Impact of Preeclampsia on the Relationship between Maternal Asthma and Offspring Asthma

An Observation from the VDAART Clinical Trial

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Abstract

Rationale: Maternal asthma and preeclampsia have independently been reported to be associated with increased asthma incidence in children of affected mothers. Maternal asthma is also associated with increased risk of preeclampsia development. However, the joint effect of these maternal conditions on child asthma risk is unknown.

Objectives: To study whether development of preeclampsia among pregnant women with asthma was associated with higher risk of childhood asthma in the VDAART (Vitamin D Antenatal Asthma Reduction Trial).

Methods: A total of 806 pregnant women and their offspring at high risk of asthma or atopy, who were followed from VDAART enrollment (10–18 wk of gestation) through the child's third birthday, were included in this cohort analysis. Preeclampsia status was determined by chart review, obstetrician diagnosis, and adjudication by a panel of obstetricians. Child asthma was the main outcome as determined by parental report of a physician diagnosis, and the risk of child asthma was also examined if accompanied by recurrent wheeze. The main risk variable of interest was a four-level ordered variable defined for each mother, with values without asthma without preeclampsia, without asthma with preeclampsia, with asthma without preeclampsia, and with asthma with preeclampsia during their pregnancy. We examined the trend of outcome proportions across these categories. To account for differences in maternal and child characteristics, we used a Weibull regression model for interval-censored data to compare the incidence of child asthma by age of 3 years across the maternal variable categories.

Measurements and Main Results: The incidence of asthma in 3-year-old children was 9.90% (44/445), 17.95% (7/39), 22.11% (65/294), and 32.14% (9/28) among those born to mothers without asthma and without preeclampsia, mothers without asthma with preeclampsia, mothers with asthma without preeclampsia, and mothers with asthma with preeclampsia, respectively. The incidences demonstrated an increasing trend in risk of child asthma across the maternal groups (P for trend <0.001). After accounting for potential confounders and using time to report of childhood asthma as analysis outcome, risk of asthma was greater among children born to mothers with asthma without preeclampsia, compared with mothers without asthma without preeclampsia (adjusted hazard ratio, 2.18; 95% confidence interval, 1.46–3.26). This risk was 50% greater for children born to mothers with asthma who developed preeclampsia during pregnancy (adjusted hazard ratio, 2.68; 95% confidence interval, 1.30–5.61). The trend in asthma and recurrent wheeze proportions across the maternal groups' children also indicated a higher risk for children born to mothers with asthma with preeclampsia (adjusted hazard ratio, 4.73; 95% confidence interval, 2.20–10.07; P for trend <0.001).

Conclusions: Preeclampsia is associated with increased risk of early life childhood asthma in children less than 3 years old over and above that associated with maternal asthma alone. The results implicate the interplay between maternal factors as strong predictors of offspring asthma and *in utero* maternal–fetal immune perturbations and developmental dysregulations associated with preeclampsia.

Keywords: pregnancy; preeclampsia; maternal asthma; child asthma; perinatal development

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At a Glance Commentary

Scientific Knowledge on the

Subject: Maternal asthma and preeclampsia have independently been reported to be associated with increased asthma incidence in children of affected mothers. Maternal asthma is also associated with increased risk of preeclampsia development. This evidence raises an unanswered question about whether maternal asthma, in whole, might drive the association of preeclampsia with an increased risk of childhood asthma or the two conditions could confer independent and additive effects on child asthma risk.

What This Study Adds to the

Field: This study is a cohort analysis of paired mothers and infants who were participants in VDAART (Vitamin D Antenatal Asthma Reduction Trial). The results demonstrate that the joint effect of maternal asthma and preeclampsia development during pregnancy on the risk of childhood asthma is stronger than the independent effects of each condition. The study implicates pregnancy and maternal–fetal interface as a crucial window for prenatal developmental and immune programming and impact on long-term child health as well as the importance of identification of high-risk pregnancies and preventive antenatal measures in this population.

Intrauterine perturbations during sensitive prenatal developmental periods could predispose offspring to the increased risk of permanent changes or conditions

that persist throughout one's lifespan (1). Preeclampsia is a heterogeneous pregnancy-specific condition, characterized by hypertension with proteinuria or other systemic disturbances. The incidence (3–8%) has increased over the last two decades (2–5). Preeclampsia can cause maternal–fetal physiologic imbalance with considerable maternal, fetal, and neonatal morbidity and mortality (6).

Recently, primary results from the COPSAC (Copenhagen Prospective Studies on Asthma in Childhood) suggested that children whose mothers developed preeclampsia during pregnancy were more likely to develop childhood asthma. The nationwide extension of the study using the national registry-based cohort with information on almost 1.70 million children whose 3.70% of their mothers suffered from preeclampsia confirmed the observed relationship (7). The study also reported the association of maternal asthma with increased risk of preeclampsia. This key additional finding could raise the issue that maternal asthma could, in whole or in part, drive the association of preeclampsia with increased risk of childhood asthma. The notion is further supported by several prior studies demonstrating that maternal asthma increased risk of asthma and recurrent wheeze in early life (8–10) and asthma during pregnancy also increased the risk of preeclampsia (11–13).

Maternal asthma could impose substantial risk of offspring asthma by gene–environment interactions or uncontrolled asthma-induced biologic perturbations during either *in utero* life or after (14–16). Excessive maternal inflammation in pregnancy is a feature of preeclampsia. Recent studies suggest that preeclampsia-induced immunologic perturbations may predate the clinical stage

of disease (17). The preclinical and clinical biologic alterations could contribute to developmental dysregulations and cytokine imbalances during *in utero* and early postnatal life (18, 19), predisposing offspring to long-term immunopathologic conditions originating during the window of developmental plasticity (20, 21). If these conjectures are true, it would be expected that comorbidity (joint effect) of maternal asthma and preeclampsia during pregnancy might further increase the risk of childhood asthma. Accordingly, we hypothesized that there is a trend toward a higher risk of childhood asthma among offspring from mothers with asthma who had *in utero* exposure to excessive inflammation caused by preeclampsia relative to the children from pregnancies with or without asthma but uncomplicated by preeclampsia. We investigated this hypothesis in the VDAART (Vitamin D Antenatal Asthma Reduction Trial) cohort. VDAART is a randomized trial that was conducted to investigate the effect of vitamin D treatment during pregnancy on preeclampsia and early life offspring asthma and recurrent wheeze (22, 23).

Methods

Ethics and Oversight

In VDAART, pregnant women were recruited from three clinical sites across the United States: Boston Medical Center, Boston, Massachusetts; Washington University at St. Louis, St. Louis, Missouri; and Kaiser Permanente Southern California Region, San Diego. The data coordinating center was based in the Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, Massachusetts. All women provided written informed consent. The data safety monitoring board convened by the NHLBI met every

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Author Contributions: H.M. conceptualized and designed the project, performed statistical analyses and interpretation, and drafted the manuscript. R.S.Z., L.B., G.T.O'C., T.F.M., and B.W.H. contributed to design, coordination, and conduction of the trial. R.S.Z. and T.F.M. provided guidance on the revision of the manuscript draft. W.Q. and V.J.C. assisted in data preparation and the analyses as well as and manuscript preparation. S.T.W. and A.A.L. were the principal investigators of VDAART. S.T.W. supervised and conceptualized the trial and supervised the analysis, result interpretation, and manuscript preparation. All authors contributed to the relevant sections and approved the final manuscript. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

This study is a secondary analysis on the data from the VDAART. The VDAART protocol was approved by the institutional review boards at each participating institution and at the Brigham and Women's Hospital and registered with ClinicalTrials.gov (NCT00920621).

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6 months to review recruitment, adherence, adverse events, data quality, and protocol changes.

VDAART Design and Participants

VDAART is a randomized, double blind, placebo-controlled clinical trial of vitamin D supplementation (4,000 IU plus a multivitamin with 400 IU daily) versus placebo (placebo pill plus a multivitamin with 400 IU daily) in pregnant women to prevent preeclampsia and asthma and recurrent wheeze in their children. In this cohort study, we included all the enrolled pregnant women who were randomized according to the intent-to-treat paradigm and their live children with follow-ups for the primary and secondary trial outcomes “asthma or recurrent wheeze” by age of 3 years (Figure 1, study flow diagram) and “preeclampsia.” Eligible participants were women between the ages of 18 and 39 years

with the estimated gestational ages of 10 and 18 weeks (singleton), nonsmoker, a history of physician-diagnosed asthma or atopy, or a partner (biologic father of the child) with a history of physician-diagnosed asthma or atopy. Eligible participants were screened per VDAART protocol and enrolled if eligible. Details of the trial design, protocol, and primary and secondary outcomes have been published (17, 22, 23).

Clinical Endpoints

Offspring asthma or asthma and recurrent wheeze. In this cohort analysis using VDAART intent-to-treat population (806 mothers and their children), offspring asthma by age of 3 years was considered as the main outcome and examined in association with maternal asthma and preeclampsia status. The diagnosis of

asthma was defined as a parental report of physician’s diagnosis of asthma on the prospective study questionnaires. To assess recurrent wheeze frequency among children diagnosed with asthma in the study groups, we further included recurrent wheeze as an additional criterion (i.e., child asthma was considered an outcome event if patents reported recurrent wheeze in addition [child asthma with recurrent wheeze]). We examined the effect of maternal asthma and preeclampsia status on the child’s asthma accompanied by recurrent wheeze and compared it with child asthma regardless of wheeze status. Recurrent wheeze was defined by the occurrence of at least one of the following five conditions: 1) parental report of wheeze after child’s second birthday preceded by at least one report of wheeze before second birthday; 2) report of child’s use of asthma controller medication (defined as report

Figure 1. The VDAART (Vitamin D Antenatal Asthma Reduction Trial) participant flow. IVF = *in vitro* fertilization.

of use of steroid inhalers or nebulizers, leukotriene modifiers, or steroid pills or liquids) after the second birthday, preceded by a report of wheeze before the second birthday; 3) two or more distinct parental reports of wheeze after the second birthday; 4) at least one parental report of wheeze and use of asthma controller medications at distinct visits, both subsequent to the second birthday; or 5) two distinct reports of use of asthma controller medications after the second birthday.

Preeclampsia. The occurrence of preeclampsia during pregnancy was both a prespecified secondary outcome of the trial and an adverse event. Pregnant women with known chronic hypertension were excluded from entry into VDAART. After all participants delivered, medical records were abstracted for all participants. The diagnosis was validated by a committee of four board-certified obstetricians who reviewed 276 abstracted charts flagged for any evidence of hypertension, proteinuria, or preeclampsia. The diagnosis of preeclampsia, at the time of record reviews, was based on the American Congress of Obstetricians and Gynecologists guidelines, which included the identification of high blood pressure and either proteinuria (≥ 300 mg per 24-hour collection or $\geq 1^+$ on urine dipstick) or presence of elevated liver enzymes, high platelet count, headache, or visual disturbances after 20 weeks of gestation (24). The blood pressure included either systolic blood pressure greater than or equal to 140 mm Hg, diastolic blood pressure greater than or equal to 90 mm Hg, or both, with a second recorded elevated measurement at least 6 hours after the first measure (24).

Study Groups and Main Variables

Similar to prior studies investigating the association of maternal asthma and offspring asthma, the main comparison groups were mothers with and without asthma. Completed questionnaires at enrollment provided the information on absence or presence of maternal asthma, constructing the two main study groups (no asthma and asthma). A pregnant woman was considered to have asthma if she reported physician-diagnosed asthma at any time in her life. To examine the joint effect of maternal asthma and preeclampsia on childhood asthma, occurrence or nonoccurrence of preeclampsia during pregnancy was considered as an additional morbidity criterion to construct the subgroups

in the main study groups. Therefore, the main variable of interest included a four-level ordered variable: women without asthma who did not develop preeclampsia (reference level), women without asthma who developed preeclampsia, women with asthma who did not develop preeclampsia, and women with asthma who developed preeclampsia.

Additional Study Variables

A priori covariates known to be risk factors for offspring asthma and potential confounders of the measure of association for the main variables of interest with the outcomes were extracted from the study questionnaires and data records (25, 26). These maternal variables included: trial arm (placebo vs. vitamin D supplementation), parity (first child or more), maternal age, race (African American, white, and other), body mass index (mg/kg^2) at first appointment, gestational age at delivery, gestational diabetes, mode of delivery, child sex, child birth weight, study center, annual household income, maternal marital and educational status, maternal partner's asthma status, and plasma 25-hydroxyvitamin D at enrollment (ng/ml). Total 25-hydroxyvitamin D levels were measured using a chemiluminescence assay on the DiaSorin Liaison machine at the data coordinating center.

Statistical Analysis

Mothers' baseline and study characteristics were compared according to asthma status (no asthma, asthma) using Student's *t* test, chi-square, or Fisher exact test. Mantel-Haenszel chi-square for linear and dose-response association with continuity correction for *P* value was used to investigate the trend of offspring "asthma" and "asthma with recurrent wheeze" among mothers with no asthma without preeclampsia, no asthma with preeclampsia, asthma without preeclampsia, and asthma with preeclampsia (27). Furthermore, offspring asthma free proportions during first 3 years of life were derived according to the levels of the main variable of interest, log-rank trend test was conducted, and Kaplan-Meier survival curves were depicted.

Subsequent to observing a trend across the ordered levels of the maternal variable, we used interval-censored event-time analysis using Weibull regression models (28) to make full use of all available 3-year

observation times with adjustment for potential confounders and obtain instantaneous risks of the outcomes over the study time period as opposed to cumulative event rates. Weibull univariable regression was used to reduce the number of potential confounders for inclusion in a multivariable model. Any potential confounder that had at least a modest ($P < 0.20$) relation with both the outcome variable and the predictor of interest or caused more than 10% change in baseline coefficient of the predictor of interest in the bivariable analysis was included in later stepwise models. Thereafter, stepwise multivariable Weibull regression models incorporating covariates were used to assess the effects of ordered levels of the maternal variable on the offspring asthma and offspring asthma with recurrent wheeze. Crude and adjusted hazard ratios (HR and aHR) were calculated with 95% confidence intervals (CI) and corresponding *P* values were calculated with the use of the Weibull model. R version 3.4.3 was used for all analyses (R Foundation for Statistical Computing; packages interval, survival, SurvRegCensCov, ggplot2). All tests were two-sided, and the significance level was prespecified at *P* less than 0.05.

Results

Study Groups

Table 1 demonstrates the pregnant women's characteristics according to their asthma status. A total of 806 mothers and their children were used for this analysis, 322 mothers with asthma versus 484 mothers without asthma (VDAART subjects' flowchart) (Figure 1). The incidence of preeclampsia was not different among 322 subjects with asthma and 484 mothers without asthma (8.70% [28/322] vs. 7.60% [37/484], respectively; relative risk [RR], 1.14; 95% CI, 0.71–1.82). Maternal body mass index greater than or equal to $25 \text{ mg}/\text{kg}^2$ at first appointment was slightly more prevalent among subjects with asthma compared with subjects without asthma (57.43% [278/422] and 65.60% [98/322], respectively; chi-square $P = 0.044$); no other differences were observed in comparisons of study group characteristics. Among all newborns from mothers in the study groups, 125 were diagnosed with asthma by age of 3 years, of whom 96 had also recurrent wheeze by

Table 1. Pregnant Women's Characteristics by History of Physician-diagnosed Asthma Whose Children Were Included in the Intention-to-Treat Population of VDAART and This Analysis ($N_{\text{Total}} = 806$ Mother–Child Pairs)

Features	Maternal Asthma ($n = 322$)	No Maternal Asthma ($n = 484$)
Preeclampsia, n (%)		
Yes	28 (8.7)	39 (8.06)
No	294 (91.3)	445 (91.94)
Missing	0	0
Maternal monthly visits during pregnancy, n		
Median	5	5
Range*	0–7	0–7
Gestational age at enrollment, wk		
Mean (SD)	14.2 (2.78)	14.13 (2.75)
Range	9.86–18.71	2.1–19.0
95% central range [†]	10.30–18.70	10.3–18.60
Maternal age, yr		
Mean (SD)	26.7 (5.40)	27.8 (5.50)
Range	18.0–38.80	18.0–39.52
95% central range	18.7–35.30	19.0–36.60
Enrollment time to delivery, wk		
Mean (SD)	24.84 (3.43)	24.85 (3.43)
Range	11.14–31	13.60–35.30
95% central range	19.15–29.70	19.6–29.60
Gestational age at delivery		
Mean (SD), wk	38.8 (1.80)	38.9 (2.10)
Range, wk	26.0–42.10	26.2–42.3
95% central range, wk	36.2–41.0	36.0–41.10
<34 wk, n (%)	6 (1.86)	13 (3.08)
≥34 wk, n (%)	316 (98.14)	469 (96.51)
Missing, n (%)	0	2 (0.41)
Trial arm, n (%)		
Vitamin D intervention	171 (53.10)	234 (48.35)
Placebo	151 (46.90)	250 (51.65)
25-OHD levels		
10–18 wk of gestation (maternal baseline), ng/ml		
Mean (SD), ng/ml	22.64 (10.33)	23.18 (10.18)
Range, ng/ml	4.35–65.30	4.50–0.80
95% central range, ng/ml	7.60–42.40	8.30–39.60
Missing, n	2	3
Sufficiency status, n (%)		
<30 ng/ml	250 (77.6)	375 (77.70)
≥30 ng/ml	70 (21.71)	106 (21.70)
Number of pregnancies		
Median	2	2
Range	1–11	1–13
95% central range	1–6	1–5
Category status, n (%)		
First	105 (32.61)	176 (36.36)
>1	217 (67.39)	306 (63.74)
Clinical site, n (%)		
Boston	93 (28.88)	147 (30.37)
San Diego	112 (34.78)	162 (33.47)
St. Louis	117 (36.34)	175 (36.16)
Gestational diabetes, n (%)		
Yes	19 (5.90)	28 (5.90)
No	302 (94.10)	454 (94.10)
Maternal eczema, n (%)		
Yes	108 (33.54)	149 (30.79)
No	214 (66.46)	335 (69.21)
Maternal allergic rhinitis, n (%) [‡]		
Yes	227 (70.50)	289 (59.71)
No	95 (29.50)	195 (40.29)

(Continued)

3 years age (76.19% [96/126]) (Table 2). The incidence of asthma in children born to mothers with preeclampsia during pregnancy was higher than those born to mothers without preeclampsia (16/67 [23.88%] vs. 109/739 [14.75%], respectively; RR, 1.62; 95% CI, 1.02–2.57). These values for incidence of asthma in children whose parents also reported recurrent wheeze were 14/67 (20.90%) versus 82/739 (11.10%), respectively (RR, 1.88; 95% CI, 1.13–3.13).

Dose–Response Association of Ordered Maternal Asthma and Preeclampsia Status with Asthma in 3-Year-Old Children

The incidence of child asthma was 9.90% (44/445), 17.95% (7/39), 22.11% (65/294), and 32.14% (9/28) among those born to mothers without asthma without preeclampsia, mothers without asthma with preeclampsia, mothers with asthma without preeclampsia, and mothers with asthma with preeclampsia, respectively. The trend test indicated that an increase in maternal morbidity across ordered levels (no asthma without preeclampsia, no asthma with preeclampsia, asthma without preeclampsia, asthma with preeclampsia) increased the risk of child asthma by age of 3 years. The highest risk was observed among mothers with asthma who developed preeclampsia during their pregnancy relative to mothers without asthma without preeclampsia (odds ratio, 4.32; P for trend <0.0001) (Table 3). This risk was relatively lower if the mother had asthma and did not have preeclampsia or did not have asthma but developed preeclampsia (odds ratio, 2.59 and 1.99, respectively) (Table 3).

The incidence of child asthma with recurrent wheeze was 7.4% (33/445), 12.82% (5/39), 16.67% (49/294), and 32.14% (9/28) among those born to mothers without asthma without preeclampsia, mothers without asthma with preeclampsia, mothers with asthma without preeclampsia, and mothers with asthma with preeclampsia, respectively (Table 2). The test for linear association still demonstrated increasing trend in proportions of child asthma with recurrent wheeze across maternal levels of the ordered variable. However, higher risk of child asthma was estimated among mothers with asthma with preeclampsia compared with those subjects without asthma without preeclampsia (odds ratio, 5.91) (Table 2).

Table 1. (Continued)

Features	Maternal Asthma (n = 322)	No Maternal Asthma (n = 484)
Partner's asthma, n (%) [‡]		
Yes	57 (17.70)	130 (26.86)
No	264 (81.99)	354 (73.14)
Unknown	1 (0.31)	0
Partner's eczema, n (%)		
Yes	47 (14.60)	86 (17.77)
No	274 (85.09)	396 (81.82)
Unknown	1 (0.31)	2 (0.41)
Partner's allergic rhinitis, n (%) [‡]		
Yes	96 (29.81)	248 (51.24)
No	225 (69.88)	235 (48.55)
Unknown	1 (0.31)	1 (0.21)
Body mass index at first appointment, n (%) [‡]		
<25 kg/m ²	98 (30.43)	179 (36.98)
≥25 kg/m ²	208 (64.60)	278 (57.46)
Missing	16 (4.97)	27 (5.56)
Race, n (%)		
African American	147 (45.65)	200 (41.32)
Non-African American	175 (54.35)	284 (58.68)
White	125 (38.82)	201 (41.53)
American Indian or Alaska Native	5 (1.60)	5 (1.0)
Asian	9 (2.80)	27 (5.58)
Native Hawaiian	4 (1.24)	7 (1.45)
Other	32 (9.89)	44 (9.12)
Child sex, n (%)		
Male	178 (54.28)	243 (50.20)
Female	144 (44.72)	241 (49.80)
Child weight at delivery, kg		
Mean (SD)	3.24 (0.54)	3.3 (0.58)
Range	0.92–4.63	0.80–4.70
Mode of delivery, n (%)		
Caesarean section	92 (28.57)	147 (30.37)
Vaginal	229 (71.12)	335 (69.22)
Missing	1 (0.31)	2 (0.41)
Maternal marital status, n (%)		
Not married/divorced	187 (58.10)	252 (52.07)
Married	135 (41.90)	232 (47.93)
Maternal education completed, n (%)		
Less than college	226 (70.19)	307 (63.43)
Less than high school	47 (14.60)	53 (10.95)
High school, technical school	97 (30.12)	144 (29.75)
Some college	82 (25.47)	110 (22.73)
Above college		
College graduate/graduate school	96 (29.81)	177 (36.57)
Annual family income, n (%)		
<\$50,000	73 (22.67)	125 (25.83)
≥\$50,000	172 (53.42)	240 (49.60)
Unknown or refused	77 (23.91)	119 (24.57)

Definition of abbreviations: 25-OHD = 25-hydroxyvitamin D; VDAART = Vitamin D Antenatal Asthma Reduction Trial.

*Two participants (one with asthma and one subject without asthma) did not provide monthly visits. With exclusion of these cases the ranges for both study groups are one to seven visits.

[†]Within the 2.5th and 97.5th percentiles of values.

[‡]All *P* values of pairwise comparisons between characteristics of subjects with and without history of asthma diagnosis >0.05 with the exception of obesity status by body mass index at first appointment, maternal and partner's allergic rhinitis, and partner's asthma.

Effect of Maternal Asthma and Preeclampsia Status on Time to Event of Offspring Asthma

The free proportions of child asthma during first 3 years of life by maternal asthma and preeclampsia status (no asthma without

preeclampsia, no asthma with preeclampsia, asthma without preeclampsia, and asthma with preeclampsia) were demonstrated using Kaplan-Meier survival curves (Figure 2). Test for a trend in survival across maternal ordered categories

confirmed the expected unequal survival distributions and prior observed graduated relationship with child asthma (*P* for trend <0.001) (Figure 2). Using time to report of childhood asthma (regardless of wheezing status) as analysis outcome, crude risk estimates of asthma was greater among children born to mothers with asthma without preeclampsia, compared with mothers without asthma without preeclampsia (HR, 2.40; 95% CI, 1.64–3.53; *P* < 0.001). The risk of asthma was greater if mothers with asthma developed preeclampsia during their pregnancies (HR, 3.70; 95% CI, 1.80–7.50; *P* < 0.001) (Table 4). After adjustments for potential confounders, the adjusted risk of child asthma among mothers with asthma with and without preeclampsia was 2.18 (95% CI, 1.46–3.26; *P* < 0.001) and 2.68 (95% CI, 1.30–5.61; *P* = 0.013), respectively, as compared with mothers without asthma (Table 4).

Using time to report of childhood asthma who also had recurrent wheeze as the analysis outcome (asthma with recurrent wheeze), slightly higher risk of child asthma was observed among mothers with asthma without preeclampsia compared with mothers without asthma without preeclampsia (aHR, 2.38; 95% CI, 1.50–3.79; *P* < 0.001). However, the estimated risk of asthma was substantially greater among mothers with asthma with preeclampsia who also reported recurrent wheeze in their children compared with mothers without asthma without preeclampsia (aHR, 4.73; 95% CI, 2.20–10.07; *P* < 0.001) (Table 5).

Discussion

Primary Findings

The present cohort study using the VDAART population demonstrated an increasing trend in risk of childhood asthma by the age of 3 years as the level of maternal morbidity by preeclampsia and asthma status increases. Children born to mothers with a history of physician-diagnosed asthma had almost two times higher risk of asthma by the age of 3 years as compared with children born to mothers who did not have a history of asthma. This comparative risk increased by 50%, if the pregnancy of child's mother was complicated with the occurrence of preeclampsia, demonstrating a synergistic effect of maternal asthma and preeclampsia on the risk of child asthma. The results from

Table 2. Trend in Risk of Child Asthma Accompanied by Recurrent Wheeze by Age 3 Years across Pregnant Women Groups according to Their Asthma and Preeclampsia Status

Maternal (Co)morbidity Status	Offspring Asthma with Recurrent Wheeze by Age of 3 Years			Trend in Proportions	
	Yes	No	Total	Odds Ratio	Trend P Value with Correction for Continuity*
No asthma					<0.0001
Without preeclampsia	33	412	445	1 (Reference)	
With preeclampsia	5	34	39	1.84	
Asthma					
Without preeclampsia	49	245	294	2.50	
With preeclampsia	9	19	28	5.91	
Total	96	710	806		

*Extended Mantel-Haenszel chi-square test for linear trend = 22.77; P value for trend (1 degree of freedom) with continuity correction <0.0001.

time to report of childhood asthma in children who also had recurrent wheeze is suggestive that preeclampsia could be associated with up to two times higher risk of early life childhood asthma in children of 3 years old over and above that associated with maternal asthma alone. We have previously shown that VDAART women with asthma were at higher risk of preeclampsia (13). Taken together, our result suggests that the effect of preeclampsia as an intermediate pregnancy condition is associated with higher risk of asthma development in children whose mothers had a history of asthma as compared with mothers without asthma with or without preeclampsia.

The adjusted estimated effect of preeclampsia on the risk of childhood asthma among mothers without asthma in

this study is suggestive of a weaker effect of preeclampsia among this group of women (aHR, 1.10–1.20). Consistently, the nationwide registry-based cohort study of Danish children demonstrated almost 10% increase risk of asthma in children born to mothers with preeclampsia (adjusted incidence rate ratio, 1.05–1.17) (7).

In Light of Other Studies

In utero and postnatal development are crucial for the origin of childhood asthma (29). A few studies have shown an association between preeclampsia and wheezing (both early transient and persistent) and asthma in offspring (7, 30). Maternal asthma is also a risk factor for offspring asthma (31), which could, *per se*, increase the risk of preeclampsia

development during pregnancy compared with pregnant women without asthma (11, 12, 32). The results from studies that investigated the independent relationship of maternal asthma and preeclampsia with offspring asthma are suggestive that the associated risk of maternal asthma with offspring asthma is larger than that of preeclampsia with offspring asthma. These studies did not investigate a potential joint effect and interaction of the two conditions, therefore, they are not conclusive whether the effect from preeclampsia is an inherent part of maternal asthma or an additive effect. Our results help to explain these associations and supports the overall results from prior studies that the maternal asthma effect is more prominent than preeclampsia as a risk factor for early life child asthma. Furthermore, the joint effect of maternal asthma and preeclampsia in the present study is suggestive of an additive effect of preeclampsia on risk of offspring asthma. Such an additive effect is greater than the observed effect of preeclampsia among mothers without asthma, potentially caused by an augmented induced prenatal inflammation (33).

Immune Responses

Low-grade proinflammatory responses might start in early pregnancy and increase excessively in women who develop preeclampsia later during their pregnancy (17). Maternal inflammatory cytokines during pregnancy have been shown to correlate with corresponding cytokines in the offspring at early life that might predispose offspring to asthma and atopic disease (18, 34, 35). Preeclampsia is associated with an increase in circulating maternal cytokines, such as IFN- γ and a decrease in IL-4 and decrease in IL-10, most probably caused by an increase in T-helper 1 (Th1)/T-helper 2 (Th2) balance (36). These altered cytokine balances have also been observed in early life of neonates from mothers with preeclampsia (18).

Because asthma is typically thought to be a Th2-cell driven inflammatory disease (37), it might be expected that the skewness of the child's Th1/Th2 cytokine balance after birth from a mother with preeclampsia protects against the development of asthma or atopy. However, preeclampsia is a complex inflammatory condition characterized by a variety of proinflammatory cytokines beyond the Th1 type of cytokines (38, 39). Furthermore,

Table 3. Trend in Risk of Child Asthma by Age 3 Years (Regardless of Wheeze Status) across Pregnant Women Groups according to Their Asthma and Preeclampsia Status

Maternal (Co)morbidity Status	Offspring Asthma by Age 3 Years			Trend in Proportions	
	Yes	No	Total	Odds Ratio	Trend P Value with Correction for Continuity*
No asthma					<0.0001
Without preeclampsia	44	401	445	1 (Reference)	
With preeclampsia	7	32	39	1.99	
Asthma					
Without preeclampsia	65	229	294	2.59	
With preeclampsia	9	19	28	4.32	
Total	125	681	806		

*Extended Mantel-Haenszel chi-square test for linear trend = 22.77; P value for trend (1 degree of freedom) with continuity correction <0.0001.

Figure 2. Kaplan-Meier survival curves demonstrating offspring asthma-free proportion by maternal morbidity status of asthma and preeclampsia (P for trend <0.001 across all four-level maternal variable). The hazard ratios for the time to the first event of child asthma (regardless of wheeze status) obtained using Weibull regression model were 2.41 (95% confidence interval [CI], 1.64–3.53; $P < 0.001$) for mothers with asthma who did not develop preeclampsia and 3.65 (95% CI, 1.78–7.47; $P < 0.001$) for mothers with asthma who developed preeclampsia. The estimated risks after adjustment for potential confounders using Weibull model were adjusted hazard ratio of 2.18 (95% CI, 1.46–3.26; $P < 0.001$) and 2.68 (95% CI, 1.30–5.61; $P = 0.013$), respectively.

asthma is a heterogeneous collection of clinical phenotypes and recent studies suggest that the new T-cell subsets and interplay between the innate and adaptive immune system are essential for the initiation and propagation of different clinical phenotypes of asthma and atopic immune responses (37). Further investigation is warranted to specifically investigate postnatal immune responses among children from mothers with asthma who had preeclampsia during their pregnancy as compared with those who did not develop preeclampsia.

Potential Shared Mechanisms

Both maternal asthma and preeclampsia could induce developmental perturbations during pregnancy, predisposing the child to asthma (29, 40, 41). Long-term longitudinal studies on postnatal growth and health

have further supported the notion that these alterations are caused by altered fetal programming (42, 43). There is evidence that some of the pathways in fetal programming might be shared between asthma and preeclampsia-induced perturbations and developmental dysregulations. For example, pregnancies with asthma have been shown to have increased placental vascular resistance, which could predispose to defective placentation and vascular dysfunction, an early observed change in preeclampsia (40, 44). Maternal asthma could also alter homeostatic control through inducing hormonal imbalances. Syncytiotrophoblast and villous cytotrophoblast 11β -hydroxysteroid dehydrogenase 2 protects the fetus from of harmful effects of high concentrations of maternal glucocorticoids. This enzyme is reduced in preeclampsia. Similarly,

reduced 11β -hydroxysteroid dehydrogenase 2 activity has been shown among women with asthma who do not use inhaled corticosteroids, and resulted in smaller neonates at term (45). In the presence of maternal asthma during pregnancy, studies have shown alterations in placental mitochondrial and sex-specific placental global gene expression associated with reduced fetal growth (40, 46). It has been shown that inhaled corticosteroid usage by pregnant women for treatment of asthma during pregnancy could change the pattern of mitochondrial gene expression in the placenta (47). Preeclampsia is also shown to affect mitochondrial and global placenta mRNA levels (48, 49).

Although transferring genetic susceptibility is essentially evidenced for maternal asthma, epidemiologic studies suggest that these two conditions might share some genetic or environmental factors. Preeclampsia has been reported to be more common in pregnant women with male fetus, similar to asthma with higher prevalence in boys up to adolescence (50, 51). Furthermore, asthma has been reported more in first born children (52), similar to more common presentation of preeclampsia among nulliparous women (53). Prenatal dietary exposure to certain nutrients might also affect risk of wheezing phenotypes in early life (54). These thought-provoking observations raise the question to what extent predisposition to childhood asthma during pregnancy might be caused by maternal genetic and/or epigenetic susceptibility to asthma and preeclampsia. In contrast, such a predisposition might reflect *in utero* developmental dysregulation associated with preeclampsia and uncontrolled asthma, potentially with some overlaps in conditional biologic features. Further studies are warranted to investigate the overlapping biologic pathways in asthma and preeclampsia during pregnancy to identify potential preventive measures.

Low birth weight in some studies has been reported with higher risk of childhood asthma and hospitalization in early life (55). In our study, lower birth weight ($<2,500$ g) was associated with higher risk of asthma in children but after adjustment for the main variables and covariates, it was not a predictor of child asthma. This observation is likely caused by adjustment for preterm

Table 4. Estimated Risk of Events (Asthma) at 3-Year Follow-up in the Offspring by Maternal Asthma and Preeclampsia Status Using Time-to-Event Analysis

Variable	Univariable Analysis			Stepwise Multivariable Analysis		
	HR	95% CI	P Value	Adjusted HR	95% CI	P Value
Maternal asthma and morbidity status						
Without asthma						
Without preeclampsia	1 (Ref)			1 (Ref)		
With preeclampsia	1.89	0.85–4.19	0.12	1.21	0.51–2.91	0.63
With asthma						
Without preeclampsia	2.41	1.64–3.53	<0.001	2.18	1.46–3.26	<0.001
With preeclampsia	3.65	1.78–7.47	<0.001	2.68	1.30–5.61	0.013
Maternal age	0.93	0.90–0.96	<0.001	—	—	—
Gestational age at delivery						
≥34 vs. <34 wk	0.31	0.15–0.63	0.017	0.36	0.15–0.84	0.021
Trial arm						
Vitamin D intervention vs. placebo	0.90	0.63–1.30	0.55	—	—	—
Maternal baseline vitamin D						
≥30 vs. <30 ng/ml	0.43	0.25–0.75	0.004	0.53	0.28–0.99	0.051
Clinical center						
Boston	1 (Ref)	0.30–0.84	0.02	—	—	—
San Diego	0.5	0.65–1.26	0.20			
St. Louis	0.9					
Race						
White	1 (Ref)	1.28–2.73	0.02	1.17	0.74–1.84	0.50
African American	1.87	0.18–0.99	0.03	0.33	0.14–0.78	0.014
Other	0.40					
Maternal marital status						
Married vs. unmarried or divorced	0.40	0.27–0.60	<0.001	0.63	0.39–1.01	0.06
Maternal education						
College and above vs. less than college	0.49	0.32–0.76	0.002	—	—	—
Body mass index at first appointment						
<25 vs. ≥25 kg/m ²	0.65	0.44–0.98	0.04	0.90	0.59–1.36	0.61
Gestational diabetes						
Yes vs. no	0.67	0.27–1.64	0.38	—	—	—
Mode of delivery						
Vaginal vs. cesarean section	0.91	0.63–1.33	0.63	—	—	—
Child's sex						
Male vs. female	1.64	1.14–2.36	0.01	1.44	0.98–2.10	0.060
Parity						
1 vs. >1	0.95	0.66–1.38	0.80	—	—	—
Child's weight at birth						
<2.5 vs. ≥2.5 kg	1.87	1.11–3.17	0.02	—	—	—
Paternal asthma						
Yes vs. no	0.95	0.62–1.44	0.79	1.10	0.71–1.68	0.69

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; Ref = reference.

Hazard ratios for the outcome were estimated using a Weibull model; HRs and CIs are two-sided.

birth and the fact that children born to mothers with preeclampsia with preterm delivery might also have lower birth weight (56, 57).

Strengths and Limitations

VDAART is a well-designed trial of vitamin D with meticulous clinical and data monitoring and follow-up of pregnant women for preeclampsia development during pregnancy and their children for asthma and recurrent wheeze by age 3 years. This trial provided an exquisite prospective cohort for the purpose of this study to investigate the joint effect of maternal asthma and preeclampsia on childhood

asthma. Nevertheless, this cohort is enriched for pregnant women with asthma with a 40% prevalence compared with an 8% prevalence of asthma among pregnant women (58). This feature might affect the estimated risks as opposed to the general population. In the COPSAC study, the authors reported the cumulative incidence of childhood asthma (7). This approach did not allow the investigator to observe the trend of incidences across the study period. Conversely, the VDAART design allowed us to explore the child asthma incidence trend across study time and present the instantaneous incidences for maternal asthma categorized levels. One observation from

this approach was that children with an asthma diagnosis born to mothers without asthma with preeclampsia were under the age of 1.5 years as opposed to the three other maternal groups, potentially implicating preeclampsia-related immunologic dysregulations at an earlier stage of childhood, particularly among mothers without asthma (Figure 2). In the VDAART study, completed questionnaires at enrollment and monthly maternal health questionnaires thereafter provided the information on absence or presence of parental asthma (as a parental report of physician's diagnosis of asthma). Offspring were evaluated

Table 5. Estimated Risk of Events (Asthma Diagnosis with Recurrent Wheeze) at 3-Year Follow-up in the Offspring by Maternal Asthma and Preeclampsia Status Using Time-to-Event Analysis

Variable	Univariable Analysis			Multivariable Model*		
	HR	95% CI	P Value	Adjusted HR	95% CI	P Value
Maternal asthma and morbidity status						
Without asthma						
Without preeclampsia	1 (Ref)			1 (Ref)		
With preeclampsia	1.37	0.50–3.87	0.49	1.10	0.38–3.14	0.87
With asthma						
Without preeclampsia	2.39	1.54–3.72	<0.001	2.38	1.50–3.79	<0.001
With preeclampsia	5.38	2.57–11.25	<0.001	4.73	2.20–10.07	<0.001

For definition of abbreviations, see Table 4.

Hazard ratios for the outcome were estimated using a Weibull model; HRs and CIs are two-sided.

*HRs are adjusted for race, maternal age, gestational age at delivery, trial arm, maternal baseline vitamin D, clinical center, maternal marital status, maternal education, maternal body mass index at first appointment, gestational diabetes, mode of delivery, child's sex, parity, child's weight at birth, and maternal partner's asthma status.

quarterly through questionnaires and yearly during in-person visits until the third birthday of the child. The study design minimized the possibility of recall bias, particularly for prospectively followed-up pregnant women and their children; however, the potential

should be pointed out. Maternal smoking was a VDAART exclusion criterion. Although 28% of mothers in this study were either living with their partners or divorced, the potential of second-hand smoke exposure during pregnancy of mothers living with their partners and

their children after birth is another limitation.

Conclusions

Preeclampsia is a risk factor for childhood asthma that has an additive effect to maternal asthma as a strong prenatal risk factor among pregnant women. In this population, children born to pregnant women who have asthma and further develop preeclampsia during pregnancy demonstrate a higher risk asthma or asthma in their early life. These results implicate pregnancy and maternal–fetal interface as a crucial window for prenatal developmental and immune programming and impact on long-term child health and highlight the importance of prenatal care in high-risk pregnancies, particularly women with asthma, and identification of preventive measures for preeclampsia. ■

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