METHODS

Subject recruitment

From March 2009 to June 2010, children in San Juan, Puerto Rico, were chosen from randomly selected households to participate in a study of genetics, environmental/lifestyle exposures, and asthma. As previously described,[E1,E2] households in the metropolitan area of San Juan were selected by using a multistage probability sampling design. Primary sampling units were randomly selected neighborhood clusters based on the 2000 US Census, and secondary sampling units were randomly selected households within each primary sampling unit. A household was eligible if 1 or more residents were children age 6 to 14 years. In households with more than 1 eligible child, only 1 child was randomly selected for screening. On the basis of the sampling design, 7073 households were selected, and 6401 (approximately 91%) were contacted. Of these 6401 households, 1111 had 1 or more children within the age range of the study who met other inclusion criteria (see below). In an effort to reach a target sample size of approximately 700 children (which would give us >90% power to detect an OR of ≥2 for exposures with a prevalence of ≥25%), we attempted to enroll a random sample (n = 783) of these 1111 children. Parents of 105 of these 783 eligible households refused to participate or could not be reached. There were no significant differences in age, sex, or area of residence between eligible children who did (n = 678 [86.6%]) and did not (n = 105 [13.4%]) agree to participate. We selected as cases children who had physician-diagnosed asthma and wheeze in the previous year (n = 351). We selected as control subjects children who had neither physician-diagnosed asthma nor wheeze in the prior year (n = 327). All study participants had to have 4 Puerto Rican grandparents to ensure that they were of Puerto Rican descent.

Study procedures

Study participants completed a protocol that included administration of questionnaires, spirometry, and collection of blood samples (for measurement of serum total and allergen-specific IgE levels). One of the child's parents (usually [for approximately 93% of subjects] the mother) completed a questionnaire that was slightly modified from one used in the Collaborative Study of the Genetics of Asthma.[E3] This questionnaire was used to obtain information about the child's general and respiratory health (including a history of low birth weight and prematurity or prematurity requiring NICU admission); sociodemographic characteristics; family history of asthma, allergic rhinitis, or eczema; current exposure to ETS; and early-life exposure to ETS (*in utero* or before 2 years of age).

Height and weight were measured to the nearest centimeter and pound, respectively. Spirometry was conducted with an EasyOne spirometer (NDD Medical Technologies). All participants had to be free of respiratory illnesses for 4 or more weeks, and they were also instructed to avoid (when possible) the use of inhaled short- and long-acting bronchodilators for 4 or more and 12 or more hours before testing, respectively. Forced expiratory maneuvers were judged to be acceptable if they met or exceeded American Thoracic Society criteria modified for children.[E4] The best FEV_1 and FVC values were selected for data analyses. Serum levels of total IgE and IgE specific to common allergens (dust mite [Der p 1], cockroach [Bla g 2], cat dander [Fel d 1], dog dander [Can f 1], and mouse urinary protein [Mus m 1]) were determined by using the UniCAP 100 system (Pharmacia & Upjohn). For each allergen, an IgE level of 0.35 IU/mL or greater was considered positive.

Written parental consent was obtained for participating children, from whom written assent was also obtained. The study was approved by the Institutional Review Boards of the University of Puerto Rico (San Juan, Puerto Rico), Brigham & Women's Hospital (Boston, Mass), and the University of Pittsburgh (Pittsburgh, Pa).

Statistical analysis

For our primary analysis, prematurity was treated as a binary variable based on parental response to the following question: "Was your child born prematurely?" For our secondary analysis, prematurity requiring NICU admission was treated as a binary variable based on a positive response to the question on prematurity, as well as the following question: "Was your child kept in a neonatal intensive care unit?" Our outcome of interest was asthma (defined as physician-diagnosed asthma and wheeze in the previous year).

For each continuous variable, to compare 2 groups, we used 2-sample *t* tests. For the comparison of each binary variable between 2 groups, we used Fisher exact tests. For multivariate analyses, we used a stepwise approach to build logistic regression models. Because of their well-established association with prematurity, asthma, or both, all models included age,[E5] sex,[E6] household income (<$15,000/y vs ≥$15,000/y [near the median income for households in Puerto Rico in 2008-2009]),[E7-E9] maternal history of asthma, and early-life exposure to ETS.[E10] The following covariates were also included in the initial multivariate models if they were associated with asthma at a *P* value of .20 or less in bivariate analyses: body mass index as a *z* score (based on 2000 Centers for Disease Control and Prevention growth charts),[E11,E12] low birth weight (<2500 g), mode of delivery (cesarean vs vaginal birth), total IgE (transformed to a logarithmic [log_{10}] scale), atopy (≥1 positive allergen-specific IgE level), current exposure to ETS, parental education (≥1 parent completed high school vs none), type of health insurance (private or employer-based health insurance vs others), maternal history of 1 or more atopic diseases (asthma, allergic rhinitis, or eczema), and measures of lung function (FEV_1 and FEV_1/FVC ratio). These additional covariates remained in the final models if they were associated with asthma at a *P* value of less than .05 or if they changed the parameter estimate (β) by 10% or greater. After the final models were built, we tested for first-order interactions between prematurity or prematurity requiring NICU admission and the other covariates in the models. We assessed the overall goodness of fit of each model using the Hosmer-Lemeshow test.

As a confirmatory step, we repeated the analysis of prematurity and asthma after matching cases and control subjects through propensity scoring. To this end, we first estimated the propensity score using the following covariates: age, sex, household income, and early-life exposure to ETS. We then randomly sorted the data set and matched cases and control subjects on the basis of the logit of their propensity score and within a prespecified caliper distance using a one-to-one matching algorithm with no replacement.[E13,E14] The caliper distance selected was 0.2 of the pooled SD of the logit of the propensity score because this has been shown to eliminate most of the bias caused by the measured confounders.[E14] Next, we assessed whether the matching had been adequately conducted by comparing descriptive statistics between groups before and after matching. Lastly, we examined the relation between prematurity and asthma in the matched sample using statistical techniques that take into account the paired nature of the sample (ie, paired *t* tests and McNemar tests for unadjusted analysis and conditional logistic regression for adjusted analysis).[E15]

Statistical significance was defined as a *P* value of less than .05. All statistical analyses were performed with SAS version 9.3 software (SAS Institute).

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TABLE E1. Baseline characteristics of participating children according to case-control status and prematurity requiring admission to the NICU*†

	Control subjects		Cases		All	
	Prematurity requiring NICU admission		Prematurity requiring NICU admission		Prematurity requiring NICU admission	
Covariate	**No (n = 317)**	**Yes (n = 6)**	**No (n = 328)**	**Yes (n = 21)**	**No (n = 645)**	**Yes (n = 27)**
Age (y)	10.5 (2.7)	8.8 (3.2)	10.0 (2.6)	9.9 (2.0)	10.3 (2.7)	9.7 (2.3)
Female sex	162 (51.1%)	4 (66.7%)	140 (42.7%)	10 (47.6%)	302 (46.8%)	14 (51.9%)
Body mass index (*z* score)	0.5 (1.1)	−0.34 (1.2)	0.7 (1.2)	1.0 (1.2)	0.6 (1.1)	0.6 (1.3)
Total IgE (IU/mL)§	151.4 (4.7)	173.8 (3.8)	288.4 (4.8)	323.6 (4.2)	208.9 (4.9)	275.4 (4.1)
Atopy (≥1 positive allergen-specific IgE)	139 (50.2%)	2 (33.3%)	194 (67.8%)	14 (82.4%)	333 (59.2%)	16 (69.6%)
Current exposure to ETS	110 (34.7%)	2 (33.3%)	142 (43.3%)	12 (57.1%)	252 (39.1%)	14 (51.9%)
Exposure to ETS *in utero* or before age 2 y	127 (40.1%)	3 (50.0%)	162 (49.4%)	11 (52.4%)	289 (44.8%)	14 (51.9%)
Household income <$15,000/y	189 (62.6%)	5 (83.3%)	210 (65.2%)	14 (70.0%)	399 (63.9%)	19 (73.1%)
No parent graduated from high school	61 (19.2%)	2 (33.3%)	57 (17.4%)	6 (28.6%)	118 (18.3%)	8 (29.6%)
No private or employer-based health insurance	198 (62.5%)	4 (66.7%)	222 (67.7%)	16 (76.2%)	420 (65.1%)	20 (74.1%)
Maternal history of asthma	65 (20.7%)	2 (33.3%)	162 (49.5%)	8 (40.0%)	227 (35.4%)	10 (38.5%)
Maternal history of asthma, allergic rhinitis, or eczema	84 (26.8%)	2 (33.3%)	179 (55.1%)	9 (45.0%)	263 (41.2%)	11 (42.3%)
Low birth weight (<2500 g)	12 (3.9%)	2 (33.3%)‡	7 (2.2%)	11 (52.4%)‡	19 (3.0%)	13 (48.2%)‡
Birth by cesarean section	106 (33.7%)	2 (33.3%)	120 (36.7%)	10 (47.6%)	226 (35.2%)	12 (44.4%)
FEV_1 (L)‖	2.1 (0.7)	1.6 (0.8)	1.9 (0.7)	2.1 (0.4)	2.0 (0.1)	1.9 (0.6)
FEV_1/FVC ratio	0.8 (0.1)	0.9 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)

*Data are presented as numbers (percentages) for binary variables or means (SDs) for continuous variables.

†Percentages were calculated for children with complete data. For example, 592 (287 control subjects and 305 cases) of the 678 participating children had allergen-specific IgE.

‡$P < .05$ for the comparison between groups (performed by using 2-sample *t* tests or Fisher exact tests, as appropriate).

§Total IgE transformed to a logarithmic (log_{10}) scale. Results are shown as geometric means (SDs).

‖FEV_1 values are presented as absolute values because of lack of predicted values for Puerto Rican subjects.

TABLE E2. Comparison of cases and control subjects that were and were not included in the multivariate analysis of prematurity and asthma*†

	Control subjects		Cases	
	Included in analyses		Included in analyses	
Covariate	**No (n = 40)**	**Yes (n = 287)**	**No (n = 46)**	**Yes (n = 305)**
Age (y)	10.1 (2.7)	10.5 (2.7)	9.9 (2.5)	10.1 (2.6)
Female sex	19 (47.5%)	149 (51.9%)	22 (47.8%)	128 (42.0%)
Body mass index (*z* score)	0.8 (1.2)	0.5 (1.1)	0.6 (1.4)	0.7 (1.2)
Exposure to ETS *in utero* or before age 2 y	12 (30.0%)	119 (41.6%)	21 (45.7%)	153 (50.2%)
Current exposure to ETS	9 (22.5%)	104 (36.2%)	16 (34.8%)	139 (45.6%)
Household income <$15,000/y	17 (44.7%)	179 (65.3%)‡	22 (47.8%)	203 (68.1%)‡
No parent graduated from high school	4 (10.0%)	60 (20.9%)	5 (10.9%)	58 (19.0%)
No private or employer-based health insurance	18 (45.0%)	187 (65.2%)‡	27 (58.7%)	212 (69.5%)
Maternal history of asthma	7 (18.0%)	60 (21.2%)	20 (43.5%)	152 (50.2%)
Maternal history of asthma, allergic rhinitis, or eczema	11 (28.2%)	75 (26.5%)	21 (45.7%)	169 (56.2%)
Low birth weight (<2500 g)	0	14 (5.1%)	3 (6.7%)	15 (4.9%)
Birth by cesarean section	18 (45.0%)	90 (31.8%)	15 (33.3%)	116 (38.0%)
Prematurity	0	15 (5.3%)	4 (8.7%)	27 (8.9%)
Prematurity requiring NICU admission	0	6 (2.1%)	4 (8.7%)	17 (5.6%)
FEV_1 (L)§	1.9 (0.7)	2.1 (0.7)	1.9 (0.8)	1.9 (0.7)
FEV_1/FVC ratio	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)

*Data are presented as numbers (percentages) for binary variables or means (SDs) for continuous variables.
†Percentages were calculated with children with complete data.
‡$P < .05$ for comparison between groups (performed by using 2-sample *t* tests or Fisher exact tests, as appropriate).
§FEV_1 values are presented as absolute values because of lack of predicted values for Puerto Rican subjects.

TABLE E3. Multivariate analysis of prematurity and asthma in participating children after stratification by atopy (≥1 positive allergen-specific IgE) and using alternate measures of socioeconomic status*†‡

Covariate	OR (95% CI)	
	Nonatopic children (n = 239)	Atopic children (n = 353)
Type of health insurance‡		
Prematurity	0.5 (0.1-1.6), $P = .2$	4.8 (1.6-14.7), $P = .006$
No private or employer-based health insurance	1.4 (0.7-2.7), $P = .4$	1.1 (0.7-1.9), $P = .6$
Parental education‡		
Prematurity	0.5 (0.1-1.7), $P = .3$	4.9 (1.6-15.2), $P = .005$
No parent graduated from high school	0.8 (0.4-1.6), $P = .5$	1.0 (0.5-1.7), $P = .8$

*Allergen-specific IgE levels were available for 592 (287 control subjects and 305 cases) of the 678 participating children.
†Asthma was defined as physician-diagnosed asthma and wheeze in the previous year.
‡Multivariate logistic regression models were adjusted for age, sex, maternal history of asthma, and exposure to ETS *in utero* or before 2 years of age in addition to the covariates listed in the first column.

TABLE E4. Multivariate analysis of prematurity and asthma in participating children after stratification by atopy (≥1 positive allergen-specific IgE), replacing maternal history of asthma with maternal history of atopic disease*†‡

Covariate	OR (95% CI)	
	Nonatopic children (n = 239)	Atopic children (n = 353)
Prematurity	0.4 (0.1-1.5), $P = .2$	4.9 (1.6-15.2), $P = .01$
Maternal history of asthma, allergic rhinitis, or eczema	3.9 (2.1-7.1), $P < .001$	3.7 (2.3-6.1), $P < .001$

*Allergen-specific IgE levels were available for 592 (287 control subjects and 305 cases) of the 678 participating children.
†Asthma was defined as physician-diagnosed asthma and wheeze in the previous year.
‡Multivariate logistic regression models were adjusted for age, sex, household income, and exposure to ETS *in utero* or before 2 years of age in addition to the covariates listed in the first column.

TABLE E5. Multivariate analysis of prematurity and asthma after stratification by atopy (≥1 allergen specific IgE) and additional adjustment for low birth weight or lung function measures*†

Covariate	OR (95% CI)	
	Nonatopic children (n = 239)	Atopic children (n = 353)
Original multivariate model + low birth weight‡§		
Prematurity	0.5 (0.1-2.0), $P = .3$	4.5 (1.2-16.2), $P = .02$
Low birth weight (<2500 g)	0.3 (0.1-1.8), $P = .2$	1.1 (0.3-4.1), $P = .9$
Original multivariate model + prebronchodilator FEV_1‡§		
Prematurity	0.4 (0.1-1.9), $P = .2$	4.2 (1.3-13.1), $P < .001$
FEV_1 (L)	0.3 (0.1-0.8), $P = .02$	0.4 (0.2-0.9), $P = .02$
Original multivariate model + prebronchodilator FEV_1/FVC ratio‡§		
Prematurity	0.3 (0.1-1.7), $P = .2$	4.4 (1.4-13.6), $P = .01$
FEV_1/FVC ratio	0.02 (<0.001-0.7), $P = .03$	0.04 (0.002-0.8), $P = .03$

*Allergen-specific IgE levels were available for 592 (287 control subjects and 305 cases) of the 678 participating children.
†Asthma was defined as physician-diagnosed asthma and wheeze in the previous year.
‡Original multivariate model presented in Fig 1.
§Multivariate logistic regression models were adjusted for age, sex, household income, maternal history of asthma, and exposure to ETS *in utero* or before 2 years of age in addition to the covariates listed in the first column. The model for FEV_1 was additionally adjusted for height.

TABLE E6. Multivariate analysis of prematurity and asthma after stratification by atopy (≥1 positive allergen-specific IgE) in a matched sample of cases and control subjects (n = 594)*†‡

Covariate	Nonatopic children (n = 213)	Atopic children (n = 308)
Prematurity	1.0 (0.1-16.0), $P = 1.0$	3.3 (1.0-11.3), $P = .06$
Maternal history of asthma	3.2 (1.2-8.7), $P = .02$	4.0 (1.7-9.5), $P = .001$

*Cases and control subjects were matched by using a one-to-one propensity score matching algorithm. Please see the text for details.
†Asthma was defined as physician-diagnosed asthma and wheeze in the previous year.
‡Results from conditional logistic regression in the matched sample.