Association of Prenatal Maternal and Infant Vitamin D Supplementation with Offspring Asthma

Lourdes G. Ramirez[1,2], Kathleen Lee-Sarwar[1,2], Rachel S. Kelly[1], Scott T. Weiss[1], and Augusto A. Litonjua[3]

[1]Channing Division of Network Medicine and [2]Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and [3]Division of Pediatric Pulmonary Medicine, Golisano Children's Hospital at Strong, University of Rochester Medical Center, Rochester, New York

ORCID ID: 0000-0003-3023-1822 (R.S.K.).

Abstract

Rationale: The role and timing of vitamin D supplementation in the prevention of asthma has not been fully elucidated.

Objective: To describe the association between prenatal and postnatal vitamin D with offspring asthma outcomes in participants of the Vitamin D Antenatal Asthma Reduction Trial.

Methods: We classified 748 mother–offspring pairs into four groups based on the mother's randomization to receive high-dose versus low-dose (4,400 IU vs. 400 IU) vitamin D supplementation during pregnancy and the offspring parent-reported high-dose versus low-dose (≥400 IU vs. <400 IU) vitamin D supplementation as estimated by intake of vitamin D drops or infant formula. We used logistic regression to test the association of the four vitamin D exposure groups—"mother-low/infant-low (reference)," "mother-high/infant-high," "mother-high/infant-low," and "mother-low/infant-high"—with offspring asthma and/or recurrent wheeze at age 3 years, active asthma at age 6 years, and atopic asthma at age 6 years.

Results: The risk of asthma and/or recurrent wheeze at 3 years was lowest in the mother-high/infant-low group (adjusted odds ratio vs. mother-low/infant-low, 0.39; 95% confidence interval, 0.16–0.88, $P = 0.03$). When stratifying by history of exclusive breastfeeding until age 4 months, the protective effect in the mother-high/infant-low group was seen only among exclusively breastfed infants (odds ratio vs. mother-low/infant-low, 0.19; 95% confidence interval, 0.04–0.68; $P = 0.02$). We did not observe any significant associations with active or atopic asthma at age 6 years.

Conclusions: We observe that high-dose prenatal and low-dose postnatal vitamin D supplementation may be associated with reduced offspring asthma or recurrent wheeze by age 3 years, but this association may be confounded by the protective effect of breastfeeding.

Keywords: asthma, wheezing, atopy, cholecalciferol, vitamin D

(Received in original form June 2, 2023; accepted in final form December 5, 2023)

Supported by National Health, Lung and Blood Institute (NHLBI) grants R01 HL091528 (S.T.W. and A.A.L.), UH3 OD023268 (S.T.W. and A.A.L.), K08HL148178 (K.L.-S.), and K01HL146980 (R.S.K.) and NHLBI T32 Training grant T32 HL007427 (L.G.R.).

Author Contributions: L.G.R., K.L.-S., R.S.K., S.T.W., and A.A.L. contributed substantially to the conception and design of this study. L.G.R. drafted the manuscript. All authors contributed substantially to data acquisition, data analysis, interpretation, and critical review of the manuscript. All authors approved the final version of the manuscript.

Correspondence and requests for reprints should be addressed to Lourdes G. Ramirez, M.D., Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115. E-mail: lgramirez@bwh.harvard.edu.

This article has a data supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Ann Am Thorac Soc Vol 21, No 2, pp 279–286, Feb 2024

DOI: 10.1513/AnnalsATS.202306-504OC
Internet address: www.atsjournals.org

Asthma is a common chronic disease of the airways that affects more than 6 million children in the United States (1). The onset of asthma occurs before the age of 6 years in approximately 80–90% of patients, and approximately 70% of cases develop before the age of 3 years (2, 3). The exact etiology of asthma appears to be multifactorial, and, given its early onset, early nutrition, including prenatal dietary exposures and early postnatal exposures, are plausible risk factors.

Vitamin D has a role in immunomodulation *in utero* and postnatally that may be important in the development of allergic disease (4, 5). Additionally, vitamin D *in utero* is known to play a role in fetal lung development (6, 7). Postnatally, vitamin

D may enhance the ability to fight respiratory infections in early life (8) and likely continues to affect lung and immune system development throughout early childhood. Vitamin D crosses the placenta freely in humans, and the levels can be modulated by diet. Given the *in utero* effects of vitamin D, the prenatal effects of vitamin D on modifying asthma and allergic diseases in offspring have been previously evaluated, and higher doses of vitamin D intake have been shown to be associated with a decreased risk of asthma and wheeze in offspring (9–12). A combined analysis of the Vitamin D Antenatal Asthma Reduction Trial (VDAART) and the Copenhagen Prospective Studies on Asthma in Childhood 2010, two independent randomized controlled trials of vitamin D supplementation during pregnancy, demonstrated a 25% reduced risk of offspring asthma or wheeze by 3 years of age (13). Camargo and colleagues showed in a prospective prebirth cohort study that greater prenatal vitamin D intake reduces the risk of asthma in early life irrespective of low (defined as $<$200 IU/d) or high ($\geq$200 IU/d) infant vitamin D intake (9). A more recent randomized clinical trial of vitamin D supplementation in 300 preterm Black infants found that sustained supplementation with 400 IU/d of vitamin D until 6 months of age decreased the incidence of wheeze by 1 year of age (14). Thus, there still remain open questions in regard to the optimal timing of vitamin D intake and whether prenatal and postnatal supplementation impact asthma differently.

In this study, we hypothesize that high-dose prenatal and postnatal vitamin D exposure are associated with reduced offspring asthma compared with low-dose vitamin D exposure prenatally and postnatally. Our primary outcome of interest is asthma or recurrent wheeze by 3 years of age. Our secondary outcomes of interest are the development of active asthma and atopic asthma by 6 years of age.

Preliminary results of this study were presented at the 2023 American Thoracic Society International Conference (15).

Methods

Study Design and Participants

This is a secondary analysis of VDAART that was designed *post hoc*. VDAART is a randomized, double-blind, placebo-controlled trial that began enrollment in October 2009, with participants recruited from three different centers in the United States: Kaiser Permanente Southern California Region, San Diego, CA; Washington University in St. Louis, St. Louis, MO; and Boston Medical Center, Boston, MA. The study included 881 pregnant, nonsmoking women between 18 and 39 years of age who were at high risk of having children with asthma because of a history of asthma, allergic rhinitis, or eczema in the study participant or the child's biological father. These participants were randomized at 10–18 weeks' gestation to receive 4,400 IU/d or 400 IU/d of vitamin D (Figure 1). The results of the original trial showed that, in these pregnant women at high risk of having a child with asthma, randomization to receive 4,400 IU/d of vitamin D supplementation significantly increased serum vitamin D levels, and their offspring had a 6.1% lower incidence of asthma and recurrent wheeze at 3 years of age, compared with participants who were randomized to receive 400 IU/d (16). Written consent was obtained from the mothers, and the study was approved by the institutional review boards of the three sites and Brigham and Women's Hospital (Boston, MA).

Vitamin D Exposures

We classified mother–offspring pairs with available clinical and vitamin D supplementation data into four groups based on mothers' randomization to receive high- versus low-dose vitamin D supplementation and offspring randomization to receive high- versus low-dose vitamin D exposure. Data on postnatal vitamin D exposure were obtained from questionnaires completed by parents at the children's visits at 6 and 12 months of age. We defined postnatal vitamin D exposure as high-dose if infants received $>$4 d/wk of vitamin D drops or multivitamin drops or $\geq$32 oz/d of infant formula at 6 and 12 months of age. We defined low-dose postnatal vitamin D exposure as any drop or formula intake that did not meet these criteria. Infant vitamin D drops (one drop per day) and 32 ounces of infant formula each deliver 400 IU of vitamin D, which is the recommended amount of vitamin D supplementation during infancy according to the American Academy of Pediatrics (17).

The group termed "mother-low/infant-low" was used as the reference in our models and included mothers randomized to receive low-dose vitamin D supplementation whose offspring received low-dose vitamin D. The group termed "mother-high/infant-high" consisted of mothers who were randomized to receive high-dose vitamin D supplementation during pregnancy whose offspring received high-dose vitamin D; the group termed "mother-high/infant-low" included mothers randomized to receive high-dose vitamin D supplementation whose offspring received low-dose vitamin D; and the group termed "mother-low/infant-high" included mothers randomized to receive low-dose vitamin D supplementation whose offspring received high-dose vitamin D (17). Offspring plasma 25-hydroxyvitamin D levels were measured at 1 year of age and are reported in ng/ml.

Offspring Asthma Outcomes

Our primary outcome was offspring asthma or recurrent wheeze by age 3 years. This was selected as the primary outcome in view of evidence that prenatal vitamin D prevents this specific asthma outcome (13). Data on doctor-diagnosed asthma and recurrent wheezing at 3 years of age were obtained from parent-reported quarterly questionnaires. As previously described (16), asthma by age 3 years was defined by a parental report of physician-diagnosed asthma during the child's first 3 years of life, and recurrent wheeze was defined by the presence of at least one of the following conditions: *1*) parental report of wheeze after the child's second birthday with at least one preceding episode of reported wheeze before the child's second birthday, *2*) report of the child's use of any asthma-control medication after their second birthday with a preceding episode of reported wheeze before their second birthday, *3*) at least two distinct reports of wheeze after the child's second birthday, *4*) at least one report of wheeze and the use of asthma-control medication at distinct visits after the child's second birthday, or *5*) two reports of asthma-control medication use at distinct visits after the child's second birthday (16). We included two secondary asthma outcomes: atopic asthma and active asthma at age 6 years. Atopic asthma was defined by parent-reported doctor-diagnosed asthma by age 6 years and aeroallergen sensitization at 3 or 6 years of age (18). Aeroallergen sensitization was defined by a positive serum-specific immunoglobulin E (IgE) level of $\geq$0.35 kU/L to at least one of seven tested aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat dander, dog dander, grass mix, German cockroach, and *Alternaria alternata*) (19).

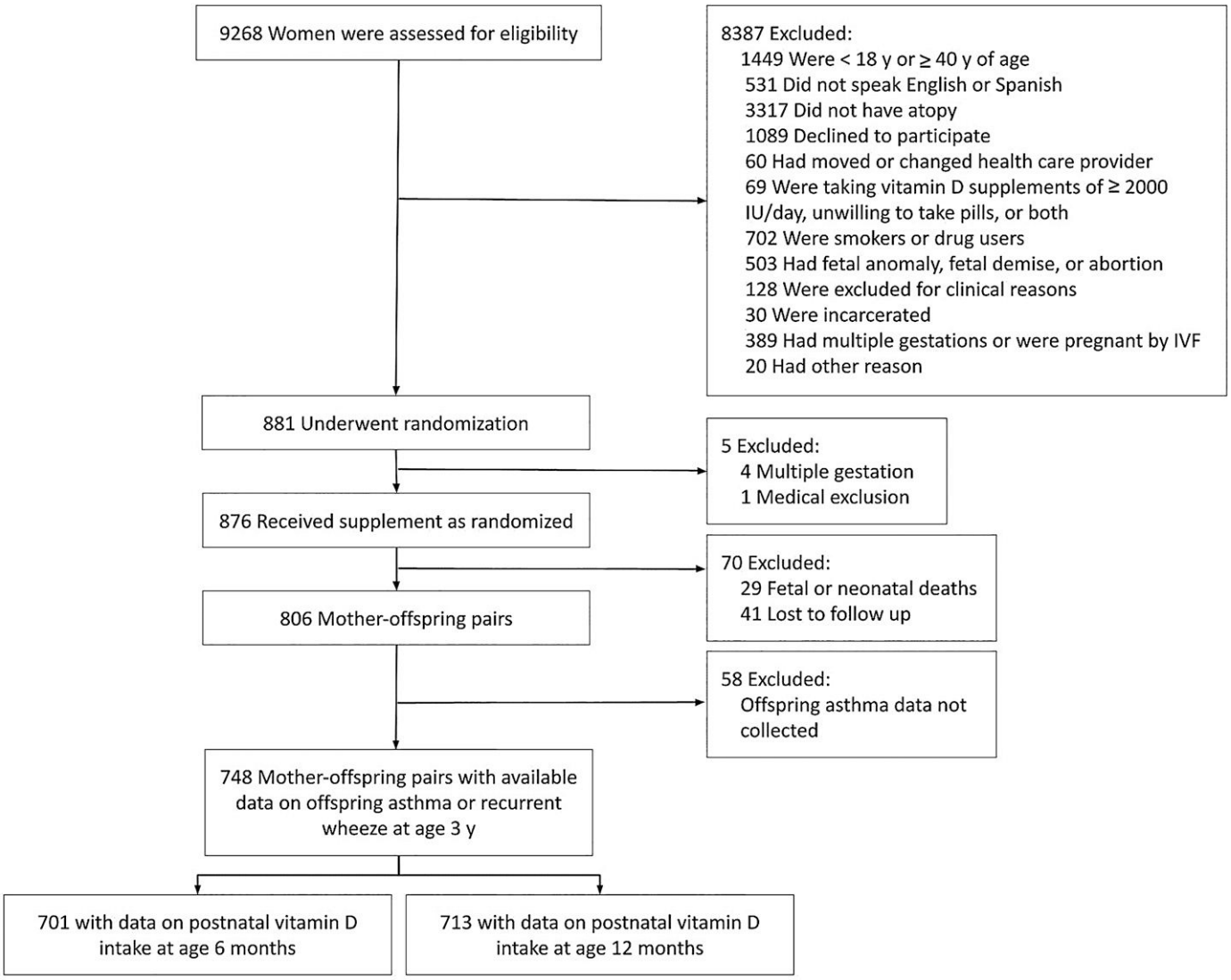

Figure 1. Flow diagram of study participants included in the study. IVF = *in vitro* fertilization.

Specific IgE levels were measured using the UniCAP system (Phadia AB). Active asthma was defined by parent-reported doctor-diagnosed asthma at any time in the first 6 years of the child's life in addition to a report of the child's use of any asthma medication or a report of wheeze after the child's fifth birthday (19).

Statistical Analysis

Our statistical analyses were performed using the R statistical package (version 4.1.3) with a prespecified α significance level of 0.05. We used descriptive statistics to summarize the baseline characteristics of all mother–infant pairs based on the primary outcome.

We calculated the offspring mean plasma vitamin D levels at 1 year of age and used Wilcoxon rank sum tests to identify differences in circulating vitamin D levels among all infants receiving high- versus low-dose vitamin D. We used a Kruskal-Wallis test to identify differences in circulating plasma vitamin D levels among infants in each of the four mother–offspring vitamin D exposure groups.

We used logistic regression to test the association of the four-category vitamin D exposure variable (using the mother-low/infant-low group as the reference) and our primary and secondary asthma outcomes. We adjusted our models for the following confounding variables selected on the basis of a directed acyclic graph, adjusting for variables that may be associated with the exposure and outcome: study site, maternal asthma, maternal age, child's race and ethnicity, preterm birth, and breastfeeding status at 6 months of age (Figure E1 in the data supplement). We obtained crude and adjusted odds ratios with confidence intervals (CIs) and *P* values.

Results

Baseline Characteristics

Among the 806 mother–offspring pairs in the original VDAART study, 748 had complete data on offspring asthma outcomes at age 3 years and prenatal/offspring vitamin D status and were included in this analysis. Baseline characteristics of the study participants are shown in Table 1. Of the 748 infants, 29%

Table 1. Baseline characteristics in the study population by primary outcome at age 3 years

Subject Characteristic	Asthma/Wheeze by 3 yr ($n = 218$)	No Asthma/Wheeze by 3 yr ($n = 530$)
Maternal age, yr	26.1 ± 5.6	27.9 ± 5.4
Maternal education		
College or graduate school	57 (26.1%)	202 (38.1%)
Some college	54 (24.8%)	118 (22.3%)
High school, technical school	72 (33%)	149 (28.1%)
Less than high school	35 (16.1%)	61 (11.5%)
Study site		
Boston, MA	76 (34.9%)	138 (26%)
San Diego, CA	50 (22.9%)	195 (36.8%)
St. Louis, MO	92 (42.2%)	197 (37.2%)
Female sex	82 (37.6%)	269 (50.8%)
Child race and ethnicity		
Black	110 (50.5%)	192 (36.2%)
Hispanic/other	75 (34.4%)	224 (42.3%)
White	33 (15.1%)	114 (21.5%)
Preterm birth	35 (16.1%)	32 (6.0%)
Birth by Caesarean section	66 (30.4%)	159 (30.0%)
Sensitization to environmental allergens	72 (60.5%)	162 (52.3%)
Maternal asthma	115 (52.8%)	188 (35.5%)

Data are presented as mean ± standard deviation or number (percentage) of individuals. Missingness includes preterm birth ($n = 1$ in the asthma/wheeze by 3 yr group), sensitization to environmental allergens ($n = 99$ in the asthma/wheeze by 3 yr group and $n = 220$ no asthma/wheeze by 3 yr group), and birth by Caesarean section ($n = 1$ in the asthma/wheeze by 3 yr group and $n = 1$ in the no asthma/wheeze by 3 yr group).

had asthma and/or recurrent wheeze by age 3 years and 71% did not. Offspring with asthma and/or wheeze at age 3 years were more likely to have younger mothers (mean maternal age at enrollment, 26.1 vs. 27.9 yr) and mothers with less education than a college degree (73.9% vs. 61.9%); they were also more likely to be male (62.4% vs. 49.2%) and have a history of preterm birth (16.1% vs. 6%) and maternal asthma (52.8 vs. 35.5%).

Association between Vitamin D Exposure and Asthma or Recurrent Wheeze by Age 3 Years

We evaluated our four-category vitamin D variable with respect to the outcome of asthma or recurrent wheeze by age 3 years when infant vitamin D intake was ascertained at 6 months and 12 months. The mean plasma vitamin D levels at 1 year of age were not significantly higher among infants with high- ($n = 353$) versus low-dose ($n = 360$) vitamin D intake at 12 months of age (30.38 ± 9.55 vs. 29.12 ± 10.53 ng/ml, respectively; Wilcoxon test, $P = 0.06$). The mean plasma vitamin D levels at 1 year of age in infants with high- ($n = 457$) versus low-dose ($n = 244$) vitamin D intake at 6 months of age were not significantly different (29.89 ± 9.97 vs. 28.71 ± 8.98 ng/ml, respectively; Wilcoxon test, $P = 0.24$). No significant differences between plasma vitamin D levels at 1 year of age among the four mother–offspring vitamin D exposure groups were found by a Kruskal-Wallis test (Table 2).

In the analyses of the four-category vitamin D exposure variable when infant vitamin D intake was ascertained at age 6 months, there were 125 mother–offspring pairs in the mother-low/infant-low group, 233 in the mother-high/infant-high group, 119 in the mother-high/infant-low group, and 224 in the mother-low/infant-high group. Asthma or wheeze at 3 years was least frequent in the mother-high/infant-low group (mother-high/infant-low vs. mother-low/infant-low: adjusted odds ratio, 0.39; 95% CI, 0.16–0.88; $P = 0.03$; Figure 2A).

To disentangle whether associations of vitamin D and asthma are modified by exclusive breastfeeding in early life, we stratified our four-category vitamin D exposure variable by history of exclusive breastfeeding until 4 months of age. We did not have a sufficient sample size within every mother–offspring vitamin D exposure group to stratify by exclusive breastfeeding at 6 months. There were a total of 234 mother–offspring pairs whose infants were exclusively breastfed until 4 months of age (mother-low/infant-low, $n = 54$; mother-high/infant-high, $n = 69$; mother-high/infant-low, $n = 50$; mother-low/infant-high, $n = 61$; Table E1). Again, only the mother-high/infant-low group had a reduced risk of asthma and/or wheeze at age 3 years compared with the mother-low/infant-low group (adjusted odds ratio, 0.19; 95% CI, 0.04–0.68; $P = 0.02$). Among the infants who were not exclusively breastfed, there were no significant associations with asthma outcomes for any of the vitamin D exposure groups (Figure 3).

We next analyzed associations between the four-category vitamin D variable and offspring asthma when infant vitamin D exposure was ascertained at age 12 months. We did not find significant associations between the vitamin D exposure groups and asthma and/or wheeze at 3 years (Figure 2B). We did not have a sufficient sample size in

Table 2. Mean offspring plasma 25-hydroxyvitamin D levels at 1 year of age

Infant Vitamin D Exposure*	Plasma 25-Hydroxyvitamin D Level (*ng/ml*)				Kruskal-Wallis *P* Value
	Mother-Low/ Infant-Low	Mother-High/ Infant-High	Mother-High/ Infant-Low	Mother-Low/ Infant-High	
6 mo	29.45 ± 11.94	29.90 ± 9.68	28.76 ± 8.79	30.93 ± 9.39	0.17
12 mo	28.42 ± 10.28	29.13 ± 9.05	29.02 ± 7.46	30.69 ± 10.83	0.18

Data are presented as mean ± standard deviation.
*Mean plasma 25-hydroxyvitamin D levels were calculated for each vitamin D exposure group based on infant vitamin D intake at 6 or 12 months.

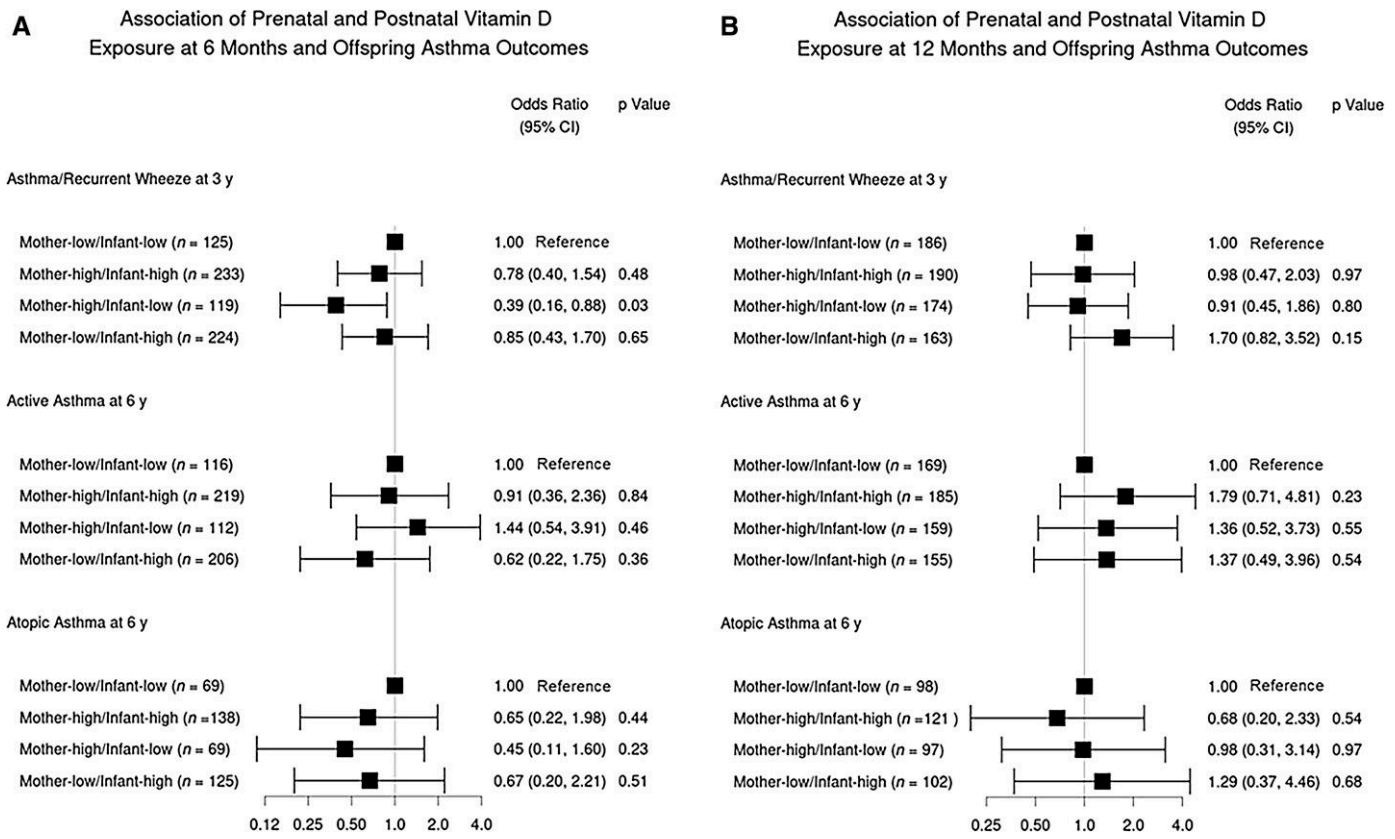

Figure 2. Forest plots depict odds ratios and 95% confidence intervals of the associations of prenatal and postnatal vitamin D exposure and offspring asthma outcomes. Postnatal vitamin D intake was ascertained at ages 6 months (*A*) and 12 months (*B*). Logistic regression models were adjusted for the child's race and ethnicity, preterm birth, study site, maternal asthma, maternal age, and breastfeeding status at 6 months. The "mother-low/infant-low" group is the reference group. CI = confidence interval.

each mother–offspring exposure category to stratify this analysis by history of exclusive breastfeeding (*see* Table E1).

Our sample sizes in each vitamin D exposure group allowed us to detect moderate (Cohen's $f \geq 0.15$) and large (Cohen's $f \geq 0.35$) effect sizes in the overall and stratified analyses, respectively. Of note, additional adjustment of our models for prenatal and postnatal tobacco smoke exposure did not affect our results (Tables E2 and E3).

Association of Vitamin D Exposure with Active Asthma

Among the 695 offspring with available data on active asthma at 6 years, active asthma developed in 130 (19%). There were no significant associations between our four-category vitamin D exposure variable and active asthma at age 6 years when vitamin D exposure was ascertained at 6 and 12 months of age (Figure 2). Our sample sizes in each vitamin D exposure group allowed us to detect moderate effect sizes (Cohen's $f \geq 0.15$). We did not stratify these associations by history of exclusive breastfeeding as a result of insufficient sample size (*see* Table E1).

Association of Vitamin D Exposure with Atopic Asthma

Among 429 offspring with available data on atopic asthma at age 6 years, atopic asthma developed in 77 (18%). Our analysis of the association of our four-category vitamin D exposure variable and atopic asthma when infant vitamin D exposure was ascertained at 6 and 12 months did not reveal any statistically significant associations (Figure 2). Our sample sizes in each vitamin D exposure group allowed us to detect moderate effect sizes (Cohen's $f \geq 0.15$). We were not able to stratify our vitamin D exposure groups by history of exclusive breastfeeding as a result of insufficient sample size in at least one of the mother–offspring vitamin D exposure groups (*see* Table E1).

Discussion

This study aimed to evaluate the effect of prenatal and postnatal vitamin D on childhood asthma risk and contribute to the evidence regarding the optimal timing for dosing of vitamin D supplementation. We found a significant association between mother–offspring pairs classified as receiving high-dose prenatal and low-dose postnatal vitamin D supplementation at 6 months of life and reduced offspring asthma or recurrent wheeze at 3 years of age. The benefit of high-dose prenatal vitamin D is consistent with prior knowledge on the protective effect of prenatal vitamin D supplementation (9–11). However, our results were unexpected because we hypothesized that the mother-high/infant-high group, which included mothers randomized to receive high-dose vitamin D during pregnancy whose infants received a vitamin D intake of ⩾400 IU/d for ⩾5 d/wk, would show the most protection or show

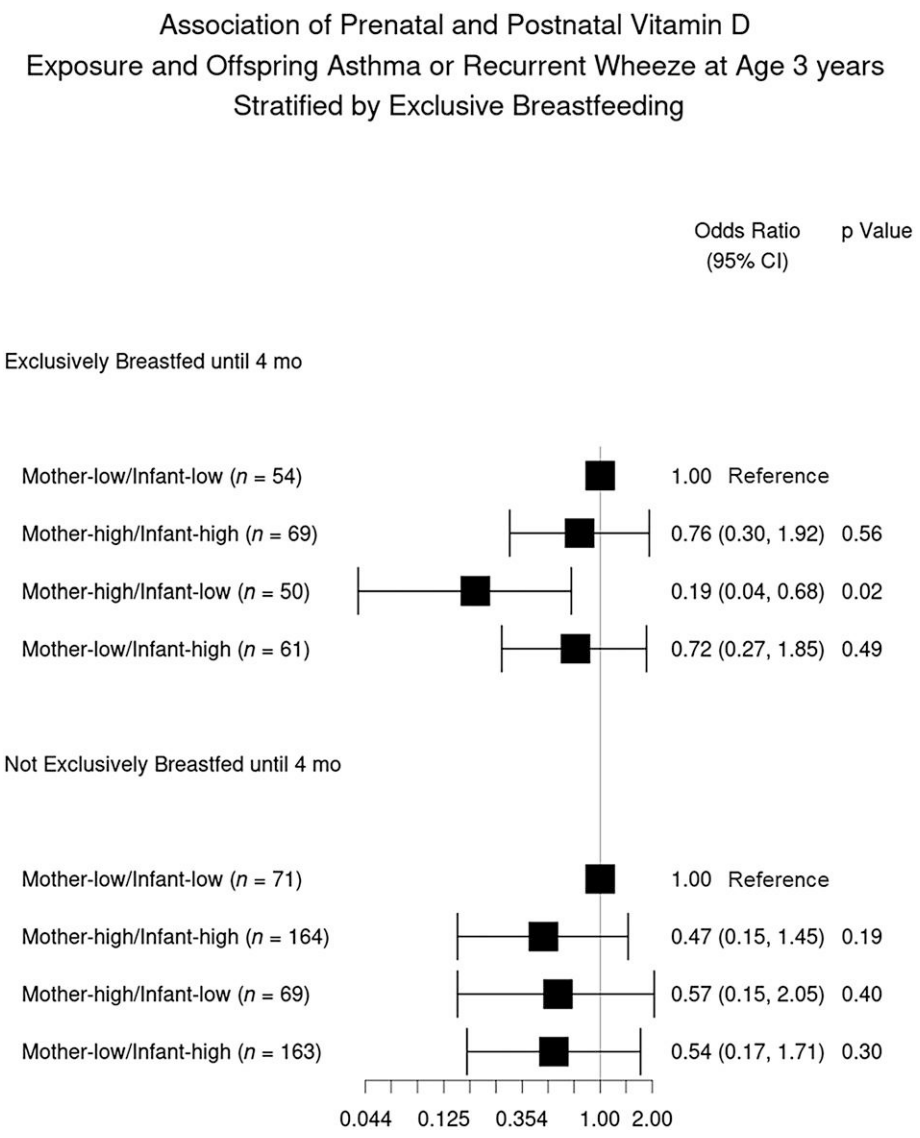

Figure 3. Forest plots depict odds ratios and 95% confidence intervals of associations of prenatal and postnatal vitamin D exposure and offspring asthma outcomes stratified by history of exclusive breastfeeding until age 4 months. Postnatal vitamin D intake was ascertained at age 6 months. Logistic regression models were adjusted for the child's race and ethnicity, preterm birth, study site, maternal asthma, maternal age, and breastfeeding status at 6 months. The "mother-low/infant-low" group is the reference group. CI = confidence interval.

similar results to the mother-high/infant-low group. The lack of significant associations in the mother-high/infant-high may be due to an insufficient sample size that precluded us from detecting small effect sizes. We did not see significant associations between our vitamin D exposure groups and active asthma or atopic asthma at 6 years when ascertaining infant vitamin D intake at 6 and 12 months of age.

When stratifying by exclusive breastfeeding until age 4 months, the protective association in the high-dose prenatal vitamin D and low-dose postnatal vitamin D supplementation group was seen in only those children who were exclusively breastfed. A modified response of vitamin D on asthma outcomes in a subgroup of exclusively breastfed infants has not been previously noted. Recent studies show that vitamin D status alters the expression of genes in two chromosomal loci, Chr17q12-21.1 and Chr17q21.2, which are associated with chronic inflammation and autoimmune disease. In mouse models, the vitamin D receptor has been shown to be expressed in lung CD4 $Th2^{+}$ cells, and activation of the vitamin D/VDR pathway was shown to significantly suppress production of Th2 cytokines via suppression of the IL-2/STAT5 signaling pathway (20). Although these findings are incongruous to this study, it is plausible that there is a complex interplay between the immunomodulatory effects of high-dose prenatal/low-dose postnatal vitamin D and breastfeeding that results in a true association with reduced offspring asthma. It is also possible that the protective effects in our results are due to other protective effects of breastfeeding beyond vitamin D. The protective effects of breastfeeding on asthma risk have been reported (21), including a recent study by Wilson and colleagues that showed a duration-dependent protective association of exclusive breastfeeding and childhood asthma (22).

Prior analyses from VDAART have shown an association between high-dose vitamin D supplementation in pregnancy and reduced allergic rhinitis and aeroallergen sensitization by 6 years of age (23). Other reports showing the relationship between vitamin D and reduced aeroallergen sensitization in childhood include the cross-sectional study by Searing and colleagues that demonstrated inverse associations between plasma vitamin D levels and IgE sensitization to environmental aeroallergens, lung function, and use of inhaled or oral steroids in asthmatic children (24). Additionally, vitamin D levels have been inversely associated with airway smooth muscle mass in children with severe therapy-resistant asthma (25).

Although prior analyses from VDAART have shown the protective effect of prenatal vitamin D in offspring asthma risk, the present study uniquely investigates vitamin D exposure by comparing four levels of prenatal and postnatal exposure. Camargo and colleagues showed that postnatal vitamin D exposure does not have a significant association with asthma or recurrent wheeze at 3 years of age; however, our study used a higher threshold of vitamin D intake to define a high versus a low dose (9). Furthermore, our study closely controlled maternal vitamin D supplementation, whereas the aforementioned study was an observational study with vitamin D intake derived from food-frequency questionnaires. Interestingly, Hibbs and colleagues showed a reduced risk of asthma by 1 year of age in Black preterm infants with 6 months of

sustained vitamin D supplementation, supporting the theory of a role for vitamin D in the postnatal developing lung as well as the influence of race (14).

Our study had several strengths, including that the mother–offspring pairs were followed longitudinally with questionnaires ascertaining parent-reported intake of vitamin D drops and formula and doctor-diagnosed asthma. This cohort is racially and ethnically diverse, which allows for greater generalizability. In addition, this cohort is enriched with offspring with a high risk for atopy, increasing the power to detect associations with atopic outcomes.

This study had several limitations. Unlike prenatal vitamin D supplementation, postnatal supplementation was not part of the intervention in this clinical trial. Infant vitamin D intake was not closely monitored, and parental reports of vitamin D intake may have been subject to recall bias. Another limitation inherent to nutrient studies is that there is vitamin D already present in the low-dose groups for which we are not accounting. We are also not accounting for vitamin D in solid foods infants may have been introduced to, which are typically introduced at 4–6 months of age. Additionally, the study did not find significant differences in plasma vitamin D levels at 1 year of age among infants from the four-category vitamin D exposure groups. The vitamin D dose received by mothers in the high-dose vitamin D arm (4,400 IU/d) far exceeded the dose received by infants, which raises the possibility that greater postnatal vitamin D supplementation could have stronger associations with reduced childhood asthma. The upper limits of vitamin D doses safely tolerated in infants are 1,000 IU until 6 months of age and 1,500 IU at 6–12 months of age (26). Given the clinical associations of vitamin D and reduced atopic disease and the more recent mechanistic evidence of vitamin D as a regulator of allergic inflammatory pathways, perhaps additional studies with vitamin D supplementation at higher doses postnatally may yield significant associations with reduced childhood asthma. Another limitation to the present study is the lack of correction for multiple testing in this exploratory analysis as well as the effect of unmeasured factors not accounted for.

In conclusion, this study shows that there may be an association between high-dose prenatal and low-dose postnatal vitamin D supplementation at age 6 months and reduced risk of asthma or recurrent wheeze at age 3 years in a subset of exclusively breastfed patients at high risk of asthma. Although the observed benefit of high-dose prenatal vitamin D aligns with the findings of prior studies, the present study underscores the potential clinical relevance of vitamin D supplementation strategies, particularly for pregnant mothers and their exclusively breastfed infants at high risk of asthma, as part of a comprehensive approach to asthma prevention. The ongoing uncertainty regarding the role and optimal dosing of postnatal vitamin D for asthma protection highlights the need for further investigation and a nuanced approach to vitamin D supplementation in early infancy. Given the broad effects of vitamin D beyond asthma, adherence to the American Academy of Pediatrics guidelines regarding supplementation with 400 IU/d of vitamin D in infants who are exclusively breastfed or consume <32 oz/d of formula is important in early life. Although it may be challenging to draw definitive conclusions from this limited study, our findings serve as a stepping stone toward a more comprehensive understanding of the multifaceted role of vitamin D in early childhood and its role in modifying asthma risk. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the study coordinators, especially Nancy Laranjo, B.A., M.P.H., and the participants of VDAART for their contribution.

References

1 U.S. Centers for Disease Control and Prevention. Most recent national asthma data. Atlanta, GA: U.S. Centers for Disease Control and Prevention; 2022 [updated 2023 May 10; accessed 2022 Dec 25]. Available from: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm.

2 Wainwright C, Isles AF, Francis PW. Asthma in children. *Med J Aust* 1997;167:218–223.

3 Yunginger JW, Reed CE, O'Connell EJ, Melton LJ III, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma. Incidence rates, 1964-1983. *Am Rev Respir Dis* 1992;146:888–894.

4 Mirzakhani H, Al-Garawi A, Weiss ST, Litonjua AA. Vitamin D and the development of allergic disease: how important is it? *Clin Exp Allergy* 2015;45:114–125.

5 Litonjua AA. Vitamin D deficiency as a risk factor for childhood allergic disease and asthma. *Curr Opin Allergy Clin Immunol* 2012;12:179–185.

6 Weiss ST, Litonjua AA. The in utero effects of maternal vitamin D deficiency: how it results in asthma and other chronic diseases. *Am J Respir Crit Care Med* 2011;183:1286–1287.

7 Zosky GR, Berry LJ, Elliot JG, James AL, Gorman S, Hart PH. Vitamin D deficiency causes deficits in lung function and alters lung structure. *Am J Respir Crit Care Med* 2011;183:1336–1343.

8 Beard JA, Bearden A, Striker R. Vitamin D and the anti-viral state. *J Clin Virol* 2011;50:194–200.

9 Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, *et al.* Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr* 2007;85:788–795.

10 Devereux G, Litonjua AA, Turner SW, Craig LC, McNeill G, Martindale S, *et al.* Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am J Clin Nutr* 2007;85:853–859.

11 Erkkola M, Kaila M, Nwaru BI, Kronberg-Kippilä C, Ahonen S, Nevalainen J, *et al.* Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy* 2009;39:875–882.

12 Lu M, Litonjua AA, O'Connor GT, Zeiger RS, Bacharier L, Schatz M, *et al.* Effect of early and late prenatal vitamin D and maternal asthma status on offspring asthma or recurrent wheeze. *J Allergy Clin Immunol* 2021;147:1234–1241.e3.

13 Wolsk HM, Chawes BL, Litonjua AA, Hollis BW, Waage J, Stokholm J, *et al.* Prenatal vitamin D supplementation reduces risk of asthma/recurrent wheeze in early childhood: a combined analysis of two randomized controlled trials. *PLoS One* 2017;12:e0186657.

14 Hibbs AM, Ross K, Kerns LA, Wagner C, Fuloria M, Groh-Wargo S, *et al.* Effect of vitamin D supplementation on recurrent wheezing in Black infants who were born preterm: the D-Wheeze randomized clinical trial. *JAMA* 2018;319:2086–2094.

15 Ramirez L, Zeiger RS, O'Connor GT, Sandel M, Bacharier LB, Carey V, *et al.* Association of prenatal maternal and infant vitamin D supplementation with offspring asthma outcomes [abstract]. *Am J Respir Crit Care Med* 2023;207:A1001.

16 Litonjua AA, Carey VJ, Laranjo N, Harshfield BJ, McElrath TF, O'Connor GT, *et al.* Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 years: the VDAART randomized clinical trial. *JAMA* 2016;315:362–370.

17 Wagner CL, Greer FR; American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics* 2008;122:1142–1152.
18 Chen YS, Lee-Sarwar KA, Mirzakhani H, O'Connor GT, Bacharier LB, Zeiger RS, *et al.* The association of prenatal C-reactive protein levels with childhood asthma and atopy. *J Allergy Clin Immunol Pract* 2022; 10:3213–3219.e11.
19 Litonjua AA, Carey VJ, Laranjo N, Stubbs BJ, Mirzakhani H, O'Connor GT, *et al.* Six-year follow-up of a trial of antenatal vitamin D for asthma reduction. *N Engl J Med* 2020;382:525–533.
20 Kılıç A, Halu A, De Marzio M, Maiorino E, Duvall MG, Brueggemann T, *et al.* Vitamin D constrains inflammation by modulating the expression of key genes on Chr17q12-21.1. *eLife* 2023;12:RP89270.
21 Hou W, Guan F, Xia L, Xu Y, Huang S, Zeng P. Investigating the influence of breastfeeding on asthma in children under 12 years old in the UK Biobank. *Front Immunol* 2022;13:967101.
22 Wilson K, Gebretsadik T, Adgent MA, Loftus C, Karr C, Moore PE, *et al.* The association between duration of breastfeeding and childhood asthma outcomes. *Ann Allergy Asthma Immunol* 2022;129:205–211.
23 Chen YS, Mirzakhani H, Lu M, Zeiger RS, O'Connor GT, Sandel MT, *et al.* The association of prenatal vitamin D sufficiency with aeroallergen sensitization and allergic rhinitis in early childhood. *J Allergy Clin Immunol Pract* 2021;9:3788–3796.e3.
24 Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DYM. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. *J Allergy Clin Immunol* 2010;125:995–1000.
25 Gupta A, Sjoukes A, Richards D, Banya W, Hawrylowicz C, Bush A, *et al.* Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. *Am J Respir Crit Care Med* 2011; 184:1342–1349.
26 Golden NH, Abrams SA; Committee on Nutrition. Optimizing bone health in children and adolescents. *Pediatrics* 2014;134:e1229–e1243.