



Incidence and timing of offspring asthma, wheeze, allergic rhinitis, atopic dermatitis, and food allergy and association with maternal history of asthma and allergic rhinitis

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Background: Studying the developmental precursors of allergy may help explain the mechanisms (or etiology) of allergic disease. We studied childhood respiratory and allergic diseases in a pre-birth cohort from the United States.

Objective: We assessed the associations between maternal history of asthma and the development of respiratory and allergic diseases in offspring. We also assessed associations with maternal history of allergic rhinitis.

Methods: Maternal history of asthma and allergic rhinitis was self-reported during early pregnancy. Offspring respiratory and allergy information was obtained from electronic medical records. Adjusted Cox proportional hazard models assessed the associations between maternal history of asthma and development of respiratory and allergic diseases in the offspring up to 8 years. A similar approach was used for maternal history of allergic rhinitis.

Results: Children born to women with a history of asthma had a 77% greater risk of developing asthma, a 45% greater risk of atopic dermatitis/eczema, and a 65% greater risk of wheeze (all $p < 0.01$), but no significantly increased risk of allergic rhinitis or food allergies, compared to children born to women with no history of asthma. Maternal history of allergic rhinitis was not associated with any child allergy outcome, and maternal history of both asthma and allergic rhinitis was associated with child atopic dermatitis/eczema only.

Conclusions: Maternal history of asthma was significantly associated with offspring respiratory and allergic diagnoses. The association between maternal history of asthma and offspring asthma and atopic dermatitis is a novel finding. Our findings may guide physicians who counsel families with a history of maternal asthma and allergic rhinitis about their child's risk of developing respiratory and allergic diseases.

Keywords: Allergic diseases, Maternal history, Risk factors, Prevention, Allergies

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INTRODUCTION

Allergy is the sixth most common chronic condition in the United States, affecting more than 50 million Americans.¹ The Institute of Medicine² and the World Allergy Organization¹ state that allergic diseases are an increasing public health concern. The 4 major presentations of allergic diseases include asthma, allergic rhinitis, atopic dermatitis/eczema, and food allergies.¹ Children with 1 allergic presentation are more likely to develop another.³ Genetic,^{4,5} environmental^{4,6} and dietary factors^{7,8} differentially affect the development of allergic diseases, and a developmental origins component has been recently proposed.^{9,10}

Parental¹¹ and paternal^{12,13} history of atopic disease are well-established risk factors for the development of offspring allergic outcomes. Maternal history of allergy is, however, of particular relevance,¹⁴ as it may infer an increased risk of allergy in the offspring due to genetic risk,^{15,16} intra-uterine factors,^{17,18} and maternal dietary factors.¹⁹ Maternal history of asthma²⁰ is considered a risk factor for the development of asthma and wheeze²¹ in the offspring. It is unclear, however, whether maternal history of asthma confers risk to offspring for other allergic diseases as well. The role of maternal history of allergic rhinitis on offspring allergy outcomes also needs further clarification.

We assessed the associations between maternal history of asthma and the development of offspring allergies up to 8 years. We also assessed associations with maternal history of allergic rhinitis. We used data from a longitudinal pre-birth cohort of mother-offspring dyads in the United States. We hypothesized that maternal history of asthma would be associated with increased offspring risk of all allergic outcomes. We suspected that the same association would hold for maternal history of allergic rhinitis.

METHODS

Study participants

This analysis included data from a longitudinal pre-birth cohort of 1410 mother-child dyads.

Pregnant women aged 16 years or older with singleton pregnancies were recruited from obstetrics clinics at the local hospital from 2009 to 2014. The study protocol was approved by the Institutional Review Board. Further details regarding the study have been published elsewhere.^{22,23}

At recruitment, the cohort included 1410 mother-child dyads. Following written consent, pregnant women completed questionnaires on medical history at enrollment in early pregnancy, and were asked to give consent for the review of offspring electronic medical records up to age 4 years. Additional consent for review of offspring electronic medical records up to age 8 was requested when mothers and children came in for a follow-up visit after age 4.

Participants were excluded from this analysis if they did not provide consent for child medical record review from birth up to 4 years of age ($n = 9$), had offspring who died prior to birth ($n = 6$), or who had insufficient data available to search for the child in the electronic medical records system ($n = 66$) (Fig. 1). Among the 1329 participants eligible for inclusion in the electronic medical record search, 68 children had no records in the electronic medical record system, resulting in a total of 1261 participants in the analytic data set. In order to assess whether selection bias was present, we compared demographic characteristics of the participants who were identified and those who were not identified in the electronic medical records system.

Electronic medical record search

Medical record numbers (MRNs) were found by searching the electronic medical records using the child's name and date of birth. The MRNs were recorded by 2 independent researchers and any discrepancies were reviewed and resolved. The final list of MRNs was sent to the electronic medical record search team. The electronic medical records were searched using previously published terms¹⁰ for allergic diseases. The following search terms related to allergic presentations of the skin and airways were used to identify offspring diagnoses of allergic rhinitis, asthma, atopic dermatitis/eczema, and wheeze: 1) allergic

rhinitis: "allergic rhinitis", "allergic rhinoconjunctivitis", "hay fever", "rhinitis", "seasonal allergies"; 2) asthma: "asthma"; 3) atopic dermatitis/eczema: "atopic dermatitis", "eczema"; and 4) wheeze: "wheeze." Search terms related to IgE-mediated food allergies and food allergens included: "food allergy", "almond", "cashew", "clam", "crab", "egg", "fin fish", "fish", "milk", "pecan", "peanut", "salmon", "sesame seed", "scallop", "shellfish", "shrimp", "soy", "sunflower seed", "tree nut", "tuna", and "wheat". For each participant, each time there was a text recognition for one of the search terms or part of the search terms, the corresponding medical record notes were recorded verbatim as a text field, as well as the date of the service. The dataset received from the electronic medical record search team included multiple rows for each participant at different service dates.

Medical record verified child respiratory and allergy outcomes

Any text field identified from the search of the electronic medical records was reviewed by 2

clinician researchers who assigned diagnoses for asthma, wheeze, allergic rhinitis, atopic dermatitis/eczema, and food allergies, after extensive review of medical notes. Diagnosis was based on the diagnosis assigned by the physician based on the medical notes (eg, if the physician used wheeze as a diagnosis, the child was considered to have a diagnosis of wheeze). Children with a diagnosis of hay fever or seasonal allergies were considered to have allergic rhinitis, as the common terms often appear interchangeably in the medical record. Child's age at diagnosis was calculated using their date of birth and the service date associated with their diagnosis. If a participant did not return a hit for any of the search terms, they were considered to have no respiratory or allergy diagnoses between birth and the age at which the medical record search was conducted. All children were counted in the analyses regardless of respiratory or allergy status.

To differentiate between those with no food allergies and those with food allergy or food intolerance or sensitivity, a more complicated protocol

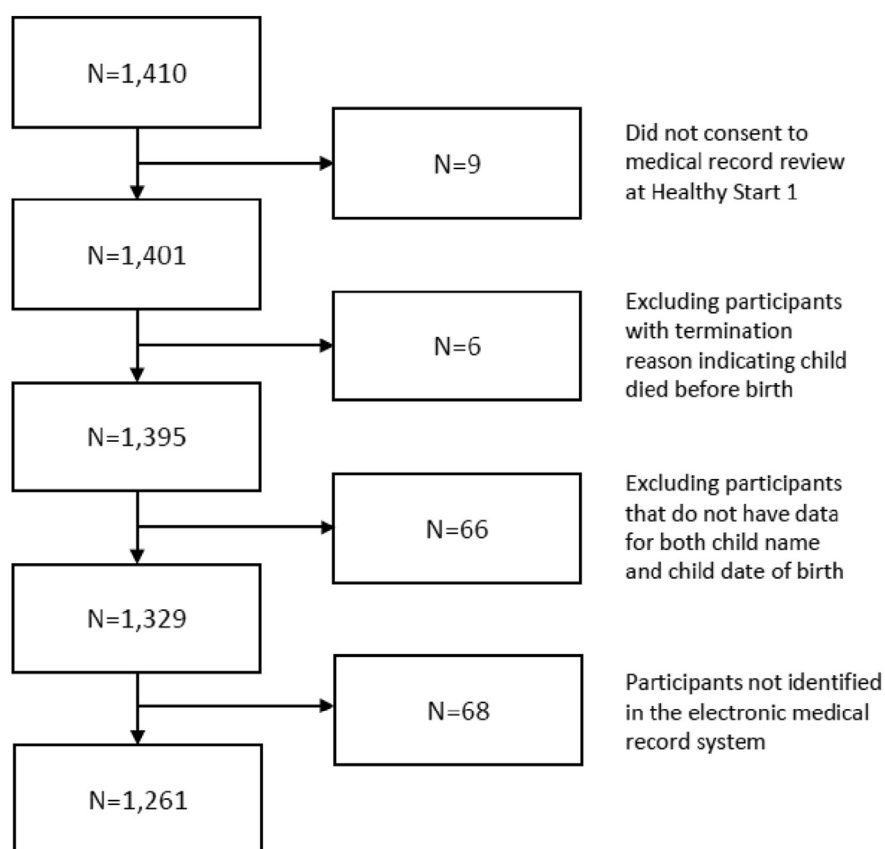


Fig. 1 Number of participants in the present study

was followed. Records flagged as having a search term associated with food allergy were reviewed and coded as a suspected food allergy diagnosis, a suspected food intolerance/sensitivity diagnosis or no diagnosis. Participants who had no hits for any food allergy search term were considered to have no food allergy diagnoses. For any participant with suspected food allergy or food intolerance/sensitivity, the full electronic medical record was individually inspected. The full record included clinic notes, information on allergy testing, oral food challenge information if conducted and medical letters. For each participant, we recorded whether the child had IgE-mediated food allergy, the age of diagnosis, and the age at development of tolerance to the food if tolerance had been developed. Children with Eosinophilic Esophagitis (EoE) or Food Protein induced enterocolitis (FPIES) were not considered to have IgE-mediated food allergies unless they also had co-existing IgE-mediated food allergies. Any unclear diagnoses were re-reviewed by 2 clinician researchers, and diagnosis made by consensus.

Demographic data

Maternal questionnaires completed at the first research visit, which occurred between 13 and 23 weeks gestation, collected data on child's race/ethnicity, number of previous pregnancies and births, and maternal history of allergic diseases.²⁴ A maternal history of asthma was considered present if pregnant women answered "yes" to the question, *"Has a health professional such as a doctor, physician assistant, or nurse practitioner ever told you that you have asthma?"* A maternal history of allergic rhinitis was considered present if pregnant women answered "yes" to the question, *"Has a health professional such as a doctor, physician assistant, or nurse practitioner ever told you that you have hay fever, seasonal allergies or allergic rhinitis?"* In addition, participants were considered to have a double maternal history of both asthma and allergic rhinitis if mothers answered "yes" to both of the preceding questions. Information regarding gestational smoking, breastfeeding duration, and age of introduction of solid foods were also obtained by maternal report. Pre-pregnancy weight was collected from either medical records or self-reported early in pregnancy, and maternal

height was measured via stadiometer at the first research visit. Feeding information reported at the 18 months postnatal interview was used to calculate breastfeeding duration as breastmilk months, a product of breastfeeding duration and intensity.²⁵ Mode of delivery, child's sex and birth year were obtained from electronic medical record data.

Statistical analysis

Descriptive statistics for participants' demographic data were computed as frequencies and percentages or means and standard deviations for categorical or continuous variables, respectively. Likelihood ratio chi-squared tests and Cochran-Mantel-Haenszel tests were used to compare demographic characteristics between the participants who were identified in the electronic medical record system and those who were not, in order to assess for potential selection bias.

We computed cumulative incidence as the number of new cases of disease during a specified time interval, reflecting the definition from the US Centers for Disease Control and Prevention (CDC).²⁶ We computed cumulative incidence of the medical record verified respiratory and allergy outcomes up to 6 months, 2 years, and 5 years of age to describe the burden of allergic diseases in the cohort.

We fit Cox proportional hazards models to examine the associations between maternal history of asthma and medical record verified childhood respiratory and allergic diseases (allergic rhinitis, asthma, atopic dermatitis/eczema, food allergy, wheeze) up to 8 years. We used a similar approach for maternal history of allergic rhinitis. For each combination of maternal allergic disease history by child disease outcome, we fit two models. The first model (Model 1) adjusted for the following potential prenatal confounders: child's race/ethnicity,^{27,28} sex,²⁹ firstborn,³⁰ gestational smoking,³¹ and pre-pregnancy BMI.³² The second model (Model 2) additionally adjusted for perinatal or early life characteristics including Caesarean section,³³ breastfeeding duration,³⁴ and age of introduction of solid foods,³⁵ as these have also been associated with child allergy outcomes in some, but not all studies. The follow-up age was different for each child. This occurred

for 1 of 2 reasons: 1) consent was only given to review child medical records from birth up to age 4 years, but not from age 4–8 years; or 2) consent was given to review child medical records from birth up to age 8 years, but the child had not yet reached 8 years of age at the time of the electronic medical record search (eg, the child was only 6 years old when the search was conducted). The Cox proportional hazards modeling approach allowed us to censor participants at the latest follow-up age for which they had available electronic medical record data, due to 1 of the 2 reasons described. For children with multiple recorded diagnoses of a disease outcome, their age at their first diagnosis was used. We computed the hazard ratios (HR) and 95% confidence intervals. We checked that the assumption of proportional hazards was met prior to interpreting the results of these models. Significance for all

statistical hypothesis testing was assessed at an alpha level of 0.05.

As a sensitivity analysis, we fit Cox proportional hazard models as described above, but used double maternal history of both asthma and allergic rhinitis as the primary predictor.

RESULTS

There were no significant differences in demographic characteristics between the 1261 participants who were identified in the electronic medical record system, and therefore included in the search, and the 68 participants who were not identified in the electronic medical record system, and therefore were not included in the search (data not shown). Table I reports descriptive statistics of maternal history of allergic diseases

	n (%)
Child's race/ethnicity	
Non-Hispanic white	631 (50)
Non-Hispanic black	163 (13)
Hispanic	323 (26)
Other ^a	144 (11)
Child's sex, female	601 (48)
Firstborn	601 (48)
Gestational smoking	107 (8)
Maternal history of asthma	209 (17)
Maternal history of allergic rhinitis	333 (26)
Ever breastfed	1034 (93)
Caesarean section	270 (22)
Birth year	
2010	137 (11)
2011	266 (21)
2012	323 (26)
2013	341 (27)
2014	194 (15)
	mean (SD)
Pre-pregnancy BMI (kg/m ²)	25.75 (6.2)
Breastfeeding duration (breastmilk months)	8.34 (6.8)
Age of introduction of solid foods (months)	6.17 (2.0)

Table I. Demographic characteristics of study participants included in the electronic medical record search (N = 1261) a. Other race/ethnicity includes non-Hispanic Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, and multiracial

		Up to 6 months	Up to 2 years	Up to 5 years
Allergic rhinitis/hay fever/seasonal allergies	n/N	13/1261	65/1261	99/731
	%	1.03%	5.15%	13.54%
	95% CI	0.55–1.76%	4.00–6.52%	11.15–16.24%
Asthma	n/N	45/1261	119/1261	121/731
	%	3.57%	9.44%	16.55%
	95% CI	2.61–4.75%	7.88–11.19%	13.93–19.45%
Atopic dermatitis/eczema	n/N	108/1261	266/1261	187/731
	%	8.56%	21.09%	25.58%
	95% CI	7.08–10.25%	18.87–23.45%	22.45–28.91%
Food allergy	n/N	2/1261	31/1261	20/731
	%	0.16%	2.46%	2.74%
	95% CI	0.02–0.57%	1.68–3.47%	1.68–4.19%
Wheeze	n/N	48/1261	183/1261	161/731
	%	3.81%	14.51%	22.02%
	95% CI	2.82–5.02%	12.61–16.58%	19.07–25.21%

Table II. Cumulative incidence of medical record verified child allergy outcomes

and covariates for the analytic sample. [Table II](#) presents cumulative incidence of the medical record verified child respiratory and allergy outcomes up to 6 months (N = 1261), 2 years (N = 1261), and 5 years (N = 731).

Maternal history of asthma and medical record verified child respiratory and allergy outcomes

The models adjusted for potential prenatal confounders (Model 1) found that maternal history of asthma was significantly associated with an increased risk of child development of atopic dermatitis/eczema (HR = 1.45; 95% CI: 1.13, 1.86; $p < 0.01$; [Table III](#)), asthma (HR = 1.77; 95% CI: 1.30, 2.40; $p < 0.01$; [Table IV](#)), and wheeze (HR = 1.65; 95% CI: 1.24, 2.19; $p < 0.01$; [Table V](#)). The effect of maternal history of asthma remained significant in the models that further adjusted for perinatal and early life factors (Model 2). None of the perinatal or early life factors included in Model 2 were significantly associated with child development of atopic dermatitis/eczema ([Table III](#)). Breastfeeding duration was significantly associated with child

development of asthma ([Table IV](#)) and wheeze ([Table V](#)). Longer duration of breastfeeding was associated with a lower risk of child asthma (HR = 0.95; 95% CI: 0.93, 0.98; $p < 0.01$) and wheeze (HR = 0.96; 95% CI: 0.93, 0.98; $p < 0.01$). Maternal history of asthma was not significantly associated with child development of allergic rhinitis ([Table VI](#)) or food allergies ([Table VII](#)) in either the model adjusted for prenatal confounders (Model 1), or the model that additionally adjusted for perinatal and early life factors (Model 2). [Figure 1–5 in the supplementary material](#) illustrate the associations between maternal history of asthma and development of each child allergy outcome, as observed from the models adjusted for potential prenatal confounders (Model 1).

Maternal history of allergic rhinitis and medical record verified child respiratory and allergy outcomes

The models adjusted for potential prenatal confounders (Model 1) found that maternal history of allergic rhinitis was not significantly associated

with child development of atopic dermatitis/eczema (HR = 1.13; 95% CI: 0.89, 1.43; $p = 0.32$), asthma (HR = 1.12; 95% CI: 0.83, 1.52; $p = 0.45$), wheeze (HR = 0.98; 95% CI: 0.73, 1.30; $p = 0.87$), allergic rhinitis (HR = 1.01; 95% CI: 0.72, 1.42; $p = 0.95$), or food allergy (HR = 1.37; 95% CI: 0.75, 2.51; $p = 0.31$). In the models that additionally adjusted for perinatal and early life factors (Model 2), maternal history of allergic rhinitis remained non-significantly associated with the development of child respiratory and allergic diseases (data not shown).

Sensitivity analyses

The models adjusted for potential prenatal confounders (Model 1) found that double maternal history of both asthma and allergic rhinitis was significantly associated with offspring development of atopic dermatitis/eczema (HR = 1.71; 95% CI: 1.24, 2.36; $p < 0.01$), but was not significantly associated with offspring development of asthma, wheeze, allergic rhinitis, or food allergy (data not shown). In the models that additionally adjusted for perinatal and early life factors (Model 2) similar results were observed (data not shown).

DISCUSSION

We found that a maternal history of asthma was significantly associated with offspring development of asthma, wheeze, and atopic dermatitis/eczema, but not allergic rhinitis or food allergies. Maternal history of allergic rhinitis was not associated with offspring development of any of the allergic diseases examined. Having both a maternal history of asthma and allergic rhinitis was associated with atopic dermatitis/eczema only. These findings will allow clinicians to provide specific information about risk of allergic disease to families. In addition, the findings also will allow those designing interventions to target families who are at highest risk.

It is widely accepted that the predisposition to atopy is passed on from parents to the child, although which gene or genes have effects on offspring allergy has not been fully established.³⁶ It is also unclear whether the disease seen in the mother is associated specifically with the same disease in the offspring, or with other allergic diseases.³⁷ In our study, maternal history of asthma was associated with a number of allergic diseases in offspring. Our data indicated that

Predictor ^a	Model 1 (N = 1260)			Model 2 (N = 970)		
	HR	95% CI	p-value	HR	95% CI	p-value
Maternal asthma	1.45	1.13, 1.86	0.0037	1.62	1.21, 2.16	0.0011
Child race/ethnicity						
Hispanic	2.24	1.73, 2.90	<0.0001	2.28	1.67, 3.11	<0.0001
Non-Hispanic black	3.66	2.75, 4.86	<0.0001	3.80	2.69, 5.39	<0.0001
Other ^b	1.23	0.84, 1.81	0.2826	1.05	0.66, 1.68	0.8283
Child sex - female	0.85	0.69, 1.05	0.1404	0.83	0.65, 1.06	0.1327
Firstborn	1.28	1.04, 1.59	0.0229	1.30	1.01, 1.68	0.0403
Gestational smoking	1.51	1.09, 2.09	0.0133	1.38	0.88, 2.19	0.1631
Pre-pregnancy BMI	1.00	0.99, 1.02	0.6301	1.01	0.99, 1.03	0.3038
Caesarean section	-	-	-	0.78	0.57, 1.07	0.1201
Breastfeeding duration	-	-	-	0.99	0.97, 1.01	0.4916
Age solids introduced	-	-	-	0.99	0.93, 1.05	0.6950

Table III. Results of Cox proportional hazard models examining the association between maternal history of asthma and child atopic dermatitis/eczema diagnosis. ^a The reference category for the hazard ratios presented for child race/ethnicity was non-Hispanic white. The hazard ratios presented for pre-pregnancy BMI represent a one kg/m² increase in pre-pregnancy BMI. The hazard ratios presented for breastfeeding duration represent a one-unit increase in breastmilk-months. The hazard ratios presented for age solids were introduced represent a one-month increase in age when solid foods were introduced. ^b Other race/ethnicity includes non-Hispanic Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, and multiracial.

Predictor ^a	Model 1 (N = 1260)			Model 2 (N = 970)		
	HR	95% CI	p-value	HR	95% CI	p-value
Maternal asthma	1.77	1.30, 2.40	0.0003	1.79	1.25, 2.57	0.0014
Child race/ethnicity						
Hispanic	2.82	2.01, 3.96	<0.0001	2.49	1.67, 3.71	<0.0001
Non-Hispanic black	2.53	1.68, 3.80	<0.0001	2.58	1.61, 4.13	<0.0001
Other ^b	2.34	1.53, 3.56	<0.0001	1.68	0.99, 2.84	0.0558
Child sex - female	0.75	0.57, 0.98	0.0373	0.79	0.57, 1.08	0.1343
Firstborn	1.50	1.14, 1.97	0.0041	1.56	1.13, 2.17	0.0072
Gestational smoking	1.63	1.08, 2.46	0.0211	1.16	0.65, 2.07	0.6266
Pre-pregnancy BMI	1.02	1.00, 1.04	0.0483	1.02	1.00, 1.05	0.0587
Caesarean section	-	-	-	0.92	0.63, 1.35	0.6793
Breastfeeding duration	-	-	-	0.95	0.93, 0.98	0.0010
Age solids introduced	-	-	-	1.04	0.96, 1.11	0.3417

Table IV. Results of Cox proportional hazard models examining the association between maternal history of asthma and child asthma diagnosis. *a.* The reference category for the hazard ratios presented for child race/ethnicity was non-Hispanic white. The hazard ratios presented for pre-pregnancy BMI represent a one kg/m² increase in pre-pregnancy BMI. The hazard ratios presented for breastfeeding duration represent a one-unit increase in breastmilk-months. The hazard ratios presented for age solids were introduced represent a one-month increase in age when solid foods were introduced. *b.* Other race/ethnicity includes non-Hispanic Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, and multiracial.

children with a maternal history of asthma have a 77% greater risk of developing asthma, 45% greater risk of developing atopic dermatitis/

eczema, and 65% greater risk of developing wheeze, when compared to children of mothers with no history of asthma.

Predictor ^a	Model 1 (N = 1260)			Model 2 (N = 970)		
	HR	95% CI	p-value	HR	95% CI	p-value
Maternal asthma	1.65	1.24, 2.19	0.0006	1.67	1.20, 2.31	0.0023
Child race/ethnicity						
Hispanic	2.75	2.02, 3.75	<0.0001	2.33	1.62, 3.34	<0.0001
Non-Hispanic black	2.84	1.99, 4.07	<0.0001	2.76	1.83, 4.16	<0.0001
Other ^b	2.11	1.42, 3.15	0.0002	1.62	1.00, 2.63	0.0508
Child sex - female	0.79	0.62, 1.01	0.0635	0.79	0.59, 1.04	0.0963
Firstborn	1.09	0.85, 1.40	0.5044	0.99	0.74, 1.33	0.9361
Gestational smoking	1.55	1.06, 2.25	0.0227	1.21	0.72, 2.01	0.4721
Pre-pregnancy BMI	1.00	0.98, 1.02	0.9294	1.00	0.97, 1.02	0.7252
Caesarean section	-	-	-	0.99	0.70, 1.39	0.9323
Breastfeeding duration	-	-	-	0.96	0.93, 0.98	0.0004
Age solids introduced	-	-	-	1.00	0.93, 1.07	0.9253

Table V. Results of Cox proportional hazard models examining the association between maternal history of asthma and child wheeze diagnosis. *a.* The reference category for the hazard ratios presented for child race/ethnicity was non-Hispanic white. The hazard ratios presented for pre-pregnancy BMI represent a one kg/m² increase in pre-pregnancy BMI. The hazard ratios presented for breastfeeding duration represent a one-unit increase in breastmilk-months. The hazard ratios presented for age solids were introduced represent a one-month increase in age when solid foods were introduced. *b.* Other race/ethnicity includes non-Hispanic Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, and multiracial.

Predictor ^a	Model 1 (N = 1260)			Model 2 (N = 970)		
	HR	95% CI	p-value	HR	95% CI	p-value
Maternal asthma	1.31	0.92, 1.87	0.1399	1.36	0.90, 2.05	0.1452
Child race/ethnicity						
Hispanic	2.80	1.91, 4.12	<0.0001	2.69	1.73, 4.18	<0.0001
Non-Hispanic black	3.56	2.32, 5.44	<0.0001	3.42	2.08, 5.64	<0.0001
Other ^b	2.17	1.33, 3.52	0.0019	1.51	0.82, 2.80	0.1882
Child sex - female	0.81	0.60, 1.10	0.1774	0.80	0.57, 1.13	0.2044
Firstborn	1.36	1.00, 1.84	0.0502	1.29	0.90, 1.84	0.1609
Gestational smoking	1.65	1.07, 2.57	0.0252	1.32	0.72, 2.40	0.3687
Pre-pregnancy BMI	1.01	0.99, 1.03	0.5102	1.01	0.98, 1.04	0.6283
Caesarean section	-	-	-	1.00	0.66, 1.50	0.9880
Breastfeeding duration	-	-	-	0.98	0.95, 1.01	0.1446
Age solids introduced	-	-	-	1.04	0.96, 1.12	0.3601

Table VI. Results of Cox proportional hazard models examining the association between maternal history of asthma and child allergic rhinitis diagnosis. *a.* The reference category for the hazard ratios presented for child race/ethnicity was non-Hispanic white. The hazard ratios presented for pre-pregnancy BMI represent a one kg/m² increase in pre-pregnancy BMI. The hazard ratios presented for breastfeeding duration represent a one-unit increase in breastmilk-months. The hazard ratios presented for age solids were introduced represent a one-month increase in age when solid foods were introduced. *b.* Other race/ethnicity includes non-Hispanic Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, and multiracial

Our finding of an association between maternal history of asthma and risk of offspring asthma is similar to results from a systematic review.²⁰ Our

finding of an association between maternal history of asthma and offspring atopic dermatitis/eczema appears to be novel, as neither Tariq

Predictor ^a	Model 1 (N = 1260)			Model 2 (N = 970)		
	HR	95% CI	p-value	HR	95% CI	p-value
Maternal asthma	1.23	0.60, 2.48	0.5740	0.89	0.37, 2.18	0.8021
Child race/ethnicity						
Hispanic	1.05	0.50, 2.21	0.9012	1.37	0.57, 3.26	0.4806
Non-Hispanic black	1.67	0.75, 3.71	0.2089	2.02	0.74, 5.48	0.1696
Other ^b	1.41	0.59, 3.34	0.4379	1.47	0.53, 4.05	0.4567
Child sex - female	0.60	0.33, 1.08	0.0898	0.53	0.27, 1.06	0.0708
Firstborn	1.01	0.57, 1.81	0.9692	1.00	0.51, 1.96	0.9922
Gestational smoking	0.91	0.32, 2.58	0.8633	0.49	0.06, 3.66	0.4828
Pre-pregnancy BMI	1.00	0.95, 1.05	0.9674	1.00	0.95, 1.06	0.8846
Caesarean section	-	-	-	0.73	0.30, 1.79	0.4962
Breastfeeding duration	-	-	-	1.02	0.97, 1.08	0.4028
Age solids introduced	-	-	-	0.98	0.84, 1.16	0.8525

Table VII. Results of Cox proportional hazard models examining the association between maternal history of asthma and child food allergy diagnosis. *a.* The reference category for the hazard ratios presented for child race/ethnicity was non-Hispanic white. The hazard ratios presented for pre-pregnancy BMI represent a one kg/m² increase in pre-pregnancy BMI. The hazard ratios presented for breastfeeding duration represent a one-unit increase in breastmilk-months. The hazard ratios presented for age solids were introduced represent a one-month increase in age when solid foods were introduced. *b.* Other race/ethnicity includes non-Hispanic Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, and multiracial

et al³⁸ nor any of the 27 studies in the systematic review²⁰ reported an association between maternal asthma and childhood atopic dermatitis/eczema. It is unclear whether the association between maternal history of asthma and atopic dermatitis/eczema is due to genetic, environmental, and/or maternal dietary factors. The role of genetic factors is supported by a twin study, which showed that twins with asthma often have a twin with atopic dermatitis.³⁹ Environmental and dietary factors need further investigation to clarify the association between maternal asthma and offspring atopic dermatitis/eczema.⁴⁰

We expected that maternal history of asthma would confer an increased risk of offspring development of all allergic diseases; however, we did not find significant associations between maternal asthma and offspring allergic rhinitis or food allergy. A possible explanation as to why maternal asthma was not significantly associated with offspring allergic rhinitis could be that the heterogeneity involved in diagnosing allergic rhinitis⁴¹ may make it difficult to have a clear definition that truly captures allergic rhinitis diagnoses that represent atopic disease compared to diagnoses more representative of symptoms of the common cold. Due to the small number of food allergy diagnoses observed in our cohort, it is likely that a much larger sample size would be needed to detect a significant association between maternal asthma and offspring food allergy development. We confirmed the possibility of this explanation by performing a power analysis to compute the sample size required to detect a significant difference in development of food allergy between offspring with and without maternal history of asthma. Results indicated a sample size of approximately 2100–3500 would be needed to have 80–95% power to detect a significant effect size similar to what we observed in our study (HR = 1.23), which is larger than our analytic sample size of 1261. Maternal history of allergic rhinitis showed no association with sibling allergy outcomes and having both a maternal history of asthma and allergic rhinitis was associated with atopic dermatitis/eczema only. This may again reflect difficulty in diagnosis and capturing reported information on allergic rhinitis correctly.

We controlled for a number of covariates, including prenatal and early life factors, which have previously been associated with child allergy outcomes in some, but not all, studies. In our study, race/ethnicity was significantly associated with atopic dermatitis/eczema, asthma, wheeze, and allergic rhinitis, but not food allergy. Race/ethnicity has previously been shown to be associated with atopic dermatitis,²⁷ asthma,⁴² and food allergy.^{28,43} We found that longer duration of breastfeeding showed a protective association against child development of asthma and wheeze, but breastfeeding duration showed no association with child development of allergic rhinitis, atopic dermatitis/eczema, or food allergy. This provides additional data supportive of the guidelines of the American Academy of Pediatrics, which suggest that longer duration of breastfeeding may be protective against the development of asthma.⁴⁴ Having a Caesarian section and the age of introduction of solid foods were not significantly associated with any of the allergy outcomes. These factors have inconsistently been implicated in allergy development in the past.^{30,31,35}

We are also presenting novel data on the incidence of childhood allergy outcomes using electronic medical record data. We considered a doctor's diagnosis of allergic diseases, which are similar to the ISAAC questions (eg, "Has your child ever had a doctor's diagnosis of asthma?"), but in addition we were able to add the exact date of diagnosis. There are currently no data to address the sensitivity and specificity of this approach, however medical record data have been used in European cohort studies to report on asthma outcomes and to validate these methods of reporting.⁴⁵ There are limited studies or surveys from the United States using medical record data. Hill et al⁴⁶ used electronic medical record data in a patient population in Pennsylvania. They reported prevalence data in children between 3 and 5 years of age. Their estimated prevalence of asthma (19.4%) was higher than in our cohort (16.5%), similar for allergic rhinitis (13.7% vs 13.5% in our study) and lower for atopic dermatitis/eczema (7.7% vs 25.6% in our study). In the current study, the cumulative incidence of IgE-mediated food allergy (2.74% up to 5 years) was in line with studies using oral food challenges

from the United Kingdom (2.4% up to 3 years)⁴⁷ and Australia (3.8% at 4 years).³

A strength of our study is that the data come from following participants in a longitudinal pre-birth cohort, obtaining information prospectively. We did not have to rely on data from tertiary referral center patients, which may overrepresent allergic disease prevalence and severity. Other strengths of our study include utilizing available data from electronic medical records and the racially and ethnically diverse sample. Studies reporting on ethnic diverse populations, particularly in relation to food allergies are scarce.⁴⁸ Allergic diseases reduce quality of life and may lead to fatalities.¹ Prevention strategies are therefore urgently needed, but other than early introduction of food allergens to prevent specific food allergies,⁴⁹ have been unsuccessful. Our results increase our knowledge and understanding about the risk of allergy outcomes in children conferred by specific maternal allergic diseases. These findings will enable physicians to better counsel families with atopic disease and enable researchers to develop targeted prevention strategies.

We acknowledge some limitations of our study. We did not have data on maternal history of atopic dermatitis/eczema or food allergy, and could not investigate the associations between these potential risk factors and offspring allergies. We were also not able to separate mothers with a history of allergic asthma from those with non-allergic asthma. We did not perform specific IgE tests or skin prick test to confirm atopic status in the pregnant women or their offspring. We have only used sensitization information from the electronic medical record to confirm the food allergy diagnosis. We were unable to define the different clinical sub-types of wheeze and in our study cohort. Subsequent follow-up will allow us to better characterize early wheezes, transient wheezers, and those with late-onset wheeze.⁵⁰ We based all diagnoses on the reported terminology used in the electronic medical records and therefore depended on a valid diagnosis by the physician. In addition, we did not have any information on paternal or sibling history of allergic diseases. Further studies focusing on maternal diet and environmental exposures during pregnancy are needed. We need to better understand the

association between maternal history and risk of allergic and respiratory diseases in offspring.

The study provides novel findings regarding the associations between maternal history of asthma and maternal history of allergic rhinitis and the development of allergic diseases in the offspring. We found that maternal history of asthma was associated with increased offspring risk of asthma, wheeze, and atopic/dermatitis, but not food allergy or allergic rhinitis. Maternal history of allergic rhinitis, by contrast, was not significantly associated with offspring risk of any allergic outcomes. Maternal history of allergic rhinitis was not associated with offspring development of any of the allergic diseases examined. Having both a maternal history of asthma and allergic rhinitis was associated with atopic dermatitis/eczema only. Our findings will enable physicians to provide individualized information to families regarding risk of offspring development of allergic diseases. Furthermore, these data will allow those designing interventions to target families who are at highest risk for offspring development of allergic diseases.

ABBREVIATIONS

MRN, Medical record number; EoE, Eosinophilic esophagitis; FPIES, Food protein induced enterocolitis syndrome; CDC, Centers for Disease Control; NHANES, National Health and Nutrition Examination Survey.

Ethics

The Healthy Start study protocol was approved by the Colorado Multiple Institutional Review Board. Protocol # 09-0563 Version 25 02-16-2016.

Author contribution

We can confirm that: Each person given authorship meets all of the following criteria: (1) made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafted the article or reviewed it critically for important intellectual content; (3) given final approval of the version to be published; and (4) agrees to be accountable for all aspects of the work related to its accuracy or integrity.

Specifically, author contributions included

Carina Venter drafted the paper. Michaela Palumbo performed the data analysis and drafted the methods and results section, with Debra Glueck. Andrew Liu and Ivan

Yang provided guidance on the respiratory allergy data. David Fleischer provided guidance on the atopic dermatitis and food allergy data. Katherine Sauder and Dana Dabelea (PI of the Healthy Start study), provided data from the Healthy Start study and guided the epidemiology aspects of the project. All authors read the paper and contributed to interpretation of the data.

Submission declaration

This manuscript is original, has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

Consent for publication

All authors have reviewed and consented to publication of the work.

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The funders had no input in obtaining data, data analysis, or manuscript preparation.

Availability of data and materials

The study investigators have primary rights to data collected during the study. Data collected during the study will be made available to the research community through scientific publications and presentations at local, national and international conferences. Study investigators will entertain requests for access to the study data from qualified scientists for specific analyses. The procedures for data sharing ensure that: 1) confidential information is not disclosed; 2) data are released in a form that does not endanger national security or compromise law enforcement activities; and that 3) proprietary data are not released inadvertently.

Declaration of competing interest

Venter C provided educational material or reviewed educational materials for Abbott Laboratories, Danone, and Reckitt Benckiser. Fleischer D is a consultant to Aquestive, Aravax, Genentech, Nasus, AllerGenis, Intrimmune and DOTS Technology Corp. He has provided educational material for Nutricia. He has the following organizational declarations: DBV Technologies - Clinical Medical Advisory Board; Food Allergy & Anaphylaxis Connection Team - Medical Advisory Board; Food Allergy Research & Education -

Clinical Advisory Board; National Peanut Board - Allergy Education Advisory Council. Liu A.H. has received a grant from the National Institutes of Health, is a member of the Data Monitoring Committee for an asthma study for GSK, and has received payment for lectures from Merck. Yang I.V. is a consultant to Eleven P15, outside of the submitted work. The other authors declare no conflicts of interest.

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Appendix A Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.waojou.2021.100526>.

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