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Original Research Article

Title: Prenatal Vitamin D Levels and Child Wheeze and Asthma

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ABSTRACT

BACKGROUND: Maternal vitamin D status during pregnancy may influence lung development and risk of childhood wheeze and asthma. We investigated the relationship between prenatal

vitamin D and child asthma in a racially diverse cohort with a high burden of vitamin D insufficiency and child asthma.

METHODS: We included mother-child dyads in the prenatal Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) cohort (2006-2011, Shelby County, Tennessee). Maternal plasma vitamin D [25(OH)D] was measured from 2nd trimester (n=1091) and delivery specimens (n=907). At age 4-6 years, we obtained parent report of current child wheeze (symptoms within the past 12 months) and asthma (physician diagnosis and/or medication or symptoms within the past 12 months). We used multivariable logistic regression to assess associations of 25(OH)D and child wheeze/asthma, including an interaction term for maternal race.

RESULTS: Median 2nd trimester 25(OH)D levels were 25.1 and 19.1 ng/ml in White (n=366) and Black women (N=725), respectively. We detected significant interactions by maternal race for 2nd trimester plasma 25(OH)D and child current wheeze (p=0.014) and asthma (p=0.011). Odds of current wheeze and asthma decreased with increasing 25(OH)D in dyads with White mothers and increased in dyads with Black mothers, e.g., adjusted odds ratio (95% confidence interval) for asthma: 0.63 (0.36-1.09) and 1.41 (1.01-1.97) per interquartile range (15-27 ng/ml 25[OH]D) increase, respectively. At delivery, protective associations in White dyads were attenuated.

CONCLUSION: We detected effect modification by maternal race in associations between prenatal 25(OH)D and child wheeze/asthma. Further research in racially diverse populations is needed.

Keywords: Vitamin D, 25(OH)D, Asthma, Wheezing, Race, Prenatal Programming

Abbreviations: 25(OH)D: 25-hydroxyvitamin D3; OR: Odds Ratio; CI: Confidence Interval

Introduction

Asthma is a common chronic disease in childhood with the majority of cases presenting at less than 6 years of age.[1, 2, 3] The medical, psychosocial, and healthcare burdens associated with asthma are substantial as asthma is a leading cause of missed school days, emergency department visits, and hospitalizations.[4] Given the prevalence of asthma and the potentially profound effect on quality of life of patients and their families, it is important to investigate factors that may help prevent disease development. Asthma is a complex disease with contributions of both genetic and environmental factors: family history of asthma, parental smoking, and caesarian delivery are a few important risk factors for asthma, while nutritional factors have been associated with decreased risk.[5, 6] Maternal vitamin D levels during pregnancy have recently been investigated with respect to the development of asthma and wheeze in childhood, but the relationship between maternal vitamin D and childhood asthma remains unclear.

Vitamin D is a pro-hormone obtained from either diet or synthesis in the skin upon sunlight exposure.[7] The primary circulating form of vitamin D is 25-hydroxyvitamin D(25[OH]D) which is metabolized into 1,25-dihydroxyvitamin D, the biologically active form of vitamin D capable of binding to the vitamin D receptor transcription factor to control gene expression.[7, 8] Vitamin D is essential in bone health and maintaining calcium/phosphate homeostasis,[9] as well as influencing aspects of cardiovascular, endocrine, neurologic, and respiratory and immune health.[7, 10] Prenatally, vitamin D may influence normal lung and immune system development, contributing to its possible role in the development of asthma. Vitamin D receptors are present within fetal lung cells [11] and immune cells.[12] Vitamin D-regulated genes have been shown to be expressed in developing lung of both mice and humans. [13] Maternal vitamin D deficiency has been associated with increased airway smooth muscle mass and altered lung function in mice,[14] whereas supplementation of vitamin D deficient rats during pregnancy has been shown to decrease airway contractility and lower airway resistance

in offspring.[15] In humans, several observational epidemiologic studies have investigated the association between prenatal vitamin D intake or biomarker concentrations and wheeze or asthma in young children (reviewed in [16, 17, 18, 19]), generating inconsistent results, while recent, recent randomized clinical trials report suggestive protective associations with prenatal vitamin D supplementation and child recurrent wheeze, asthma and related symptoms at age 3 years.[20, 21, 22]

Vitamin D levels differ by race, with Black populations being at increased risk of vitamin D deficiency.[23] Some investigations have found inconsistent associations between vitamin D levels (including concurrent and prenatal) and respiratory and atopic disease outcomes by race.[24, 25, 26] However, such differences were not detected in a secondary analysis of data from a recent randomized controlled trial,[27] or in paired analysis of two racially distinct cohorts.[28] Here, using data from a large, racially diverse prospective cohort, we investigate the association of maternal plasma vitamin D levels (25(OH)D) and current wheeze and asthma at age 4-6 years, examining whether this association is modified by maternal race.

Materials and Methods

Study population

This investigation included mother-child dyads enrolled in the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study, a prospective cohort study based in Shelby County (Memphis), TN designed to study the relationship between prenatal and early life exposures and early childhood health and development. CANDLE recruited women in the 2nd trimester of pregnancy from community obstetric practices and one obstetric clinic. Eligible women were 16-40 years old and intended to deliver at a study hospital. Women with certain chronic medical conditions requiring medication (e.g., hepatitis, human immunodeficiency virus) or pregnancy complications (e.g., oligohydramnios, complete placenta previa) at study entry were excluded, however women with asthma remained eligible.[29, 30]

CANDLE enrolled 1,503 pregnant women between December 2006 and June 2011. [30] Women provided demographic information, medical histories and biospecimens during the 2nd and 3rd trimesters and at delivery.[29] Postnatally, the study conducted annual in-person clinic visits with mother-child dyads through age 3, and again when the children were between 4-6 years of age. For the current study, we included dyads with a maternal plasma 25(OH)D determination from either the 2nd trimester or delivery, estimated gestational age ≥ 32 weeks, and completion of a 4-6 year visit between age 3.7 and 6.5 years. Inclusion was also limited to dyads with White or Black mothers because women of other races were too few to study (n = 31). Written informed consent was obtained from each woman for herself and her child at enrollment and the 4-6 year follow-up visit. The study protocol was approved by the Institutional Review Boards of Vanderbilt University, The University of Tennessee Health Science Center, the Tennessee Department of Health, and by representatives of Tennessee Medicaid (Bureau of TennCare).

Vitamin D Assessment

Maternal plasma 25(OH)D levels were assessed from biospecimens collected during the 2nd trimester and at delivery. Biospecimens were maintained and stored at the Department of Pathology, University of Tennessee Health Science Center.[30] Following collection, biospecimens were transported on ice and frozen at -20 degrees Celsius within 6 hours. At the time of analysis, biospecimens were thawed and analyzed with a commercially available enzyme immunoassay (Immunodiagnostic Systems, IDS, Boldon, Tyne & Wear, UK). The assay has precision within 1 standard deviation of the mean and uses NIST SRM972 as the standard. Maternal 25(OH)D levels were assessed with a minimum detection range of 2 ng/ml with an interassay variability of <6%.[30]

Childhood Wheeze and Asthma Assessment

Primary outcomes were current wheeze and current asthma ascertained at the 4-6 year visit. Research assistants assessed these outcomes using questionnaires based on the International

Study of Asthma and Allergies in Children [31] and parent report of child asthma-specific medication and healthcare use.[32] We defined current wheeze as a positive response to the question, “Has your child ever had wheezing or whistling in the chest in the last 12 months?” We defined current asthma as 1) parent report of physician diagnosis of asthma (or reactive airway disease) and report of wheeze or asthma-specific medication use in past 12 months, *or* 2) wheeze and asthma-specific medication use in past 12 months.

Statistical Analysis

Descriptive analyses were used to summarize cohort characteristics. The Pearson χ^2 and Wilcoxon rank sum tests were used for univariate analyses comparing categorical and continuous variables, respectively. We used multivariable logistic regression to assess the association of maternal 25(OH)D levels (ng/ml) in the 2nd trimester and at delivery with child current wheeze and current asthma outcomes at 4-6 years. We tested for interactions by including a cross-product term of race and vitamin D level in each model and using the likelihood ratio test.

We analyzed prenatal 25(OH)D levels as continuous exposures and by sufficiency status, using current recommendations by the Institute of Medicine for bone health (≥ 20 ng/ml),[33] modeling 2nd trimester and delivery levels separately. Because physiologically driven 25(OH)D cut points regarding sufficiency for respiratory health have not been clearly established [34] we also categorized vitamin D levels in tertiles with the lowest (T¹) as referent. Final models were adjusted for the following covariates, based on their association with both the exposure and the outcomes:[35, 36] maternal age, race, education level (greater than high school, high school or less), smoking during pregnancy (yes, no), and history of maternal asthma (yes, no), as assessed at enrollment; delivery route (vaginal, caesarean), child sex (male, female), and season of birth (Winter, Spring, Summer, Fall), as assessed at delivery; and breastfeeding initiation history (yes, no), as assessed at 4-6 year follow-up. Birth season served to control for season of maternal delivery sample collection as seasonality may affect levels.[25] All analyses were conducted in R

version 3.4.0 (The R Foundation, Vienna, Austria) and, two-sided, type 1 error rates of 0.05 were used for statistical significance.

Results

We included 1,095 dyads with either 2nd trimester or delivery plasma 25(OH)D determinations. Among 1,091 women with 2nd trimester 25(OH)D determinations, 66% were Black. Forty-two percent had greater than high school education, 9% reported smoking, and 12% reported having asthma (Table 1). Similar descriptive characteristics for 907 women contributing determinations at delivery are shown in Table S1. Overall, median (interquartile range [IQR]) plasma concentrations were 21.1 (15.2, 26.9) ng/ml and 22.6 (16.1, 28.6) ng/ml for 2nd trimester and delivery, respectively. White women had higher 25(OH)D levels (ng/ml) than Black women at the 2nd trimester (median [IQR]), White: 25.1 (20.1, 29.7); Black: 19.1 (14.1, 25.0), $p < 0.001$) and delivery (median (IQR), White: 26.9 (22.1, 34.1); Black: 19.4 (14.9, 25.9), $p < 0.001$). Women with sufficient 25(OH)D at both time points were less likely to have Medicaid insurance and were more likely to be older, White, better educated, to have given birth in the Fall, and to report breastfeeding compared to women with insufficient levels. Overall, infants born to women with sufficient 25(OH)D had higher birth weights than infants born to women with insufficient levels ($p < 0.001$) (Table 1, S1).

The median age of children at the 4-6 year visit was 4.2 years (range: 3.8-6.4 years), and 95% of children were ≥ 4.0 years at time of visit. Overall, 19% of children met criteria for current wheeze and 15% of children met criteria for current asthma. There were no differences in the prevalence of child wheeze or child asthma by sufficiency of maternal 2nd trimester ($P = 0.44$ wheeze; $P = 0.5$ asthma) or delivery 25(OH)D levels ($P = 0.4$ wheeze; $P = 0.68$ asthma) (Tables 1 and S1).

Current Wheeze

In multivariable analyses of 2nd trimester 25(OH)D, we found evidence for effect modification by maternal race (p interaction = 0.014) with an overall statistically significant association between continuous 25(OH)D and current wheeze at age 4-6 years ($p=0.049$). Figure 1A illustrates that higher vitamin D levels were associated with lower odds of wheeze in children of White mothers (adjusted odds ratio [aOR] 0.62, 95% confidence interval [CI] 0.38-1.01 per IQR increase in 25(OH)D), but the opposite association is seen in children of Black mothers (aOR 1.25, 95% CI 0.91-1.71 per IQR increase). At delivery, there was borderline significant effect modification (P for interaction = 0.087), also suggesting higher delivery vitamin D levels were associated with lower odds of current wheeze in dyads with White mothers but not Black mothers (Figure 1B). Analysis of current wheeze by 25(OH)D sufficiency status and tertiles in the 2nd trimester and at delivery yielded similar results (Table 2). For example, 2nd trimester 25(OH)D sufficiency was associated with decreased odds of current wheeze in dyads with White mothers (aOR 0.57; 95% CI 0.30-1.09), but not in dyads with Black mothers (aOR 1.38, 95% CI: 0.93-2.05).

Current Asthma

In our multivariable analysis of 2nd trimester vitamin D, we found an association between 25(OH)D levels and current asthma ($p=0.026$), with effect modification by maternal race (p interaction=0.011) (Figure 1C). At delivery, we observed a marginal association between 25(OH)D levels and current asthma ($p=0.068$) with statistically significant effect modification by race (p interaction=0.027) (Figure 1D). For an IQR increase, 2nd trimester 25(OH)D was associated with decreased odds of asthma in children of White women (aOR 0.63, 95% CI: 0.36-1.09) and increased odds in children of Black women (aOR 1.41, 95% CI: 1.01-1.97) (Table S2). We observed similar results in analyses of 2nd trimester 25(OH)D sufficiency status and tertiles (Table 3). At delivery, we also observed a suggestive protective association of 25(OH)D sufficiency in dyads with White but not Black mothers, however several estimates were attenuated relative to the 2nd trimester (Table 3, Table S2). Among Black dyads, the highest

tertile of 25(OH)D at delivery was associated with a 92% increase in odds of current asthma (T³versus T¹: aOR 1.92, 95% CI: 1.08-3.41).

Discussion

Asthma is a leading cause of morbidity and mortality worldwide.[2, 3, 37] Vitamin D is important for lung function and immune development *in utero*, potentially by influencing airway smooth muscle proliferation as well as impacting immune tolerance to allergens.[12, 14, 38, 39] Vitamin D deficiency is associated with several chronic medical conditions, including asthma, and thus is a potentially modifiable risk factor for disease.[10, 40] In the current study, we examined maternal plasma vitamin D (25[OH]D) and child wheeze and asthma outcomes at age 4-6 years in a large, racially diverse cohort. We observed evidence of effect modification by maternal race in the associations between prenatal vitamin D and child current wheeze and asthma. Among dyads with White mothers, 25(OH)D was inversely associated with current wheeze and asthma in children age 4 -6 years. Among dyads with Black mothers, however, 25(OH)D was positively associated with current wheeze and asthma in children.

The association between maternal or cord blood vitamin D and child respiratory outcomes has been examined in several observational cohorts, generating mixed results potentially due to variability in outcome ascertainment and timing of vitamin D exposure assessment.[16, 17, 18, 19] Recent clinical trials include the Vitamin D Antenatal Asthma Reduction Trial (VDAART),[22] which examined early pregnancy vitamin D supplementation on asthma and wheeze at age 3 among dyads with parental history of atopic disease, and the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) trial, which studied supplementation later in pregnancy on respiratory outcomes at age 3.[20] Both VDAART and a combined analysis of both trials demonstrated modest protective associations between vitamin D supplementation during pregnancy and asthma and recurrent wheeze,[21, 22] while COPSAC alone observed an association with troublesome lung symptoms but not persistent wheeze.[20]

Several previous studies have described potential racial differences in the association between maternal vitamin D status and wheeze/asthma outcomes,[25, 26, 41] and similar differences have been observed with respect to other pediatric and perinatal health outcomes, such as neurodevelopment.[42] We previously reported a potentially protective association between prenatal 25(OH)D and current wheeze at age 3 among White but not Black dyads.[26] Similarly, Wegienka *et al.* found a stronger inverse relationship between cord blood 25(OH)D and allergen sensitization at age 2 in White compared to Black children.[25] Findings from a cross-sectional survey reported that vitamin D insufficiency was associated with increased current wheeze and asthma in non-Hispanic White children, but not among children of other races.[24] In contrast, a cohort in the United Kingdom reported no association between prenatal vitamin D and wheeze in White children, but a protective association among British-born Pakistani children (p for interaction = 0.04).[41] A secondary analysis of VDAART data demonstrated no significant interaction between vitamin D supplementation and maternal race, defined as African American ($n=312$) and non-African American ($n=400$) (p for interaction=0.77).[27]

The clinical implications of our findings are unclear, as are the reasons we detected different associations between prenatal 25(OH)D and child respiratory outcomes by race. While genetic variability may play a role in our observed associations,[43] race/ethnic-specific metabolic demands for vitamin D are poorly understood, including during pregnancy. Vitamin D sufficiency levels range from 20 to 50 ng/ml,[44] but no evidence-based consensus on race/ethnic-specific or pregnancy-specific requirements has been reached.[45] Racial differences in vitamin D binding protein and, consequently, vitamin D bioavailability have been demonstrated in some studies,[46] but not others.[47, 48] Studies of bone health suggest that Black women are less sensitive to vitamin D deficiency than White women, having increased bone mineral density despite lower 25(OH)D.[49] However, it is not clear how this so-called “paradox” in bone health translates to prenatal development and whether that is a factor in our findings. Examination

of additional vitamin D biomarkers (e.g., vitamin D binding protein, vitamin D metabolites, or free versus total 25(OH)D) in future studies may clarify the relationships we observed. In VDAART, the greatest reduction in asthma/wheeze risk was observed among children of women randomized to treatment (4000 IU/day vitamin D supplementation) who had also high levels of baseline (first trimester) 25(OH)D, suggesting early pregnancy vitamin D is important for protection from child recurrent wheeze/asthma.[27] Black women in our cohort had lower 2nd trimester 25(OH)D levels than White women, but first trimester levels were not measured. While 25(OH)D levels tend to be stable over time,[50] it is plausible that our results may be attributable, in part, to low early pregnancy vitamin D levels in Black women, despite many achieving relatively high levels later in pregnancy. Lastly, findings may be related to unmeasured confounders.

A strength of this study is that it represents one of the largest investigations of prenatal vitamin D and child asthma to date that includes Black mother-child dyads. We studied maternal 25(OH)D levels at two different time points and we assessed our outcomes in a cohort in which the participants were not selected based on parental atopic disease. Finally, we characterized wheeze/asthma outcomes when children were primarily four years or older and less likely to have transient wheezing.

There are several limitations to note as well. As acknowledged above, we did not assess maternal 25(OH)D before the 2nd trimester or in childhood. In addition, due to the limited number of women with vitamin D levels ≥ 30 ng/ml, we were unable to assess the association of vitamin D with current asthma and current wheeze at this particular cut point. However, we did analyze our outcomes based on tertiles which allowed us to examine the high end of our exposure distribution.

In conclusion, in this large prospective prenatal cohort, there was evidence of interaction in the association of 2nd trimester and delivery 25(OH)D and child current wheeze and asthma outcomes at 4-6 years by maternal race. Higher levels of 25(OH)D tended to be protective in

White but not Black dyads. These findings deserve further study in large epidemiologic cohorts with racially diverse populations that include wide variability in vitamin D levels and additional vitamin D biomarkers and associated proteins. The follow-up of children through older ages with postnatal vitamin D assessment and exploration of potential mechanisms may also help explain these relationships.

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Table 1. Characteristics of mother-child dyads in the CANDLE cohort, enrolled 2006-2011, by vitamin D sufficiency status in the second trimester

	25(OH)D Status		
	Insufficient (<20 ng/ml)	Sufficient (≥ 20 ng/ml)	Total
	482	609	1091
	391 (81)	334 (55)	725 (66)
	91 (19)	275 (45)	366 (34)
	331 (69)	299 (49)	630 (58)
	151 (31)	310 (51)	461(42)
	330 (68)	267 (44)	597 (55)
	152 (32)	342 (56)	494 (45)
	53 (11)	73 (12)	126 (12)
	42 (9)	53 (9)	95 (9)
	429 (89)	590 (97)	1019 (93)
	152 (32)	256 (42)	408 (38)
	25 (21-29)	27 (23-31)	26 (22-30)
	3.19 (2.96-3.49)	3.30 (2.30-3.62)	3.26 (2.98-3.57)
	39 (38-40)	39 (38-40)	39 (38-40)
	247 (51)	306 (50)	553 (51)

	144 (30)	82 (13)	226 (21)
	172 (36)	134 (22)	306 (28)
	86 (18)	235 (39)	321 (29)
	80 (17)	158 (26)	238 (22)
	266 (55)	444 (73)	710 (65)
	85 (18)	118 (20)	203 (19)
	70 (15)	97 (16)	167 (15)

CANDLE: Conditions Affecting Neurocognitive Development and Learning in Early Childhood; 25(OH)D: 25-hydroxyvitamin D3; missing data: prenatal smoking (n = 1); prenatal vitamin use (n = 18); ^aValues reported as medians and interquartile range (IQR) ^b 4 subjects had estimated gestational age imputed from linked birth certificates

Table 2. Association of 25(OH)D levels and child current wheeze (age 4 to 6 years) by maternal race in the CANDLE cohort

		Black				White			
Maternal Vitamin D	Current wheeze		Unadjusted odds ratio (95% CI)	Adjusted odds ratio ^a (95% CI)	Current wheeze		Unadjusted odds ratio (95% CI)	Adjusted odds ratio ^a (95% CI)	
	No	Yes			No	Yes			
Sufficiency, Second Trimester									
<20 ng/ml	323	67			72	18	1.00	1.00	
≥20 ng/ml	253	78			233	40	0.69 (0.37-1.27)	0.57 (0.30-1.09)	
Tertiles, Second Trimester									
<17.2 ng/ml	253	50	1.00	1.00	51	10	1.00	1.00	
≥17.2 - <25.2 ng/ml	190	54	1.44 (0.94-2.21)	1.45 (0.93-2.27)	93	29	1.59 (0.72-3.52)	1.44 (0.63-3.26)	
≥25.2 ng/ml	133	41	1.56 (0.98-2.48)	1.42 (0.86-2.34)	161	19	0.60 (0.26-1.38)	0.52 (0.22-1.23)	
Sufficiency, Delivery									
<20 ng/ml	258	52			51	11	1.00	1.00	
≥20 ng/ml	205	60			222	41	0.86 (0.42-1.78)	0.81 (0.37-1.76)	
Tertiles, Delivery									
<18.3 ng/ml	211	43			40	8	1.00	1.00	
≥18.3 - <26.7 ng/ml	153	39			90	21	1.17 (0.48-2.86)	1.08 (0.43-2.73)	

≥ 26.7 ng/ml	99	30		143	23	0.80 (0.33-1.93)	0.73 (0.29-1.85)
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^a Adjusted for: maternal age, education, asthma, prenatal smoking, delivery route, child sex, birth season, and history of breastfeeding.

Table 3. Association of 25(OH)D levels and child current asthma (age 4 to 6 years) by maternal race in the CANDLE cohort

		Black				White			
Maternal Vitamin D	Current asthma		Unadjusted odds ratio (95% CI)	Adjusted odds ratio ^a (95% CI)	Current asthma	Unadjusted odds ratio (95% CI)		Adjusted odds ratio ^a (95% CI)	
No Yes			No Yes						
Sufficiency, Second Trimester									
<20 ng/ml	336	55			75	15	1.00	1.00	
≥20 ng/ml	263	69			245	28	0.57 (0.29-1.13)	0.49 (0.24-1.01)	
Tertiles, Second Trimester									
<17.2 ng/ml	264	40	1.00	1.00	51	10	1.00	1.00	
≥17.2 - <25.2 ng/ml	198	46	1.53 (0.97-2.43)	1.56 (0.97-2.52)	104	18	0.88 (0.38-2.05)	0.82 (0.34-1.95)	
≥25.2 ng/ml	137	38	1.83 (1.12-2.99)	1.72 (1.01-2.91)	165	15	0.46 (0.20-1.1)	0.41 (0.17-1.01)	
Sufficiency, Delivery									
<20 ng/ml	268	43			53	9	1.00	1.00	
≥20 ng/ml	216	50			234	29	0.73 (0.33-1.63)	0.67 (0.29-1.55)	
Tertiles, Delivery									
<18.3 ng/ml	221	34			41	7	1.00	1.00	
≥18.3 - <26.7 ng/ml	163	29			95	16	0.99 (0.38-2.58)	0.89 (0.33-2.41)	
≥26.7 ng/ml	100	30			151	15	0.58 (0.22-1.52)	0.52 (0.19-1.43)	

^a Adjusted for maternal age, education, asthma, prenatal smoking, delivery route, child sex, birth season, and history of breastfeeding

Figure 1.

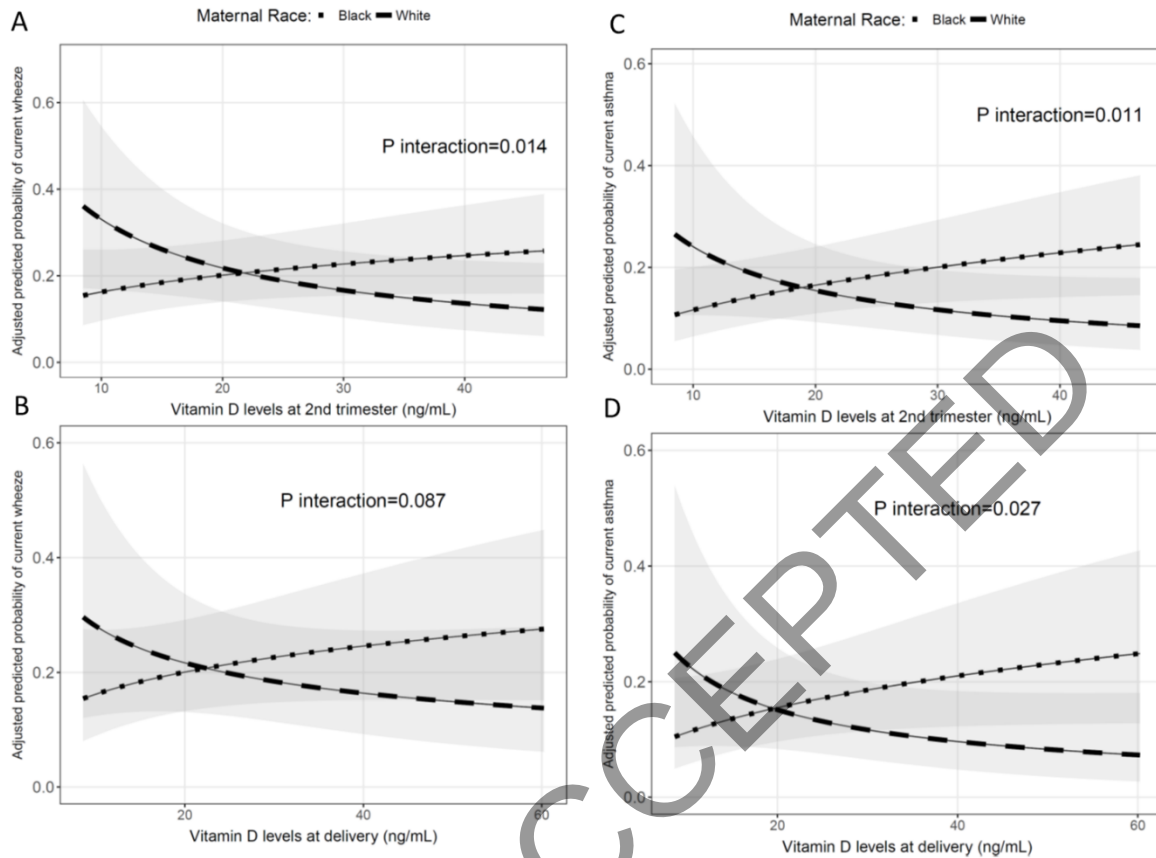


Figure 1. Multivariable analyses characterizing (A) child current wheeze and continuous 25(OH)D levels (ng/ml) at the 2nd trimester; (B) child current wheeze and continuous 25(OH)D levels (ng/ml) at delivery; (C) child current asthma and continuous 25(OH)D levels (ng/ml) at the 2nd trimester; (D) child current asthma and continuous 25(OH)D levels (ng/ml) at delivery, by maternal race.