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.