JOURNAL OF WOMEN'S HEALTH
Volume 23, Number 7, 2014

DOI: 10.1089/jwh.2013.4598

Association of Serum Vitamin D with Symptoms of Depression and Anxiety in Early Pregnancy

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Abstract

Objective: To evaluate associations between early pregnancy 25-hydroxyvitamin D (25[OH]D) concentrations and antepartum depression and anxiety symptoms and potential modifiers thereof.
Materials and Methods: In a pregnancy cohort ($N = 498$), we examined cross-sectional associations of early pregnancy (mean = 15.4 weeks gestation) serum 25[OH]D concentrations and depression and anxiety symptoms. Symptoms were measured using Depression, Anxiety, and Stress Scales (DASS-21) and Patient Health Questionnaire Depression Module (PHQ-9) instruments. Regression models were fit and effect modification by prepregnancy body mass index and leisure-time physical activity (LTPA) were assessed using interaction terms and stratified analyses.
Results and Discussion: Mean 25[OH]D concentration was 34.4 ng/mL. Approximately 12% had ''moderate'' anxiety (score ≥ 10) and depression (score ≥ 10) symptoms by DASS-21 Anxiety and PHQ-9 instruments, respectively. A 1 ng/mL lower 25[OH]D was associated with 0.043 and 0.040 higher DASS-21 Anxiety and PHQ-9 Scores (p-values = 0.052 and 0.029, respectively). Participants in the lowest quartile of 25[OH]D (< 28.9 ng/mL) had 1.11 higher PHQ-9 scores than those in the highest quartile (≥ 39.5 ng/mL, $p < 0.05$). However, associations were attenuated and statistically insignificant in fully adjusted models. Inverse associations of 25[OH]D with depression symptoms were significant among participants who reported no LTPA, but not among women who reported any LTPA (interaction $p = 0.018$).
Conclusions: Our study provides modest evidence for inverse cross-sectional associations of early pregnancy maternal vitamin D concentrations with antepartum depression symptoms. We also observed that these associations may be modified by physical activity.

Introduction

Depression, anxiety, and other mood disorders are common among women, particularly those of childbearing age. Estimates of lifetime prevalence of self-reported mood and anxiety disorders among US women are as high as 22%.[1] Approximately 15%–30% of women experience mood and anxiety disorders during pregnancy.[2,3] Self-reported symptoms of antenatal mood disorders are associated with risk behaviors (e.g., smoking[4] and substance use during pregnancy[5]), pregnancy complications (e.g., preeclampsia[6,7,8] and low birth weight[9]), and long term adverse outcomes in the mother (e.g. poor postpartum mental health[5]) and her offspring (e.g. childhood obesity[10]). Therefore, understanding determinants of antenatal mood disorders, such as depression and anxiety, has broad implications. Recent research in the general population on novel risk factors of mood and anxiety disorders indicates potentially significant roles of vitamin D deficiency.[11]

Vitamin D is an important regulator of gene expression in a broad range of cellular functions.[12] Vitamin D receptors are abundant across brain tissue; and several biological pathways (e.g., insulin/serotonin mediated pathways and the hypothalamic-pituitary-adrenal axis) have been postulated to link vitamin D deficiency with depression, anxiety, and other mood disorders.[13,14] Epidemiologic evidence for potential relationships between vitamin D and mood disorders have mainly come from studies conducted among men, the elderly, or nonpregnant women.[15–18] Several small randomized controlled trials have supported the benefit of vitamin D

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supplementation on improvements in depressive symptoms among overweight patients,[19] mood among healthy patients during the winter season,[20] or depressive symptoms among sufferers of seasonal affective disorders.[21] However, the association of vitamin D with mood and anxiety symptoms during pregnancy is under-investigated. In the two available published reports in this research area to date, conducted among African American[22] and European women,[23] second trimester vitamin D was inversely related to depression symptoms. Since vitamin D deficiency is potentially preventable, such investigations can provide potential opportunities to improve mood and anxiety disorder related pregnancy outcomes.

Prior studies on vitamin D and mood disorders among nonpregnant populations have examined potential effect modification by characteristics such as overweight/obesity status and leisure time physical activity (LTPA).[24,25] Adipose tissue may reduce bioavailability of vitamin D and alter vitamin D metabolism, consequently reducing basal concentrations of vitamin D.[26–28] Similarly, LTPA may be related to vitamin D homeostasis[28] and has been shown to be a strong determinant of vitamin D status in several studies, including large US cohorts of healthy middle-aged men and women.[29,30] Therefore, the relationship between vitamin D concentrations and depression may differ based on the presence of either overweight/obesity or physical activity. Despite this, past studies within pregnant populations have not explicitly tested effect modification by prepregnancy body mass index or LTPA during pregnancy.[22–23]

Given the promising link between vitamin D deficiency and antenatal mood and anxiety disorders, and, the significant knowledge gap in the understanding of the relationships, we investigated cross-sectional associations of early pregnancy serum vitamin D concentrations with self-reported depressive and anxiety symptoms, assessed using validated survey instruments. We also evaluated potential effect modification of these associations by prepregnancy body mass index and LTPA.

Materials and Methods

Study setting and study population

This study was conducted among participants of the Pregnancy Migraine study, a prospective pregnancy cohort study designed to examine maternal risk factors for migraine in pregnancy and its relation to adverse pregnancy outcomes. Pregnant women were eligible for participation if they were 18 years or older, spoke and read English, initiated prenatal care at or prior to 20 weeks of gestation, and planned to deliver at the Swedish Medical Center in Seattle, Washington. The study population for this report is from the first 500 participants who were enrolled and were interviewed during the period of April 2009 and December 2010 as part of the Pregnancy Migraine study. Of these, all completed a blood draw for serum Vitamin D measurement and only two did not complete survey instruments. Consequently, 498 pregnancies were available for analysis.

Data collection

Study participants were asked to complete an interviewer-administered questionnaire at or near the time of enrollment (mean = 15.4 weeks of gestation) to collect information on sociodemographics, anthropometric characteristics, and reproductive and medical histories, including information on maternal age, race/ethnicity, marital status, educational attainment, antenatal smoking, history of depression or anxiety, history of diabetes or hypertension, and any leisure time physical activity (LTPA) during pregnancy. Any LTPA was defined as responding in the affirmative to a binary yes/no question regarding whether the participant had engaged in any ''recreational physical activity'' or exercise during the current pregnancy. In addition, information on height, weight, and physician-diagnosed depression and/or anxiety disorder during pregnancy was abstracted from the electronic medical records of Swedish Medical Center. Prepregnancy Body Mass Index was calculated from prepregnancy height and weight (kg/m^2).

Survey instruments

During the time of initial interview, participants were asked to complete two brief survey instruments to assess symptoms of depression, anxiety, and stress: the Depression, Anxiety, and Stress Scales 21-item Short Form (DASS-21) and Patient Health Questionnaire Depression Module (PHQ-9). The DASS-21 is a self-administered questionnaire containing 7 questions regarding each of the three domains (depression, anxiety, and stress), with respondents asked to score each statement on a four-point scale, from 0 indicating ''does not apply at all'' to 3 indicating ''applied very much / almost all of the time.''[31] This score is then doubled (to correspond to the full DASS instrument), producing a possible 42 points in each domain. The DASS-21 has been shown to be effective in distinguishing between symptoms of depression, anxiety, and stress[32,33] and potentially useful in perinatal populations due to its exclusion of somatic symptoms such as sleep disturbance, lack of energy, and poor concentration.[34]

The PHQ-9 is a self-administered questionnaire which asks respondents to rate the frequency of nine *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition depression criteria from 0 (''not at all'') to 3 (''nearly every day'') for a score range of 0 to 27.[35] The PHQ-9 has been evaluated in various settings including in pregnant populations and shown to have good sensitivity and specificity in detecting clinical and subclinical depression.[36] Cutoffs for severity for each instrument were defined to be consistent with DASS-21 documentation and previous literature. A DASS-21 Depression domain score of 0–9 was considered ''normal''; 10–13 ''mild''; 14–20 ''moderate''; 21–27 ''severe''; and ≥28 ''extremely severe.''[31] The corresponding cutoff scores for anxiety are 0–7, 8–9, 10–14, 15–19, and ≥20. The cutoff scores for stress are 0–14, 15–18, 19–25, 26–33, and ≥34. A PHQ-9 score of 0–4 was considered ''minimal'' depression; 5–9 ''mild''; 10–14 ''moderate''; 15–19 ''moderately severe''; and 20–27 ''severe.''[35] Women with DASS scores above ''normal'' or PHQ-9 scores above ''mild'' have been shown to have higher risk of pregnancy complications.[37,38]

Vitamin D measurements

At the time of enrollment, concurrent with completion of survey instruments to measure depression and anxiety, study participants provided a 20 mL nonfasting sample of peripheral blood. The samples were immediately fractionated and stored at −80°C until analysis. Serum 25-hydroxyvitamin D (25[OH]D) concentrations were measured using liquid chromatography–tandem mass spectroscopy (LC-MS/MS)

by ZRT Laboratory (ZRT Laboratory, Portland, OR). Both 25[OH]D2 and 25[OH]D3 concentrations were measured, with the sum giving total serum 25[OH]D concentration. In our analyses, we used total serum 25[OH]D concentrations to characterize vitamin D levels. The assay reportable range was 2–800 ng/mL with a coefficient of variation ranging between 6% and 11%. Measurements were conducted blinded to knowledge of mood or anxiety symptoms.

Statistical analyses

Study population characteristics were described using mean (and standard deviations) for continuous variables and count (and percentages) for categorical variables, across quartiles of the serum total 25[OH]D distributions (quartiles based on distributions among all study participants). The distribution of serum total 25[OH]D concentrations was normally distributed and thus were not log-transformed. We examined associations of serum total 25[OH]D concentration with each of the instrument scores (DASS-Depression, DASS-Anxiety, DASS-Stress, and PHQ-9) using multivariate linear regression with robust standard errors. We fit unadjusted, minimally adjusted, and maximally adjusted regression models. Potential confounders were chosen *a priori*, drawing from past literature and causal diagramming (not shown). Minimally adjusted models included covariates for season and gestational age at blood draw, age at enrollment, and prepregnancy body mass index (BMI). Maximally adjusted models included covariates in the minimally adjusted models as well as additional behavioral and socioeconomic characteristics (smoking, race, education, and marital status) which may be potential confounders. The exposure variable, serum total 25[OH]D concentrations, was evaluated as a continuous variable as well as a categorical variable (based on quartiles). In analyses involving quartiles, the trend *p*-value was examined to assess significant linear relationships.

We evaluated effect modification by prepregnancy overweight/obese status or antenatal LTPA using stratified analyses (stratified by prepregnancy overweight/obesity status [BMI $\geq 25\,kg/m^2$] or any self-reported LTPA during pregnancy, respectively). We assessed statistical significance of the effect modification by evaluating the *p*-value of interaction terms in models that include terms for main effects and the interaction. Statistical significance was evaluated at the $\alpha \leq 0.050$ level. All analyses were conducted using STATA Version 12 (STATA, College Station, TX).

Results

Study participants were predominantly non-Hispanic white (86.8%), married (90.4%), and educated (89.8% at least college graduates) (Table 1). Mean prepregnancy BMI

Table 1. Selected Study Participant Characteristics, by Quartiles of Serum Vitamin D

		Serum vitamin D concentrations (ng/mL)			
*% (N) or mean (SD) (denoted by *)*	*Overall (N = 498)*	*Quartile 1 ≥ 39.5 (n = 125)*	*Quartile 2 34.1–39.4 (n = 124)*	*Quartile 3 28.9–34.0 (n = 124)*	*Quartile 4 < 28.9 (n = 125)*
Demographics					
Maternal age (years)*	33.4 (4.2)	33.9 (4.0)	32.8 (4.1)	33.3 (4.2)	33.5 (4.6)
Non-Hispanic white	86.8% (429)	94.3% (116)	90.2% (111)	91.9% (113)	71.2% (89)
Married	90.4% (450)	92.8% (116)	89.5% (111)	92.7% (115)	86.4% (108)
College graduate or higher	89.8% (447)	91.2% (114)	90.3% (112)	91.1% (113)	86.4% (108)
Medical / life style history					
Smoked during pregnancy	4.2% (21)	4.0% (5)	4.8% (6)	3.2% (4)	4.8% (6)
History of depression	12.5% (58)	11.8% (14)	18.8% (21)	10.2% (12)	9.5% (11)
Depression diagnosis	4.9% (24)	5.6% (7)	3.3% (4)	3.3% (4)	7.5% (9)
Anxiety diagnosis	2.9% (14)	3.2% (4)	5.7% (7)	0.8% (1)	1.7% (2)
Leisure-time physical activity	76.8% (381)	86.2% (106)	71.0% (88)	79.0% (98)	71.2% (89)
History of diabetes	0.2% (1)	0% (0)	0% (0)	0.8% (1)	0% (0)
History of hypertension	2.2% (11)	1.6% (2)	3.2% (4)	0.8% (1)	3.2% (4)
BMI and vitamin D measurements					
Prepregnancy BMI (kg/m^2)*	23.5 (4.7)	22.7 (3.9)	23.4 (4.3)	23.8 (4.5)	24.2 (5.8)
Total serum 25[OH]D (ng/mL)*	34.4 (8.7)	45.4 (6.1)	36.5 (1.4)	31.6 (1.4)	24.1 (4.7)
GA at blood draw (weeks)*	15.4 (2.6)	16.0 (2.5)	15.7 (2.5)	15.0 (2.7)	14.7 (2.5)
Winter season blood draw	15.9%	8.8% (11)	12.9% (16)	16.1% (20)	25.6% (32)
Depression instruments					
*Depression subscale (0–42)**	4.4 (5.1)	4.3 (5.5)	4.4 (4.8)	3.7 (4.4)	5.4 (5.4)
At least ''moderate'' depression (14+)	5.8% (29)	4.0% (5)	7.3% (9)	4.0% (5)	8.0% (10)
*Anxiety subscale (0–42)**	4.2 (4.6)	3.5 (4.3)	4.5 (4.4)	4.1 (5.5)	4.6 (4.3)
At least ''moderate'' anxiety (10+)	12.4% (62)	12.0% (15)	14.5% (18)	10.5% (13)	12.8% (16)
*Stress subscale (0–42)**	8.9 (6.8)	8.3 (5.8)	9.0 (6.4)	8.7 (7.7)	9.7 (7.1)
At least ''moderate'' stress (19+)	7.6% (38)	3.2% (4)	8.1% (10)	9.7% (12)	9.6% (12)
PHQ-9 (0–27)*	5.5 (3.5)	5.3 (3.5)	5.6 (3.2)	4.8 (3.2)	6.4 (3.8)
At least ''moderate'' depression (10+)	12.2% (61)	12.0% (15)	11.3% (14)	8.1% (10)	17.6% (22)

25[OH]D, 25-hydroxyvitamin D; BMI, body mass index; GA, gestational age; PHQ, Patient Health Questionnaire Depression Module.

Table 2. Instrument Scores by Vitamin D Concentrations (Continuous)

Model	*β [95% confidence interval]*	p-*value*
Difference in DASS 21 depression score per 1 ng/mL decrease in total serum vitamin D		
Unadjusted	0.040 [−0.012, 0.091]	0.130
Minimum	0.017 [−0.037, 0.070]	0.543
Maximum	0.017 [−0.038, 0.071]	0.547
Difference in DASS 21 anxiety score per 1 ng/mL decrease in total serum vitamin D		
Unadjusted	0.043 [−0.001, 0.086]	0.052
Minimum	0.034 [−0.009, 0.076]	0.118
Maximum	0.019 [−0.025, 0.062]	0.398
Difference in DASS 21 stress score per 1 ng/mL decrease in total serum vitamin D		
Unadjusted	0.062 [−0.009, 0.132]	0.087
Minimum	0.039 [−0.028, 0.105]	0.255
Maximum	0.037 [−0.030, 0.105]	0.281
Difference in PHQ-9 (depression) score per 1 ng/mL decrease in total serum vitamin D		
Unadjusted	0.040 [0.004, 0.077]	0.029*
Minimum	0.024 [−0.013, 0.061]	0.204
Maximum	0.019 [−0.020, 0.058]	0.335

Minimum: Adjusted for season and gestational age at blood draw, age at enrollment, and prepregnancy BMI. Maximum: Also adjusted for smoking status, white race, education, and marital status.
*$p < 0.050$.

was 23.5 kg/m^2, and 76.8% of participants reported any LTPA during pregnancy. Mean 25[OH]D concentration among participants was 34.4 ng/mL. Among participants, 40% were vitamin D insufficient/deficient (≤ 32 ng/mL), while 4.2% of were vitamin D deficient (≤ 20 ng/mL). Based on medical records, 12.5% had physician-diagnosed history of depression. Based on responses to the PHQ-9 or DASS-21 questionnaires, 12.2% had at least ''moderate'' depression (PHQ-9 > 10); 12.4% had at least ''moderate'' anxiety (DASS-21 anxiety > 10) symptoms; and 7.6% had at least ''moderate'' stress (DASS-21 stress > 19) symptoms (Table 1).

Overall, women in our study with lower 25[OH]D concentrations had higher DASS-21 and PHQ-9 scores (Table 2). A 1 ng/mL decrease in 25[OH]D was associated with 0.043 and 0.040 higher DASS-21 anxiety and PHQ-9 scores (*p*-values 0.05 and 0.03, respectively, Table 2). Participants with the lowest 25[OH]D concentrations (quartile 4: 25[OH]D < 28.9 ng/mL) had 1.11 higher PHQ-9 scores compared with participants with the highest 25[OH]D concentrations (quartile 1: 25[OH]D ≥ 39.5 ng/mL; $p < 0.05$; Table 3). However, associations were attenuated and became statistically insignificant in fully adjusted models. While associations were not different among groups of participants stratified by prepregnancy overweight/obese status (Table 4), observed inverse associations of 25[OH]D with depression symptoms (using both DASS-21 Depression and PHQ-9 measures) were more pronounced among participants who reported no LTPA during current pregnancy than those who reported any LTPA during current pregnancy (interaction *p*-value = 0.018) (Table 5). Among those reporting no LTPA, participants in the lowest quartile (quartile 4) of 25[OH]D concentrations had a 2.6-point higher DASS-21 Depression score (95% confidence interval [95% CI]: −0.40, 5.56) compared with participants in the highest quartile (quartile 1) of 25[OH]D concentrations in the maximally adjusted model (linear trend *p*-value = 0.025). The corresponding beta and (95% CI) among participants who reported any LTPA was −0.32 (−1.92, 1.28) for DASS-21 Depression score (linear trend *p*-value = 0.423). Similar differences were observed for PHQ-9 depression scores (interaction *p*-value = 0.051).

We did not observe evidence for statistical interactions between prepregnancy overweight/obesity status or LTPA

Table 3. Instrument Scores by Vitamin D Quartiles (Relative to Quartile 1: ≥ 39.5 ng/mL)

Model	*Quartile 2 (34.1–39.4 ng/mL)*	*Quartile 3 (28.9–34.0 ng/mL)*	*Quartile 4 (< 28.9 ng/mL)*	*Trend* p-*value*
Difference in DASS 21 depression score (β [95% confidence interval])				
Crude	0.15 [−1.14, 1.43]	−0.55 [−1.78, 0.69]	1.09 [−0.27, 2.45]	0.233
Minimum	−0.0002 [−1.32, 1.32]	−0.90 [−2.22, 0.42]	0.54 [−0.88, 1.96]	0.751
Maximum	−0.05 [−1.37, 1.28]	−0.82 [−2.15, 0.52]	0.57 [−0.88, 2.02]	0.731
Difference in DASS 21 anxiety score (β [95% confidence interval])				
Crude	0.93 [−0.14, 2.00]	0.53 [−0.70, 1.75]	1.02 [−0.034, 2.08]	0.123
Minimum	0.72 [−0.39, 1.84]	0.29 [−0.97, 1.55]	0.80 [−0.29, 1.89]	0.261
Maximum	0.60 [−0.53, 1.74]	0.27 [−0.98, 1.52]	0.43 [−0.71, 1.57]	0.593
Difference in DASS 21 stress score (β [95% confidence interval])				
Crude	0.68 [−0.85, 2.21]	0.42 [−1.27, 2.12]	1.36 [−0.25, 2.97]	0.145
Minimum	0.13 [−1.42, 1.68]	0.063 [−1.68, 1.81]	0.65 [−0.92, 2.21]	0.463
Maximum	0.02 [−1.57, 1.60]	0.14 [−1.59, 1.88]	0.58 [−1.03, 2.19]	0.475
Difference in PHQ-9 (depression) score (β [95% confidence interval])				
Crude	0.32 [−0.52, 1.16]	−0.51 [−1.34, 0.33]	1.11 [0.20, 2.02]*	0.083
Minimum	0.13 [−0.73, 1.00]	−0.76 [−1.63, 0.12]	0.64 [−0.29, 1.58]	0.484
Maximum	0.09 [−0.79, 0.98]	−0.74 [−1.64, 0.15]	0.55 [−0.42, 1.52]	0.656

Minimum: Adjusted for season and gestational age at blood draw, age at enrollment, and prepregnancy BMI.
Maximum: Also adjusted for smoking status, white race, education, and marital status.
*$p < 0.050$.

Table 4. Depression Instrument Scores by Vitamin D Quartiles and Prepregnancy Body Mass Index (Relative to Quartile 1: ≥39.5 ng/mL)

		Vitamin D quartiles (ng/mL)				
Model	*ppBMI*	*Quartile 2 (34.01–39.4)*	*Quartile 3 (28.9–34.0)*	*Quartile 4 (<28.9)*	*Trend* p-*value*	*Interaction* p-*value*[†]
Difference in DASS 21 depression scores (β [95% confidence interval])						
Crude	<25 kg/m^2	0.46 [−0.96, 1.89]	−0.07 [−1.48, 1.35]	1.33 [−0.11, 2.78]	0.167	0.567
	≥25 kg/m^2	−0.96 [−3.63, 1.70]	−2.12 [−4.84, 0.62]	0.08 [−2.51, 2.66]	0.965	
Minimum	<25 kg/m^2	0.42 [−1.05, 1.88]	−0.38 [−1.84, 1.08]	0.85 [−0.68, 2.38]	0.542	0.628
	≥25 kg/m^2	−1.35 [−4.16, 1.45]	−2.47 [−5.38, 0.43]	−0.25 [−2.93, 2.44]	0.792	
Maximum	<25 kg/m^2	0.34 [−1.14, 1.82]	−0.32 [−1.80, 1.16]	0.81 [−0.78, 2.40]	0.580	0.609
	≥25 kg/m^2	−1.29 [−4.13, 1.55]	−2.20 [−5.15, 0.75]	−0.22 [−3.08, 2.64]	0.749	
Difference in PHQ-9 scores (β [95% confidence interval])						
Crude	<25 kg/m^2	0.50 [−0.51, 1.51]	−0.25 [−1.25, 0.76]	1.46 [0.44, 2.49]*	0.042*	0.532
	≥25 kg/m^2	−0.30 [−1.96, 1.36]	−1.30 [−3.00, 0.40]	0.05 [−1.56, 1.66]	0.870	
Minimum	<25 kg/m^2	0.40 [−0.63, 1.44]	−0.49 [−1.52, 0.55]	1.00 [−0.08, 2.08]	0.271	0.669
	≥25 kg/m^2	−0.54 [−2.29, 1.20]	−1.30 [−3.10, 0.51]	−0.16 [−1.83, 1.51]	0.746	
Maximum	<25 kg/m^2	0.29 [−0.75, 1.34]	−0.47 [−1.51, 0.57]	0.80 [−0.32, 1.92]	0.453	0.531
	≥25 kg/m^2	−0.58 [−2.35, 1.19]	−1.26 [−3.10, 0.58]	−0.10 [−1.88, 1.69]	0.761	

[†]Likelihood ratio testing the model with and without an interaction term between indicator variable of vitamin D quartiles and prepregnancy overweight/obesity status (≥25 kg/m^2).

*$p < 0.05$.

ppBMI, prepregnancy body mass index.

and 25[OH]D on either DASS-21 Anxiety or DASS-21 Stress scores (*not shown*).

Discussion

In the current study, we found some evidence to support cross-sectional associations of lower concentrations of 25[OH]D with increased symptoms of antenatal depression. However, several of the relationships were not statistically significant after adjustment. We also found evidence that the relationships between 25[OH]D and depression symptoms were stronger among those that reported no LTPA during pregnancy using two different measures of depression.

To our knowledge, only two prior cross-sectional studies investigated vitamin D concentrations and depression symptoms among pregnant women.[22,23] In a study conducted

Table 5. Depression Instrument Scores by Vitamin D Quartiles and Leisure-Time Physical Activity (Relative to Quartile 1: ≥39.5 ng/mL)

		Vitamin D quartiles (ng/ml)				
Model	*LTPA*	*Quartile 2 (34.01–39.4)*	*Quartile 3 (28.9–34.0)*	*Quartile 4 (<28.9)*	*Trend* p-*value*	*Interaction* p-*value*[†]
Difference in DASS 21 depression score (β [95% confidence interval])						
Crude	None	−0.16 [−2.95, 2.63]	−0.27 [−3.23, 2.69]	3.23 [0.44, 6.02]*	0.011*	0.075
	Any	0.40 [−1.04, 1.85]	−0.55 [−1.95, 0.86]	0.35 [−1.09, 1.79]	0.980	
Minimum	None	−0.70 [−3.57, 2.17]	−1.11 [−4.11, 1.90]	2.76 [−0.08, 5.60]	0.016*	0.023*
	Any	0.31 [−1.19, 1.80]	−0.84 [−2.32, 0.63]	−0.31 [−1.86, 1.24]	0.438	
Maximum	None	−1.14 [−4.05, 1.77]	−0.98 [−4.01, 2.05]	2.58 [−0.40, 5.56]	0.025*	0.018*
	Any	0.28 [−1.23, 1.78]	−0.81 [−2.29, 0.68]	−0.32 [−1.92, 1.28]	0.423	
Difference in PHQ-9 score (β [95% confidence interval])						
Crude	None	−0.93 [−3.03, 1.18]	−1.33 [−3.56, 0.90]	1.41 [−0.70, 3.51]	0.087	0.122
	Any	0.63 [−0.33, 1.59]	−0.36 [−1.29, 0.58]	0.80 [−0.16, 1.76]	0.378	
Minimum	None	−1.42 [−3.56, 0.72]	−2.04 [−4.29, 0.20]	0.82 [−1.31, 2.94]	0.183	0.050*
	Any	0.48 [−0.51, 1.48]	−0.54 [−1.52, 0.43]	0.34 [−0.69, 1.36]	0.983	
Maximum	None	−1.59 [−3.77, 0.59]	−1.88 [−4.14, 0.69]	0.78 [−1.46, 3.01]	0.184	0.051
	Any	0.46 [−0.53, 1.46]	−0.52 [−1.51, 0.46]	0.22 [−0.84, 1.27]	0.801	

Minimum model: Adjusted for season and gestational age at blood draw, age at enrollment, and prepregnancy BMI.

Maximum model: Also adjusted for smoking status, white race, education, and marital status.

[†]Likelihood ratio testing the model with and without an interaction term between indicator variable of vitamin D quartiles and Leisure-Time Physical Activity (LTPA).

*$p < 0.05$.

among participants of the Amsterdam Born Children and Their Development cohort, Brandenbarg, et al. reported that women who were vitamin D deficient (25[OH]D ≤29.9 nM) or insufficient (30–49.9 nM) at 13 weeks gestation were more likely to report high levels of depressive symptoms (score ≥16 on the Center for Epidemiologic Studies Depression Scale, CES-D) at 16 weeks gestation compared to women who were vitamin D sufficient (≥50 nM) (adjusted odds ratio [OR] = 1.48 [95% CI: 1.13–1.95] and adjusted OR = 1.44 [95% CI: 1.12–1.85] for vitamin D deficient and insufficient, respectively).[23] Each 10-nM decrease in vitamin D status was associated with 1.05-fold increase in odds of high level of depressive symptoms (95%CI: 1.02–1.08).[23]

In their study among African American women, using the CES-D scale, Cassidy-Bushrow, et al. found that women with elevated depressive symptoms (CES-D ≥16) had significantly lower 25[OH]D concentrations ($p = 0.003$) and were significantly more likely to be in the vitamin D deficient (25[OH]D < 20ng/mL) category ($p = 0.016$).[22] Further, they reported a 46% lower odds of clinical depression (CES-D ≥16) for each 1 log-unit higher 25[OH]D serum concentration.[22]

In line with previous studies, we found that lower 25[OH]D concentrations were generally associated with higher depression scores. Nonetheless, we did not find strong evidence overall of linear association between 25[OH]D concentrations and depression scores (Table 2). However, among women reporting no LTPA during pregnancy, the associations were stronger and statistically significant. Our investigations extend previous work by examining associations among a US study population at otherwise low risk for adverse outcomes; using both DASS-21 and PHQ-9 scores, validated instruments for depression and mood disorder screening; and assessing potential modifiers of vitamin D and depression associations.

There are potential reasons for differences, mostly in strength of associations, between our findings and previous reports. First, different instruments were used to measure depressive symptoms in studies. While the measures of depression used in previous studies, CES-D, has been validated for clinical diagnoses of depression using other instruments, to our knowledge, it has not been specifically tested against the DASS-21 and PHQ-9 used in our study. Therefore, there may be a difference in the constructs measured by these instruments. Second, differences in the study populations may account for observed differences in associations. For example, the Cassidy-Bushrow study was conducted among African American women who had a very high frequency (82.6%) of vitamin D deficiency (25[OH]D < 20ng/mL). Our study population was predominantly non-Hispanic white (86.8%) with a much lower frequency of vitamin D deficiency (4.2%). To the extent that the associations of vitamin D with mood/anxiety disorders differ by study population characteristics, as demonstrated by our effect modification analyses, findings may differ between studies. Finally, differences in exposure categorization may have contributed to observed differences in findings. Prior studies used a binary indicator for vitamin D deficiency while we used a continuous variable for vitamin D concentrations. Since vitamin D deficiency is not prevalent among our participants, we were unable to conduct comparable analyses using a binary indicator for vitamin D deficiency. The two previous studies on vitamin D and antepartum depression suggested further work to assess the role of physical activity in observed relationships. In the current study, we found significant interactions between vitamin D and LTPA on depressive symptoms. Inverse associations of 25[OH]D concentrations and depressive symptoms were stronger and statistically significant among women who did not report any LTPA. As noted by Brandenbarg, et al., evaluating the role of physical activity in the relationship between vitamin D and depression is important.[23] There are several reasons why physical activity may play a role in the vitamin D-depression relationship. First, physical activity, particularly outdoor physical activity, is related to sun exposure, the main determinant of endogenous vitamin D production.[12] Physical activity has also been associated with improved mood and less frequent symptoms of depression.[39–41] Of note, hypothesized mechanisms for physical activity and mood/anxiety associations include alterations in the HPA stress response axis, which is also the hypothesized target mechanism for vitamin D activity in relation to depressive symptoms.[42]

Some strengths of our study include the following: We used state-of-the-art LC-MS/MS methods to measure maternal early pregnancy serum 25[OH]D concentrations. We used two validated scales to measure mood/anxiety disorders, particularly depression. In analyses of data collected in our study, conducted among a well-characterized study population, we adjusted for relevant covariates and assessed effect modification by overweight/obese status and LTPA. Moreover, we tested the sensitivity of our observed relationships to confounding by comorbid conditions or prior medical history by adding history of chronic hypertension, diabetes, anxiety, and depression to our maximally adjusted models. The estimate from these models did not differ greatly from our reported values: for example, the difference in DASS-21 Depression score per 1 ng/mL lower serum 25[OH]D was 0.021 ([95% CI: −0.032, 0.075], $p = 0.425$). This was not substantively different from our original estimate when not including these covariates: 0.017 ([95% CI: −0.038, 0.071], $p = 0.547$). Notably, Cassidy-Bushrow, et al. also found history of depression to have a minimal effect on their estimates.[22]

Some limitations of our study deserve mention. First, our study, which is moderate in size, may not be powered to assess statistically significant associations. While we observed beta estimates that support inverse associations between vitamin D and mood/anxiety symptoms, the confidence intervals for most of these estimates included zero. Second, misclassification of information collected from participants, particularly from self-report, is a potential limitation. For example, self-report of LTPA may be over-reported among those with other behaviors that improve vitamin D status. Participants who report LTPA may otherwise be spending more time in outdoor activities regardless of the level of physical exertion. Physical activity would then be a direct proxy for greater sun exposure, and thus endogenous vitamin D production. Generalizability of our findings may be limited to a middle-class and largely non-Hispanic white population. Finally, given the cross sectional nature of our study we cannot rule out non-causal reasons for observed associations, including reverse causality or associations with other unmeasured confounders. Our sensitivity analysis suggests that, at least in our population, comorbidities and prior history may not substantially confound the observed relationship.

Conclusions

In sum, our findings suggest that vitamin D may be related to self-reported symptoms of depression in early pregnancy independent of factors including: BMI, skin color, season, age, and smoking. This relationship may be strongest among those who report no physical activity. Future studies should evaluate temporal relationships between vitamin D and depressive symptoms and the potential role of physical activity in these relationships.

Acknowledgments

This research was supported by grants from the National Institutes of Health (HD/HL 355566, T32HD052462-06, and K01HL103174). The authors are indebted to participants of the Migraine study and staff of Center for Perinatal Studies, Swedish Medical Center, Seattle, Washington.

Disclosure Statement

No competing financial interests exist.

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