

The Influence of Asthma and/or Hay Fever on Pregnancy: Data from the 1995 National Survey of Family Growth



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What is already known about this topic? Asthma is associated with adverse pregnancy outcomes (spontaneous pregnancy loss, preterm birth, low-birth-weight infants).

What does this article add to our knowledge? Statistically significant increases in adverse pregnancy outcomes are observed in women with asthma only (without hay fever) in the 1995 National Survey of Family Growth. Women with asthma and hay fever or hay fever only, in contrast, do not have a statistically significant increase in adverse pregnancy outcomes.

How does this study impact current management guidelines? Although women with asthma and hay fever and hay fever only are observed to have healthy pregnancies, special precautions need to be taken in the care of pregnant women with asthma only.

BACKGROUND: Asthma is associated with adverse pregnancy outcomes. At the same time there is a worldwide increase in asthma and hay fever.

OBJECTIVE: This study addresses whether asthma and/or hay fever adversely influence pregnancy outcomes.

METHODS: Data from the 1995 National Survey of Family Growth that include a history of diagnosed asthma, hay fever, and adverse pregnancy outcomes in 10,847 women representative of the US population aged 15 to 44 years were analyzed.

RESULTS: Women with the allergic phenotypes asthma and hay fever and hay fever only had no significant increase in adverse pregnancy outcomes (spontaneous pregnancy loss, preterm birth, infant low birth weight), whereas women with the nonatopic phenotype asthma only (without hay fever) did. The study did not evaluate endotypes.

CONCLUSIONS: This study provides new data that the allergic phenotypes, asthma and hay fever and hay fever only, are compatible with healthy pregnancy, whereas the nonatopic asthma phenotype, asthma only, adversely impacts pregnancy. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1679-90)

Key words: Allergic rhinitis; Asthma; Spontaneous abortion; Preterm birth; Infant low birth weight; Allergy

Asthma causes adverse pregnancy outcomes, including spontaneous pregnancy loss, low birth weight,^{1,2} and preterm birth.^{3,4} Its prevalence has increased worldwide⁵⁻⁷ and is significantly higher in females.^{8,9} Overall asthma prevalence in the United States increased 12.3% from 2001 to 2009^{8,9} and ranges from 12% to 8%⁸ in women, dependent on their age (15-45 years).

Asthma and atopy are inversely associated with family size,¹⁰ raising the initial speculation that atopic disease may adversely influence fertility.¹¹ However, both atopic disease¹² and successful pregnancy^{13,14} are associated with a type 2 innate lymphoid/adaptive T_H2-cell cytokine profile, leading to the contrary speculation that the worldwide increase in the prevalence of allergic diseases may be due to atopic mothers being more fertile than nonatopic mothers.¹⁵

The speculation that atopy may be a factor in fertility led one of the authors (P.C.T.) to request inclusion of questions related to asthma and allergy in the 1995 National Survey of Family Growth (1995 NSFG) to explore the relationship of asthma/allergy phenotype to pregnancy outcomes.

METHODS

Data are drawn from the 1995 NSFG, the fifth in a series of periodic surveys of reproductive age women conducted by the National Center for Health Statistics.¹⁶ The 1995 NSFG is based on

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Abbreviations used

CRS- Chronic rhinosinusitis

ILC2- Type 2 innate lymphoid cell

OR- Odds ratio

1995 NSFG- 1995 National Survey of Family Growth

NHANES II or III- National Health and Nutrition

Examination Survey 1976-1980 or
1988-1994

PID- Pelvic inflammatory disease

VEGF- Vascular endothelial growth factor

cross-sectional multistage probability sampling of the civilian noninstitutionalized population of women who were aged 15 to 44 years on April 1, 1995, in the United States, yielding estimates that are representative of the national population of women in this age range.¹⁷ This is the only NSFG that included questions pertaining to allergy.

The 1995 NSFG is based on in-home interviews carried out between January 1995 and October 1995 with 10,847 women aged 15 to 44 years, of whom 1,553 are Hispanic, 6,483 non-Hispanic white, 2,446 non-Hispanic black, and the remaining 365 of other races and ethnic origins. For each pregnancy reported, information was obtained on several characteristics, such as date of outcome, gestational length, and birth weight; for pregnancies between January 1991 and the 1995 interview, women also were asked about pregnancy complications, prenatal care, and smoking during pregnancy.

Self-reported histories of asthma and hay fever diagnosis by a doctor or other medical care provider were operationalized as 4 mutually exclusive categories. These included neither asthma nor hay fever, asthma only, hay fever only, and both asthma and hay fever—using 3 dummy variables with neither hay fever nor asthma as the reference group. These categories are based on the differing associations of allergen skin test positivity using a conservative cutoff (mean erythema ≥ 10.5 mm) with asthma only, asthma and hay fever, and hay fever only observed in National Health and Nutrition Examination Survey 1976-1980 (NHANES II).¹⁸

Four indicators of adverse pregnancy outcome were considered. All adverse outcomes are based on pregnancies since January 1991 and the 1995 interview.

Pregnancy loss outcomes (woman-based)

A *spontaneous pregnancy loss* includes miscarriage, ectopic pregnancy, or stillbirth. An *early spontaneous pregnancy loss* includes only miscarriage or ectopic pregnancy. These outcomes were evaluated among the 3090 sample women who had at least 1 completed pregnancy during or after January 1991 and the 1995 interview that did not end in an induced abortion.

Live birth outcomes (pregnancy-based)

Low birth weight was defined as birth weight less than 2500 g or 5 lb 8 oz. *Preterm delivery* was defined as delivery before 37 weeks of gestation. The singleton live births from the NSFG interval data set were matched with the women (N = 2711) using the woman's ID number in the respondent data set for the analyses of low birth weight and preterm delivery. These outcomes were analyzed and limited to women's most recent singleton live births occurring in or after January 1991.

The adjusted odds of an adverse pregnancy outcome associated with a history of asthma or hay fever were estimated on the basis of

logistic regression. The logistic models for all outcomes controlled for age at pregnancy outcome, marital status, race and Hispanic origin, region of residence, high school graduation, history of diabetes, history of high blood pressure, cigarette smoking, and history of pelvic inflammatory disease (PID). Smoking was operationalized in 4 mutually exclusive categories, nonsmoker, former smoker, smokes less than 1 pack per day, smokes more than 1 pack per day, with nonsmoker as the reference group. Based on the relationship of body mass index to asthma¹⁹ and hay fever,²⁰ additional chi-square analyses compared the odds of asthma and hay fever among those who were underweight, overweight, and obese with the odds of the respective outcome among normal-weight individuals. Additional logistic models for all adverse pregnancy outcomes included body mass index as a covariate; if it was significant, it was added to the final model.

The possibility that smoking mediated any significant relationships between asthma and pregnancy loss was examined when both asthma and smoking were significant predictors of the pregnancy loss (in models without smoking and asthma) and asthma and smoking were correlated. Mediation was established on the basis of a reduction in the direct path between smoking and pregnancy loss, when smoking was added to a model that included all previously identified covariates except smoking.²¹ Because smoking increases the risk of asthma²² and is inversely associated with atopy,²³ but does not influence the number or size of positive allergen skin test results,¹⁸ a second set of analyses in women who never smoked provided an opportunity to evaluate the relationship between allergy and outcomes not confounded by smoking.

SPSS version 20 (IBM Corp, Armonk, NY) statistical software was used to compute accurate variances that account for the complex survey design of the NSFG. PANEL was included as the cluster variable, COL_STR as the strata variable, and POST_WT as the sampling weight in all analyses.

RESULTS

Among all women aged 15 to 44 years in 1995 NSFG, 5.5% were diagnosed with asthma only, 12.3% with hay fever only, and 5.0% with asthma and hay fever. The remaining 77.2% had neither condition.

Pregnancy loss outcomes (woman-based)

Frequencies of the pregnancy loss outcomes were estimated on the basis of complex sample design of the NSFG. An estimated 19.4% (representing a population of 3,073,565 women aged 15-44 years) experienced any spontaneous pregnancy loss, and 18.8% (2,969,342) experienced any early spontaneous pregnancy loss (Table I). The log odds of the multivariable complex samples logistic regression for the pregnancy loss outcomes are presented in Table II.

A history of asthma only is associated with 79% higher odds (adjusted odds ratio [OR], 1.79; $F_{1,186} = 5.89$; $P = .016$) of having any spontaneous pregnancy loss and an 84% higher odds (1.84; $F_{1,186} = 6.27$; $P = .013$) of any early spontaneous pregnancy loss compared with women with neither asthma nor hay fever after controlling for age at pregnancy outcome, marital status, race and Hispanic origin, region of residence, high school graduation, history of diabetes, history of high blood pressure, cigarette smoking, and PID (Table II). Asthma and hay fever (1.29; $F_{1,186} = 1.12$; $P = .29$) and hay fever only (1.13; $F_{1,186} = 0.57$; $P = .45$) are not significant independent predictors of any spontaneous pregnancy loss. Neither are asthma

TABLE I. Characteristics of the pregnancy loss sample women with at least 1 completed pregnancy in or after January 1991 not ending in an induced abortion (N = 3,090)

Variable	Mean	SD
Age (y)	22.6	5.3
Variable	N	%
Marital status		
Ever married	1,794	58.1
Never married	1,296	41.9
Race and Hispanic origin		
Hispanic	592	19.2
Non-Hispanic white	1,651	53.4
Non-Hispanic black	743	24.0
Non-Hispanic other	104	3.4
Having high school diploma or GED		
Yes	2,444	81.1
No	571	18.9
Geographic region of patient's residence		
Northeast	561	18.2
Midwest	758	24.5
South	1,039	33.6
West	732	23.7
History of diabetes		
Yes	36	1.2
No	3,054	98.8
History of high blood pressure		
Yes	202	6.5
No	2,888	93.5
Cigarette smoking		
Nonsmoker	1,845	59.7
Former smoker	446	14.4
Smoker: less than a pack (1-19 cigarettes) a day	541	17.5
Smoker: more than a pack (≥ 20 cigarettes) a day	257	8.3
PID		
Yes	265	8.6
No	2,826	91.4
Asthma and/or hay fever		
Neither	2,443	79.1
Asthma only	158	5.1
Hay fever only	360	11.7
Asthma and hay fever	129	4.2
Any spontaneous pregnancy loss		
Yes	560	18.1
No	2,530	81.9
Any early spontaneous pregnancy loss		
Yes	540	17.5
No	2,550	82.5

GED, General equivalency diploma.

TABLE II. Results of logistic regression evaluating the contribution of asthma, hay fever, and other predictors to pregnancy loss outcomes (woman-based) (N = 3,090)

Outcome	OR	95% CI for OR	
		Lower	Upper
Any spontaneous pregnancy loss			
(Intercept)	.065	.031	.135
Asthma only	1.793*	1.115	2.883
Hay fever only	1.133	.817	1.570
Asthma and hay fever	1.293	.801	2.086
Age	1.040*	1.016	1.064
Not married	2.699*	2.097	3.474
Hispanic	.704	.492	1.006
Non-Hispanic black	.655*	.476	.902
Non-Hispanic others	.850	.433	1.666
Region: Northeast	.768	.516	1.144
Region: Midwest	.898	.597	1.350
Region: South	1.024	.706	1.487
High school graduate	1.476*	1.071	2.034
Diabetes	1.912	.885	4.129
High blood pressure	1.066	.729	1.559
Former smoker	1.348	.986	1.843
Smoking <1 pack/d	1.284	.966	1.706
Smoking ≥1 pack/d	1.266	.839	1.909
PID	1.719*	1.209	2.444
Any early spontaneous pregnancy loss			
(Intercept)	.060	.028	.127
Asthma only	1.836*	1.138	2.963
Hay fever only	1.174	.844	1.632
Asthma and hay fever	1.152	.677	1.960
Age	1.042*	1.018	1.067
Not married	2.751*	2.131	3.553
Hispanic	.701	.486	1.010
Non-Hispanic black	.572*	.407	.804
Non-Hispanic others	.788	.396	1.569
Region: Northeast	.748	.498	1.122
Region: Midwest	.891	.590	1.347
Region: South	.984	.672	1.439
High school graduate	1.469*	1.063	2.029
Diabetes	2.071	.960	4.465
High blood pressure	1.015	.677	1.520
Former smoker	1.352	.985	1.856
Smoking <1 pack/d	1.284	.966	1.706
Smoking ≥1 pack/d	1.284	.842	1.958
PID	1.761*	1.232	2.516

Reference category is neither asthma nor hay fever, non-Hispanic white, West region, ever married, nonsmoker.

* $P < .05$.

and hay fever (1.15; $F_{1,186} = 0.28$; $P = .60$) and hay fever only (1.17; $F_{1,186} = 0.92$; $P = .34$) significant independent predictors of any early spontaneous pregnancy loss (Table II).

Other significant predictors of any spontaneous pregnancy loss (Table II) include age at pregnancy outcome (1.04; $F_{1,186} = 11.03$; $P = .001$), being unmarried (2.70; $F_{1,186} = 60.25$; $P < .001$), and being non-Hispanic black (0.66;

$F_{1,186} = 6.82$; $P = .01$) compared with non-Hispanic white, having graduated from high school (1.48; $F_{1,186} = 5.73$; $P = .018$), and PID (1.72; $F_{1,186} = 9.23$; $P = .003$). The same significant predictors are seen for any early spontaneous pregnancy loss (Table II).

Obese women in the pregnancy loss sample had significantly higher odds of asthma only (OR, 2.51; $P < .001$) compared with normal-weight women, whereas obese women with hay fever

TABLE III. Characteristics of the nonsmoker women in the pregnancy loss sample who had at least 1 completed pregnancy in or after January 1991 not ending in an induced abortion (N = 1,845)

Variable	Mean	SD
Age (y)	22.8	5.2
Variable	N	%
Marital status		
Ever married	1,115	60.4
Never married	730	39.6
Race and Hispanic origin		
Hispanic	433	23.5
Non-Hispanic white	806	43.7
Non-Hispanic black	524	28.4
Non-Hispanic others	82	4.4
Having high school diploma or GED		
Yes	1,492	80.9
No	304	16.5
Geographic region of patient's residence		
Northeast	306	16.6
Midwest	422	22.9
South	654	35.4
West	463	25.1
History of diabetes		
Yes	18	1.0
No	1,827	99.0
History of high blood pressure		
Yes	119	6.4
No	1,726	93.6
PID		
Yes	124	6.7
No	1,721	93.3
Asthma and/or hay fever		
Neither	1,495	81.0
Asthma only	78	4.2
Hay fever only	200	10.8
Asthma and hay fever	72	3.9
Any spontaneous pregnancy loss		
Yes	288	15.6
No	1,557	84.4
Any early spontaneous pregnancy loss		
Yes	277	15.0
No	1,568	85.0

GED, General equivalency diploma.

only (OR, 0.99; $P = .51$) or asthma and hay fever (OR, 1.18; $P = .34$) did not. Adjusting for body mass index made no difference in the risk of any of the adverse pregnancy outcomes with respect to women diagnosed with asthma only, hay fever only, or asthma and hay fever, except for overweight women who had a significantly lower risk of low-birth-weight babies (OR, 0.64; $P = .035$) compared with normal-weight women in the live birth sample, which did not affect the other predictors.

Smoking partially mediated the associations between asthma only and both spontaneous pregnancy loss and early pregnancy loss. Smoking predicted both spontaneous (1.299; $F_{1,186} = 4.12$; $P = .044$) and early spontaneous (1.33; $F_{1,186} = 4.167$; $P = .043$) pregnancy loss when all predictors except asthma

TABLE IV. Results of logistic regression of asthma, hay fever, and other predictors on nonsmoker pregnancy loss outcomes (woman-based) (N = 1,845)

Outcome	OR	95% CI for OR	
		Lower	Upper
Any spontaneous pregnancy loss			
(Intercept)	.048	.018	.126
Asthma only	1.092	.559	2.133
Hay fever only	.974	.610	1.556
Asthma and hay fever	.764	.368	1.589
Age	1.062*	1.029	1.095
Not married	2.808*	1.976	3.990
Hispanic	.691	.429	1.114
Non-Hispanic black	.705	.465	1.070
Non-Hispanic others	.774	.341	1.757
Region: Northeast	.638	.379	1.074
Region: Midwest	.936	.549	1.595
Region: South	.800	.509	1.257
High school graduate	2.247*	1.215	4.156
Diabetes	1.529	.401	5.824
High blood pressure	1.130	.680	1.878
PID	1.402	.804	2.445
Any early spontaneous pregnancy loss			
(Intercept)	.044	.016	.119
Asthma only	1.161	.594	2.272
Hay fever only	1.005	.630	1.604
Asthma and hay fever	.599	.245	1.463
Age	1.064*	1.031	1.099
Not married	2.804*	1.966	3.999
Hispanic	.719	.442	1.169
Non-Hispanic black	.620*	.404	.950
Non-Hispanic others	.797	.350	1.816
Region: Northeast	.637	.376	1.078
Region: Midwest	.948	.553	1.627
Region: South	.755	.472	1.209
High school graduate	2.603*	1.396	4.852
Diabetes	1.649	.434	6.262
High blood pressure	1.137	.670	1.931
PID	1.511	.862	2.647

Reference category is neither asthma nor hay fever, non-Hispanic white, West region, ever married, nonsmoker.

* $P < .05$.

variables were included in the model. The relationship of asthma to each outcome was reduced (3%) when smoking was added to the prediction models for each outcome.

Characteristics of the women nonsmokers in the pregnancy loss sample are presented in Table III. An estimated 16.4% (representing a population of 1,466,473 nonsmoker women aged 15–44 years) experienced any spontaneous pregnancy loss, and 15.7% (1,403,409) experienced any early spontaneous pregnancy loss. In contrast to the pregnancy loss sample that included smokers (Table II), there is no longer an association of asthma only with any spontaneous pregnancy loss (1.09; $F_{1,182} = 0.068$; $P = .80$) or early spontaneous pregnancy loss (1.16; $F_{1,182} = 0.194$; $P = .66$) (Table IV). In asthma and hay fever nonsmokers, there is no significant increase in any spontaneous (0.76; $F_{1,182} = 0.52$; $P = .47$) or any early spontaneous

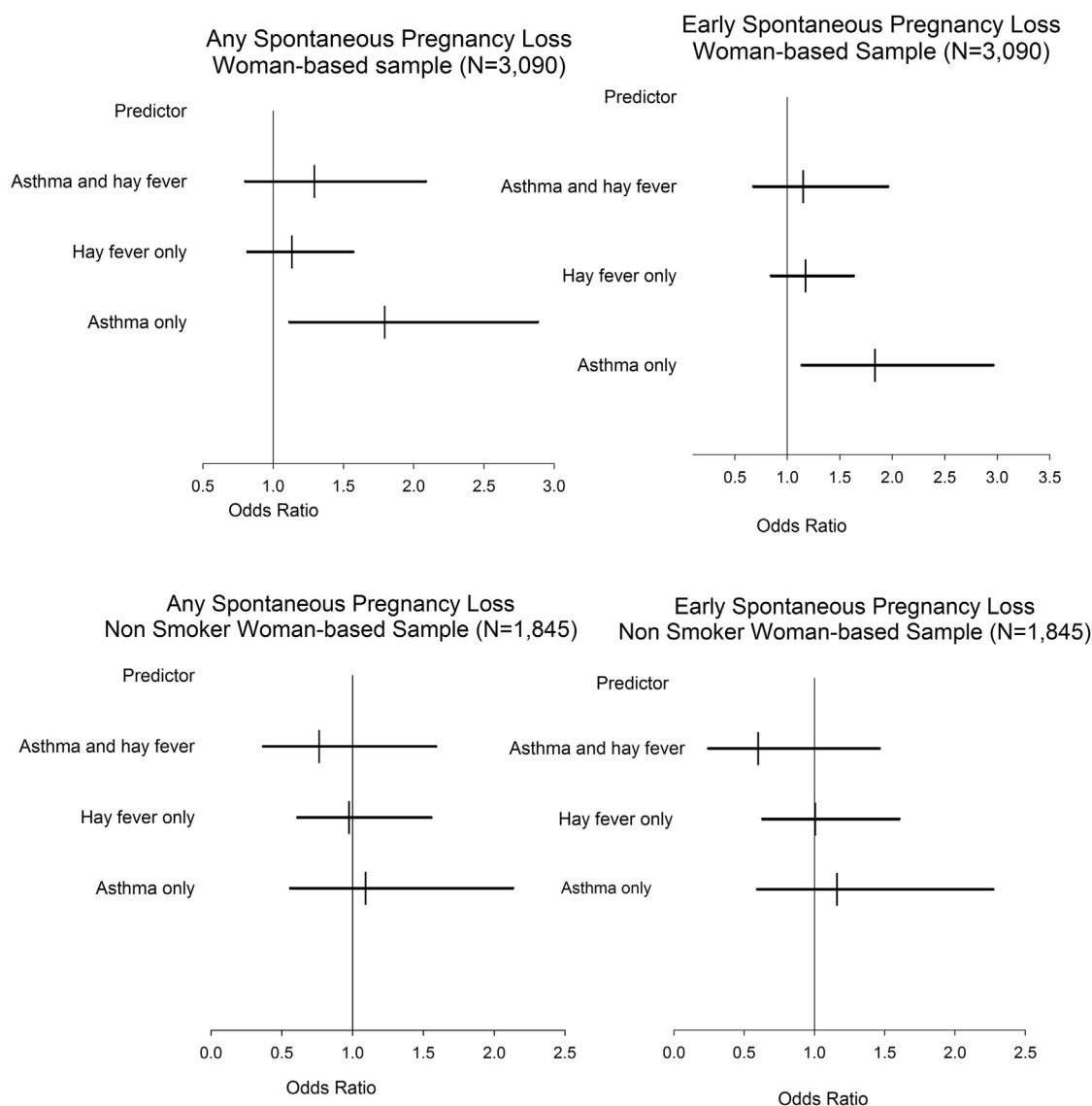


FIGURE 1. ORs with 95% CIs from logistic regression analyses evaluating the independent contributions of asthma and/or hay fever to pregnancy loss outcomes. Reference category was neither asthma nor hay fever. Additional covariates in each analysis are age at pregnancy outcome, marital status, race and Hispanic origin, region of residence, high school graduation, history of diabetes, high blood pressure, smoking, and PID.

pregnancy loss (0.60; $F_{1,182} = 1.282$; $P = .26$). Hay fever only nonsmokers also had no significant increased risk of any spontaneous pregnancy loss (0.97; $F_{1,182} = 0.12$; $P = .91$) or early spontaneous pregnancy loss (1.00; $F_{1,182} = 0.001$; $P = .98$) (Table IV), similar to the pregnancy loss sample that includes smokers (Table II).

Other significant predictors of any spontaneous pregnancy loss in nonsmokers (Table IV) are similar to the pregnancy loss sample that included smokers (Table II), in that age (1.06; $F_{1,182} = 14.487$; $P = .001$), being unmarried (2.81; $F_{1,182} = 33.598$; $P < .001$), and being a high school graduate (2.25; $F_{1,182} = 6.743$; $P = .010$) are significant, but differ in that being non-Hispanic black and PID are not significant predictors (Table IV). Other significant predictors of any early spontaneous pregnancy loss in nonsmokers (Table IV), that is, age, being unmarried, being non-Hispanic black, and being a high school

graduate, are similar to the pregnancy loss sample that included smokers (Table II), but differ in that PID is not a significant predictor (Table IV). ORs and 95% CI for the independent contributions of asthma and/or hay fever to pregnancy loss outcomes are presented in Figure 1.

Live birth outcomes (pregnancy-based)

Frequencies of the live birth outcomes were estimated on the basis of complex sample design of the NSFG. For the live birth sample that includes smokers (Table V), an estimated 9% (1,264,200) of most recent singleton live births resulted in preterm delivery (<37 weeks) and 5% (652,120) resulted in low-birth-weight babies (<2500 g). The log odds of the multivariable complex samples logistic regression for the live birth outcomes are presented in Table VI.

TABLE V. Characteristics of women who had most recent singleton live births occurring in or after January 1991 sampled for live birth outcomes (N = 2,711)

Variable	Mean	SD
Age at most recent singleton live birth (y)	27.1	5.8
Variable	N	%
Marital status		
Ever married	1,978	73.0
Never married	733	27.0
Race and Hispanic origin		
Hispanic	534	19.7
Non-Hispanic white	1,454	53.6
Non-Hispanic black	628	23.2
Non-Hispanic other	95	3.5
Having high school diploma or GED		
Yes	2,151	81.2
No	499	18.8
Geographic region of patient's residence		
Northeast	494	18.2
Midwest	663	24.5
South	925	34.1
West	629	23.2
History of diabetes		
Yes	29	1.1
No	2,682	98.9
History of high blood pressure		
Yes	165	6.1
No	2,546	93.9
Cigarette smoking		
Nonsmoker	1,655	61.0
Former smoker	392	14.5
Smoker: less than a pack (1-19 cigarettes) a day	450	16.6
Smoker: more than a pack (≥ 20 cigarettes) a day	213	7.9
PID		
Yes	218	8.0
No	2,493	92.0
Asthma and/or hay fever		
Neither	2,165	79.9
Asthma only	134	4.9
Hay fever only	307	11.3
Asthma and hay fever	104	3.8
Preterm delivery (<37 wk)		
Yes	266	9.8
No	2,445	90.2
Low birth weight (<2,500 g)		
Yes	156	5.8
No	2,555	94.2

GED, General equivalency diploma.

Asthma only is associated with a 94% higher odds (1.94; $F_{1,186} = 5.55$; $P = .019$) of preterm delivery (Table VI) compared with women with neither asthma nor hay fever after controlling for age at pregnancy outcome, marital status, race and Hispanic origin, region of residence, high school graduation, history of diabetes, history of high blood pressure, cigarette smoking, and PID. Asthma and hay fever (1.45; $F_{1,186} = 1.28$;

TABLE VI. Results of logistic regression evaluating the contribution of asthma, hay fever, and other predictors to most recent singleton live birth outcomes (pregnancy-based) (N = 2,711)

		95% CI for OR	
Outcome	OR	Lower	Upper
Preterm delivery (<37 wk)			
(Intercept)	.089	.037	.216
Asthma only	1.942*	1.114	3.386
Hay fever only	1.196	.765	1.869
Asthma and hay fever	1.454	.756	2.796
Age	.996	.968	1.026
Not married	1.276	.855	1.904
Hispanic	.847	.552	1.301
Non-Hispanic black	1.182	.752	1.856
Non-Hispanic others	.678	.288	1.596
High school graduate	.929	.630	1.369
Region: Northeast	1.008	.640	1.588
Region: Midwest	1.047	.705	1.555
Region: South	1.198	.818	1.753
Diabetes	3.024*	1.153	7.928
High blood pressure	2.012*	1.219	3.321
Former smoker	.983	.613	1.577
Smoking <1 pack/d	1.143	.761	1.715
Smoking ≥1 pack/d	1.132	.675	1.899
PID	.740	.413	1.326
Low birth weight (<2500 g)			
(Intercept)	.009	.002	.032
Asthma only	1.865	.865	4.023
Hay fever only	.877	.477	1.610
Asthma and hay fever	1.333	.482	3.684
Age	1.030	.993	1.069
Not married	1.131	.691	1.853
Hispanic	1.859*	1.063	3.252
Non-Hispanic black	2.588*	1.604	4.176
Non-Hispanic others	1.249	.370	4.221
High school graduate	.894	.528	1.513
Region: Northeast	1.675	.823	3.408
Region: Midwest	1.433	.712	2.886
Region: South	2.050*	1.108	3.793
Diabetes	2.339	.739	7.407
High blood pressure	2.033*	1.110	3.721
Former smoker	.630	.326	1.118
Smoking <1 pack/d	1.603	.972	2.645
Smoking ≥1 pack/d	2.286*	1.218	4.287
PID	.592	.259	1.351

Reference category is neither asthma nor hay fever, non-Hispanic white, West region, ever married, nonsmoker.

* $P < .05$.

$P = .260$) and hay fever only (1.20; $F_{1,186} = 0.63$; $P = .430$) are not significantly associated with preterm delivery.

Other significant predictors of preterm delivery (Table VI) include diabetes (3.02; $F_{1,186} = 5.13$; $P = .025$) and high blood pressure (2.0; $F_{1,186} = 7.59$; $P = .006$).

No significant association of asthma only, asthma and hay fever, or hay fever only is observed on the odds of low birth weight (Table VI) after controlling for age at pregnancy outcome, marital status, race and Hispanic origin, region of residence, high

TABLE VII. Characteristics of women nonsmokers with most recent singleton live births occurring in or after January 1991 (N = 1,655)

Variable	Mean	SD
Age at most recent singleton live birth (y)	26.8	5.8
Variable	N	%
Marital status		
Ever married	1,198	72.4
Never married	457	27.6
Race and Hispanic origin		
Hispanic	401	24.2
Non-Hispanic white	716	43.3
Non-Hispanic black	462	27.9
Non-Hispanic others	76	4.6
Having high school diploma or GED		
Yes	1,336	80.7
No	274	16.6
Geographic region of patient's residence		
Northeast	279	16.9
Midwest	375	22.7
South	594	35.9
West	407	24.6
History of diabetes		
Yes	16	1.0
No	1,639	99.0
History of high blood pressure		
Yes	100	6.0
No	1,555	94.0
PID		
Yes	110	6.6
No	1,545	93.4
Asthma and/or hay fever		
None	1,346	81.3
Asthma only	70	4.2
Hay fever only	177	10.7
Asthma and hay fever	62	3.7
Preterm delivery (<37 wk)		
Yes	157	9.5
No	1,498	90.5
Low birth weight (<2500 g)		
Yes	94	5.7
No	1,561	94.3

GED, General equivalency diploma.

school graduation, history of diabetes, history of high blood pressure, cigarette smoking, and PID.

Significant predictors of low birth weight (Table VI) include being Hispanic (1.86; $F_{1,186} = 4.79$; $P = .030$) and non-Hispanic black (2.59; $F_{1,186} = 15.38$; $P < .001$) compared with non-Hispanic white, living in the South (2.05; $F_{1,186} = 5.30$; $P = .022$), high blood pressure (2.03; $F_{1,186} = 5.35$; $P = .022$), and smoking 1 or more pack per day (2.29; $F_{1,186} = 6.72$; $P = .010$). The necessary criteria for mediation were not met for preterm delivery or low birth weight.

Characteristics of the live birth sample of women nonsmokers are presented in Table VII. An estimated 8.8% (704,662) of

TABLE VIII. Results of logistic regression evaluating the contribution of asthma, hay fever, and other predictors in women nonsmokers to their most recent singleton live birth outcomes (pregnancy-based) (N = 1,655)

Outcome	OR	95% CI for OR	
		Lower	Upper
Preterm delivery (<37 wk)			
(Intercept)	.087	.021	.354
Asthma only	2.264*	1.061	4.831
Hay fever only	1.403	.753	2.613
Asthma and hay fever	1.430	.582	3.516
Age	.989	.952	1.028
Not married	1.250	.678	2.305
Hispanic	.852	.515	1.409
Non-Hispanic black	.967	.559	1.672
Non-Hispanic others	.584	.199	1.717
High school graduate	1.268	.694	2.316
Region: Northeast	.911	.460	1.807
Region: Midwest	1.012	.609	1.682
Region: South	1.272	.776	2.084
Diabetes	3.808*	1.191	12.182
High blood pressure	1.743	.936	3.247
PID	.404	.136	1.195
Low birth weight (<2500 g)			
(Intercept)	.003	.000	.018
Asthma only	2.788*	1.334	5.827
Hay fever only	.637	.222	1.827
Asthma and hay fever	1.047	.231	4.742
Age	1.049*	1.003	1.097
Not married	1.353	.679	2.696
Hispanic	2.776*	1.405	5.484
Non-Hispanic black	3.015*	1.584	5.739
Non-Hispanic others	2.021	.553	7.383
High school graduate	1.257	.545	2.898
Region: Northeast	1.851	.724	4.733
Region: Midwest	2.448	.987	6.068
Region: South	2.297	.965	5.464
Diabetes	4.767*	1.325	17.147
High blood pressure	1.450	.695	3.029
PID	.648	.223	1.878

Reference category is neither asthma nor hay fever, non-Hispanic white, West region, ever married, nonsmoker.

* $P < .05$.

most recent singleton live births resulted in preterm delivery and 4.5% (363,281) resulted in low-birth-weight babies.

In the live birth sample of nonsmokers (Table VIII), women with asthma only have a significant 126% increase in the odds of preterm delivery (2.26; $F_{1,182} = 4.529$; $P = .035$), similar to the live birth sample that includes smokers (Table VI). In the live birth sample of nonsmokers, there is a 179% increase in the log odds of low birth weight in women with asthma only (2.79; $F_{1,182} = 7.535$; $P = .007$) (Table VIII). In comparison, there is no significant association of asthma only with pregnancies resulting in low-birth-weight babies in the sample that includes smokers (Table VI).

Diabetes is a significant predictor of preterm delivery in nonsmokers (Table VIII) (3.81; $F_{1,182} = 5.148$; $P = .024$), with

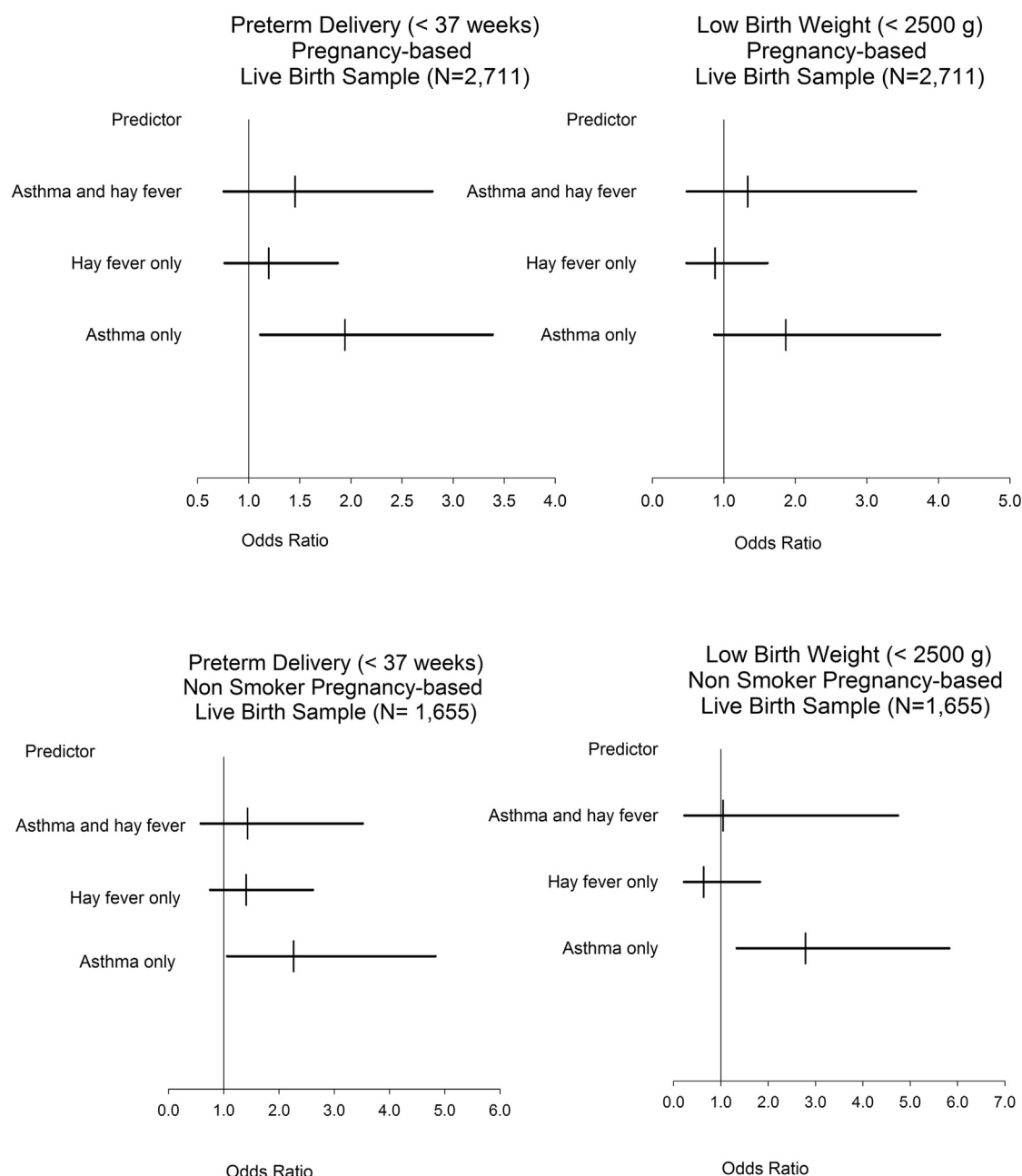


FIGURE 2. ORs with 95% CIs from logistic regression analysis evaluating the independent contributions of asthma and/or hay fever to most recent singleton live birth outcomes. Reference category was neither asthma nor hay fever. Additional covariates in each analysis are age at pregnancy outcome, marital status, race and Hispanic origin, region of residence, high school graduation, history of diabetes, high blood pressure, smoking, and PID.

odds similar to that seen in the sample that includes smokers (Table VI). High blood pressure in nonsmokers is not a significant predictor of preterm delivery (Table VIII), in contrast to the sample including smokers (Table VI). Other significant predictors of low birth weight in nonsmokers (Table VIII) are being Hispanic (2.78; $F_{1,182} = 8.751$; $P = .004$) and non-Hispanic black (3.02; $F_{1,182} = 11.439$; $P = .001$) compared with non-Hispanic white, similar to the predictors seen in the live birth sample that includes smokers (Table VI). Other significant predictors of low birth weight in nonsmokers

(Table VIII) are age (1.05; $F_{1,182} = 4.463$; $P = .036$) and diabetes (4.77; $F_{1,182} = 5.793$; $P = .017$), which differ from the live birth sample that includes smokers (Table VI). ORs and 95% CI for the independent contributions of asthma and/or hay fever to live birth outcomes are presented in Figure 2.

DISCUSSION

The 1995 NSFG overall asthma prevalence of 10.5% is within the range observed for women of reproductive age (15-45 years)

in 2001 to 2009 US population-based study.⁸ The overall US prevalence of asthma increased from 9.1% to 12.5% from 1997 to 2011.⁹ The 1995 NSFG hay fever prevalence of 17.3% falls within the 16.9% to 28.5% reported in general population surveys of Western Europe²⁴ and is similar to the prevalence reported in US adult women (18-85+ years) of 14.7% in NHANES 2005-2006.²⁰ The significantly increased odds (1.85; $P < .05$) of asthma in adult obese women compared with normal-weight women observed in NHANES 2001-2014¹⁹ are consistent with the significantly increased odds (2.51; $P < .001$) of asthma only in 1995 NSFG, but are not applicable to obese women with asthma and hay fever (1.18; $P = .34$) and obese women with hay fever only (0.99; $P = .51$). The lack of significantly increased odds of hay fever only in obese women in 1995 NSFG is consistent with NHANES 2005-2006, which also found no significant increase in hay fever in obese women.²⁰

Decreased risk of low-birth-weight babies in overweight mothers has been reported previously.²⁵ Age²⁶ and PID^{27,28} are previously reported to increase the risk of spontaneous pregnancy loss.²⁶ Other significant predictors of preterm delivery (Table V) include diabetes (3.02; $F_{1,186} = 5.13$; $P = .025$) and high blood pressure (2.0; $F_{1,186} = 7.59$; $P = .006$), which have previously been reported.²⁹ Smoking, being non-Hispanic black,³⁰ and hypertension are reported to increase the risk of low-birth-weight babies.³¹

The concern that asthma is associated with adverse pregnancy outcomes is the subject of reviews that show significantly increased risks of preterm delivery, low birth weight,^{2,32,33} and spontaneous pregnancy loss.¹ Data from the 1995 NSFG indicate that it is the phenotype asthma only that accounts for the adverse pregnancy outcomes in women of reproductive age and confirm that the previously reported risks for preterm delivery and spontaneous pregnancy loss are attributable to women with asthma only and the risk for low-birth-weight babies is attributable to asthma only in women nonsmokers.

The pathogenesis of the pregnancy loss associated with maternal asthma is attributed to various etiologies, including fetal hypoxia due to poorly controlled asthma, the adverse effects of asthma drugs, and hyperreactive uterine and bronchial smooth muscle.^{1,2,33-35}

A number of other studies report no adverse pregnancy outcomes associated with asthma³² and attribute the inconsistent association in part to differences in asthma severity and adequacy/inadequacy of asthma therapy.^{2,34} In the 1995 NSFG, it is women with the phenotype asthma and hay fever that account for the women with asthma who do not experience adverse pregnancy outcomes.

Differences in fertility are reported for women with allergy and/or asthma. Women diagnosed with asthma and hay fever or with hay fever only are significantly more fertile (live births per 1000 person-years) than women in the general population without diagnosed allergic diseases, whereas the fertility of women with asthma only is not significantly different from that of women in the general population.³⁶ Another study reports that women with a history of asthma are significantly less fertile (time to pregnancy >1 year) than healthy controls³⁷; however, the fertility of women with a history of allergy or allergy and asthma was not significantly different from that of healthy controls.³⁷ The 1995 NSFG finding that women with the phenotypes asthma and hay fever or hay fever only do not have significantly increased odds of adverse pregnancy outcomes is

consistent with these 2 studies. The 1995 NSFG finding that significantly increased adverse pregnancy outcomes impact women with the phenotype asthma only is consistent with the latter cited study.

The difference in pregnancy outcomes/fertility between women with a history of asthma only compared with women with asthma and hay fever or hay fever only may be due to their different associations with atopy, defined by allergen skin test reactivity. A significant positive association between hay fever and allergen skin test reactivity (number of positive skin test results) was observed in NHANES II to aeroallergens across all ages surveyed (12-74 years), regardless of smoking status, consistent with an atopic etiology.¹⁸ The association of asthma and hay fever with allergen skin test reactivity is significantly positive in each age group in nonsmokers.¹⁸ In contrast, a significant positive association between asthma/asthma only and allergen skin test positivity is observed in the age range of only 12 to 24 years,¹⁸ regardless of smoking status, consistent with the observation of significantly increased fertility of women with asthma in the age range 20 to 29.9 years compared with women without asthma.³⁶ If atopic asthma is defined as asthma and hay fever, then 48% of all women diagnosed with asthma in 1995 NSFG are atopic. In NHANES III, asthma attributed to atopy based on skin test reactivity to aeroallergens was 56%.³⁸

The lack of association of the phenotype asthma only with skin test positivity to aeroallergens in the age range 25 to 49 years observed in NHANES II¹⁸ indicates that the etiology of asthma only in older women is likely associated with nonatopic etiologies,^{39,40} for example, tobacco smoke, air pollution, viral infections, bacterial infections,⁴¹ and obesity.⁴²⁻⁴⁵ The nonatopic asthma phenotype is characterized by obese,^{42,45} older women with adult onset⁴⁰ who have more severe disease,^{40,46} poorly controlled asthma requiring hospital admission³⁵ during pregnancy, no IgE reactivity to allergens, or no type 2 helper T-cell adaptive immunity.⁴⁷ More severe asthma and exacerbation of asthma during pregnancy^{34,35} both increase the risk for adverse pregnancy outcomes.^{1,34} The phenotype atopic asthma, in contrast, comprises the mildest asthma severity categories,⁴⁶ has detectable IgE and/or skin test positivity to commonly inhaled/ingested allergens,⁴⁷ and does not increase the risk of asthma exacerbations during pregnancy.³⁵

Smoking significantly increases the odds (2.25; $P < .01$) of asthma only in the US population.²² Smoking neither influences the percentage of positive allergen skin test results nor the size of the cutaneous allergic responses to aeroallergens.¹⁸ This indicates that smoking is an important nonatopic etiology of the phenotype asthma only, especially in women of reproductive age.^{48,49} Smoking has been reported to be an adverse risk factor for fertility and spontaneous pregnancy loss.^{50,51}

Cigarette smoke activates innate immune cells, either directly via pattern recognition receptors on epithelial cells, macrophages, and dendritic cells, or indirectly via toxic/apoptotic⁵² release of normally endogenous-specific molecules, termed damage-associated molecular patterns, from smoke-damaged airway cells resulting in release of proinflammatory cytokines.⁵³ Cigarette smoke increases neutrophils, macrophages, IL-6, and TGF- β , influencing both local and distal T-cell subpopulations (Tc17/T_H17).⁵² TGF- β is increased in nonatopic asthma.⁵⁴

After controlling for smoking, women with asthma only had significantly increased risk of spontaneous pregnancy loss (Table II) and preterm delivery (Table VI). Smoking was an

independent predictor of low birth weight, but asthma only was not (Table VI). Nonsmoking women with asthma only, while not having an increased risk of spontaneous pregnancy loss (Table IV), do have increased risk of low-birth-weight babies and preterm delivery (Table VIII).

The immunologic response in successful human pregnancy underlying maternal tolerance to the semi-allogeneic fetus¹⁴/foreign fetal antigens⁵⁵ is immune deviation to type 2 innate lymphoid cell (ILC2)/T_H2 cytokine profile^{13,56} and T_H17/T_H2 profile.⁵⁷ Decidualization of the stromal compartment of the endometrium to permit implantation of the semiallogeneic blastocyst in normal pregnancy is dependent on IL-33.⁵⁸ IL-33 is a crucial regulator of innate and adaptive type 2 immune responses^{59,60} and plays a major role in asthma and allergic rhinitis.^{12,56,61,62}

The immunological basis of atopy/atopic asthma also involves immune deviation to an ILC2/T_H2 cytokine profile,^{60,63,64} eliciting allergic immune responses in mild to moderate asthma.⁶⁵ More severe asthma is often nonatopic and elicited following exposure to viruses, cigarette smoke, and diesel exhaust particles that elicit T_H17/T_H1 cytokines.⁶⁵ Nonatopic asthma associated with obesity is associated with IL-17–producing ILC3s.⁴⁴ ILC3s are increased in preeclampsia and chronic diabetes and may pose risk for the developing fetus.⁶⁶ Obesity and diabetes are controlled for in the 1995 NSFG analyses of adverse pregnancy outcomes in women with asthma and/or hay fever.

Immune deviation from a type 2 cytokine profile has deleterious effects on pregnancy.^{15,67} Spontaneous abortion is associated with a shift to a T_H1 profile.^{68,69} Upregulation of T_H17 and decreased levels of regulatory T cells and IL-33 are associated with recurrent spontaneous abortion,^{58,70} whereas T_H17 or T_H17/T_H1 predominance is found in spontaneous abortion⁵⁷ and, when paired with decreased regulatory T cells, in preeclampsia.⁷⁰ Low levels of T_H17 cells/transcription factors are found in normal pregnancy,⁷⁰ whereas higher T_H17 tissue density is associated with preterm birth.⁷¹ Exposure to cigarette smoke, preterm birth, intrauterine growth restriction, and preeclampsia are associated with a predominance of T_H1 reactivity in the mother,⁷² often in response to viral/bacterial infection during pregnancy.⁷³

Deviation from a type 2 immune response in pregnancy provides an explanation for the adverse pregnancy outcomes in women with the nonatopic phenotype “asthma only.” Immune deviation to a type 2 response associated with the hay fever only or asthma and hay fever phenotypes is compatible with healthy pregnancy.

Immune deviation to T_H1 cytokines/interferon associated with viral⁷⁴ respiratory infections in nonatopic individuals is different from the immune deviation to a type 2 cytokine profile seen in mild to moderate atopic asthmatic patients infected by rhinovirus due to upregulation of IL-25.^{75,76} In normal pregnancy, decidual stromal cells have higher IL-25 levels than do decidual stromal cells from spontaneous abortion.⁷⁷ The higher IL-25 levels associated with rhinovirus infection may explain, in part, the lack of adverse pregnancy outcomes in women with asthma and hay fever, as rhinovirus accounts for nearly 50% of asthma exacerbations in adults.^{78,79}

The type 2 cytokine profile in response to aeroallergens responsible for hay fever and allergic asthma^{59,61} is directed against proteins from reproductive structures, such as pollens and mold spores^{80,81} and other allergens that are homologous with

reproductive proteins, for example, chain 1 of the major allergen of cat, Fel d 1, a secretoglobulin, homologous with uteroglobin,^{82,83} a human reproductive protein.

Women with chronic rhinosinusitis (CRS) with nasal polyps have more asthma⁸⁴ with downregulation of regulatory T cells and increased T_H17 in nasal polyps.⁸⁵ CRS without nasal polyps is increased in females^{84,86} and is associated with microbial infection.⁸⁷ Although CRS has nearly twice the prevalence of allergic rhinitis and is significantly increased by smoking,²² neither chronic rhinitis^{18,80} nor sinusitis⁸⁰ is significantly associated with allergen skin test positivity.

Allergic rhinitis, in contrast to nonallergic CRS, has increased levels of vascular endothelial growth factor (VEGF) in nasal secretions.⁸⁸ VEGF is increased in nasal lavage fluid of subjects with asthma and hay fever⁸⁹ and in skin-test-positive/allergic asthmatic patients following upper respiratory tract infection.⁹⁰ VEGF in endometrial secretions is significantly lower in women with nonatopic asthma versus atopic asthmatic women and controls.^{37,91} Low expression of VEGF is associated with recurrent spontaneous abortion.^{37,92}

The 1995 NSFG data sharpen the focus on the asthma phenotype of concern for adverse pregnancy outcomes to women with asthma only, highlighting their nonatopic etiologies and the consequent type 1 innate lymphoid cell/T_H1 immunologic response as likely contributors to impaired pregnancy outcomes. In contrast, the 1995 NSFG data point to lack of adverse pregnancy outcomes in women with the allergic phenotypes asthma and hay fever or hay fever only, highlighting their aeroallergen etiologies and consequent ILC2/T_H2 immune response as compatible with normal pregnancy and a new understanding of the role of the allergic response in health. Limitations of the 1995 NSFG include self-reports of provider-diagnosed medical conditions subject to recall bias rather than concurrent medical evaluation or review of medical records to establish atopic phenotype. Neither did it include the therapeutic interventions used to treat asthma and/or hay fever, nor their adequacy to control symptoms. The 1995 NSFG did not obtain laboratory samples/biomarkers precluding endotype assessment. Although prior or subsequent NSFGs have not included questions pertinent to asthma and hay fever, the prevalence of asthma and hay fever and the other risk factors associated with adverse pregnancy outcomes observed are consistent with the published literature cited subsequent to the 1995 NSFG.

Because of the worldwide increase in asthma and allergic disease, the potential impact of atopy on pregnancy needs to be understood. Future studies designed to address this question will require better phenotypic characterization of asthma,⁹³ better characterization of the concomitant upper airway diseases⁹⁴ associated with asthma, as well as the immune response to important aeroallergens, the immune response to infectious agents/pollutants associated with asthma, and their consequent influence on pregnancy outcomes. Interventions directed at ameliorating the allergic response that depend on immune deviation from an ILC2/T_H2 will need to consider their impact on pregnancy.

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