% CI)	*P*[4]	β (95% CI)	*P*	β (95% CI)	*P*
Early childhood	*n* = 1688		*n* = 1688		*n* = 1449	
Total problems	−0.77 (−1.37, −0.17)	0.012	−0.59 (−1.21, 0.04)	0.066	−0.75 (−1.43, −0.07)	0.030
Externalizing	−0.48 (−1.05, 0.09)	0.099	−0.38 (−0.98, 0.22)	0.215	−0.65 (−1.29, 0.00)	0.049
Internalizing	−0.66 (−1.26, −0.06)	0.031	−0.46 (−1.09, 0.17)	0.151	−0.50 (−1.18, 0.17)	0.146
Middle childhood	*n* = 1480		*n* = 1480		*n* = 1310	
Total problems	−0.48 (−1.13, 0.18)	0.152	−0.51 (−1.19, 0.17)	0.143	−0.70 (−1.43, 0.02)	0.057
Externalizing	−0.82 (−1.42, −0.22)	0.007	−0.73 (−1.36, −0.10)	0.023	−0.93 (−1.60, −0.26)	0.006
Internalizing	−0.08 (−0.69, 0.53)	0.797	−0.33 (−0.95, 0.30)	0.308	−0.39 (−1.05, 0.28)	0.257

ECHO, Environmental influences on Child Health Outcomes.
[1] Estimates for expected change in outcome per 10ng/mL increase in 25(OH)D.
[2] Minimal model adjusted for maternal age (continuous), child sex, and child age at assessment (continuous), with random intercepts accounting for within-cohort correlation.
[3] Full model adjusted for covariates in the minimal model plus maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic other, or Hispanic), maternal education (high school degree or lower, some college or associate degree, or bachelor's degree or higher), prenatal tobacco use (yes or no), prenatal alcohol use (yes or no), parity (continuous), and prepregnancy BMI(continuous).
[4] $P < 0.05$ is considered significant.

Discussion

Overall, this study confirmed a high prevalence of vitamin D deficiency among pregnant individuals in the United States, especially those who self-identified as Black. This study found evidence of an association between gestational vitamin D and childhood behavior. Greater 25(OH)D concentrations, measured in prenatal or cord blood samples, were associated with reduced externalizing behaviors in middle childhood. In a sensitivity analysis restricted to 25(OH)D measurements in prenatal samples (that is, excluding the one cohort with cord blood 25(OH)D data), we additionally found favorable associations of vitamin D with total and externalizing problems in early childhood. This finding suggests that the timing of exposure may be related to susceptibility to insult, and future research should evaluate the possible critical windows of exposure. Relationships of gestational 25(OH)D and childhood behavior did not appear to differ between races. Altogether, these results suggest that greater vitamin D status in pregnancy may confer modest protection against behavioral problems during childhood.

Published findings on the relationship between gestational 25(OH)D with offspring behavioral development are inconsistent. Among the strongest positive findings were those reported by Daraki et al. [6] based on a sample of 487 mother-child dyads in Greece. Children of mothers in the highest 25(OH)D tertile (>20.3 ng/mL) in early- to mid-pregnancy had significantly reduced total behavioral difficulties and externalizing behavior scores at age 4 compared to the lowest tertile (<15.5 ng/mL) [6]. In a sample of 218 dyads, Chawla et al. [7] found that greater 25(OH)D concentrations in the first and second trimesters were significantly associated with more favorable internalizing behavior and dysregulation scores at ages 12–24 mo among children of White mothers. However, associations were less evident among Black or Hispanic mothers [7]. In another small study, Gale et al. [45] reported that greater 25(OH)D concentrations in late pregnancy were associated with more favorable scores on the peer problems scale of the SDQ at age 9 but not with any other scales. Another study found that the odds of high total problem scores at 7 y was ~24% (95% CI: −4%, 60%) greater in children with lower gestational 25(OH)D exposure (<20 ng/mL) compared with higher (>20 ng/mL) exposure, although this did not reach statistical significance ($P = 0.09$) [46].

Several other studies have observed no association of gestational 25(OH)D with behavioral problems in early [16,18,47] or middle childhood [17,47,48], or adolescence [47]. However, these studies have important limitations. For example, both Laird [18] and López-Vicente [17] acknowledged that their study samples had few participants with vitamin D deficiency. Others included homogenous populations composed predominantly of White participants (86%–100%) [16,47,48] and often with limited geographic recruitment [16,47]. These authors recognized limitations to generalizability [16], especially to other non-White populations with a greater burden of vitamin D deficiency. In contrast, the present study examined a racially and ethnically diverse sample in which vitamin D deficiency was prevalent. Methodological differences may also underlie the differences in study conclusions. For example, the null findings reported by Whitehouse et al. [47] were based on a simple bivariate analysis examining the relationship between quartiles of prenatal 25(OH)D and the percentage of children exceeding CBCL clinical thresholds. Categorization of the exposure and outcome variables, along with the lack of control for potential confounders, could have limited the researchers' ability to detect subtle relationships. Another study reporting null findings based their behavioral assessment on a brief symptom rating completed by a psychologist following a study visit [48]. Although highly trained in this field, psychologists had limited exposure to study participants and, therefore, may report behavioral problems differently than parents, who are the primary respondents for other assessment tools such as the CBCL and SDQ. A sensitivity analysis suggested that for some behavioral outcomes, stronger relationships may be observed for vitamin D exposures assessed within pregnancy rather than at the time of delivery. Importantly, this study included only one cohort with cord blood 25(OH)D data, but other research supports this possibility, including a study by Sammallahti et al. [49] examining 2 prospective cohorts in Finland and the Netherlands. In this study, lower 25(OH)D concentrations in early- to mid-pregnancy, but not in cord blood, were associated with higher infant-negative

TABLE 3
Estimated regression coefficients (with 95% CI) for the association of gestational 25(OH)D concentration and childhood behavioral problems T-scores with the interaction of race and 25(OH)D

Outcome	Model terms[1]	Early childhood		Middle childhood	
		β (95% CI)	P[2]	β (95% CI)	P
Total problems	25(OH)D × Race (Black)	−0.89 (−2.09,0.32)	0.149	−0.85 (−2.26,0.56)	0.238
	25(OH)D, 10 ng/mL	−0.02 (−0.94,0.91)	0.973	−0.23 (−1.06,0.61)	0.595
	Maternal race (Black)	0.55 (−2.44,3.55)	0.716	0.67 (−2.66,4.00)	0.694
Externalizing	25(OH)D × Race (Black)	−0.88 (−2.04,0.27)	0.132	−0.72 (−2.02,0.58)	0.279
	25(OH)D, 10 ng/mL	0.18 (−0.70,1.06)	0.686	−0.50 (−1.28,0.27)	0.201
	Maternal race (Black)	0.33 (−2.54,3.20)	0.821	1.11 (−1.97,4.18)	0.479
Internalizing	25(OH)D × Race (Black)	−0.52 (−1.73,0.68)	0.396	−0.52 (−1.82,0.78)	0.434
	25(OH)D, 10 ng/mL	−0.08 (−1.00,0.84)	0.861	−0.17 (−0.94,0.60)	0.660
	Maternal race (Black)	−0.40 (−3.40,2.60)	0.795	−1.03 (−4.09,2.03)	0.510

[1] Models included random intercepts accounting for within-cohort correlation, in addition to terms for maternal age (continuous), child sex, and child age at assessment (continuous), maternal ethnicity (non-Hispanic or Hispanic), maternal education (high school degree or lower, some college or associate degree, or bachelor's degree or higher), prenatal tobacco use (yes or no), prenatal alcohol use (yes or no), parity (continuous), and prepregnancy BMI (continuous).
[2] $P < 0.05$ is considered significant.

affectivity [49], an outcome linked with internalizing and externalizing behaviors in childhood [50]. Two of the largest human studies examining this relationship, which reported null findings, utilized 25(OH)D measurements from relatively late in pregnancy, at 26 wk [48] or 29.6 wk [46]. In contrast, reports by Daraki [6] and Chawla [7], which provide the greatest support for the role of vitamin D, analyzed 25(OH)D concentrations in the first and second trimesters. Consistent with these findings, our sensitivity analysis restricted to second trimester exposure showed either similar or strengthened relationships with behavioral outcomes compared with the main analysis.

Early pregnancy is a critical window during which vitamin D performs numerous biological functions critical to early brain development, such as cytokine regulation, neurotransmitter synthesis, antioxidant activity, and the expression of genes involved in neuronal differentiation, structure, and metabolism [51]. In animal models, prenatal vitamin D deficiency has been associated with morphological changes [52] that may result in abnormal behaviors in adulthood [53,54]. However, studies in humans are limited, and specific biological mechanisms remain unclear. Additionally, existing data from human studies have yet to clarify optimal 25(OH)D concentrations for promoting offspring behavioral health. The most recent recommendations for vitamin D intake from the Institute of Medicine were released in 2011 and are based on achieving circulating 25(OH)D concentrations of 20 ng/mL, including in pregnancy [44]. These guidelines were based on skeletal health outcomes; key limitations acknowledged within the report were the lack of data on the role of vitamin D in nonskeletal health outcomes and during pregnancy and lactation [44]. The results of our IPTW analysis suggested that targeting 30 ng/mL may provide greater protection against behavioral problems compared to 20 ng/mL, yet few studies have directly examined this. Many observational studies have not evaluated relative risks for this higher exposure level [6,16,46], but others have documented benefits for mental and psychomotor development among those with 25(OH)D $\geq$ 30 ng/mL compared to those between 20 and 30 ng/mL [55].

This study had multiple strengths. First, using multi-cohort data from the ECHO program provided a large sample size for this analysis with rich geographic, socioeconomic, and racial diversity. We also maximized our sample size using a newly developed crosswalk conversion between the CBCL and SDQ scores [40]. The parent-reported SDQ and CBCL both have high predictive validity for behavioral problems [56,57] and are often used as a "gold standard" to which other tools are compared [58]. However, a sensitivity analysis suggested that the conversion may not have fully harmonized scores from the 2 instruments. Our study is the first, to our knowledge, to utilize this crosswalk in a large epidemiological investigation, and future research should evaluate its performance in other populations.

This study may also be affected by residual confounding. For example, a recent review pointed out that many investigations of this subject fail to control for other dietary nutrients [37]. We did not include other dietary factors and nutrient supplements in this analysis, as most cohorts did not collect this information. Positive associations of prenatal diet quality with children's executive functioning were recently reported in a Canadian cohort [59], yet other researchers have seen no clear association between prenatal diet quality and childhood behavior [60]. Additionally, although adequate infant vitamin D status may potentially mitigate the harmful effects of gestational vitamin D deficiency on childhood outcomes, we did not include information on infant feeding or supplementation practices. Future research assessing vitamin D status throughout early life might be especially helpful in encouraging adherence to the recommendation in the United States Dietary Guidelines to provide infants with vitamin D supplements soon after birth [61]. Due to limited data availability, we were unable to assess the potential importance of the season of biospecimen collection, which may influence 25(OH)D concentrations. However, results from Darling et al. [46] indicated a minimal change in effect estimates for the association of maternal 25(OH)D with childhood neurocognitive outcomes when the season of vitamin D measurement was added to models already adjusted for sociodemographic and lifestyle factors. Concentrations of 25(OH)D were measured for each cohort by a different laboratory. Method-related differences in 25(OH)D analyses are well recognized and could have influenced our findings. However, each laboratory performed rigorous quality control procedures, and most participated in measurement standardization protocols. Furthermore, a sensitivity analysis showed no remarkable differences in findings when any single cohort was omitted from the analysis. Finally, 25(OH)D has been shown to exhibit a diurnal rhythm with lower values overnight compared to midday [62], and we were unable to account for this in our models. This may have increased random error in our exposure assessment, possibly biasing our findings toward the null hypothesis.

In conclusion, this study supports the hypothesized association between gestational vitamin D and childhood behavioral outcomes. Vitamin D deficiency is prevalent among pregnant women in the United States, which may increase risks for adverse birth outcomes, neonatal mortality, and impaired neurocognitive development [4,5,63,64]. Interventions to prevent or correct vitamin D deficiency in pregnancy may be warranted to promote childhood health and should be evaluated in future studies.

Acknowledgments

The authors wish to thank our ECHO colleagues; the medical, nursing, and program staff; and the children and families participating in the ECHO cohorts. We also acknowledge the contribution of the following ECHO program collaborators: ECHO Components, Coordinating Center: Duke Clinical Research Institute, Durham, North Carolina (Smith PB, Newby KL); Data Analysis Center: Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland (Jacobson LP); Research Triangle Institute, Durham, North Carolina (Catellier DJ); and Person-Reported Outcomes Core: Northwestern University, Evanston, Illinois (Gershon R, Cella D). ECHO Awardees and Cohorts: University of Colorado Denver, Denver, CO (Dabelea D); University of Washington, Department of Environmental and Occupational Health Sciences, Seattle, WA (Karr C); University of Tennessee Health Science Center, Memphis, TN (Mason A); Brigham and Women's Hospital, Boston, MA (Weiss S); Boston University Medical Center, Boston, MA (O'Connor G);

Kaiser Permanente, Southern California, San Diego, CA (Zeiger R); Washington University of St. Louis, St Louis, MO (Bacharier L); and Harvard Pilgrim Health Care Institute, Boston, MA (Oken E).

The authors' responsibilities were as follows—MMM, SS, and MM: designed the research; ML and MP: analyzed the data; MMM and SS: wrote the article; MMM: had primary responsibility for the final content, and all authors: participated in a critical review of the manuscript drafts and read and approved the final manuscript.

Data availability statement

Researchers can request to access de-identified ECHO data through the Data and Specimen Hub (DASH), a centralized resource established by the National Institute of Child Health and Human Development.

Funding

Research reported in this publication was supported by the Environmental influences on Child Health Outcomes program, Office of The Director, NIH, under Award Numbers U2COD023375 (Coordinating Center), U24OD023382 (Data Analysis Center), U24OD023319 with cofunding from the Office of Behavioral and Social Science Research (PRO Core), UH3OD023318 (ALD), UH3OD023271(Karr), UH3OD023244 (AEH), UH3OD023286 (Oken), UH3OD023248 (Dabelea), UH3OD023268 (Weiss), UH3OD023285 (JMK), UH3OD023249 (Stanford), UH3OD023342 (Lyall), UH3OD023344 (MacKenzie).

Author disclosures

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2023.03.005.

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