

The Association of Maternal Asthma and Early Pregnancy Vitamin D with Risk of Preeclampsia: An Observation From Vitamin D Antenatal Asthma Reduction Trial (VDAART)



Hooman Mirzakhani, MD, PhD, MMSc^{a,b}, Vincent J. Carey, PhD^{a,b}, Thomas F. McElrath, MD, PhD^{b,c}, Nancy Laranjo, MS^a, George O'Connor, MD, MS^d, Ronald E. Iverson, MD, MPH^d, Aviva Lee-Parritz, MD^e, Robert C. Strunk, MD^{f,†}, Leonard B. Bacharier, MD^f, George A. Macones, MD, MSCE^g, Robert S. Zeiger, MD, PhD^h, Michael Schatz, MD, MS^h, Bruce W. Hollis, PhDⁱ, Augusto A. Litonjua, MD, MPH^{a,b,j}, and Scott T. Weiss, MD, MS^{a,b,k} Boston, Mass; St Louis, Mo; San Diego and Pasadena, Calif; and Charleston, SC

What is already known about this topic? History of a diagnosis of maternal asthma and asthma control during pregnancy have been linked to increased risk of preeclampsia. Vitamin D status during pregnancy might be a potential factor moderating the risk of asthma exacerbations and the subsequent risk of preeclampsia.

What does this article add to our knowledge? The present study found the association of uncontrolled asthma during pregnancy with the risk of preeclampsia and revealed that maternal vitamin D status at early pregnancy could possibly affect the extent to which uncontrolled asthma may be associated with a higher risk of preeclampsia.

How does this study impact current management guidelines? Attention to vitamin D levels in pregnant women with asthma as well as optimal asthma control may decrease the risk of preeclampsia. Future study is warranted to define the optimal level of vitamin D concentrations during pregnancy for maternal-fetal health.

BACKGROUND: Maternal asthma, uncontrolled asthma, and low vitamin D levels during pregnancy have been individually linked to increased risk of preeclampsia.

OBJECTIVE: To investigate the association of history of physician-diagnosed asthma and uncontrolled asthma status during pregnancy with the risk of preeclampsia and the effects

^aChanning Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Mass

^bHarvard Medical School, Boston, Mass

^cDivision of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, Mass

^dDepartment of Medicine, Boston Medical Center, Boston University, Boston, Mass

^eDepartment of Obstetrics and Gynecology, Boston Medical Center, Boston University, Boston, Mass

^fDivision of Pediatric Allergy, Immunology and Pulmonary Medicine, Department of Pediatrics, Washington University, St Louis, Mo

^gDivision of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Washington University, St Louis, Mo

^hDepartment of Allergy and Research and Evaluation, Kaiser Permanente Southern California Region, San Diego and Pasadena, Calif

ⁱDepartment of Pediatrics, University of South Carolina College of Medicine, Charleston, SC

^jDivision of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Mass

^kPartners Center for Personalized Medicine, Partners Health Care, Boston, Mass

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Corresponding author: Scott T. Weiss, MD, MS, Brigham and Women's Hospital, Channing Division of Network Medicine, Department of Medicine, 181 Longwood Ave, Boston, MA 02114. E-mail: scott.weiss@channing.harvard.edu.

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Abbreviations used

25OHD- 25-hydroxyvitamin D

aOR- adjusted odds ratio

BIC- Bayesian information criterion

BMI- body mass index

BP- blood pressure

IU- international unit

IVF- intrauterine fertilization

OR- odds ratio

p-ACT- Pregnancy-Asthma Control Test

VDAART- Vitamin D Antenatal Asthma Reduction Trial

of early pregnancy vitamin D concentrations on this relationship.

METHODS: A total of 816 subjects with available pregnancy outcome data and risk factors of interest were analyzed. A group of experienced obstetricians and gynecologists from 3 study centers validated the preeclampsia diagnoses. Vitamin D was measured using the DiaSorin method at 10 to 18 weeks of gestation. The Pregnancy-Asthma Control Test was used to assess asthma control during pregnancy. Criterion-based stepwise variable selection algorithm was applied to investigate the relationships of risk factors of interest (history of asthma diagnosis, uncontrolled asthma during pregnancy, and vitamin D) to preeclampsia.

RESULTS: The incidence of preeclampsia was not related to the presence of asthma diagnosis (8.9% with vs 7.4% without). The adjusted odds of preeclampsia controlled for maternal serum 25-hydroxyvitamin D (25OHD) concentrations was higher for women with a higher proportion of uncontrolled asthma months per visit during pregnancy (adjusted odds ratio, 3.55; 95% CI, 1.15-13.0). Adjusting for asthma control status during pregnancy, an additional decrease in the associated preeclampsia risk by 7% was observed for a 10-unit (ng/mL) increase in early pregnancy 25OHD levels (adjusted odds ratio_{10-unit}, 0.60; 95% CI, 0.43-0.82) as compared with the previous risk estimate of preeclampsia associated with low maternal 25OHD unadjusted for asthma control status.

CONCLUSIONS: Uncontrolled asthma during pregnancy is associated with an increased risk of preeclampsia. Early pregnancy 25OHD contributes to the association of uncontrolled asthma status with preeclampsia. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:600-8)

Key words: Asthma; Exacerbation; Pregnancy; Vitamin D; 25OHD; Preeclampsia

Asthma is one of the most common serious medical problems during pregnancy affecting up to 8% of pregnant women.¹ Some studies have shown that maternal history of asthma diagnosis or uncontrolled asthma during pregnancy might increase the risk of adverse pregnancy and prenatal outcomes such as low birth weight and preeclampsia, whereas other reports do not support these findings.²⁻⁴ A few studies have particularly investigated the association of maternal history of asthma diagnosis or asthma control status during pregnancy with preeclampsia. Two studies showed that pregnant women with symptomatic asthma had 2 to 3 times higher odds of preeclampsia as compared with those without asthma symptoms.^{5,6} In contrast, the results from 2

earlier studies had been inconsistent with these 2 recent observations.^{7,8} The conflicting results in relating asthma and preeclampsia might be due to differences in study populations and inadequate control for confounding. None of the studies investigated the asthma-preeclampsia relationship adjusted for vitamin D status during pregnancy, which might be a potential moderating factor contributing to both risk of preeclampsia occurrence and asthma exacerbations.⁹⁻¹² This notion is principally conceived from systematic reviews and meta-analyses of clinical trials suggesting that vitamin D supplementation and higher serum levels of 25-hydroxyvitamin D (25OHD) might be associated with reduced risk of asthma exacerbations.^{13,14} The most recent meta-analysis study suggested that vitamin D supplementation could result in a reduced rate of exacerbations (rate ratio, 0.63; 95% CI, 0.45-0.88) and the risk of having at least 1 of the exacerbation requiring emergency room visit or hospitalization (odds ratio [OR], 0.39; 95% CI, 0.19-0.78).¹³ Furthermore, epidemiological studies have provided evidence on the association of lower serum vitamin D levels with increased asthma prevalence in general population samples.¹⁵ Therefore, the main objective of this study was to investigate the association of asthma diagnosis and asthma control during pregnancy with preeclampsia development and determine the impact of maternal 25OHD levels on this relationship.

METHODS

Vitamin D Antenatal Asthma Reduction Trial and study population

To attain the objective of the study, we used the data on the outcomes of pregnancy from the Vitamin D Antenatal Asthma Reduction Trial (VDAART). VDAART (www.vdaart.com) is a multicenter clinical trial conducted at 3 study centers across the United States (Washington University in St Louis, Boston Medical Center, and Kaiser Health Care San Diego). The trial was sponsored by the National Heart, Lung, and Blood Institute and registered at ClinicalTrials.gov (NCT00920621). The institutional review boards of the participating clinical centers and the data coordinating center in Brigham Women's Hospital (Partners Health Care, Boston, Mass) approved VDAART, and written consent was obtained from all the participating pregnant women at the first enrollment visit. Pregnant women were randomized between September 2009 and July 2011. The study population consisted of pregnant women with singleton pregnancies at 10 to 18 weeks who were enrolled in a multicenter, double-blind, randomized trial to investigate the effect of vitamin D supplementation during pregnancy. The VDAART aims were to investigate a reduction in risk of predefined pregnancy outcomes including preeclampsia as well as wheezing and asthma in the born children from mothers who received vitamin D supplementation. All the pregnant participants received prenatal vitamins containing 400 international unit (IU) (10 µg/d) of cholecalciferol; thus, the vitamin D treatment arm received a total of 4400 IU/d (110 µg/d) and the placebo arm received 400 IU/d (10 µg/d). The participants were 18 up to 39 years old, who had either a personal history of physician-diagnosed asthma and/or allergies (ie, allergic rhinitis and eczema) or a partner who had either asthma or allergies. The pregnant women's clinical course was followed prospectively from randomization to the end of the pregnancy.^{16,17} Exclusion criteria for VDAART enrollment included current smoking and user of other nicotine products (eg, nicotine patch for at least 1 month before enrollment), chronic conditions (ie, diabetes mellitus and

current treatment for chronic hypertension), multiple gestation pregnancy, pregnancy achieved by assisted reproduction techniques (eg, intrauterine insemination and intrauterine fertilization), parathyroid and thyroid disease, kidney stones and sarcoidosis, intake of vitamin D supplements more than 2000 IU/d, and taking illicit drugs in the last 6 months. The details of the trial design and clinical trial outcomes for the vitamin D supplementation effect on preeclampsia occurrence and wheezing in the offspring of the mothers have been published.¹⁶⁻¹⁸ In brief, administration of 4000 IU vitamin D at 10 to 18 weeks of gestation did not reduce the risk of study outcomes; however, further analyses demonstrated that pregnant women with higher 25OHD concentrations (≥ 30 ng/mL) at enrollment experienced a lower risk of preeclampsia during their pregnancy and wheezing in the first 3 years of their infants' lives.^{16,18}

Data collection

Throughout the VDAART, the selected 10-member Data and Safety Monitoring Board monitored the trial. The enrollment visit occurred at the subjects' prenatal visit between 10 and 18 weeks of gestation, and serum 25OHD levels were measured at enrollment. A completed questionnaire at enrollment and monthly thereafter, in addition to medical record review, obtained information on maternal health characteristics during pregnancy.

Main outcome measure: Preeclampsia diagnosis and validation

The occurrence of preeclampsia was a prespecified secondary outcome of the trial and was also an adverse event. Every month, study coordinators performed a medical record review for cases of preeclampsia as part of the protocol for identifying severe adverse events in the trial. After all participants completed their deliveries, medical records were abstracted for all participants. A committee of 4 board-certified obstetricians reviewed 276 abstracted charts with any evidence of hypertension, proteinuria, or preeclampsia diagnosis in a blinded fashion to determine or validate preeclampsia status. The diagnosis of preeclampsia at the time of record reviews was based on the American Congress of Obstetricians and Gynecologists' guidelines¹⁹; the identification of high blood pressure (BP) with proteinuria (≥ 300 mg per 24-hour collection or $\geq 1+$ on urine dipstick) or the presence of elevated liver enzymes, high platelet count, headache, or visual disturbances after 20 weeks of gestation. The BP criteria included either systolic BP of 140 mm Hg or more or diastolic BP of 90 mm Hg or more, or both, with a second elevated measurement at least 6 hours after the first measure in the medical record.

Primary and secondary exposure variables: Maternal asthma status and serum vitamin D

Maternal asthma and its control status during pregnancy. Completed questionnaires at the first appointment (enrollment visit) and monthly maternal health questionnaires thereafter provided the information on absence or presence of maternal asthma and monitored asthma control throughout the study, from enrollment until delivery (Figure 1). A subject was considered to have asthma if she reported physician-diagnosed asthma at any time in her life. Thereafter, the monthly questionnaires prospectively collected all the information characterizing uncontrolled status of asthma, if any. The Pregnancy-Asthma Control Test (p-ACT), a 5-item questionnaire included in the monthly questionnaires, was used to assess a multidimensional perspective of asthma control on the basis of activity limitation,

frequency of shortness of breath due to asthma, nighttime symptoms, use of rescue medication, and self-perception of asthma control over a period of 4 weeks.²⁰ A p-ACT score of 16 or less was considered the cutoff for discrimination of uncontrolled asthma from controlled asthma during pregnancy.²⁰⁻²² Accordingly, occurrence (p-ACT score ≤ 16) or nonoccurrence (p-ACT score > 16) of uncontrolled asthma month was abstracted from the monthly questionnaires of each subject. Thereafter, the number of uncontrolled asthma months during study time (from enrollment until delivery) in each woman was defined as the total number of p-ACT scores of 16 or less. To avoid any potential bias due to differences in subjects' study time, the proportion of uncontrolled asthma months to the number of total study visits in each subject was used as the main exposure variable of interest for asthma control status during pregnancy (expressed as uncontrolled months per visit).

Vitamin D assay. Serum assays of 25OHD were performed at the Channing Division of Network Medicine. The applied method for quantitative determination of 25OHD is a Food and Drug Administration—approved, direct, competitive chemiluminescence immunoassay using the DiaSorin LIAISON 25-OH Vitamin D Total assay.²³ This assay is cospecific for 25-hydroxyvitamin D₃ and 25-hydroxyvitamin D₂. All assays were performed at the data coordinating center blinded for treatment assignment, and for quality control, the laboratory used US National Institute of Standards and Technology level 1 protocol.

Additional variables

A priori covariates as risk factors for preeclampsia and potential confounders of the measure of association for the main variables of interest with preeclampsia were extracted from the study questionnaires and data records. These variables included the number of previous pregnancies, maternal age, gestational diabetes in the present pregnancy, race (African American, white, and other), treatment arm of the trial (placebo vs vitamin D supplementation), serum 25OHD concentrations, body mass index (BMI) at first appointment, clinical centers, annual household income, marital status, and educational status (Table 1).

Statistical analysis

We conducted a secondary analysis of the VDAART data using a cohort design. The cohort consisted of all randomized subjects included in the intent-to-treat analysis of VDAART (N = 816; see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Missing data were assumed to be completely at random as was confirmed by Little's Missing Completely at Random test. R version 3.3.2 was used for all analyses. Differences in means of continuous variables for groups by the primary exposure of interest (asthma vs no asthma) were evaluated with *t* tests, and differences in proportions were evaluated with chi-square tests (Table 1). Stepwise logistic regression analyses were used to explore the relationship of self-reported asthma, asthma control status (uncontrolled asthma months per visit), and early pregnancy vitamin D (25OHD) in association with the response variable (preeclampsia) after adjustment for demographic characteristics of pregnant women and additional potential confounding variables. Stepwise regression is a semi-automated process of building a model by successively adding or removing variables on the basis of solely *t* statistics of their estimated coefficients and is especially useful for examining a large number of potential independent variables. Previous studies to investigate the risk factors of preeclampsia considered either maternal asthma or vitamin D levels in different population samples or neither

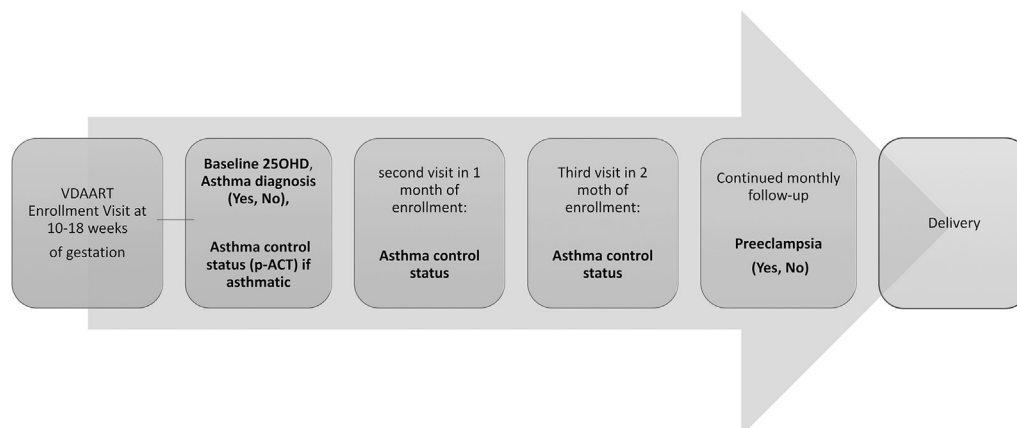


FIGURE 1. The follow-up scheme of VDAART study to collect the data on the variable of interest (history of physician-diagnosed asthma, asthma control status, vitamin D levels at enrollment, and preeclampsia diagnosis).

of them. Accordingly, we included asthma, asthma control status, baseline vitamin D, potential confounding variables, and *a priori* known risk factors in the regression models using comparative approaches and the same study population to represent procedures in the previous studies. In these approaches, the key assumption is that one of the fitted models is true, in the sense that it contains all possible important predictors and no unimportant predictors. To this end, a criterion with a high probability of discovering that model is needed. The best-recommended procedure tailored for this goal is Bayesian information criterion (BIC). Accordingly, we used BIC as our model selection tool to determine the model resulting in the lowest BIC over the whole set of included variables during the above steps. BIC decreases the risk of overfitting by introducing the penalty term $d \times \log(N)$, which increases with the number of parameters resulting in more accurate estimation of several parameters on a given data set of size N .²⁴

Univariate and comparative criterion-based stepwise regression models were as follows:

- Univariate test of association to independently explore the relationship of each exploratory variable with preeclampsia.
- Assessing the relationship of maternal asthma, uncontrolled asthma months per visit during pregnancy, and baseline 25OHD level with preeclampsia controlling for potential confounders or covariates (Kitchen Sink regression, model 1).
- Assessing the relationship of all exploratory variables with preeclampsia excluding asthma diagnosis, uncontrolled asthma months per visit, and baseline 25OHD level using stepwise logistic regression (model 2).
- Assessing the relationship of asthma diagnosis and uncontrolled asthma months per visit along with other exploratory variables with exclusion of baseline 25OHD level using stepwise logistic regression (model 3).
- Assessing the association of baseline 25OHD level with preeclampsia including other exploratory variables with exclusion of asthma diagnosis and uncontrolled asthma months per visit using stepwise logistic regression (model 4).
- Assessing the relationship of asthma, uncontrolled asthma months per visit in the presence of 25OHD, and other exploratory variables and measure of their association with preeclampsia using stepwise logistic regression (model 5: stepwise logistic regression of model 1).

Model calibration was assessed with the use of Hosmer-Lemeshow chi-square test to avoid overfitting. Using the fitted model with the lowest BIC adjusted for all other variables, we displayed the scaled risk of uncontrolled asthma months per visit in association with preeclampsia. We also tested for possible interactions by fitting interaction terms into the multivariable models. No significant interactions were identified. Continuous variables are presented as mean $\pm$ SD and 95% CIs. ORs are reported with 95% CIs. For interval variable, median and range were used. Tests with 2-sided P values of less than .05 were considered to indicate statistical significance.

RESULTS

The baseline characteristics of the women included in this study are presented in Table I. A total of 816 randomized subjects to the trial arms who were included in the intent-to-treat analysis for VDAART main outcomes were used in this analysis.^{16,18} Of these women, 67 developed preeclampsia. The mean of weeks of gestation at enrollment was 14.20 ± 2.8 and it was not different among women with or without asthma diagnosis (Table I). Pairwise comparisons of groups' characteristics (asthma vs no asthma) were not statistically different (Table I). There was no difference in distributions of preeclampsia among women with or without self-reported physician-diagnosed asthma (8.87% and 7.36%, respectively). Among 327 women with asthma, 31.5% experienced at least 1 episode of uncontrolled asthma status during their pregnancy.²⁵

Table II demonstrates results from univariate associations of study variables (asthma diagnosis, uncontrolled asthma months per visit, early pregnancy 25OHD, and other potential confounders) with preeclampsia and adjusted measure of associations including all variables in a multivariable logistic regression model with the lowest BIC. The details of results from other compared models and BIC values have been provided in Table E1 in this article's Online Repository at www.jaci-inpractice.org. In univariate analysis, both uncontrolled asthma months per visit and maternal serum 25OHD at enrollment but not self-reported physician-diagnosed asthma were associated with preeclampsia (OR, 0.95; 95% CI, 0.92-0.98; OR, 4.15; 95% CI, 1.70-12.53; and OR, 1.15; 95% CI, 0.69-1.90, respectively; Table II and Table E1).

TABLE 1. Pregnant women's characteristics by history of physician-diagnosed asthma according to the intention-to-treat population of VDAART (N = 816)*

Feature	Asthma (N = 327)	No asthma (N = 489)
Preeclampsia, n (%)		
Yes	29 (8.9)	38 (7.4)
No	298 (91.1)	451 (92.6)
Maternal monthly visits during pregnancy, n		
Median	5	5
Range	1-7	1-7
Gestational age (wk)		
Mean $\pm$ SD	14.2 $\pm$ 2.8	14.26 $\pm$ 2.8
Median	13.7	13.7
Range	10-18	10-18
Age (y)		
Mean $\pm$ SD	25.67 $\pm$ 5.45	27.79 $\pm$ 5.49
Range	18.0-38.77	18-39.52
Vitamin D level at 10-18 wk (ng/mL)		
Mean $\pm$ SD	22.65 $\pm$ 10.3	23.15 $\pm$ 10.2
Range	4.6-65.3	4.5-80.8
95% central range†	6.3-46.2	6.9-44.6
Sufficiency status at 10-18 wk (ng/mL), n (%)		
<15	74 (22.63)	104 (21.27)
15-29.9	180 (55.05)	276 (56.44)
$\geq$ 30	71 (21.71)	106 (21.68)
n missing	2 (0.61)	3 (0.61)
No. of pregnancies		
Median	2	2
Range	1-11	1-13
95% central range	1-6	1-6
Category status, n (%)		
First	107 (32.7)	179 (36.1)
Second	81 (24.8)	126 (25.8)
Third	63 (19.3)	100 (20.4)
>3	76 (23.2)	84 (17.7)
Site, n (%)		
Boston	112 (34.2)	165 (37.3)
San Diego	96 (29.4)	147 (30.3)
St Louis	119 (36.4)	177 (32.4)
Trial arm, n (%)		
Vitamin D intervention	173 (52.9)	235 (48.1)
Control	154 (47.1)	254 (51.9)
Gestational diabetes, n (%)		
Yes	19 (6.0)	28 (5.7)
No	307 (94.0)	461 (94.3)
BMI at first appointment (kg/m ²)		
Mean $\pm$ SD	30 $\pm$ 8.25	28.2 $\pm$ 7.1
Range	17.9-61.9	16.3-56.4
95% central range	24.1-53.1	23.1-45.2
Race, n (%)		
African American	152 (46.5)	203 (42.5)
Non-African American	175 (53.5)	286 (58.5)
White	125 (38.2)	204 (41.7)
American Indian or Alaska	5 (1.5)	4 (0.8)

(continued)

TABLE 1. (Continued)

Feature	Asthma (N = 327)	No asthma (N = 489)
Asian	9 (2.8)	28 (5.7)
Native Hawaiian	4 (1.2)	7 (1.4)
Other	32 (9.8)	43 (8.8)
Gestational age at delivery (wk)		
Mean $\pm$ SD	38.75 $\pm$ 2.1	38.8 $\pm$ 2.4
Range	23.3-42.1	21-42.3
Maternal marital status, n (%)		
Not married/divorced	190 (58.1)	254 (51.1)
Married	137 (51.9)	235 (48.9)
Education completed, n (%)		
Less than high school	49 (14.9)	53 (10.8)
High school, technical school	98 (30)	146 (29.9)
Some college	84 (25.7)	110 (22.5)
College graduate/graduate school	96 (29.7)	180 (36.8)
Annual family income		
<\$50,000	151 (46.2)	193 (39.5)
$\geq$ \$50,000	95 (29.0)	177 (36.2)
Unknown or refused	81 (24.8)	119 (24.3)

*All *P* values of pairwise comparisons between characteristics of subjects with and without asthma are $>.05$ except BMI at first appointment ($P = .001$ using Welch's *t*-test).
†95% central range is defined by the 2.5th and 97.5th percentiles of the values.

After adjustment for all variables except baseline vitamin D (25OHD) and applying stepwise multivariable logistic regression, BMI at first appointment and number of pregnancies but not uncontrolled asthma months per visit were associated with preeclampsia (adjusted odds ratio [aOR], 1.04; 95% CI, 1.01-1.08; aOR, 0.71; 95% CI, 0.57-0.87; and aOR, 2.97; 95% CI, 0.85-10.40, respectively). On addition of baseline vitamin D to the model and re-running the algorithm did not change the associated odds of preeclampsia with BMI and the number of pregnancies. However, this adjustment substantially increased the associated odds of preeclampsia with uncontrolled asthma months per visit by 27% and the association became significant (aOR, 3.75; 95% CI, 1.15-13.0; $P = .038$). This model demonstrated the lowest BIC as compared with all other models and showed no change in associated odds of preeclampsia with vitamin D as compared with other models (aOR, 0.95; 95% CI, 0.92-0.98; $P = .002$) as well as those of number of pregnancies and BMI at first appointment (Table E1). Furthermore, Hosmer-Lemeshow test indicated an acceptable fit for the model with the lowest BIC ($P = .51$). Of note, the results of comparative models using BIC were also consistent with those attained applying Akaike information criterion (Table E1).

Adjusting for the variables derived from the final best-fit logistic regression model, we demonstrated the probability of preeclampsia affected by uncontrolled asthma months per visit among pregnant women with asthma during pregnancy. The plot showed a trend in increased risk of preeclampsia by the increase in uncontrolled asthma months (Figure 2). The results from this model showed that a 10-unit increase in maternal serum 25OHD (ng/mL) at 10 to 18 weeks of gestation decreased the odds of preeclampsia by 40% (aOR_{10-unit}, 0.60; 95% CI, 0.43-0.82). The associated adjusted odds of preeclampsia for 20- and 30-unit increase in early pregnancy vitamin D were 0.36 (95% CI, 0.19-0.68) and 0.22 (95% CI, 0.10-0.56), respectively.

TABLE II. Univariate and multivariable logistic regression to investigate the relationship of asthma diagnosis, uncontrolled asthma status during pregnancy, and early pregnancy 25OHD (10-18 wk of gestation) with preeclampsia including other potential confounders (N_{subjects} = 816)

Variable	Univariate model, OR (95% CI)	Multivariable model including all variables* (with lowest BIC), adjusted OR (95% CI)
Physician-diagnosed asthma		
No	Reference	—
Yes	1.15 (0.69-1.90)	
Uncontrolled asthma month per monthly visit†	4.15 (1.2-12.53)	3.75 (1.15-13.0)
Serum 25OHD at enrollment (10-18 wk) (ng/mL)	0.95 (0.92-0.98)‡	0.95 (0.92-0.98)‡
Age >35 y		
No	Reference	—
Yes	0.78 (0.23-1.99)	
No. of pregnancies§	0.79 (0.64-0.96)	0.69 (0.55-0.86)
Site		
Boston	Reference	
San Diego	0.99 (0.48-2.0)	—
St Louis	2.0 (1.10-3.90)	
Trial arm		
Control	Reference	
Vitamin D intervention	0.97 (0.57-1.60)	—
Gestational diabetes		
No	Reference	
Yes	1.35 (0.46-3.25)	—
BMI at first appointment (kg/m ²)	1.05 (1.02-1.08)	1.04 (1.01-1.07)
Race		
White	Reference	
African- American	1.65 (0.95-2.94)	—
Other	1.20 (0.53-2.57)	
Maternal marital status		
Not married/divorced	Reference	—
Married	0.95 (0.92 0.99)	
Education completed		
College graduate/graduate school	Reference	
Less than high school	3.83 (1.68-8.94)	
High school, technical school	2.75 (1.35-5.94)	
Some college	2.31 (1.07-5.20)	—
Annual family income		
<\$50,000	Reference	
≥\$50,000	0.98 (0.94-1.02)	—
Unknown or refused	1.03 (0.98-1.08)	

BIC was applied to identify the model with important variables (lowest BIC) using a step-by-step inclusion and exclusion of confounders and main variable of interests (please see Table E1 for additional comparative models).

* $P = .51$ By Hosmer-Lemeshow test for goodness of fit.

†Total number of uncontrolled asthma months during study time until delivery/number of monthly visits during study time until delivery.

‡Values were rounded by 2 digits.

§Total number of previous and current pregnancies.

DISCUSSION

In this secondary analysis of VDAART cohort, we showed that self-reported physician-diagnosed asthma was not associated with an increased risk of preeclampsia and that pregnant women with controlled asthma during pregnancy do not have a higher risk of preeclampsia as compared with pregnant women without asthma. We also showed that the increased frequency of uncontrolled asthma status during pregnancy was associated with an increased risk of preeclampsia (Figure 2). Our investigation suggests that controlled status of asthma during pregnancy might reduce the risk of preeclampsia. Our study also suggests that

maternal 25ODH status might have a moderating role in the association of maternal asthma control status with the risk of preeclampsia. This observation implicates the potential role of higher vitamin D levels in reducing the risk of uncontrolled asthma during pregnancy and the subsequent risk of preeclampsia development.

The lack of association of physician-diagnosed asthma with preeclampsia is consistent with other reports.^{5,6} Our adjusted risk assessment of preeclampsia controlling for maternal vitamin D status is in contrast with some researchers' findings of no association between asthma control status and preeclampsia.^{2,9} There

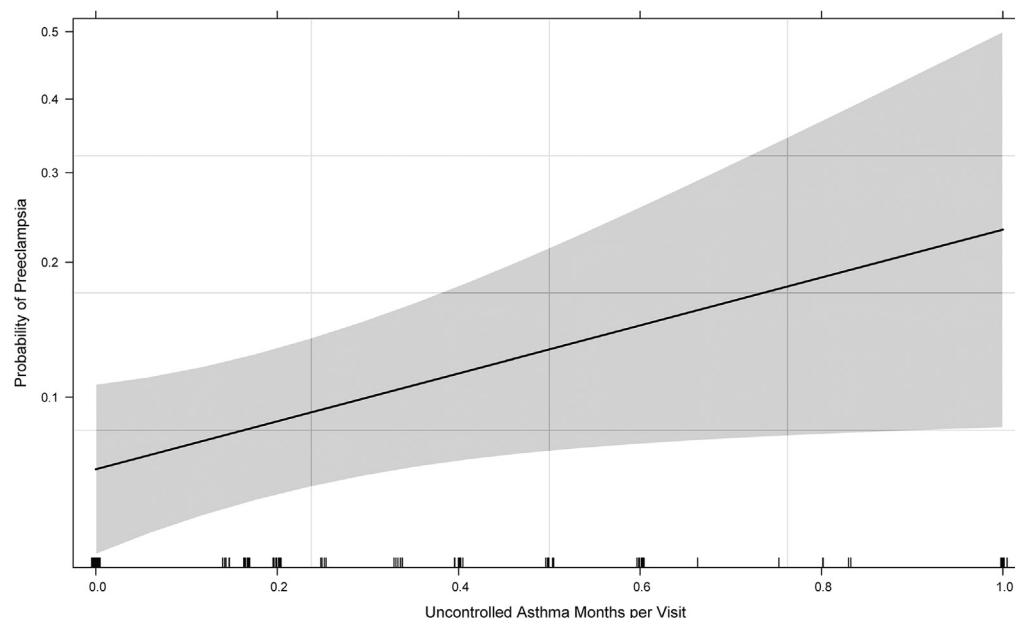


FIGURE 2. The associated effect of asthma control during pregnancy after approximately 10 weeks of gestation with risk of preeclampsia controlling for other covariates and plausible confounders derived from criterion-based stepwise logistic regression. The model with lowest BIC was used for construction of the effect plot representing the relationship of uncontrolled asthma month per visit with risk of preeclampsia occurrence (Table II and Table E1). The solid line demonstrates the point risk estimate and the gray shade its 95% point-wise confidence band. The ticks on the horizontal axis represent the subjects with uncontrolled asthma status assessed by proportion of uncontrolled asthma months to number of visits in each subject.

are 2 important points to be considered regarding previous investigations. First, most of these studies had a retrospective case-control design and used *International Classification of Diseases, Ninth Revision* codes to identify subjects with asthma and preeclampsia. Second, although these studies considered varying risk factors or potential confounders, none of them included maternal 25OHD status. In the present study, the association of uncontrolled asthma status during pregnancy with an increased risk of preeclampsia after controlling for maternal vitamin D status agrees with several other studies demonstrating that women with asthma who were symptomatic during pregnancy had a higher risk of preeclampsia.^{5,6} The relatively recent meta-analysis investigating adverse perinatal outcomes in women with asthma concluded that there could be at least 50% increased risk of preeclampsia development in pregnant women with asthma.⁹ Furthermore, the subgroup analysis by active asthma management showed a higher imposed risk of maternal asthma on preeclampsia occurrence in studies without active management (relative risk [RR], 1.70; 95% CI, 1.11-2.59). In our recent work, we demonstrated the inverse dose-response effect of early pregnancy 25OHD on the risk of preeclampsia adjusted for other covariates and confounders.¹⁸ In contrast with our previous report from VDAART, controlling for the effect of uncontrolled asthma status in this study not only did not change the previous observed inverse association of maternal early pregnancy 25OHD serum concentrations with risk of preeclampsia but also resulted in an additional reduction in the associated preeclampsia risk by 7%, 6%, and 8% for 10-, 20-, and 30-unit increase in early pregnancy 25OHD levels, respectively. Accordingly, our findings suggest that maternal vitamin D status during pregnancy might play an important role in the association

of uncontrolled asthma status with an increased risk of preeclampsia and should be considered along with uncontrolled asthma status during pregnancy as risk factors of preeclampsia. This finding also highlights the potential effect of vitamin D on asthma control during pregnancy, which has been widely investigated in nonpregnant adults with asthma and children.^{15,26} In a recent study, Confino-Cohen et al²⁶ investigated this association in a cohort of 308,000 adults with known vitamin D status. According to their study, although there was no significant association between vitamin D status and physician-diagnosed asthma, low vitamin D status was associated with 25% higher odds of asthma exacerbations as compared with vitamin D sufficiency (20-40 ng/mL). The authors also found an inverse linear association between the proportion of patients with asthma with exacerbations and vitamin D levels.²⁶ It is noted that the approximate 30 to 40 ng/mL circulating vitamin D level has been suggested by some experts as the cutoff for vitamin D deficiency in adults and during pregnancy.²⁷⁻²⁹ However, the 2011 US Institute of Medicine report defines values above 20 ng/mL (50 nmol/L) as the adequate level, which was based solely on skeletal integrity, and not considering any extraskeletal effects of vitamin D during pregnancy (2011). VDAART was not specifically designed to investigate the effect of vitamin D supplementation on asthma control status during pregnancy as one of the outcomes of the trial. However, we have shown a graduated inverse relationship of 25OHD with the risk of preeclampsia development and uncontrolled asthma status as early as 10 weeks of gestation with maximum effect for values above 30 ng/mL.^{18,25} Accordingly, it is advisable that clinicians pay attention to the current recommendation by the Institute of Medicine for vitamin

D concentrations of at least 20 ng/mL in adults, particularly at preconception in women until further studies define the optimal concentration of vitamin D during pregnancy.

A few studies provide information on the potential mechanisms involved in the association of asthma control during pregnancy and preeclampsia, but the mechanisms linking uncontrolled asthma to preeclampsia require further investigation. Tamasi et al³⁰ observed a higher proliferation of IFN- γ ⁺ and IL-4⁺-producing T cells (T_{H1} and T_{H2}) in pregnant women with asthma who developed preeclampsia than in pregnant women with asthma without preeclampsia.³⁰ There is substantial evidence that 1,25(OH)₂D directly affects both T_{H1} and T_{H2} cells and modulates the production of IFN- γ ⁺ and IL-4⁺, 2 cytokines that are involved in asthma severity. In addition, vitamin D controls regulatory T cells, which are pivotal for T-cell balance.³¹⁻³³ The potential effects of vitamin D sufficiency on reducing respiratory infections as a trigger of uncontrolled asthma and better response to inhaled corticosteroids should also be added to the potential effect modulation of vitamin D on asthma and its severity.^{34,35}

The VDAART cohort is a unique population in which to investigate the relationship of maternal asthma diagnosis, asthma control status, and vitamin D status with preeclampsia. However, VDAART's inclusion criteria, a maternal or paternal history of allergies or asthma, might limit the generalizability of the findings to pregnant women with these conditions rather than all pregnant women. Because clinical control of asthma varies in different clinical settings because of its multidimensional and heterogeneous nature,³⁶ we considered the cutoff p-ACT score of 16 or less as the threshold for any occurrence of uncontrolled asthma. This cutoff has demonstrated an objectively validated higher accuracy in discriminating controlled and uncontrolled asthma during pregnancy as compared with the recommended cutoff score of 19 for adults with asthma²² and is consistent with findings and applied cutoff in 2 other studies.^{20,21} However, sample size of patients with asthma, low occurrence of uncontrolled asthma during pregnancies, and lack of study predefined objective assessment of asthma control limited our ability to assess the risk domain of asthma control. Adherence to treatment with inhaled corticosteroid may be one of the contributors to asthma exacerbations in patients with asthma, particularly pregnant women.^{2,37}

CONCLUSIONS

Our data indicate that physician-diagnosed asthma does not increase the risk of preeclampsia development. However, pregnant women with uncontrolled asthma might have 3 times higher risk of preeclampsia than women with asthma with well-controlled asthma or pregnant women without asthma. Pregnant women with asthma that is not well controlled and at high risk of preeclampsia may benefit from increased surveillance to achieve and maintain optimal control of asthma. Early pregnancy vitamin D (25OHD) might contribute to the association of uncontrolled asthma status with preeclampsia such that early pregnancy correction of 25OHD deficiency in pregnant women might decrease the risk of uncontrolled asthma and the degree of its effect on the subsequent associated risk of preeclampsia. Our study further highlights the potential application of early pregnancy p-ACT (as early as 10 weeks of gestation) as a clinical tool with easy applicability and interpretability for evaluation of

asthma control during pregnancy. A study that considers vitamin D supplementation at early pregnancy and asthma control intervention during pregnancy might be beneficial to women who are at risk of adverse pregnancy outcomes including preeclampsia. Such an investigation also helps to understand the mechanisms by which asthma control influences pregnancy complications.

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TABLE E1. Univariate and multivariable logistic regression to investigate the relationship of uncontrolled asthma status during pregnancy and early pregnancy 25OHD (10-18 wk of gestation) with preeclampsia

Variable	Univariate model, OR (95% CI)	aOR (95% CI)				
		Model 1: Full model	Model 2	Model 3	Model 4	Model 5
Physician-diagnosed asthma						
No	Reference	Reference	Not included	—	Not included	—
Yes	1.15 (0.69-1.90)	0.89 (0.49-1.63)				
Uncontrolled asthma month per monthly visit*	4.15 (1.2- 12.53)	3.59 (0.86- 15.02)	Not included	2.97 (0.85-10.40)	Not included	3.75 (1.15-13.0)
Serum 25OHD at enrollment (10-18 wk) (ng/mL)	0.95 (0.92-0.98)	0.96 (0.92-0.99)	Not included	Not included	0.96 (0.93-0.99)	0.95 (0.92-0.98)
Age >35 y			—	—	—	—
No	Reference	Reference				
Yes	0.78 (0.23-1.99)	0.93 (0.26-3.35)				
No. of pregnancies†	0.79 (0.64-0.96)	0.70 (0.55-0.88)	0.71 (0.58-0.89)	0.70 (0.57-0.87)	0.70 (0.56-0.87)	0.69 (0.55-0.86)
Site				—	—	—
Boston	Reference	Reference	Reference			
San Diego	0.99 (0.48-2.0)	1.38 (0.55-3.48)	1.44 (0.67-3.11)			
St Louis	2.0 (1.10-3.90)	1.84 (0.90-3.74)	1.96 (1.02-3.78)			
Trial arm			—	—	—	—
Control	Reference	Reference				
Vitamin D intervention	0.97 (0.57-1.60)	0.97 (0.57-1.65)				
Gestational diabetes			—	—	—	—
No	Reference	Reference				
Yes	1.35 (0.46-3.25)	1.57 (0.55-4.52)				
BMI at first appointment (kg/m ²)	1.047 (1.02-1.08)	1.03 (1.001-1.07)	1.04 (1.01-1.08)	1.04 (1.01-1.08)	1.04 (1.01-1.08)	1.04 (1.006-1.073)
Race			—	—	—	—
White	Reference	Reference				
African- American	1.65 (0.95-2.94)	0.74 (0.33-1.67)				
Other	1.20 (0.53-2.57)	1.08 (0.46-2.57)				
Maternal marital status			—	—	—	—
Not married/divorced	Reference	Reference				
Married	0.95 (0.92 0.99)	0.85 (0.39-1.85)				
Education completed						—
College graduate/graduate school	Reference	Reference	Reference	Reference	Reference	
Less than high school	3.83 (1.68- 8.94)	3.95 (1.29- 12.15)	4.08 (1.61-10.32)	2.51 (1.16-5.43)	2.97 (1.21-7.32)	
High school, technical school	2.75 (1.35- 5.94)	2.75 (1.02- 7.42)	2.56 (1.15-5.66)	3.59 (1.49-8.64)	2.13 (0.97-4.70)	
Some college	2.31 (1.07- 5.20)	2.61 (1.01- 6.76)	2.5 (1.18-5.83)	2.44 (1.07-5.53)	2.08 (0.91-4.79)	
Annual family income			—	—	—	—
<\$50,000	Reference					
≥\$50,000	0.98 (0.94- 1.02)	1.60 (0.69-3.73)				
Unknown or refused	1.03 (0.98- 1.08)	1.08 (0.56-2.09)				
BIC	NA	530.94	469.41	464.03	460.67	449.37

NA, Not available/applicable.

A criterion-based stepwise logistic regression was applied to identify the model with the lowest BIC using a step-by-step inclusion and exclusion of confounders and main variable of interests.

*Total number of uncontrolled asthma months during study time until delivery/number of monthly visits during study time until delivery.

†Total number of previous and current pregnancies.

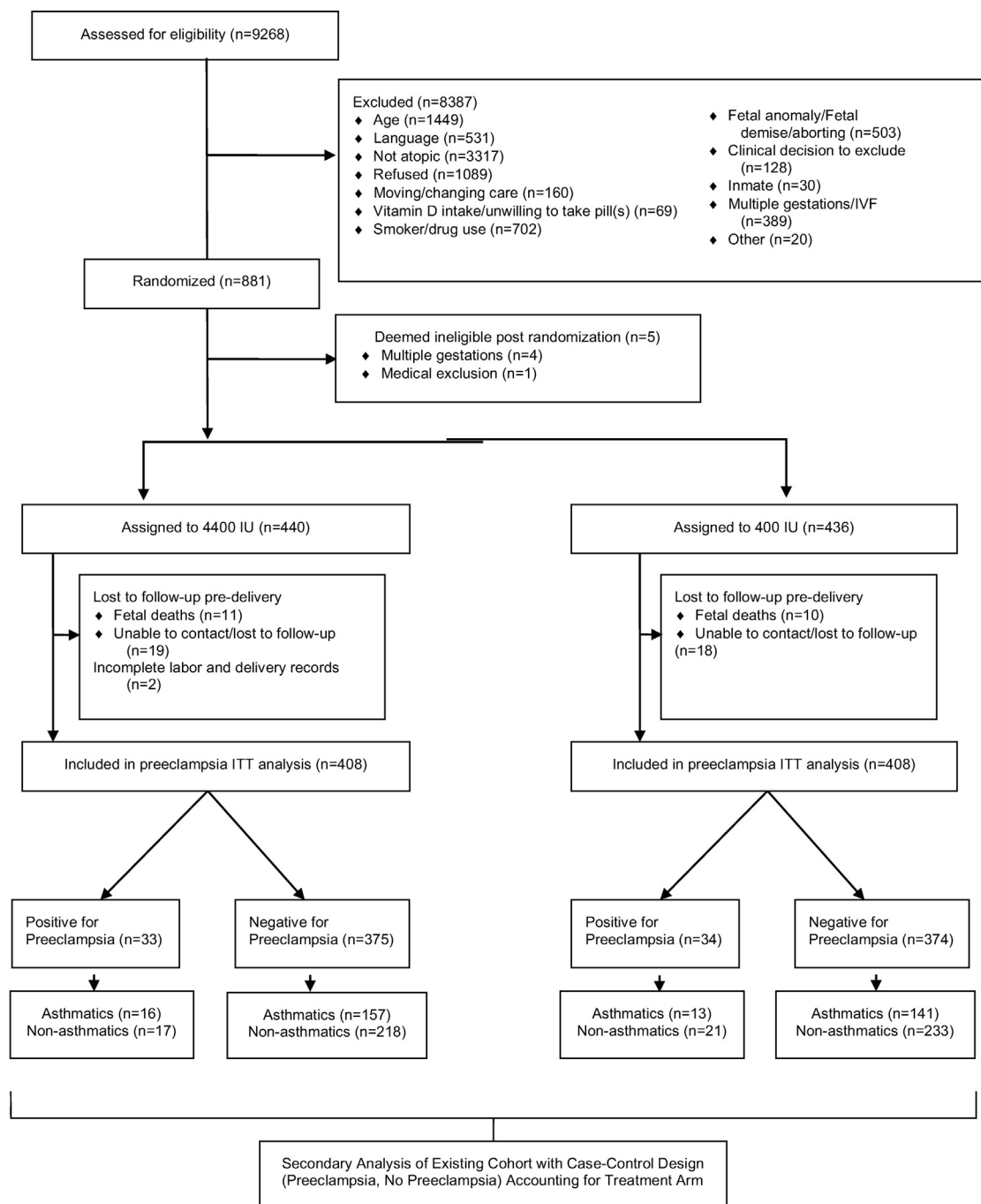


FIGURE E1. VDAART preeclampsia consort diagram.

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