

Influence of male sex and parental allergic disease on childhood wheezing: role of interactions

E. Melén^{*†}, J. Kere[‡], G. Pershagen^{*§}, M. Svartengren^{§¶} and M. Wickman^{*§||}

^{*}*Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden*, [†]*Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden*, [‡]*Department of Biosciences at Novum and Clinical Research Centre, Karolinska Institutet, Stockholm, Sweden*, [§]*Department of Occupational and Environmental Health, Stockholm County Council, Stockholm, Sweden*, [¶]*Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden* and ^{||}*Sachs's Children's Hospital, Institute of Södersjukhuset, Karolinska Institutet, Stockholm, Sweden*

Summary

Background Boys have been reported to be more susceptible to childhood wheezing, whereas girls are more susceptible later in life. This difference might be related to both genetic and environmental factors.

Objective To investigate the influence of male sex and parental allergic disease on the development of childhood wheezing.

Methods Infants ($n = 4089$) born in Stockholm were recruited in a prospective study, BAMSE. Data on parental allergic diseases were obtained from questionnaires answered at the children's birth and on symptoms of wheezing at 1, 2 and 4 years of age. Sensitization to inhalant allergens and lung function was investigated at the age of 4 years.

Results Children were classified as having recurrent, transient ($n = 266$), early-onset persistent ($n = 319$) and late-onset wheezing ($n = 195$). Boys were over-represented in all groups of wheezing (odds ratio, OR = 1.4–1.5) and both maternal and paternal allergic disease was of importance for the wheezing outcomes. A dominating influence from maternal allergic disease was only seen in children with persistent wheezing. An interaction exceeding additivity was found between male sex and parental allergic disease, particularly in children with persistent wheezing (OR = 2.9 and 95% confidence interval, CI 95% 2.1–4.0 for boys with any parental history vs. OR = 1.4, CI 95% 1.0–2.1 for girls). Interaction between male sex and parental allergic disease was also observed in children who wheezed at the age of 4 years and were sensitized to inhalant allergens.

Conclusion Our data suggest an interaction between male sex and parental allergic disease in childhood wheezing, which may represent a sex-specific genetic influence.

Keywords asthma, child, genetics, IgE, respiratory function tests

Submitted 29 April 2003; revised 14 December 2003; accepted 4 February 2004

Introduction

There is good evidence that both inherited and environmental factors influence the risk of allergic disease in childhood. Studies on twins support the genetic impact of asthma and in a study on 4-year-old twins, the heritability of asthma has been suggested to be as high as 68% [1]. Analyses of families with more than one affected individual have linked asthma and allergy to many chromosomal regions, and several candidate genes are under study [2]. Various environmental risk factors have been in focus over the past decades, but so far no data conclusively explain the rising prevalence of allergic diseases. The worldwide variations in prevalence of symptoms of asthma and other allergic manifestations suggest that in different parts of the world, different risk

factors may cause susceptible individuals to develop allergic disease [3].

Although wheezing and asthma is clearly heritable, the disease is genetically complex and probably a result of several genetic and environmental interactions. The pattern of inheritance is not fully understood and there are inconsistent findings regarding the influence of maternal and paternal allergic disease and effects in the offspring [4]. In general, boys have been reported to be more susceptible to childhood asthma, whereas girls are more susceptible later in life [5–7]. In the early years of life, boys have smaller airways relative to lung size than girls and may therefore be more sensitive to airway irritants such as infections or other airborne triggers [8]. Still, there are uncertainties about sex-specific effects on asthma development.

The birth cohort study BAMSE offers a careful mapping of the development of allergic diseases from birth to the age of 4 years [9,10]. The purpose of the study was to identify environmental and genetic risk factors for disease development. Here we present the influence of male sex and parental allergic disease on childhood wheezing and allergic sensitization up to the age of 4 years.

Correspondence: Erik Melén, Department of Occupational and Environmental Health, Norrbacka, Karolinska Hospital, SE-171 76 Stockholm, Sweden.

E-mail: erik.melen@imm.ki.se

Materials and methods

Study design

Between 1994 and 1996, 4089 infants were recruited from Child Health Centres in a prospective study, BAMSE [9, 10]. Families planning to move within a year, those without sufficient knowledge in Swedish and families whose infant suffered from a severe disabling disease were not included. This study base comprised 75% of all eligible children born in predefined areas of both urban and suburban districts of Stockholm. Data on parental allergic diseases, pet exposure, detailed residential characteristics and socio-economic factors were requested in questionnaires filled out by the parents when the child was 2 months old (median age). When the children were 1, 2 and 4 years old, a similar questionnaire was mailed to all parents, this time with the main focus on the children's symptoms related to wheezing and other allergic diseases, and information on current exposure factors (response rates 96%, 94% and 91%, respectively). At 4 years of age, 2965 children attended a clinical investigation (73%) and lung function tests (peak expiratory flow (PEF) using the normal range Ferraris Peak Flow Meter[®], Ferraris Medical Limited, Hertford, UK) were performed on 2926 (72%) children. The best of the three PEF recordings were used for analysis and acceptable tests were obtained from 2828 children. Blood samples were drawn also from 2614 children (64%) and analysed for serum IgE antibodies to inhalant allergens (cat, dog, *Dermatophagoides pteronyssinus*, *Cladospodium*, mixed grass and birch pollen) with Phadiatop[®] (Pharmacia Diagnostics AB, Uppsala, Sweden). A positive result was defined as a concentration ≥ 0.35 kU_A/L. Data from 3531 children with all four complete questionnaires (86% of the original cohort) are presented here. The corresponding number of children with complete questionnaires and acceptable PEF test is 2675 (65%) and 2487 (61%), with complete questionnaires and a blood sample drawn. The study was approved by the ethical committee of Karolinska Institutet, Stockholm.

Definitions

Recurrent, transient wheezing was defined as ≥ 3 episodes of wheezing between 3 months and 2 years of age, but no episode in the last 12 months at 4 years. Early-onset persistent

wheezing was defined as ≥ 1 episode of wheezing between 3 months and 2 years of age and ≥ 1 episode in the last 12 months at 4 years, and late-onset wheezing as no episode of wheezing between 3 months and 2 years of age, but ≥ 1 episode in the last 12 months at 4 years. Steroid-treated wheezing at 4 years was defined as at least one episode of wheezing in the last 12 months and prescription of inhaled steroids.

Parental allergic disease was defined as doctor-diagnosed asthma and/or allergy (hayfever or allergy to pollen/pets) in mother, father or both.

Statistics

A multinomial logistic regression model was used to analyse associations between wheezing phenotypes and hereditary factors. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs) adjusted for potential confounders; sex, parental allergic disease, socio-economic status (based on the parents' profession), mother's age at enrolment, maternal smoking during pregnancy or at enrolment, and pet ownership (cat, dog or rodents in the home or at relatives at enrolment), which were identified by running several models with a number of covariates. Large-sample statistics were used to test equality between proportions, Wald test for difference between the influence of maternal vs. paternal allergic disease and linear regression to test differences in PEF values (adjusted for sex, height, age and body weight). Interaction effects (or the relative excess risk due to interaction, described by Rothman and Greenland) with CI 95% between parental allergic disease and male sex were estimated from an additive scale [11,12]. The following categories were used: (a) female sex and no parental disease (reference group); (b) male sex and no parental disease; (c) female sex and parental disease and (d) male sex and parental disease. The interaction effect was calculated as follows: $(OR_d - OR_a) - (OR_c - OR_a) - (OR_b - OR_a)$ and takes the value of zero if the joint effect of the two factors is only additive. All statistical analyses were performed with Stata, Statistical Software: release 7.0 (College Station, TX, USA).

Results

According to our definitions, 266 children (8%) were classified as having recurrent, transient wheezing, 319 (9%)

Table 1. Male sex and parental allergic diseases in children with wheezing up to the age of 4 years

	No defined wheezing (<i>n</i> = 2751)	Recurrent transient wheezing (<i>n</i> = 266)			Early persistent wheezing (<i>n</i> = 319)			Late-onset wheezing (<i>n</i> = 195)		
	(%)	%	OR*	CI 95%	%	OR*	CI 95%	%	OR*	CI 95%
Male sex	48.7	58.3	1.5	1.1–2.0	58.0	1.5	1.2–1.9	57.4	1.4	1.1–1.9
Parental allergic disease†										
Maternal	16.5	24.4	1.8	1.3–2.4	27.0	2.2	1.7–3.0	21.5	1.8	1.2–2.6
Paternal	16.3	16.9	1.3	0.9–1.8	16.9	1.5	1.1–2.1	22.6	2.0	1.3–2.9
Both	5.0	6.8	1.7	1.0–2.8	12.2	3.6	2.4–5.4	8.7	2.5	1.5–4.4

*Odds ratio (OR) adjusted for maternal/paternal asthma and allergy (the other parent's condition), sex, maternal perinatal smoking, maternal age at delivery, socio-economic status and keeping of furred pets at home. †Parental allergic disease is defined as doctor-diagnosed asthma and/or allergy (hayfever or allergy to pollen/pets) in mother (maternal), father (paternal) or both parents.

CI, confidence interval.

Table 2. Sensitization and lung function in children with wheezing up to the age of 4

	No defined wheezing (<i>n</i> = 1909)	Recurrent transient wheezing (<i>n</i> = 191)	Early persistent wheezing (<i>n</i> = 242)	Late-onset wheezing (<i>n</i> = 145)
		<i>P</i> -value*	<i>P</i> -value*	<i>P</i> -value*
Sensitization at 4 years†				
Airborne allergens (%)	13.5	12.6 0.73	22.7 <0.001	29.9 <0.001
Lung function at 4 years	(<i>n</i> = 2049)	(<i>n</i> = 204)	(<i>n</i> = 263)	(<i>n</i> = 159)
PEF, best value (mean L/min)	171.5	164.7	163.4	168.5
PEF, adjusted diff (L/min)‡	0	- 8.9 <0.001	- 8.5 <0.001	- 1.9 0.38

**P*-value for difference between outcome and reference group with no wheezing. †Sensitization to airborne allergens (Phadiatop). ‡Difference in the children's best value of peak expiratory flow (PEF) is adjusted for sex, height, weight and age at lung function investigation.

The results from the lung functions tests are based on 2675 children who managed to perform an acceptable test.

as having early persistent wheezing and 195 (6%) as having late-onset wheezing (Table 1). Children with early persistent wheezing and wheezing of late onset had the highest occurrence sensitization to inhalant allergens (23% and 30%, respectively, Table 2). Significantly lower mean PEF values were seen in children with recurrent transient wheezing and early persistent wheezing (mean difference - 8.9 and - 8.5 L/min, respectively), whereas the PEF values in children with late-onset wheezing did not significantly differ from those with no defined wheezing (mean difference - 1.9 L/min, *P*-value = 0.38).

Boys were over-represented in all three groups of wheezing (around 57–58% boys, OR = 1.4–1.5, Table 1). Both maternal and paternal allergic disease (asthma, hayfever or allergy to pollen/pets) was of importance for all wheezing outcomes in the children. Maternal allergic disease appeared slightly more associated with early persistent wheezing than paternal disease (OR = 2.2 vs. 1.5, *P* = 0.03), whereas no significant difference was seen in children with recurrent

transient or late-onset wheezing (*P* > 0.05). An interaction effect exceeding additivity was found between male sex and parental allergic disease in children with early persistent wheezing (Table 3). Compared with girls with no allergic heredity (reference group), male sex was not a risk factor for early persistent wheezing, if the boy had no allergic parent (OR = 1.0, CI 95% 0.7–1.5). Furthermore, parental allergic disease was only a minor risk factor among girls (OR = 1.4, CI 95% 1.0–2.1), but constituted 3-fold risk increase among boys (OR = 2.9, CI 95% 2.1–4.0). The interaction effect was estimated to 1.4, CI 95% 1.1–1.7. This pattern of interaction was significant for maternal allergic disease (interaction effect 2.3, CI 95% 1.8–2.7), but not for paternal disease (interaction effect 0.3, CI 95% 0.0–0.7). For the other two outcomes, recurrent transient and late-onset wheezing, no clear pattern of interaction effects was observed, even if weak interaction was found for paternal allergic disease (interaction effect 0.8, CI 95% 0.4–1.1) and the opposite effect, antagonism, for maternal disease (interaction effect - 0.8, CI 95% - 1.2

Table 3. Interaction analysis of sex and parental allergic disease in children with wheezing

Sex	Parental disease*	No defined wheezing (<i>n</i> = 2751) (%)	Recurrent transient wheezing (<i>n</i> = 266)			Early persistent wheezing (<i>n</i> = 319)			Late-onset wheezing (<i>n</i> = 195)		
			%	OR†	CI 95%	%	OR†	CI 95%	%	OR†	CI 95%
(a) Girl	None	31.4	19.9	1.0	–	21.6	1.0	–	18.0	1.0	–
(b) Boy	None	30.9	32.0	1.6	1.2–2.4	22.3	1.0	0.7–1.5	29.2	1.6	1.1–2.5
(c) Girl	Any	19.9	21.8	1.7	1.2–2.6	20.4	1.4	1.0–2.1	24.6	2.3	1.5–3.6
(d) Boy	Any	17.8	26.3	2.3	1.6–3.4	35.7	2.9	2.1–4.0	28.2	2.9	1.9–4.5
Interaction effect‡			0.0 (- 0.9)–0.8			1.4 1.1–1.7			0.0 (- 0.4)–0.4		
(a) Girl	No maternal	40.2	27.4	1.0	–	30.7	1.0	–	26.7	1.0	–
(b) Boy	No maternal	38.3	41.4	1.6	1.1–2.2	30.1	1.0	0.8–1.4	43.1	1.7	1.2–2.5
(c) Girl	Maternal	11.1	14.3	1.9	1.2–2.9	11.3	1.3	0.8–1.9	15.9	2.3	1.4–3.6
(d) Boy	Maternal	10.4	16.9	2.4	1.6–3.6	27.9	3.6	2.6–4.9	14.4	2.1	1.3–3.5
Interaction effect‡			- 0.1 (- 1.1)–1.0			2.3 1.8–2.7			- 0.8 (- 1.2)–(- 0.4)		
(a) Girl	No paternal	39.8	30.5	1.0	–	29.5	1.0	–	29.7	1.0	–
(b) Boy	No paternal	38.9	45.9	1.6	1.2–2.1	41.4	1.5	1.1–1.9	39.0	1.3	0.9–1.9
(c) Girl	Paternal	11.5	11.3	1.3	0.8–2.0	12.5	1.5	1.0–2.2	12.8	1.6	1.0–2.5
(d) Boy	Paternal	9.8	12.4	1.6	1.1–2.5	16.6	2.3	1.6–3.3	18.5	2.6	1.7–4.1
Interaction effect‡			- 0.2 (- 1.1)–0.7			0.3 0.0–0.7			0.8 0.4–1.1		

*Parental allergic disease is defined as doctor-diagnosed asthma and/or allergy (hayfever or allergy to pollen/pets) in mother (maternal), father (paternal) or both parents. †Odds ratio (OR) stratified by heredity and sex and adjusted for maternal/paternal asthma and allergy (the other parent's condition), maternal perinatal smoking, maternal age at delivery, socio-economic status and keeping of furred pets at home. ‡Relative excess risk due to interaction: (OR_d–OR_a)-(OR_c–OR_a)-(OR_b–OR_a). CI, confidence interval.

Table 4. Influence of sex and parental allergic disease on wheezing and sensitization to airborne allergens (Phadiatop) at the age of 4

		No wheezing at 4 years				Wheezing at 4 years†					
		No sensitization (<i>n</i> = 1818) (%)	Sensitization (<i>n</i> = 282)*			No sensitization (<i>n</i> = 289)			Sensitization *(<i>n</i> = 98)		
			%	OR‡	CI 95%	%	OR‡	CI 95%	%	OR‡	CI 95%
Male sex		48.1	57.0	1.5	1.2–1.9	54.6	1.3	1.0–1.7	70.9	2.7	1.8–4.3
Parental allergic disease§											
	Maternal	17.2	20.3	1.5	1.0–2.0	24.8	1.8	1.3–2.4	18.8	1.6	0.9–2.9
	Paternal	16.3	18.6	1.5	1.0–2.0	17.7	1.4	1.0–2.0	23.8	2.3	1.4–4.0
	Both	4.3	12.0	3.5	2.2–5.4	9.0	2.9	1.8–4.7	17.8	7.1	3.8–13.3
Interaction analysis											
Sex	Parental disease										
(a) Girl	None	32.5	17.7	1.0	–	22.8	1.0	–	13.3	1.0	–
(b) Boy	None	29.8	32.3	2.0	1.4–2.9	26.0	1.2	0.9–1.7	26.5	2.2	1.1–4.4
(c) Girl	Any	19.4	24.8	2.4	1.6–3.5	21.8	1.6	1.1–2.3	16.3	2.0	0.9–4.2
(d) Boy	Any	18.4	25.2	2.6	1.8–3.9	29.4	2.3	1.7–3.3	43.9	6.1	3.2–11.5
Interaction effect¶				–0.8	(–1.9)–0.4		0.5	0.2–0.8		2.8	2.1–3.6

*Sensitization to airborne allergens (Phadiatop). †Wheezing at 4 years corresponds to early persistent and late-onset wheezing. §Parental allergic disease is defined as doctor-diagnosed asthma and/or allergy (hay fever or allergy to pollen/pets) in mother (maternal), father (paternal) or both parents. ‡Odds ratio (OR) adjusted for maternal/paternal asthma and allergy (the other parent's condition), sex, maternal perinatal smoking, maternal age at delivery, socio-economic status and keeping of furred pets at home. Stratification by sex and heredity was performed in the interaction analysis. ¶Relative excess risk due to interaction: $(OR_d - OR_a) - (OR_c - OR_a) - (OR_b - OR_a)$. CI, confidence interval.

to –0.4) in children with late-onset wheezing. However, the interaction effect for any parental allergic disease in this group was zero (0.0, CI 95% –0.4 to –0.4).

Additional analyses were performed to assess the influence of diagnostic criteria on the interaction results. If data from children with early persistent and late-onset wheezing were analysed together, thus representing wheezing at 4 years, significant interaction effects were also obtained (e.g. 0.9, CI 95% 0.3–1.5 for any parental allergic disease, data not shown). Even stronger interaction was observed if children with steroid-treated wheezing at 4 years were used as outcome (*n* = 185, interaction effect 2.4, CI 95% 1.0–3.8, data not shown).

Children with wheezing at 4 years (early persistent wheezing and late-onset wheezing) were further subgrouped regarding sensitization to inhalant allergens at the age of 4 years. Parental allergic diseases were associated with sensitization to inhalant allergens, even if the child had no defined wheezing at 4 years (OR = 3.5, CI 95% 2.2–5.4 if both parents had asthma or allergy, Table 4), whereas male sex showed a moderate effect (OR = 1.5, CI 95% 1.2–1.9). Approximately the same influence of parental allergic disease and male sex was found in children with wheezing at 4 years, but no sensitization. However, male sex was clearly a stronger risk factor in children with wheezing and sensitization (OR = 2.7, CI 95% 1.8–4.3). The influence of parental asthma or allergy was also much greater in these children (OR = 7.1, CI 95% 3.8–13.3, both parents affected). No significant differences were seen between maternal and paternal influence for the subgroups of wheezing and sensitization (*P* > 0.05, data not shown). A substantial interaction effect between male sex and parental allergic disease heredity was found in children with wheezing and sensitization (2.8, CI 95% 2.1–3.6), whereas much less effects were seen in the other two subgroups.

No difference was seen between children included in these analyses (*n* = 3531) and those with missing data (*n* = 558)

concerning sex, parental allergic diseases and pets at home (*P* > 0.05 for difference, data not shown). However, a few other variables differed between children included in the analyses and those with missing data: smoking mothers (13% vs. 19%), mothers below 25 years of age (7% vs. 11%) and both parents having an university degree (10% vs. 6%), *P* < 0.05 for all differences. Among those included in the analyses, children with any type of wheezing were more likely to participate in the PEF tests compared with children with no wheezing, 79% vs. 74% (*P* < 0.05 for difference) and to have a blood sample drawn, 74% vs. 69% (*P* < 0.05, data extracted from Table 2).

Discussion

We present the influence of parental allergic diseases and male sex on the development of childhood wheezing and sensitization in a large prospective birth cohort. In general, less effect of heredity was seen on recurrent, transient wheezing, compared with early persistent and late-onset wheezing, suggesting that the genetic influence may differ between the groups. In this study, 86% of the parents filled in the questionnaire with heredity questions together when the child was 2 months old. Over- or underrating of heredity by one parent should therefore not bias the results to any major extent [13]. Some studies indicate that maternal asthma is most strongly associated with childhood asthma, especially in children < 5 years of age [14, 15], whereas other show that maternal and paternal asthma confer similar risk [16]. There is supportive evidence of the maternal effects in that the development of atopic disease can be initiated already *in utero* and that this influence may be regulated by the maternal environment [17]. Linkage studies have attempted to disentangle sex-related effects genetically, and both maternal and paternal imprinting has been suggested for allergic sensitiza-

tion [18, 19]. Genomic imprinting refers to the differential expression of genes depending on whether they come from the mother or father, and has been reported to play a role in several complex diseases, among them diabetes mellitus [20]. Although not directly suggested by our data, imprinting remains a plausible mechanism for some parental effects in allergic diseases.

Several studies have reported that boys not only have an increased risk of wheezing and asthma but also of sensitization, which may partially account for the higher prevalence of asthma in boys [21–23]. A study on Swedish 8–9-year-old twins showed that boys had a higher incidence of asthma than girls, whereas girls had a higher incidence of eczema [24]. Allergic diseases may thus be expressed in different target organs depending on sex and sex-related environmental factors. The joint effect of parental allergic diseases and male sex found in this study was more than additive and may represent an important biological interaction [11]. The interaction effect was most pronounced in children with early-onset persistent wheezing, but was also seen if data from all children with wheezing at the age of 4 years were analysed together and was substantial in children with atopy-associated wheezing. Nevertheless, genetic influence may even differ between children with early persistent wheezing and those with late-onset wheezing, since there is an observed difference in interaction effect. The sex-specific hereditary effect observed in this study might diminish with age, since several studies have shown that girls are more susceptible to asthma later in life [5–7]. Results from a large population-based study on wheezing in 6–7-year-old children did not show any effect of modification by sex when analyses of risk factors, including heredity, were run separately for boys and girls [25]. However, an interaction effect has been observed in 1-year-old children, where the lung function in male infants was affected more by maternal history of asthma than in female infants [8]. Other groups have found joint effects of parental history of asthma and allergy and exposure to tobacco smoke during pregnancy or in early life [15, 16]. Still, few other studies have actually addressed the possibility of biological interaction between sex and heredity in childhood wheezing and asthma.

Our results suggest that there may be a sex-specific hereditary component that affects the susceptibility to wheezing in early life. The pattern of inheritance could be congruent with X-linked genes, which are more likely to be unmasked in boys, who have only one X-chromosome. The IL-9 receptor gene (IL-9R), located on the pseudoautosomal region of X and Y chromosomes, has previously been associated with asthma and may thus be a candidate gene in this region [26]. IL-9 has many biological effects that are important for the development of allergic diseases, e.g. stimulation of IgE synthesis as well as mast cell growth and maturation. However, polymorphism in the IL-9 gene itself has not convincingly been linked to asthma or allergy [27]. Sex of the affected individual and age at onset of wheezing may contribute to locus heterogeneity at some wheezing susceptibility loci and there is evidence for linkage between specific autosomal loci and affected individuals of a particular sex and age of onset of wheezing [28]. Recently, sex-specific effects of genotypes of IL-1 β (a pro-inflammatory cytokine) in male adults with asthma have also been reported [29].

Asthmatic disease in children is associated with a number of intermediate phenotypes, such as transient wheezing induced by infections and atopy-associated asthma [30]. Wheezing is considered to be the major criterion for childhood asthma and a certain number of episodes within the last 12 months usually constitute a basis for the asthma diagnosis [31,32]. Definitions may also include steroid treatment, and the alternative outcome used in this study, 'steroid-treated wheezing at 4 years', has for instance been used as a criterion for asthma at 4 years in the BAMSE study [33]. In small children, the term asthma has been proposed to be replaced by wheezing, which also may include symptoms over time; transient, persistent and late-onset wheezing [34]. Since the children in this study are only 4 years of age and manifest asthma is often not established by that age, we have used such wheezing definitions, although the children's age and the number of episodes do not exactly match with the original reference [34].

Our results show that already at the age of 2 and 4 years, different risk factors and disease characteristics are associated with the three wheezing phenotypes. Children with early persistent wheezing and wheezing of late onset were more often sensitized to airborne allergens. Furthermore, lung function at age 4 years, measured as the best PEF, was significantly lower in children with recurrent transient wheezing and early persistent wheezing, whereas no difference was seen in children with late-onset wheezing compared with those with no defined wheezing. The pattern of sensitization and the lung function results are relatively consistent with data from the Tucson Children's Respiratory Study on children up to the age of 6 years [34].

Some quality aspects of the study deserve attention. Of the 4089 children initially recruited in the study, 3531 (86%) had complete data for multivariate analyses. The children with missing data seem to differ somewhat from those included in the analyses in e.g. socio-economic status and exposure to tobacco smoke, but the number of missing children is relatively small and no difference was seen in sex and parental allergic diseases. Non-response is therefore unlikely to influence our interpretation to any major extent. Unfortunately, willingness to perform PEF tests and have a blood sample drawn at the clinical investigation was obviously dependent on the children's history of wheezing, which introduces some selection bias. In cohort studies of this kind with mostly healthy children included, this problem is difficult to avoid since participation is entirely on a voluntary basis. The overall difference in participation rate between healthy and wheezy children was, however, only 5% for both PEF tests and blood sampling. The questionnaire information on risk factors was obtained before the children developed allergic symptoms, minimizing the risk of disease-related misclassification. However, the reporting of children's symptoms may have been influenced by awareness related to parental allergic disease. Obviously, this would not explain our main finding of an influence by allergic heredity mainly in boys.

In summary, we have presented the influence of allergic heredity and male sex on the development of childhood wheezing and allergic sensitization in a large prospective birth cohort. An interaction between these factors exceeding additivity was found, especially in children with early

persistent wheezing, which may represent a sex-specific genetic influence. This study also shows the importance of stratification of data in order to find effects that may be obscured if only multiple regression models are used. Identification of important interactions will improve our understanding of the causes of allergic diseases, including the great variability between different wheezing and asthma phenotypes.

Acknowledgements

We thank all children and parents in the BAMSE cohort and all nurses at the Health Care Centers; Eva Hallner, André Lauber, and Lena Tollin for database administration and Magnus Lundqvist for statistical help, all at the Department of Occupational and Environmental Health, Stockholm County Council. Sources of research support: Stockholm County Council, The Swedish Asthma and Allergy Association, The Swedish Foundation for Health Care Science and Allergy Research, The Swedish Council for Building Research and Konsul Th. C. Bergh's Foundation.

References

- Koeppen-Scomerus G, Stevenson J, Plomin R. Genes and environment in asthma: a study of 4 year old twins. *Arch Dis Child* 2001; 85:398–400.
- Cookson WO. Asthma genetics. *Chest* 2002; 121:7S–13S.
- The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; 351:1225–32.
- Moffatt MF, Cookson WO. Maternal effects in atopic disease. *Clin Exp Allergy* 1998; 28 (Suppl. 1):56–61.
- Weitzman M, Gortmaker S, Walker DK, Sobol A. Maternal smoking and childhood asthma. *Pediatrics* 1990; 85:505–11.
- Skobeloff EM, Spivey WH, St Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. *JAMA* 1992; 268:3437–40.
- Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. *Thorax* 1992; 47:537–42.
- Young S, Sherill DL, Arnott J, Diepeven D, LeSouëf PN, Landau LI. Parental factors affecting respiratory function during the first year of life. *Pediatr Pulmonol* 2000; 29:331–40.
- Lannerö E, Kull I, Tollin L, Wickman M, Nordvall SL. Environmental risk factors for allergy and socio-economic status in a birth cohort (BAMSE). *Pediatr Allergy Immunol* 2002; 13:182–7.
- Kull I, Wickman M, Lilja G, Nordvall SL, Pershagen G. Breastfeeding and allergic diseases in infants – a prospective birth-cohort study. *Arch Dis Child* 2002; 87:478–81.
- Rothman KJ, Greenland S. *Modern epidemiology*. Philadelphia: Lippincott Williams and Wilkins, 1998.
- Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology* 1992; 3:452–6.
- Bergmann KE, Bergmann RL, Schulz J, Grab T, Wahn U. Prediction of atopic disease in the newborn: methodological aspects. *Clin Exp Allergy* 1990; 20:21–6.
- Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? *Am J Respir Crit Care Med* 1998; 158:176–81.
- Jaakkola JJ, Nafstad P, Magnus P. Environmental tobacco smoke, parental atopy and childhood asthma. *Environ Health Perspect* 2001; 109:579–82.
- London SJ, Gauderman WJ, Avol E, Rappaport E, Peters JM. Family history and the risk of early-onset persistent, early-onset transient, and late onset asthma. *Epidemiology* 2001; 12:577–83.
- Jones CA, Holloway JA, Warner JO. Does atopic disease start in early life? *Allergy* 2000; 55:2–10.
- Lee YA, Wahn U, Kehrt R et al. A major susceptibility locus for atopic dermatitis maps to chromosome 3q21. *Nat Genet* 2000; 26:470–3.
- Strauch K, Bogdanow M, Fimmers R, Baur MP, Wienker TF. Linkage analysis of asthma and atopy including models with genomic imprinting. *Genet Epidemiol* 2001; 21 (Suppl. 1):204–9.
- Huxtable SJ, Saker PJ, Haddad L et al. Analysis of parent-offspring trios provides evidence for linkage and association between the insulin gene and type 2 diabetes mediated exclusively through paternally transmitted class III variable number tandem repeat alleles. *Diabetes* 2000; 49:126–30.
- Johnson CC, Peterson EL, Ownby DR. Gender differences in total and allergen-specific immunoglobulin E (IgE) concentrations in a population-based cohort from birth to age four years. *Am J Epidemiol* 1998; 147:1145–52.
- Sears MR, Burrows B, Flannery EM, Herbison GP, Holdaway MD. Atopy in childhood. I. Gender and allergen related risks for development of hay fever and asthma. *Clin Exp Allergy* 1993; 23:941–8.
- Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin Exp Allergy* 1993; 23:504–11.
- Lichtenstein P, Svartengren M. Genes, environments, and sex: factors of importance in atopic diseases in 7–9-year-old twins. *Allergy* 1997; 52:1079–86.
- Rusconi F, Galassi C and the SIDRIA Collaborative Group. et al. Risk factors for early, persistent, and late-onset wheezing in young children. *Am J Respir Crit Care Med* 1999; 160:1617–22.
- Kauppi P, Laitinen T, Ollikainen V, Mannila H, Laitinen LA, Kere J. The IL9R region contribution in asthma is supported by genetic association in an isolated population. *Eur J Hum Genet* 2000; 8:788–92.
- Laitinen T, Kauppi P, Ignatius J et al. Genetic control of serum IgE levels and asthma: linkage and linkage disequilibrium studies in an isolated population. *Hum Mol Genet* 1997; 6:2069–76.
- Srivastava A, Cotton C, Paterson AD. Sex- and age-of-onset-based locus heterogeneity in asthma. *Genet Epidemiol* 2001; 21 (Suppl. 1): 154–9.
- Karjalainen J, Nieminen MM, Aromaa A, Klaukka T, Hurme M. The IL-1 β genotype carries asthma susceptibility only in men. *J Allergy Clin Immunol* 2002; 109:514–6.
- Martinez FD. Development of wheezing disorders and asthma in preschool children. *Pediatrics* 2002; 109:362–7.
- Bergmann RL, Edenharter G, Bergmann KE et al. Atopic dermatitis in early infancy predicts airway disease at 5 years. *Clin Exp Allergy* 1998; 28:965–70.
- Koopman LP, Brunekreef B, de Jongste JC, Neijens HJ. Definition of respiratory symptoms and disease in early childhood in large prospective birth cohort studies that predict the development of asthma. *Pediatr Allergy Immunol* 2001; 12:118–24.
- Almqvist C, Egmar A-C, Hedlin G et al. Direct and indirect exposure to pets – risk of sensitization and asthma at 4 years in a birth cohort. *Clin Exp Allergy* 2003; 33:1190–7.
- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; 332:133–8.