Maternal Hypertensive Disorders of Pregnancy and the Risk of Childhood Asthma

To the Editor:

Approximately 6% of children living in the United States have asthma (1). Critical immunological changes occur during pregnancy to prevent maternal rejection of the fetus (2), and the prenatal environment may influence the development of recurrent wheezing and asthma in children (3). Hypertensive disorders of pregnancy (HDP), including preeclampsia, are estimated to affect 2–8% of pregnancies worldwide (4–7) and may alter immune regulation at the maternal–fetal interface and T-helper 1/T-helper 2 balance (8, 9); however, the impact of HDP on childhood asthma remains undefined (10, 11).

Several prior studies, primarily based in Europe, have shown that preeclampsia may be associated with increased risk of wheezing and asthma at various time points during childhood (12–17); however, this association has not been consistently observed (18, 19). Because preeclampsia is rare, affecting only 3% of live births (18, 20), prior studies have been largely underpowered to establish this association. Furthermore, prior population-based studies have not used robust clinical data in the definitions for preeclampsia or examined a diverse North American population.

Our objective was to investigate whether HDP, and specifically preeclampsia, increase the risk of developing childhood asthma in a large U.S. maternal–child health cohort.

Methods

We used data from the Massachusetts General Hospital (MGH) Maternal–Child Cohort (MMCC), comprising 37,510 pregnant individuals linked to 53,802 children born between 1998 and 2016 at MGH. The MMCC was created by linking multiple datasets, including the MGH Maternal Health Cohort, the MGH Birth Cohort (21), the Mass General Brigham (MGB) Research Patient Data Registry, and Massachusetts Department of Public Health birth certificate data. This study was approved by the MGB Human Research Committee. The requirement for informed consent was waived, as data were solely obtained by linking electronic health records.

For the analytic cohort, we included mother–child pairs if the mother delivered and the child received care at an MGB facility, with the child having at least one encounter in the electronic medical record after birth and before age 1 year, and at least one health care encounter from 3 to 5.9 years.

We excluded pregnant individuals with first prenatal visit after 20 weeks, with multiple gestations, or with preexisting chronic hypertension, defined as antihypertensive medication use or systolic blood pressure (SBP) $\geq$ 140 mm Hg or diastolic blood pressure (DBP) $\geq$ 90 mm Hg before 20 weeks' gestation. We excluded children with the following International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic codes on three or more encounters (14): cystic fibrosis (277.0x), congenital abnormalities of the respiratory system (748.xx), immunodeficiency (279.0x, 279.1x, or 279.3x), or congenital heart disease (745.xx, 746.xx, or 747.xx).

Based on the American College of Obstetricians and Gynecologists' clinical practice guidelines (20, 22), HDP were defined by: *1*) SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg at two or more prenatal visits at $\geq$20 weeks' gestation; *2*) documentation of a hypertensive disorder of pregnancy as the indication for induction or cesarean delivery, or as a labor complication in the delivery record; or *3*) meeting criteria for preeclampsia (*see below*).

Preeclampsia was defined as evidence of new-onset hypertension after 20 weeks' gestation and either *1*) laboratory evidence of preeclampsia; or *2*) International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic code of eclampsia (642.6x). Evidence of new-onset hypertension was defined as either: *1*) SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg after 20 weeks' gestation at one or more prenatal visits; or *2*) documentation of a hypertensive disorder of pregnancy as the indication for induction or cesarean delivery or complication of labor in the delivery record. Laboratory evidence of preeclampsia was defined by at least one of the following: *1*) $\geq$300 mg protein per 24-hour urine collection; *2*) urine protein to creatinine ratio $\geq$ 0.3; *3*) urine dipstick protein $\geq$ 2+ if 24-hour urine or protein to creatinine ratio was not available; *4*) serum creatinine $\geq$ 1.1 mg/dl; *5*) thrombocytopenia (platelets $< 100 \times 10^9$ L); or *6*) elevated liver transaminases (aspartate transaminase or alanine transaminase $>$ 40 IU/L).

Asthma was defined by primary diagnosis (493.xx) in the electronic medical record billed between age 3.0 and 4.99 years, or two or more asthma medication "events" within a 12-month period between age 3.0 and 4.99 years in either inpatient or outpatient locations (23). Asthma medications included short-acting bronchodilators, inhaled corticosteroids, inhaled corticosteroids plus long-acting bronchodilators, and oral leukotriene modifiers. Case definitions were validated through chart review by two physicians (including an asthma specialist) in a sample of 100 randomly selected cases.

We used logistic regressions to quantify the odds of asthma in children born from pregnant individuals with HDP, adjusting for maternal and child factors.

Results

A total of 14,929 mother–child pairs were included in the analytic cohort, and 2,153 children (14.4%) were diagnosed with asthma by age 5 years (Table 1). There were 1,975 (14.3%) children with asthma born to 13,790 individuals without HDP, 178 (15.6%) children with asthma born to 1,139 individuals with HDP, and 92 (14.7%) children with asthma born to 624 individuals with preeclampsia.

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Table 1. Maternal and child characteristics among those with and without childhood asthma

	Full Analytical Cohort ($n = 14,929$)	Without Asthma ($n = 12,776$)	With Asthma ($n = 2,153$)
Maternal			
Maternal age at delivery (continuous), mean (SD)	30.3 (6.2)	30.4 (6.2)	30.1 (6.3)
Race and/or ethnicity			
Non-Hispanic White	7,508 (50.3)	6,554 (51.3)	954 (44.3)
Non-Hispanic Black	1,091 (7.3)	907 (7.1)	184 (8.6)
Non-Hispanic Asian or Pacific Islander	1,220 (8.2)	1,042 (8.2)	178 (8.3)
Hispanic	3,192 (21.4)	2,674 (20.9)	518 (24.1)
None of the above	1,918 (12.9)	1,599 (12.5)	319 (14.8)
Payor at birth			
Private insurance	8,244 (55.2)	7,200 (56.4)	1,044 (48.5)
Public insurance	5,253 (35.2)	4,340 (34.0)	913 (42.4)
Limited insurance or no insurance	1,432 (9.6)	1,236 (9.7)	196 (9.1)
Marital status			
Yes (married)	9,700 (65.0)	8,407 (65.8)	1,293 (60.1)
No	5,229 (35.0)	4,369 (34.2)	860 (39.9)
BMI at the first PNV, mean (SD)	25.7 (5.4)	25.6 (5.3)	26.4 (5.7)
BMI at the first PNV			
BMI $< 30\ kg/m^2$	11,947 (80.0)	10,306 (80.7)	1,641 (76.2)
BMI $\geq 30\ kg/m^2$	2,982 (20.0)	2,470 (19.3)	512 (23.8)
Gestational weight gain, mean (SD)	28.4 (11.4)	28.6 (11.3)	27.6 (11.9)
Gestational weight gain (lb)			
<15	1,471 (9.9)	1,199 (9.4)	272 (12.6)
15–24	3,824 (25.6)	3,267 (25.6)	557 (25.9)
25–34	5,506 (36.9)	4,748 (37.2)	758 (35.2)
35–44	3,017 (20.2)	2,603 (20.4)	414 (19.2)
≥45	1,111 (7.4)	959 (7.5)	152 (7.1)
Maternal smoking 3 mo before pregnancy or during pregnancy			
Yes	1,090 (7.3)	906 (7.1)	184 (8.6)
No	13,839 (92.7)	11,870 (92.9)	2,004 (91.6)
Maternal history of asthma			
Yes	1,162 (7.8)	885 (6.9)	277 (12.9)
No	13,767 (92.2)	11,891 (93.1)	1,876 (87.1)
Mode of delivery			
Vaginal	10,985 (73.6)	9,461 (74.1)	1,524 (70.8)
Cesarean	3,944 (26.4)	3,315 (26.0)	629 (29.2)
Maternal HDP (yes)	1,139 (7.6)	961 (7.5)	178 (8.3)
Preeclampsia	624 (4.2)	532 (4.3)	92 (4.5)
Child			
Gestational age at birth, wk, mean (SD)	39.3 (1.8)	39.4 (1.7)	39.1 (2.4)
≥37	14,152 (94.8)	12,161 (95.2)	1,991 (92.5)
32–36	660 (4.4)	544 (4.3)	116 (5.4)
<32	117 (0.78)	71 (0.56)	46 (2.1)
Sex			
Female	7,147 (47.9)	6,321 (49.5)	826 (38.4)
Male	7,782 (52.1)	6,455 (50.5)	1,327 (61.6)
Birth weight, kg, mean (SD)	3.4 (0.55)	3.4 (0.54)	3.3 (0.64)

Definition of abbreviations: BMI = body mass index; HDP = hypertensive disorders of pregnancy; PNV = prenatal visit; SD = standard deviation.
Data are presented as *n* (%) unless otherwise noted.

In the unadjusted and adjusted analyses (Table 2), children born from pregnancies affected by HDP did not have a higher risk of asthma (odds ratio [OR], 1.09; 95% confidence interval [CI], 0.92–1.29; $P = 0.34$; adjusted OR, 1.10; 95% CI, 0.92–1.31; $P = 0.29$, respectively). Similarly, in the unadjusted and adjusted analyses, children born from pregnancies affected by preeclampsia did not have a higher risk of asthma (OR, 1.01; 95% CI, 0.80–1.28; $P = 0.91$; adjusted OR, 0.95; 95% CI, 0.74–1.20; $P = 0.64$, respectively).

Discussion

In a large diverse U.S.-based maternal–child cohort, we found that HDP, including preeclampsia, were not significantly associated with childhood asthma by age 5 years. To our knowledge, this is the largest U.S.-based maternal–child cohort to examine the relation of HDP to asthma. Prior studies, primarily from European national registries and allergy-enriched cohorts, have shown inconsistent findings when examining the association between preeclampsia and asthma (12–19).

Table 2. Logistic regression models for hypertensive disorders of pregnancy and risk of childhood asthma at age 5 years

	Model 1, HDP (n = 14,929)		Model 2, Preeclampsia (n = 14,414)	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Maternal				
HDP (ref: no HDP)	1.10 (0.92–1.31)	0.29	—	
Preeclampsia (ref: no HDP)	—		0.95 (0.74–1.20)	0.64
Maternal age at delivery (continuous)	1.00 (0.99–1.01)	0.52	1.00 (0.99–1.01)	0.54
Race and/or ethnicity				
Non-Hispanic White	Ref		Ref	
Non-Hispanic Black	1.25 (1.03–1.51)	0.02	1.28 (1.06–1.56)	0.01
Non-Hispanic Asian or Pacific Islander	1.22 (1.01–1.47)	0.04	1.20 (0.99–1.45)	0.06
Hispanic	1.18 (1.02–1.36)	0.03	1.18 (1.02–1.37)	0.02
None of the above	1.28 (1.09–1.49)	0.003	1.31 (1.11–1.53)	0.001
Payer at birth				
Private insurance	Ref		Ref	
Public insurance	1.31 (1.16–1.48)	<0.001	1.30 (1.15–1.47)	<0.001
Limited insurance or no insurance	1.03 (0.86–1.24)	0.73	1.04 (0.86–1.25)	0.68
Not married (ref: married)	1.10 (0.98–1.23)	0.11	1.10 (0.98–1.23)	0.11
BMI at the first PNV ⩾ 30 kg/m^2 (ref: <30)	1.08 (0.96–1.23)	0.20	1.13 (0.99–1.28)	0.07
Gestational weight gain				
<15	1.16 (0.98–1.38)	0.08	1.12 (0.94–1.33)	0.20
15–24	1.00 (0.88–1.13)	0.98	0.99 (0.87–1.12)	0.85
25–34	Ref		Ref	
35–44	0.99 (0.87–1.13)	0.87	0.98 (0.86–1.12)	0.79
⩾45	0.90 (0.74–1.10)	0.31	0.88 (0.72–1.07)	0.20
Maternal smoking 3 mo before pregnancy or during pregnancy (ref: no)	1.07 (0.89–1.29)	0.46	1.07 (0.89–1.30)	0.46
Maternal history of asthma (ref: no)	1.96 (1.67–2.29)	<0.001	1.93 (1.65–2.27)	<0.001
Cesarean delivery (ref: vaginal)	1.13 (1.01–1.26)	0.03	1.14 (1.02–1.27)	0.03
Child				
Gestational age at birth				
⩾37 wk	Ref		Ref	
32–36 wk	1.28 (1.01–1.63)	0.04	1.29 (1.01–1.64)	0.04
<32 wk	3.77 (2.41–5.9)	<0.001	3.87 (2.46–6.09)	<0.001
Male (ref: female)	1.60 (1.45–1.76)	<0.001	1.60 (1.45–1.76)	<0.001
Birth year (continuous)	1.06 (1.04–1.07)	<0.001	1.06 (1.04–1.07)	<0.001
Birth weight (per 1,000 g; continuous)	1.03 (0.93–1.15)	0.55	1.02 (0.91–1.13)	0.78

Definition of abbreviations: BMI = body mass index; CI = confidence interval; HDP = hypertensive disorders of pregnancy; OR = odds ratio; PNV = prenatal visit; ref = reference; SD = standard deviation.

These inconsistencies may be related to geographic differences or differences in asthma phenotypes, as HDP have primarily been associated with early-life wheezing or early-onset asthma (16, 17, 19, 24), compared with null associations found in school-age children (14, 16), although our cohort consisted of preschool age children.

Our study uses data from a large diverse cohort, with rigorous definitions for HDP, including laboratory values, and validated asthma definitions. Limitations include the use of healthcare system data, which may be subject to administrative coding errors, and data from a tertiary care center, which may not be representative of the general population. In addition, only 28% of the entire cohort (n = 14,929) was included in this analysis because of exclusion criteria, with included and excluded individuals differing by race and ethnicity (e.g., non-Hispanic White individuals accounted for 63% of excluded individuals vs. 50% of included individuals). However, the final analytic cohort still is diverse, comprising 5,503 mother–child pairs (36.8%) who did not identify as non-Hispanic White. Several other prenatal factors, such as breastfeeding and viral infections, which have been associated with the development of childhood asthma, also were not included in this analysis because of data limitations; however, these data contain a large cohort of pregnant individuals with preeclampsia, a rare maternal disorder.

Further studies to understand prenatal risk factors for asthma development are critical to the development of effective strategies for the primary prevention of childhood asthma. ■

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Anna Chen Arroyo, M.D., M.P.H.*
Stanford University School of Medicine
Stanford, California

Lacey B. Robinson, M.D., M.P.H.
Beth Israel Lahey Health
Boston, Massachusetts

Kaitlyn James, Ph.D., M.P.H.
Harvard Medical School
Boston, Massachusetts

and
Massachusetts General Hospital
Boston, Massachusetts

Sijia Li, M.S.
Mohammad Kamal Faridi, M.P.H.
Massachusetts General Hospital
Boston, Massachusetts

Sarah Hsu, M.S.
Massachusetts General Hospital
Boston, Massachusetts

and

Broad Institute
Cambridge, Massachusetts

Orianne Dumas, Ph.D.
Universite Paris-Saclay
Villejuif, France

Anne Y. Liu, M.D.
Maurice Druzin, M.D.
Stanford University School of Medicine
Stanford, California

Camille E. Powe, M.D.
Carlos A. Camargo, Jr., M.D., Dr.P.H.
Harvard Medical School
Boston, Massachusetts

and

Massachusetts General Hospital
Boston, Massachusetts

ORCID ID: 0000-0002-7785-4632 (A.C.A.).

*Corresponding author (e-mail: annaarroyo@stanford.edu).

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