The effect of parental allergy on childhood allergic diseases depends on the sex of the child

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Background: The parent-of-origin effect is important in understanding the genetic basis of childhood allergic diseases and improving our ability to identify high-risk children.
Objective: We sought to investigate the parent-of-origin effect in childhood allergic diseases.
Methods: The Isle of Wight Birth Cohort (n = 1456) has been examined at 1, 2, 4, 10, and 18 years of age. Information on the prevalence of asthma, eczema, rhinitis, and environmental factors was obtained by using validated questionnaires. Skin prick tests were carried out at ages 4, 10, and 18 years, and total IgE measurement was carried out at 10 and 18 years. Parental history of allergic disease was assessed soon after the birth of the child, when maternal IgE levels were also measured. Prevalence ratios (PRs) and their 95% CIs were estimated, applying log-linear models adjusted for confounding variables.
Results: When stratified for sex of the child, maternal asthma was associated with asthma in girls (PR, 1.91; 95% CI, 1.34-2.72; $P = .0003$) but not in boys (PR, 1.29; 95% CI, 0.85-1.96; $P = .23$), whereas paternal asthma was associated with asthma in boys (PR, 1.99; 95% CI, 1.42-2.79; $P < .0001$) but not in girls (PR, 1.03; 95% CI, 0.59-1.80; $P = .92$). Maternal eczema increased the risk of eczema in girls (PR, 1.92; 95% CI, 1.37-2.68; $P = .0001$) only, whereas paternal eczema did the same for boys (PR, 2.07; 95% CI, 1.32-3.25; $P = .002$). Similar trends were observed when the effect of maternal and paternal allergic disease was assessed for childhood atopy and when maternal total IgE levels were related to total IgE levels in children at ages 10 and 18 years.
Conclusions: The current study indicates a sex-dependent association of parental allergic conditions with childhood allergies, with maternal allergy increasing the risk in girls and paternal allergy increasing the risk in boys. This has implications for childhood allergy prediction and prevention. (J Allergy Clin Immunol 2012;130:427-34.)

Key words: *Maternal, paternal, sex, cohort, parent of origin, atopy, asthma, eczema, rhinitis, allergy, IgE*

The heritability of allergic diseases has been recognized since the early 20th century. A history of asthma in the immediate family is one of the major risk factors for childhood asthma,[1] and the same is true for atopic eczema and allergic rhinitis.[2] An accurate assessment of the heritable risk is important in providing a more accurate diagnosis to parents, identifying at-risk children for preventive measures, and also investigating how environmental factors might interact with the patient's genetic predisposition. An important unresolved issue in this context is the parent-of-origin effect: the respective contribution of maternal and paternal allergic disease. A number of studies have investigated this question with conflicting results.

A common perception is that maternal asthma confers a greater risk,[3-6] although some studies indicated a stronger paternal effect[7] or no difference.[8] A stronger maternal effect might be explained by a stronger maternal parent-of-origin effect,[9] the effects of maternal environmental exposure during pregnancy, or immune interactions between mothers and their offspring *in utero*.[10] For childhood eczema, several studies reported a greater effect of maternal than paternal eczema.[7,11-15] However, a number of large studies failed to confirm a greater influence of maternal eczema.[2,16-19] For allergic rhinitis, only a few studies have investigated the parent-of-origin effect but found no significant difference in maternal or paternal rhinitis.[2,7]

Most studies did not stratify their samples according to the sex of the child, having made the assumption that maternal and paternal effects are identical in boys and girls. This also applies to a recent meta-analysis of the effect of parental history, which did not take the sex of the offspring into consideration.[6] One cross-sectional study of 9- to 11-year-olds found no differential sex-dependent effect of parental allergic disease.[7] Because allergic diseases tend to relapse and remit throughout childhood, cross-sectional studies run the risk of misclassification because those regarded as not having the disease at the time of assessment might have had it earlier or might have it later. Only 1 longitudinal study investigated the effect of parental atopy (but not asthma) on childhood wheeze (but not eczema or rhinitis) up to age 26 years.[20] The association of parental atopy was dependent on the age and sex of the child

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Abbreviations used
PR: Prevalence ratio
SPT: Skin prick test

but not in one direction. Maternal atopy was a risk factor for childhood-onset wheeze in subjects of both sexes, whereas paternal atopy increased the risk in male subjects only. For adolescent-onset wheeze, maternal history of atopy increased the risk in girls only. However, when both ages were combined, paternal history had a stronger risk in girls than boys. This conflicting outcome might be because "parental asthma and rhinitis" was combined as "parental atopy," with childhood asthma as the outcome of interest. It is well known that the heritability of childhood allergic conditions is disease specific so that parental asthma has a greater influence on childhood asthma, and the same is true for atopic eczema and allergic rhinitis.[7] In addition, early-life risk factors, such as respiratory tract infections, mode of early feeding, and exposure to environmental tobacco smoke, might also influence the outcome and thus confound the results.[21] Therefore a comprehensive investigation requires a birth cohort that is studied with prospective phenotyping, including objective tests for atopy throughout childhood with available information on early-life risk factors.

We addressed the following questions using longitudinal data collected from the Isle of Wight birth cohort (1) to estimate the effect of maternal and paternal allergic disease on the offspring's risk of respective allergic disease and (2) to determine whether the parent-of-origin effect on allergic disease varies with the age and sex of the child.

METHODS

An unselected whole population birth cohort (n = 1536) was recruited in 1989 to prospectively study the natural history of asthma and allergic conditions. After exclusion of adoptions, perinatal deaths, and refusal for follow-up, 1456 children were enrolled, with follow-up assessments conducted at 1, 2, 4, 10, and 18 years of age. At each stage, validated questionnaires, including the International Study of Asthma and Allergy in Childhood,[22] were completed on asthma and allergic diseases plus exposure to relevant environmental factors, such as tobacco smoke and pets. Information on breast-feeding duration was collected at 1 and 2 years of age. The majority of participants underwent skin prick tests (SPTs) at 4, 10, and 18 years of age to 14 common food and aeroallergens (ALK-Abelló, Hørsholm, Denmark).[23-25]

Serum for IgE assessment was collected at parturition from mothers (n = 1057 [73%]) of study subjects. Samples for determining IgE levels at age 10 and 18 years were available for 954 (66%) and 610 (42%) subjects, respectively. Maternal IgE levels and IgE levels at age 10 and 18 years were determined with PRIST (Phadia AB, Uppsala, Sweden), which is designed to measure IgE levels between 2.0 and 1000 kU/L. Detailed methodology of recruitment and follow-up has been published previously.[23-26] Ethics approval was obtained at each follow-up by local research ethics committees, and informed consent was obtained from parents, participants, or both.

Definitions

Information on parental history of allergic conditions was collected from mothers soon after birth. Maternal or paternal asthma was defined as those parents responding "yes" to the following question: "Have you ever suffered from asthma?" Information on parental reports of eczema and rhinitis was collected in the same way. If 1 or more of these allergic conditions were present in parents, they were regarded as having "a history of allergy." The definition used for asthma in a cohort child was a history of physician-diagnosed asthma plus at least 1 episode of wheezing or asthma treatment in the previous 12 months. Eczema was defined as chronic or chronically relapsing itchy dermatitis lasting more than 6 weeks with characteristic morphology and distribution, according to the Hanifin and Rajka criteria.[27] Rhinitis was defined by a positive response to the following question: "In the past 12 months have you had a problem with sneezing or a runny or a blocked nose when you did not have a cold or the flu?" Because asthma and rhinitis cannot be confidently diagnosed in early childhood (1-2 years), to reduce misclassification, we analyzed asthma and rhinitis from 4 years onward. Eczema was considered from 1 to 18 years. Atopy was defined by a positive SPT response (mean wheal diameter >3 mm than that elicited by the negative control) to at least 1 allergen. Maternal and offspring IgE levels of greater than 200 kU/L at 10 and 18 years of age were considered increased. A newborn was classified as having "low birth weight" if birth weight was less than 2.5 kg. Other environmental factors assessed were maternal smoking during pregnancy (yes vs no), birth order of the child in the family (first vs second or higher), presence of cat or dog in the home at birth, and breast-feeding duration. Breast-feeding was analyzed as breast-fed for at least 3 months versus those in whom breast-feeding ceased before this age.

Statistical methods

Data were double entered and analyzed with SPSS version 17 software (SPSS, Inc, Chicago, Ill). The prevalence of asthma, eczema, allergic rhinitis, and atopy was calculated. Univariate analyses with χ^2 tests (2-sided) were used to test for differences in proportions stratified for the sex of the child. Generalized linear mixed models were applied to examine the interaction effect of parental history of disease with sex on a multiplicative scale after adjusting for the covariates as follows:

$$\text{Conceptual model: } \text{Logit}(P[\text{Asthma in child}]) =$$

$$\text{Maternal asthma } (0/1) + \text{Paternal asthma } (0/1) + \text{Sex } (M/F)$$

$$+ \text{ Maternal asthma}^{*}\text{Sex } + \text{ Paternal asthma}^{*}\text{Sex } + \text{ covariates.}$$

This was followed by stratified analyses on statistically significant findings. For each childhood allergic manifestation (asthma, eczema, rhinitis, and atopy), the effect of a parental disease of the same type was analyzed separately for the mother and the father. By using repeated-measures analyses, changes were investigated in the prevalence of childhood asthma related to parental asthma from age 4 to 18 years, stratifying for the sex of the child. To obtain overall independent effects of the parental history, we adjusted for early childhood risk factors (in repeated-measures analysis), including maternal smoking during gestation (yes vs no), low birth weight (<2.5 kg), exposure to a dog or cat at home, and breast-feeding (≥3 months vs <3 months).

Because the prevalence of allergic diseases does not present a rare event, odds ratios are likely to overestimate relative risks.[28] To directly estimate prevalence ratios (PRs), we applied a log-linear model for prevalence. For each observation period (ages 1, 2, 4, 10, and 18 years), we estimated the association with maternal and paternal disease and present PRs and their 95% CIs. To assess long-term development in individual children, we had to consider that repeated measurements for each child represent correlated observations. Applying the method of generalized estimating equations[29] that takes the within-child effect into account, we estimated marginal probabilities for maternal and paternal history of asthma and allergy by using GENMOD in the SAS system (SAS, Inc, Gary, NC). Details of the statistical methods are provided in the Methods section in this article's Online Repository at www.jacionline.org.

RESULTS

For further information, see the Results section and Tables E1 to E5 in this article's Online Repository at www.jacionline.org.

TABLE I. Effect of maternal and paternal asthma on predisposition to childhood asthma

	Maternal asthma			Paternal asthma		
Asthma at:	**Yes, % (n/N)**	**No, % (n/N)**	**PR (95% CI); *P* value**	**Yes, % (n/N)**	**No, % (n/N)**	**PR (95% CI); *P* value**
4 y	25.6 (32/125)	13.7 (148/1082)	1.88 (1.36-2.63); .0005	23.9 (28/117)	14.0 (152/1087)	1.72 (1.21-2.46); .003
10 y	20.4 (29/142)	14.0 (170/1217)	1.46 (1.03-2.09); .04	20.6 (27/131)	14.0 (171/1220)	1.47 (1.02-2.12); .04
18 y	25.7 (35/136)	16.8 (195/1160)	1.53 (1.12-2.09); .008	23.4 (30/128)	17.2 (199/1160)	1.37 (0.97-1.92); .07
4-18 y (repeated measure)*	23.8 (96/403)	14.8 (512/3459)	1.56 (1.18-2.07); .002	22.6 (85/376)	15.0 (521/3467)	1.59 (1.19-2.12); .002

*Statistically controlling for sex, low birth weight, duration of breast-feeding, cat and dog exposure at birth, and maternal smoking during pregnancy.

TABLE II. Effect of maternal and paternal asthma on childhood asthma stratified by the sex of the child

	Maternal asthma					
	Girls			Boys		
Asthma at:	**Yes**	**No**	**PR (95% CI); *P* value**	**Yes**	**No**	**PR (95% CI); *P* value**
4 y	30.0 (18/60)	12.4 (66/532)	2.42 (1.55-3.78); .0001	21.5 (14/65)	14.8 (81/550)	1.46 (0.88-2.43); .14
10 y	20.9 (14/67)	11.3 (68/600)	1.84 (1.10-3.09); .02	20.0 (15/75)	16.5 (102/617)	1.21 (0.74-1.97); .44
18 y	31.3 (21/67)	18.2 (107/587)	1.71 (1.16-2.55); .007	20.3 (14/69)	15.4 (88/573)	1.42 (0.80-2.19); .28
4-18 y (repeated measure)*	27.3 (53/194)	14.0 (241/1719)	1.91 (1.34-2.72); .0003	20.6 (43/209)	15.6 (271/1740)	1.29 (0.85-1.96); .23
	Paternal asthma					
	Girls			**Boys**		
Asthma at:	**Yes**	**No**	**PR (95% CI); *P* value**	**Yes**	**No**	**PR (95% CI); *P* value**
4 y	16.0 (8/50)	14.1 (76/540)	1.14 (0.58-2.21); .71	29.9 (20/67)	13.7 (75/547)	2.18 (1.43-3.32); .0003
10 y	14.3 (8/56)	12.2 (74/606)	1.17 (0.60-2.30); .65	25.3 (19/75)	15.8 (97/614)	1.60 (1.04-2.46); .03
18 y	20.7 (12/58)	19.6 (116/592)	1.06 (0.62-1.79); .84	25.7 (18/70)	14.6 (83/568)	1.76 (1.13-2.75); .01
4-18 y (repeated measure)*	17.1 (28/164)	15.3 (266/1738)	1.03 (0.59-1.80); .92	26.9 (57/212)	14.8 (255/1729)	1.99 (1.42-2.79); <.0001

*Statistically controlling for low birth weight, first-born status, duration of breast-feeding, cat and dog exposure at birth, and maternal smoking during pregnancy.

Of the 1456 children enrolled in the study, 1374 (94%) were seen at the age of 1 year, 1231 (85%) at 2 years, 1214 (83%) at 4 years, 1368 (94%) at 10 years, and 1305 (90%) at 18 years. In a simple cross-tabulation, both maternal and paternal asthma were closely and consistently associated with childhood asthma (Table I). This was further confirmed by using repeated-measures analyses, with 1961 observations in boys and 1926 observations in girls. The interaction of maternal asthma with sex was insignificant ($P = .11$); however, a significant interaction of paternal asthma with sex was observed ($P = .03$). Accordingly, the stratified analyses showed that paternal asthma increased the risk of childhood asthma in boys (Table II; repeated-measures analyses: PR, 1.99; 95% CI, 1.42-2.79; $P < .0001$). Although not statistically significant on a multiplicative interaction scale, maternal asthma tended to increase the risk of childhood asthma in girls. A biparental history did not interact with sex and had a greater effect on the risk and was equally important in boys and girls (boys: PR, 3.28; 95% CI, 1.80-6.00; girls: PR, 3.19; 95% CI, 1.98-5.12; data not shown).

In simple cross-tabulation, maternal eczema increased the risk of childhood eczema at most assessments (Table III). In repeated-measures analysis (3279 observations in boys from age 1-18 years and 3206 observations in girls), a maternal effect was observed for the childhood and adolescent period from 1 to 18 years of age, which was statistically significant on a multiplicative interaction scale ($P = .01$). Paternal eczema significantly increased the risk of childhood eczema up to age 10 years, and an overall effect was also shown with repeated-measures analysis ($P = .02$); however, the interaction of paternal history and male sex of the offspring was not statistically significant on a multiplicative scale. When further stratified for child's sex, we found that maternal eczema had no statistically significant effect in boys at any age, but in girls maternal eczema increased the risk of eczema at all ages except 1 year, and a significant overall effect ($P = .009$) was noted (Table IV). For paternal effects, although the interactions were statistically insignificant, paternal eczema tended to increase the risk of childhood eczema up to age 10 years in boys, and an overall effect was observed in repeated-measures analysis ($P = .002$).

When analyzing the whole sample, maternal rhinitis was not associated with childhood rhinitis at any age (Table V). In contrast, paternal rhinitis was significantly associated with childhood rhinitis at all ages (except age 18 years, when it failed to reach statistical significance [$P = .06$]). A significant association was observed in the repeated-measures analysis adjusted for confounders ($P < .0001$). From age 4 to 18 years, there were 1962 observations in boys and 1923 observations in girls. No statistically significant parental rhinitis and sex interaction was detected. This was further supported by stratification on paternal rhinitis and offspring sex (Table VI): paternal rhinitis increased the risk of childhood rhinitis, with no differences between boys and girls at 10 years and in repeated-measures analyses (boys, $P < .001$; girls, $P = .004$). Maternal history of rhinitis had no effect.

We then examined the parent-of-origin effect on atopy (SPT response positivity) and total IgE levels. Both maternal and paternal history of allergy increased the risk of childhood atopy from age 4 to 18 years. The repeated-measures analysis of 1416 observations in boys and 1455 observations in girls corroborated an overall effect (Table VII). A significant interaction of maternal history of atopy with sex was identified ($P = .046$), whereas paternal history did not interact with sex ($P = .88$). A stratified analysis revealed that in boys a maternal history of allergy had no

TABLE III. Effect of maternal and paternal eczema on predisposition to childhood eczema

	Maternal eczema			Paternal eczema		
Eczema at:	Yes, % (n/N)	No, % (n/N)	PR (95% CI); *P* value	Yes, % (n/N)	No, % (n/N)	PR (95% CI); *P* value
1 y	12.0 (20/167)	9.4 (112/1197)	1.32 (0.80-2.20); .27	17.4 (15/86)	9.1 (116/1271)	2.10 (1.17-3.79); .02
2 y	18.0 (27/150)	9.2 (99/1075)	2.16 (1.40-3.45); .002	23.8 (19/80)	9.5 (108/1140)	2.98 (1.71-5.17); <.001
4 y	15.2 (22/145)	11.5 (120/1059)	1.37 (0.84-2.25); .22	24.4 (19/78)	11.2 (124/1124)	2.55 (1.47-4.42); .002
10 y	20.1 (32/160)	12.9 (153/1187)	1.70 (1.12-2.60); .02	20.5 (18/89)	13.0 (163/1252)	1.72 (1.0-2.96); .05
18 y	18.8 (30/160)	11.4 (129/1136)	1.80 (1.16-2.79); .01	16.9 (15/89)	11.8 (141/1199)	1.52 (0.85-2.72); .18
1-18 y (repeated measure)*	16.8 (131/782)	10.8 (613/5654)	1.48 (1.14-1.93); .004	20.4 (86/422)	10.9 (652/5986)	1.93 (1.38-2.70); .0001

*Statistically controlling for sex of the offspring, low birth weight, first-born status, duration of breast-feeding, cat and dog exposure at birth, and maternal smoking during pregnancy.

TABLE IV. Effect of maternal and paternal eczema on childhood eczema stratified by the sex of the child

	Maternal eczema					
	Girls			Boys		
Eczema at:	Yes	No	PR (95% CI); *P* value	Yes	No	PR (95% CI); *P* value
1 y	12.0 (10/83)	8.0 (47/588)	1.58 (0.76-3.26); .21	11.9 (10/84)	10.7 (65/609)	1.13 (0.56-2.30); .71
2 y	22.4 (17/76)	9.2 (49/531)	2.83 (1.53-5.24); .002	13.5 (10/74)	9.2 (50/544)	1.54 (0.75-3.19); .29
4 y	20.0 (15/75)	10.3 (51/516)	2.18 (1.16-4.11); .03	10.0 (7/70)	12.7 (69/543)	0.76 (0.34-1.73); .70
10 y	28.0 (23/82)	12.0 (70/583)	2.86 (1.66-4.92); <.001	11.7 (9/78)	13.7 (83/604)	0.83 (0.40-1.73); .73
18 y	26.8 (22/82)	14.6 (83/569)	2.15 (1.25-3.69); .009	10.3 (8/78)	8.1 (46/567)	1.29 (0.59-2.86); .51
1-18 y (repeated measure)*	21.9 (87/398)	10.8 (300/2787)	1.92 (1.37-2.68); .0001	11.5 (44/384)	10.9 (313/2867)	1.03 (0.67-1.56); .91
	Paternal eczema					
	Girls			Boys		
Eczema at:	Yes	No	PR (95% CI); *P* value	Yes	No	PR (95% CI); *P* value
1 y	12.2 (5/41)	8.2 (51/625)	1.56 (0.59-4.16); .38	22.2 (10/45)	10.1 (65/646)	2.55 (1.21-5.40); .02
2 y	24.4 (10/41)	10.1 (57/562)	2.86 (1.33-6.13); .02	23.1 (9/39)	8.8 (51/578)	3.10 (1.40-6.89); .009
4 y	22.9 (8/35)	11.0 (59/554)	2.40 (1.04-5.51); .05	25.6 (11/43)	11.4 (65/570)	2.67 (1.28-5.55); .01
10 y	16.7 (7/42)	13.6 (84/619)	1.27 (0.55-2.96); .64	23.9 (11/47)	12.5 (79/633)	2.20 (1.08-4.52); .04
18 y	22.7 (10/44)	15.4 (93/602)	1.61 (0.77-3.37); .20	11.1 (5/45)	8.0 (48/597)	1.43 (0.54-3.79); .4
1-18 y (repeated measure)*	19.7 (40/203)	11.6 (344/2962)	1.66 (1.002-2.75); .049	21.0 (46/219)	10.2 (308/3024)	2.07 (1.32-3.25); .002

*Statistically controlling for low birth weight, first-born status, duration of breast-feeding, cat and dog exposure at birth, and maternal smoking during pregnancy.

effect on atopy, whereas in girls it significantly increased the risk at all ages (from 4 to 18 years) (Table VIII).

Regarding IgE levels at 10 years of greater than 200 kU/L in offspring, we assumed that maternal IgE levels at birth (>200 kU/L) would predict increased levels in girls but not in boys. In girls 42% of those with increased maternal IgE levels also had increased IgE levels (26% if not) and in boys 35% with increased maternal IgE levels also had increased IgE levels at age 10 years (30% if not). We tested this association by using log-linear models. The PR of maternal IgE level at birth predicted increased IgE levels in girls at age 10 years (PR, 1.71; 95% CI, 1.16-2.51) but not in boys (PR, 1.1; 95% CI, 0.74-1.63; data not shown). Similar results were seen for IgE levels measured at age 18 years: 41% of the girls with increased maternal IgE levels also had increased IgE levels (26% if not), whereas in boys 33% with increased maternal IgE levels also had increased IgE levels at age 10 years (31% if not). The PRs for increased maternal IgE levels at age 18 years were 1.08 (95% CI, 0.67-1.74) in boys and 1.66 (95% CI, 1.01-2.73) in girls.

DISCUSSION

We have shown that the effect of maternal and paternal history of allergy varies with the sex of the child, whereas maternal allergic history increased the risk of asthma and eczema in girls and paternal history of allergy increases this risk in boys. This sex-specific effect was consistently present at most or all ages. When we performed repeated-measures analyses and adjusted this for various confounders to get an overall independent effect, we found statistically significant sex-specific effects for both asthma and eczema. The effect on the opposite sex (maternal to boys and paternal to girls) was weak and nonsignificant. On a multiplicative scale of interaction, for asthma, the paternal effect was stronger in boys, and for eczema, the maternal effect was statistically stronger in girls. Rhinitis, however, showed a dominant paternal effect for both boys and girls. The sex-specific effect was further confirmed by extending the observation to objective tests of atopy (allergic sensitization on skin tests and total IgE measurements), which had a similar effect. For allergic sensitization assessing differences on a multiplicative scale of interaction, the maternal effect was statistically stronger in girls.

The strengths of our study are longitudinal phenotyping from birth to 18 years of age by using validated tools, objective assessment for atopy, and availability of information on early-life environmental factors, which can confound the effect of genetic factors.[21,30] Furthermore, the information on parental history of allergy was ascertained at birth and therefore avoids the risk of biased reporting after subsequent development of allergic disease in

TABLE V. Effect of maternal and paternal rhinitis on predisposition to childhood rhinitis

	Maternal rhinitis			Paternal rhinitis		
Rhinitis at:	**Yes, % (n/N)**	**No, % (n/N)**	**PR (95% CI); *P* value**	**Yes, % (n/N)**	**No, % (n/N)**	**PR (95% CI); *P* value**
4 y	5.1 (13/256)	5.5 (51/951)	0.93 (0.50-1.73); .88	9.0 (16/177)	4.8 (49/1026)	1.98 (1.10-3.57); .03
10 y	17.3 (46/266)	14.6 (159/1089)	1.22 (0.85-1.75); .29	25.4 (51/201)	13.4 (153/1146)	2.21 (1.54-3.16); <.001
18 y	38.9 (102/262)	35.3 (366/1038)	1.17 (0.89-1.55); .28	42.3 (80/189)	35.1 (387/1103)	1.36 (0.99-1.86); .06
4-18 y (repeated measure)*	22.6 (164/727)	21.1 (577/2739)	1.07 (0.92-1.26); .36	30.3 (158/522)	19.8 (583/2944)	1.42 (1.21-1.67); <.0001

*Statistically controlling for sex of the offspring, first-born status, low birth weight, duration of breast-feeding, cat and dog exposure at birth, and maternal smoking during pregnancy.

TABLE VI. Effect of maternal and paternal rhinitis on childhood rhinitis stratified by the child's sex

	Maternal rhinitis					
	Girls			Boys		
Rhinitis at:	**Yes**	**No**	**PR (95% CI); *P* value**	**No**	**Yes**	**PR (95% CI); *P* value**
4 y	3.0 (4/133)	5.0 (23/460)	0.59 (0.20-1.73); .48	7.3 (9/123)	5.9 (29/491)	1.26 (0.58-2.73); .53
10 y	18.2 (25/137)	14.0 (74/530)	1.38 (0.84-2.26); .23	16.3 (21/129)	15.2 (85/559)	1.08 (0.64-1.83); .79
18 y	36.8 (50/136)	37.6 (195/518)	0.96 (0.65-1.42); .92	41.3 (52/126)	32.9 (171/520)	1.43 (0.96-2.14); .08
4-18 y (repeated measure)*	21.3 (81/381)	21.3 (284/1332)	1.01 (0.81-1.26); .91	24.0 (83/346)	20.8 (293/1407)	1.13 (0.92-1.40); .23
	Paternal rhinitis					
	Girls			**Boys**		
Rhinitis at:	**Yes**	**No**	**PR (95% CI); *P* value**	**No**	**Yes**	**PR (95% CI); *P* value**
4 y	8.1 (7/86)	4.0 (20/504)	2.14 (0.88-5.24); .09	9.9 (9/91)	5.6 (29/522)	1.87 (0.85-4.09); .15
10 y	24.5 (24/98)	13.1 (74/564)	2.15 (1.28-3.62); .01	26.2 (27/103)	13.6 (79/582)	2.26 (1.37-3.73); .002
18 y	44.4 (40/90)	36.5 (204/559)	1.39 (0.89-2.18); .16	40.4 (40/99)	33.6 (183/544)	1.34 (0.86-2.08); .21
4-18 y (repeated measure)*	29.8 (72/250)	20.0 (293/1463)	1.41 (1.12-1.78); .004	31.6 (86/272)	19.6 (290/1481)	1.52 (1.23-1.88); .0001

*Statistically controlling for low birth weight, first-born status, duration of breast-feeding, cat and dog exposure at birth, and maternal smoking during pregnancy.

children. In general, all potential misclassification could be affected by parental history. Hence parents with symptoms recognize and report symptoms in their offspring more often than those without symptoms (overestimation of heritability). However, this does not account for the differences seen between maternal and paternal history of the disease or for the association of maternal IgE levels with IgE levels in boys and girls at ages 10 and 18 years.

Loss to follow-up in this longitudinal cohort study was remarkably low, with information obtained from 83% to 94% of children at various follow-up visits up to age 18 years. However, it is possible that there was selective loss to follow-up influenced by parental disease or childhood disease among the 10% to 15% of children who did not attend. To explore this further, we used maternal asthma as the index disease but did not find any statistically significant difference in attrition rates among children with and without maternal asthma at each follow-up (see Table E4 in this article's Online Repository at www.jacionline.org). Similarly, we did not find any difference in attrition rates among children with and without an asthma diagnosis at the previous follow-up (see Table E5 in this article's Online Repository at www.jacionline.org). Thus there was no selective follow-up because of parental or childhood disease. A limitation of our study is that parental allergic disease was reported (by the mother) rather than physician-diagnosed disease, and there is a risk of overreporting. However, the prevalence in both the mother and father was around 10%, which is less than what has been reported previously in United Kingdom studies.[4,17] Further limitations include unavailability of SPTs for all children at ages 1 and 2 years and paternal total IgE levels at birth.

More studies report a closer association of childhood asthma with maternal asthma.[5,6] There could be several reasons for this. Inclusion of early childhood wheeze might skew the effect. In our cohort wheeze at 1 and 2 years was associated only with maternal asthma (see Table E3 in this article's Online Repository at www.jacionline.org), whereas maternal and paternal asthma had similar influence for childhood asthma (Table I). Our results are consistent with the findings of Litonjua et al,[3] who suggested that maternal history of asthma is associated with childhood asthma (wheeze) at all ages, whereas paternal history assumes significance for asthma in later childhood. Because early childhood wheeze is largely transient and has different causes than childhood asthma, we focused on asthma from 4 to 18 years of age. Similarly, it is not possible to diagnose allergic rhinitis with confidence in early childhood, and therefore we restricted data analysis to children aged 4 years and greater for rhinitis. Eczema, on the other hand, is common in early childhood and easy to diagnose. Thus eczema was included in the analysis from 1 to 18 years of age. Another explanation for a higher effect of maternal asthma might be a biased parental report of asthma because questionnaires are often completed by mothers, who might not know whether their partners had childhood asthma. We can be confident that this was not the case in our study because in the case of a maternal reporting bias, we would expect a higher prevalence of maternal than paternal asthma. In our data a lifetime prevalence (a yes answer to "Have you ever suffered from asthma?") of

TABLE VII. Effect of maternal and paternal history of allergic disease on predisposition to childhood atopy

	Maternal history of allergic disease			Paternal history of allergic disease		
Atopy at:	**Yes, % (n/N)**	**No, % (n/N)**	**PR (95% CI); *P* value**	**Yes, % (n/N)**	**No, % (n/N)**	**PR (95% CI); *P* value**
4 y	22.9 (76/341)	18.1 (116/641)	1.23 (0.95-1.59); .11	28.1 (72/256)	16.7 (120/719)	1.69 (1.31-2.17); .0001
10 y	33.2 (119/358)	23.6 (160/678)	1.41 (1.15-1.72); .0008	33.8 (91/269)	24.7 (187/756)	1.37 (1.11-1.68); .003
18 y	47.9 (139/290)	38.0 (214/563)	1.26 (1.07-1.48); .004	48.7 (113/232)	39.2 (239/610)	1.24 (1.05-1.47); .01
4-18 y (repeated measure)*	33.8 (334/989)	26.0 (490/1882)	1.26 (1.09-1.46); .002	36.5 (276/757)	26.2 (546/2085)	1.18 (1.01-1.38); .03

*Statistically controlling for sex of the offspring, low birth weight, first-born status, duration of breast-feeding, cat and dog exposure at birth, and maternal smoking during pregnancy.

TABLE VIII. Effect of maternal and paternal history of allergic disease on childhood atopy stratified by the sex of the child

	Maternal history of allergic disease					
	Girls			Boys		
Atopy at:	**Yes**	**No**	**PR (95% CI); *P* value**	**Yes**	**No**	**PR (95% CI); *P* value**
4 y	13.9 (44/317)	22.1 (38/172)	1.59 (1.08-2.37); .02	22.5 (38/169)	22.2 (72/324)	1.01 (0.72-1.43); .95
10 y	18.2 (61/335)	31.4 (58/185)	1.72 (1.26-2.35); .0006	35.3 (61/173)	28.9 (99/244)	1.22 (0.94-1.59); .13
18 y	30.9 (90/291)	44.5 (69/155)	1.44 (1.23-1.84); .004	45.6 (124/272)	51.9 (70/135)	1.14 (0.92-1.40); .22
4-18 y (repeated measure)*	32.2 (165/512)	20.7 (195/943)	1.52 (1.21-1.93); .0004	35.4 (169/477)	31.4 (295/939)	1.13 (0.94-1.35); .20
	Paternal history of allergic disease					
	Girls			**Boys**		
Atopy at:	**Yes**	**No**	**PR (95% CI); *P* value**	**Yes**	**No**	**PR (95% CI); *P* value**
4 y	25.4 (31/122)	14.0 (51/313)	1.81 (1.22-2.70); .003	30.6 (41/134)	19.4 (69/355)	1.57 (1.13-2.19); .007
10 y	28.4 (37/130)	21.3 (82/385)	1.33 (0.96-1.87); .09	38.9 (54/139)	28.3 (105/371)	1.37 (1.05-1.79); .02
18 y	41.4 (46/111)	34.0 (112/329)	1.22 (0.93-1.59); .15	55.4 (67/121)	45.2 (127/281)	1.22 (1.0-1.50); .053
4-18 y (repeated measure)*	31.4 (114/363)	22.7 (245/1078)	1.18 (0.91-1.53); .22	41.1 (162/394)	29.9 (301/1007)	1.19 (0.99-1.45); .07

*Statistically controlling for low birth weight, first-born status, duration of breast-feeding, cat and dog exposure at birth, and maternal smoking during pregnancy.

maternal asthma was 10.7% and that of paternal asthma was 9.7%, with information available from 98.8% and 97.9% of parents, respectively.

Further explanation of a greater presumed maternal effect is that the prenatal and postnatal environment of the child is more closely associated with mothers than fathers. Thus early-life environmental effects, such as exposure to cigarette smoke, can cause asthma symptoms in both the mother and child and could falsely be regarded as a genetic influence. However, adjustment for common early-life environmental factors made no significant difference to the association observed for childhood asthma in our study, which further supports the validity of the findings (Tables I to VIII).

Most previous studies investigating parent-of-origin effects assessed childhood asthma at 1 time point.[3,7,8,31] Ignoring the sex of the offspring, cross-sectional analysis of our data indicates nearly equal maternal and paternal effects (Table I), which might conceal the differential effect of parental asthma unless stratified by the sex of the child. Similarly, for childhood eczema, maternal and paternal eczema had comparable influence in our study. This is consistent with previous large studies.[16,17] To our surprise, childhood rhinitis was associated only with paternal rhinitis. A reporting bias by the mothers would amplify maternal rather than paternal effects. The effect seems to be consistent throughout childhood, and we believe that there is a greater paternal rhinitis influence. Previous cross-sectional studies that have investigated the parent-of-origin effect in patients with allergic rhinitis did not find a significant difference.[2,7] Given that allergic sensitization and, to a lesser extent, total IgE levels also show a differential parental effect based on the child's sex, our findings are supportive of an underlying immune mechanism driving the effect on asthma and eczema. Why rhinitis behaves differently to asthma and eczema is not clear.

There are 3 studies that have investigated the parent-of-origin effect in asthma with respect to the sex of the child. Melen et al[32] found a significant interaction between male sex and parental asthma, but their cohort was confined to age 1 to 4 years and thus dominated by early childhood wheezers. Bjerg et al[8] performed a sex-stratified analysis in a cross-sectional study of 7- to 8-year-olds but did not find any major difference in the effect of parental asthma. Mandhane et al[20] found a significant effect of maternal atopy (asthma or rhinitis) for childhood wheeze in both sexes, but the association of paternal atopy was restricted to boys. They did not analyze the effect of parental asthma alone on childhood asthma (which might be more specific); neither did they assess other allergic disease or sensitization. Only 1 study addressed parent-of-origin effects stratified by the child's sex for all 3 allergic conditions and did not find any significant difference.[7] However, this was a cross-sectional questionnaire survey with no longitudinal information and no supporting objective tests of allergic sensitization or IgE levels, and analyses were not adjusted for confounding variables.

This differential effect of the parent of origin might be due to genetic differences, intrauterine programming in mothers, or interaction with environmental factors.[9,21] It is plausible that epigenetic factors, such as DNA methylation, which provide

heritable information beyond the DNA sequence, contribute to the effect of parental disease status on risk of disease in offspring.[33,34] Imprinting is an epigenetic modification that is parental origin specific, leading to preferential expression of a specific parental allele in somatic cells of the offspring.[35] The vital role of imprinted genes in mammalian prenatal growth and development is shown most clearly by the abnormal development and early demise of embryos that inherit 2 copies of either a maternal or paternal genome rather than the usual one of each.[36] Furthermore, sex-specific imprinting effects have previously been observed in mammals.[37] Other possible explanations of parent-of-origin effects include transgenerational genetic and epigenetic effects.[38] Such effects have been postulated to account for the "missing heritabilty" observed when considering the proportion of heritability accounted for by loci identified in genome-wide association studies of complex disease.[39]

It is possible that the paternal effect is primarily (epi)genetic, whereas the maternal effect is also influenced by shared prenatal and postnatal environment. These environmental effects could include the effectiveness of the placenta in delivering nutrients to support fetal growth,[40] maternal smoking impeding antenatal growth,[41] or exposure of the developing airways to oxidant stress, such as acetaminophen.[42] These prenatal exposures might disproportionately affect children of asthmatic mothers and might cause wheeze in early childhood in both boys and girls. This is supported by our observations in which early childhood wheeze was associated with maternal, but not paternal, asthma (see Table E3). In contrast, the effect of paternal asthma on disease status, possibly mediated by paternal imprinting, would manifest later in childhood with development of persistent clinical symptoms of asthma in boys, whereas the same is true for girls associated with maternal asthma.

An accurate assessment of the influence of parental atopy on various allergic manifestations is critical in facilitating early diagnosis and accurate prognosis. At present, the child's sex is not considered when assessing the influence of parental allergic disease on the child's risk of the disease. We have shown that this is critical because maternal asthma does not increase the risk of asthma in boys and paternal asthma has no effect on the risk of asthma in girls. Similar effects are observed for eczema, atopy, and, to a lesser extent, total IgE levels. This information is also important to consider when identifying children at high risk for preventive measures. Lastly, it should help us to understand the pathogenesis of the different patterns of childhood asthma and allergies. Although early childhood wheeze (1-2 years) was associated with maternal asthma, childhood asthma showed the differential effect. For eczema, atopy, and total IgE level, this differential effect was observed for all time points that were analyzed. These allergic diseases are driven by atopic immune responses and possibly share genetic and epigenetic mechanisms (atopic diathesis). More studies focusing on transgenerational epigenetic programming are needed to critically appraise the differential effect of parental atopy, its origin in (epi)genetics, and the influence of the maternal environment.

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Clinical implications: We need to consider a child's sex when assessing the influence of parental atopic history on childhood allergy. This is relevant for clinical assessment, identification of children for prevention, and understanding the genetic basis of atopy.

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METHODS

Data were double entered and analyzed with SPSS version 17 software. Univariate analyses with χ^2 tests (2-sided) were used to test for differences in proportions. We focused on parental history of allergic conditions (asthma, eczema, and rhinitis) as a risk factor for the offspring's asthma, eczema, and rhinitis, respectively. Within this setting, we explored separately for maternal and paternal history and then repeated the analysis stratified for the sex of the child. To obtain independent effects of the parental history, we adjusted for early childhood risk factors, including maternal smoking during gestation (yes vs no), low birth weight (<2.5 kg), exposure to a dog or a cat at home, and breast-feeding (≥3 months vs <3 months).

Regarding parental history of allergic diseases, we also considered an overall effect of any report of asthma, eczema, or hay fever and named this "history of atopy." We investigated the effect of parental history of atopy, separately for the father and the mother, on the development of allergic sensitization by the child at various ages and then stratified by the sex of the child. To extend these investigations, we analyzed the effect of maternal total serum IgE levels on total IgE levels at age 10 years stratified for the sex of the child. IgE levels were either log-transformed (linear regression) or dichotomized (logistic regression). We adjusted the effect of maternal IgE levels for pet exposure, smoking, and birth weight. Increased IgE levels were defined as levels greater than the median.

The study represents a dynamic cohort; some children did not participate in one assessment but rejoined the next, and hence information gained through cumulative incidence is limited. Because the prevalence of asthma does not present a rare event, odds ratios are likely to overestimate relative risks. To directly estimate PRs, we applied a log-linear model for prevalence. For each observation period (ages 1, 2, 4, 10, and 18 years), we estimated the association with maternal and paternal allergic disease and present PRs and their 95% CIs. To assess long-term development in individual children, we had to consider that repeated measurements for each child represent correlated observations. Applying generalized estimating equation analysis that takes the within-child effect into account, we estimated marginal probabilities for maternal, paternal, and biparental history of atopy and asthma by using GENMOD in the SAS system. In addition, we used the age at assessment as a categorical variable and assessed risks related to early wheeze (ages 1 and 2 years) and childhood asthma (ages 4, 10, and 18 years). Also for this repeated-measures approach, we estimated PRs and their 95% CIs. To evaluate the associations between maternal and adolescence IgE levels, we used linear and logistic regressions. IgE levels were either log-transformed (linear regression) or dichotomized (logistic regression). We adjusted the effect of maternal IgE levels for pet exposure, smoking, and birth weight. Increased IgE levels were defined as levels greater than the median.

RESULTS

Of the 1456 children enrolled in the study, 1374 (94%) were seen at the age of 1 year, 1231 (85%) at 2 years, 1214 (83%) at 4 years, 1368 (94%) at 10 years, and 1305 (90%) at 18 years (Table E1). In 10% of the children, the mother reported asthma, in 8.8% the father had asthma, and in 1% both were affected (Table E2). Other early childhood risk factors were not statistically differently distributed among these groups of parental history. Maternal, but not paternal, asthma increase the risk of early childhood wheeze (Table E3).

Loss to follow-up in this longitudinal cohort study was remarkably low with information obtained from 83% to 94% children at various follow-up points up to age 18 years. However, to check for any selective loss to follow-up because of parental disease, we used maternal asthma as the index disease and compared attrition among children with and without maternal asthma at each follow-up (Table E4). To assess for any selective loss to follow-up because of childhood disease, we compared attrition among children with and without an asthma diagnosis at the previous follow-up (Table E5). There was no selective follow-up because of parental or childhood disease.

TABLE E1. Period and cumulative prevalence of asthma stratified by sex and the respective PR

Asthma symptoms	Male sex, % (n/N)	Female sex, % (n/N)	PR (95% CI); *P* value	Total, % (n/N)
1 y	12.5 (87/699)	6.8 (46/675)	1.83 (1.30-2.57); .0005	9.7 (133/1374)
2 y	12.7 (79/622)	8.7 (53/609)	1.46 (1.05-2.03); .02	10.7 (132/1231)
Early childhood (at 1 or 2 y)	18.7 (118/632)	12.9 (79/612)	1.44 (1.11-1.88); .006	15.8 (197/1244)
4 y	15.7 (97/619)	14.1 (84/595)	1.11 (0.85-1.45); .45	14.0 (181/1214)
10 y	17.0 (118/696)	12.4 (83/672)	1.37 (1.06-1.78); .02	14.7 (201/1368)
18 y	15.9 (103/646)	19.4 (128/659)	0.82 (0.65-1.04); .10	17.7 (231/1305)
Later childhood (at 4, 10, or 18 y)	34.7 (200/576)	32.3 (186/576)	1.07 (0.91-1.27); .38	33.5 (386/1152)

TABLE E2. Population characteristics (n = 1358 with information at age 1 year)

	Parental history of asthma				
	No (n = 1089 [%])	**Maternal asthma (n = 136 [%])**	**Paternal asthma (n = 120 [%])**	**Biparental asthma (n = 13 [%])**	***P* value (χ^2 test)**
Maternal smoking during pregnancy	25.0	22.8	20.8	30.8	.68
Low birth weight (<2.5 kg)	5.5	5.2	2.5	7.7	.10
Breast-feeding for <3 mo	61.3	63.2	55.8	46.2	.55
Cat in the home at birth? (2 missing)	34.6	27.2	25.8	30.8	.11
Dog in the home at birth? (2 missing)	30.6	31.6	22.5	38.5	.27
First born (225 missing)	41.4	42.3	40.8	50.0	.96

TABLE E3. Maternal and paternal asthma predisposing to early childhood wheeze

	Maternal asthma			Paternal asthma		
Wheeze	**Yes, % (n/N)**	**No, % (n/N)**	**PR (95% CI); *P* value**	**Yes, % (n/N)**	**No, % (n/N)**	**PR (95% CI); *P* value**
1 y	17.3 (26/150)	8.7 (106/1217)	1.99 (1.34-2.95); .0006	9.0 (12/134)	9.6 (118/1225)	0.93 (0.53-1.64); .80
2 y	16.4 (21/128)	10.0 (110/1100)	1.64 (1.07-2.52); .02	14.0 (16/114)	10.2 (113/1108)	1.38 (0.85-2.24); .20
Early childhood (at 1 or 2 y)	24.6 (33/134)	14.7 (163/1107)	1.67 (1.29-2.32); .003	18.3 (21/115)	15.4 (172/1120)	1.19 (0.79-1.79); .41

TABLE E4. Percentage lost to follow-up at each visit among children with and without a history of asthma in mothers

	Asthma in mothers	No asthma in mothers	*P* value
At 1 y	7/157 (4.5%)	68/1283 (5.3%)	.85
At 2 y	27/155 (17.4%)	183/1283 (14.3%)	.28
At 4 y	26/152 (17.1%)	200/1285 (15.6%)	.64
At 10 y	10/153 (6.5%)	73/1294 (5.6%)	.59
At 18 y	14/151 (9.3%)	129/1295 (10.0%)	.89

TABLE E5. Percentage lost to follow-up at each visit (from 2 years onward) in children with or without asthma at the previous visit

	Asthma at previous follow-up	No asthma at previous follow-up	*P* value
At 2 y	10/127 (7.9%)	102/1213 (8.4%)	1.0
At 4 y	10/129 (7.8%)	126/1067 (11.8%)	.19
At 10 y	5/182 (2.7%)	42/1025 (4.1%)	.53
At 18 y	19/201 (9.5%)	108/1167 (9.3%)	.90