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The association of maternal prenatal vitamin D levels and child current wheeze

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Wheezing is common in early childhood and associated with subsequent asthma and decreased lung function.¹ Prenatally, vitamin D influences immune system and lung development; a role in consequent child wheeze and asthma has been hypothesized.^{2, 3} Previous research has reported associations between 25(OH)D levels and respiratory or atopic outcomes potentially inconsistent by race.⁴ This study examines associations between maternal 2nd trimester and delivery 25(OH)D levels and child current wheeze in the third year of life by maternal race.

The Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) is a prospective cohort in Shelby County, (Memphis) TN that enrolled women December 2006–June 2011.⁵ Enrollment was not based on parental history of atopic disease.⁵ Study visits occurred during the 2nd and 3rd trimesters, delivery, and annually in early childhood. Biopecimens, demographics, and health histories were collected by trained research assistants.⁵ This study includes dyads with Black and White women who had at least one prenatal 25(OH)D determination and their non-low birth weight (> 2500 grams)

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children who were born at 36 weeks estimated gestational age, (EGA) and had a 3-year study visit including respiratory and atopic disease assessments. Women provided written informed consent. The study was approved by UTHSC Institutional Review Board.

Maternal plasma 25(OH)D levels (ng/ml) were assessed at enrollment (16 to 28 weeks gestation) and delivery using a commercially available enzyme immunoassay (Immunodiagnostic Systems, IDS, Boldon, Tyne, & Wear, UK).⁵ Child current wheeze in the third year of life was assessed by interviewer administered questionnaire and defined by affirmation to the question, “Has your child ever had wheezing or whistling in the chest at any time in the past”⁶ and report of one or more episodes of wheeze in the past 12 months. Because skin pigmentation influences cutaneous vitamin D production⁷ and potential racial differences have been reported between maternal 25(OH)D and child outcomes,⁴ we *a priori* planned to assess for interaction by maternal race and conduct race-stratified models. We used multivariable logistic regression to investigate associations of maternal 25(OH)D (continuous) in the 2nd trimester and at delivery with child current wheeze. We also categorized 25(OH)D into tertiles since there are not established guidelines regarding levels of sufficiency for respiratory or immune health.² Models were adjusted for covariates selected based on existing literature:^{4, 8} maternal education, age, asthma history, smoking in pregnancy, delivery route, and child sex, birth season, and parent report of infant RSV/ bronchiolitis hospitalization. Due to missing data (n=72), report of breastfeeding at 4 weeks was included in sensitivity analyses. The significance level was 0.05.

Of 853 women included, 63% were Black, 50% had Medicaid, 53% had a high school education or less, and 11% reported having asthma. At enrollment, 96% reported taking prenatal/multi-vitamins. Overall, 62% of births were vaginal, 31% occurred in the fall (September–November), and the median estimated gestational age and birthweight were 39.2 weeks (interquartile range (IQR): 38.5, 40.0 weeks) and 3.31 kg (IQR: 3.05, 3.61 kg), respectively. Black women had significantly lower median 25(OH)D levels (2nd trimester 20.2 ng/ml, IQR: 14.7, 25.8 ng/ml and delivery 20.25 ng/ml, IQR: 15.4, 27.2 ng/ml) than White women (2nd trimester 25.1 ng/ml, IQR: 20.0, 30.4 ng/ml and delivery 27.1 ng/ml, IQR: 22.5, 34.1 ng/ml) $p<0.0001$.

Overall, 21% (178/853) of children had wheeze in the third year of life. Significant interaction was not detected for maternal race between 2nd trimester ($p=0.39$) or delivery ($p=0.19$) 25(OH)D and child current wheeze. In continuous analyses of maternal 25(OH)D levels (2nd trimester or delivery separately) and predicted probability of child current wheeze in the 3rd year of life stratified by maternal race, we did not detect a statistically significant association in Black ($p=0.98$, 2nd trimester; $p=0.80$, delivery) or White dyads ($p=0.19$, 2nd trimester; $p=0.11$, delivery). The results did not change appreciably when breastfeeding was added. In multivariable analyses investigating tertiles of maternal 25(OH)D, children of White women with 2nd trimester levels in the highest tertile had decreased relative odds of child current wheeze compared to children of women in the lowest (OR 0.44; 95% CI: 0.19–0.99, $p=0.048$). However, significance attenuated in the smaller subset with breastfeeding data (OR 0.48; 95% CI: 0.21–1.13, $p=0.094$). Delivery associations did not reach statistical significance (highest v. lowest tertile OR 0.46; 95% CI: 0.18–1.23, $p=0.12$). Among Black dyads, higher maternal 25(OH)D concentrations in the

2nd trimester and at delivery were not associated with current wheeze among children (Table 1).

We observed a potential protective association of prenatal 25(OH)D levels and child current wheeze in dyads in which the mother was White. An investigation by Visness et al., using two high-risk asthma cohorts did not find associations between cord blood 25(OH)D and subsequent asthma.⁸ We did not select families based on atopic disease history and assessed prenatal 25(OH)D which may in part explain inconsistencies in findings. A randomized controlled trial of prenatal vitamin D supplementation, that included dyads with at least one parent with history of atopic disease, reported a marginally significant decrease in asthma and recurrent wheeze at age three in the intervention group.³ Secondary analyses found no significant interaction by race.⁹ When assessing average 25(OH)D over pregnancy there was a decreased relative of odds child recurrent wheeze/asthma in non-African American but not in African-American women.⁹ Reasons for different findings detected by race potentially include lower baseline 25(OH)D levels and limited variability in Blacks, or other physiologic factors.^{4,10}

Regarding limitations, we did not have 1st trimester 25(OH)D, however, 25(OH)D was assessed at two time-points. A limited number of Blacks had higher 25(OH)D and a smaller number of White women had lower levels, however, there was variability. Our outcome data was assessed using parent report, but differential misclassification is unlikely. We did not assess child 25(OH)D which may be important in future studies.

We found a potential protective association between prenatal 25(OH)D concentrations and child current wheeze in White but not Black dyads. Future investigations in large racially diverse cohorts that include genetic data and vitamin D binding protein, in addition to results of prenatal supplementation trials are important to consider.^{2, 10}

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Table 1

Associations between 2nd trimester and delivery 25(OH)D levels, by tertiles, and child current wheeze at age 3 in White and Black mother-child dyads.

Maternal Vitamin D levels*	Unadjusted odds ratio (95% CI)	Adjusted odds ratio [†] (95% CI)
<i>2nd trimester</i>		
White mother-child dyads		
Low (<18.2 ng/ml), n=65	1.00	1.00
Medium (18.2- <25.7 ng/ml), n=104	0.68 (0.32–1.45)	0.57 (0.25–1.30)
High (≥ 25.7 ng/ml), n=144	0.49 (0.24–1.03)	0.44 (0.19–0.99)
Black mother-child dyads		
Low (<18.2 ng/ml), n=217	1.00	1.00
Middle (18.2- <25.7 ng/ml), n=182	0.91 (0.56–1.46)	0.96 (0.56–1.64)
High (≥ 25.7 ng/ml), n=141	1.05 (0.64–1.74)	0.77 (0.46–1.28)
<i>Delivery</i>		
White mother-child dyads		
Low (<19.2 ng/ml), n=49	1.00	1.00
Medium (19.2- <27.6 ng/ml), n=98	1.00 (0.43–2.34)	0.89 (0.35–2.25)
High (≥ 27.6 ng/ml), n=139	0.58 (0.25–1.36)	0.46 (0.18–1.23)
Black mother-child dyads		
Low (<19.2 ng/ml), n= 190	1.00	1.00
Medium (19.2- <27.6 ng/ml), n=139	1.18 (0.70–1.97)	1.20 (0.70–2.06)
High (≥ 27.6 ng/ml), n=105	1.27 (0.73–2.21)	1.24 (0.68–2.24)

* Low indicates tertile 1, medium indicates tertile 2, high indicates tertile 3

[†] Adjusted for: maternal age, maternal education, maternal asthma, maternal smoking, delivery route, and child sex, birth season, and RSV in the first year of life.