

Gender-specific differences in the prevention of asthma-like symptoms in high-risk infants

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The prevalence of asthma in children has increased in the last decades, and gender-specific differences in asthma development have recently been suggested. The present study investigates whether gender differences are present in a population of young children (0–2 yr) with a high risk for the development of asthma on the basis of the presence of asthma in first-degree relative(s). The study was performed on 222 children (118 boys, 104 girls) with a familial predisposition of asthma, which received standardized recommendations to reduce exposure to allergens (dust mite, pets and food allergens) and to passive smoking. Health outcome (wheezing episodes and shortness of breath) and compliance with allergen-reducing measures were studied by means of multiple regression analyses. Boys suffered more from asthma-like complaints than girls, as diagnosed by the general practitioner (32% vs. 18%, respectively, $p = 0.023$). Compliance with intervention measures was similar for boys and girls for most allergens, but food allergen reduction was better applied for girls: duration of exclusive breastfeeding was longer in girls (median 9 wk vs. 4 wk, $p = 0.009$). Further analysis showed that 4 wk of longer breastfeeding reduced the number of wheezing episodes and shortness of breath in boys by 19% and 15%, respectively, but not in girls, suggesting sex as an effect modifier in the relationship between breastfeeding and asthma-like symptoms. The present findings indicate that application and effects of prevention strategies for children with a high risk for developing asthma might be gender-specific and suggest a special importance of breastfeeding boys.

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A gender-specific difference in asthma development in young children has recently been suggested in a number of publications (1, 2), with female the fortunate sex this time. As asthma is typically a multi-factorial disease in which genetic, environmental, pathophysiologic and immunologic aspects play a role, the reason(s) for gender-specific differences could also be multiple. Airway physiology and pathology might be under hormonal control (3), and there are known immunological differences in responses to measles vaccine (4) and risk of childhood infectious diseases (5–7) between boys and girls. Case detection bias might also contribute to the

observed differences, although this seems less likely.

As the prevalence of asthma in children has clearly increased in the past decades (8, 9), investigating which factors may cause gender differences in clinical effectiveness of prevention holds promise for both boys and girls. Recent research reported that gender might modify the effect of reduction of environmental exposure on asthma symptoms (2, 10).

If there are gender-specific differences in the prevention of asthma development in children, the question is whether these differences are based on biological [genetic (11), immunological,

hormonal] influences, on behavioural (gender) aspects or perhaps on both.

In the present study, respiratory symptoms and atopic disease in an intervention population of young children with a high risk for developing asthma are described, relating these to clinical, and to behavioural (e.g. compliance with intervention protocols) aspects, and stratified for gender.

Methods

The study population was derived from the PREVASC study, a randomized intervention study in Dutch primary care on the effectiveness of primary prevention of asthma directed towards high-risk families expecting a child (2, 10). In total, 443 children (229 boys, 214 girls) were included. Pregnant mothers were recruited by general practitioners and midwives during the first two trimesters of their pregnancy. A high risk for the development of asthma was defined when asthma was at least present in either the mother, father or sibling(s) of the unborn baby.

Twice before birth, and once 1–3 wk afterwards, an intervention group (222 children: 118 boys, 104 girls) received standardized instructions and recommendations to reduce four main environmental exposures: mite allergens (sanitation measures, mite impermeable bedding), pet allergens, food allergens (breastfeeding for at least 6 months, hypoallergenic formula milk, first solid food postponed until after 6 months) and passive smoking. A control group (221 children: 111 boys, 110 girls) received the usual care. The results of the PREVASC study have been published elsewhere (2). For the present study, where possible gender differences were investigated, only the intervention group was studied, as we were interested in the association between compliance towards preventive measures and sex, and in possible different effects of prevention between the sexes.

The following independent variables were used: compliance with advice for dust mite reduction (sanitation of baby room, of parents' room, and of living room and reduction of the number of cuddle toys), pet allergen reduction (presence of dog and cat), passive smoking ('indoors by family members' and 'in presence of infant'), and food allergen reduction (number of weeks of exclusive breastfeeding and number of weeks of exclusive hypoallergenic formula). All data on allergen reduction measures were derived from weekly diary entries by the parents. House dust mite allergens were also measured.

The occurrence of asthma-like symptoms was measured by administering questionnaires from the International Study of Asthma and Allergies in Childhood (ISAAC) (12) at 6 months, 1 and 2 yr, and also from symptoms described in the parental diaries. The following health outcome variables were examined: 'wheezing episodes' and 'shortness of breath' (at least once a week, number of weeks: derived from weekly diary entries by the parents), number of medical consultations, diagnosis asthma (ICPC R96) and diagnosis atopic eczema (ICPC S87) (0–2 yr of age, from general practitioner (GP) records).

All analyses were performed with the software package SPSS (Ver. 11.0 for Windows: SPSS). Mann–Whitney *U* tests and chi-square tests were used to determine differences between boys and girls. For a further examination of the relationships between health outcomes and feeding patterns, logistic regression procedures were used.

Results

Boys suffered statistically significantly more from asthma-like complaints than girls: they were more often seen in medical consultations, more often diagnosed with asthma, showed more wheezing episodes and were more often short of breath. Atopic eczema (ICPC code S87, as diagnosed by the GP) was also found more often in boys (see Table 1). The sequence of siblings was not different for boys or girls. Which relative (or combination of relatives) had a positive history of asthma, was also not significantly different for boys and girls.

Compliance with intervention measures did not seem to be homogeneous for boys and girls. Advices to reduce exposure to dust mite, pet allergen and passive smoking were followed

Table 1. Health outcomes for boys and girls, during the 2-yr intervention study median (range)

	Boys	Girls	p
Number of medical consultations	5 (0–36)	3 (0–29)	0.009*
Number of wheezing episodes	4 (0–81)	2 (0–29)	0.017*
Number of shortness of breath episodes	6 (0–69)	4 (0–29)	0.013*
Diagnosis: asthma†	32%	18%	0.023‡
Diagnosis: atopic eczema§	36%	17%	0.002‡

*Mann–Whitney *U* test.

†Asthma (ICPC R96) is defined as recurrent episodes of reversible acute bronchial obstruction with wheeze and/or dry cough; or diagnostic tests meeting currently accepted criteria for asthma.

‡Chi-square test.

§Atopic eczema (ICPC S87) is defined as pruritic exudative lesions with or without lichenification over face and neck, wrists and hands, chest, back of knees and front of elbows.

Table 2. Application of prevention protocol for boys and girls

	Boys	Girls	p
Dust mite reduction			
Applied in baby room	84.0%	76.3%	0.177
Applied in parents' room	70.2%	70.7%	0.944
Applied in living room	90.7%	94.6%	0.288
Applied in cuddle toys	75.7%	73.6%	0.738
Pet allergen reduction			
Dog present	20.6%	23.9%	0.570
Cat present	14.0%	8.7%	0.242
Passive smoking			
Smoking indoors by family members	17.0%	15.2%	0.737
Smoking in presence of infant	6.5%	2.2%	0.153
Food allergen reduction (median and range)			
Number of weeks exclusively breastfed	4 (0–26)	9 (0–26)	0.009*
Number of weeks of exclusively hypoallergenic formula feeding	11 (0–26)	3 (0–26)	0.089

*Statistically significant Mann–Whitney *U* test ($p < 0.05$).

similarly for both sexes in the children. Food allergen reduction, however, was better applied for girls: the duration of exclusive breastfeeding was significantly longer in girls when compared with boys ($p = 0.009$, see Table 2). Boys were fed with exclusive hypoallergenic formula for a longer period than girls, but this difference did not reach the level of statistical significance ($p = 0.089$).

As these results suggest that a better application of food allergen reduction strategies could, at least partly, explain the gender differences in asthma-like complaints, this relationship was further investigated for two outcome variables: number of wheezing episodes and shortness of breath episodes in the first 6 months. As these outcome variables were not normally distributed, a cut-off point was constructed, based on the median: (hardly) no wheezing or shortness of breath (0–1 episode in the first 6 months), suffering from wheezing or shortness of breath (two or more episodes in the first 6 months). Number of weeks of exclusive breastfeeding was compared between children with and without wheezing or shortness of breath for boys and girls (see Table 3).

These results indicate that sex could be an effect modifier in the relationship between breastfeeding and wheezing/shortness of breath. Further logistic regression analyses were carried out. Variables entered were sex, the duration of exclusive breastfeeding and the interaction variable of sex with the duration of exclusive breastfeeding. The analysis was also performed for 'duration of exclusively hypoallergenic formula feeding'. As these variables are not mutually exclusive (a baby can have 2 wk of breastfeeding followed by 24 wk of hypoaller-

Table 3. Duration of breastfeeding in weeks in boys and girls with and without complaints of wheezing or shortness of breath

	Number of weeks exclusively breastfed median (range)	p (Mann–Whitney <i>U</i> test)
Boys		
No wheezing episodes	8 (0–26)	0.012
Wheezing episodes	1.5 (0–26)	
No shortness of breath	8 (0–26)	0.015
Shortness of breath	2.5 (0–21)	
Girls		
No wheezing episodes	9 (0–26)	0.903
Wheezing episodes	9 (0–26)	
No shortness of breath	9 (0–26)	0.544
Shortness of breath	9 (0–26)	

Table 4. Results of the logistic regression analysis with 'wheezing episodes' and 'shortness of breath' (0–28 wk) as dependent variable, dichotomized (>1 vs. 0–1)

	Odds ratio (95% CI)	p-value
Wheezing episodes		
Duration of exclusive breastfeeding, per 4 wk		
For boys	0.77 (0.63–0.94)	0.011
For girls	1.00 (0.84–1.20)	0.976
Difference of boys' and girls' ORs		0.057
Shortness of breath		
Duration of exclusive breastfeeding, per 4 wk		
For boys	0.72 (0.57–0.91)	0.006
For girls	1.05 (0.88–1.26)	0.570
Difference of boys' and girls' ORs		0.011

Odds ratios indicate the change in risk per 4 wk longer exclusive breastfeeding.

genic formula!), they could not be entered in the same regression analysis.

The results of the logistic regression analyses indicate a modifying effect of sex on the effects of breastfeeding: 4 wk of longer breastfeeding reduce shortness of breath and number of wheezing episodes in boys, the odds ratios being 0.72 and 0.77, respectively, while both effects are not found in girls (see Table 4). Assuming, in this population of high-risk children, a proportion of more than one episode of wheezing and shortness of breath of about 0.40, four extra weeks of breastfeeding would mean relative risks of 81% and 85%, respectively, reducing the risks with 19% and 15%, respectively. Hypoallergenic formula feeding does not show any significant effect on the number of episodes of wheezing and/or shortness of breath, either in boys or in girls.

Discussion

Very young children (0–2 yr) with a high risk for developing asthma, apparently already show

gender-specific differences: in the present study, boys have higher risk of wheezing episodes when compared with girls and are more often presented for medical consultation.

While these results corroborate with other research publications (1, 3), the fact that food allergen reduction strategies seem to be applied differently for boys and girls has to our knowledge not been published before. By definition, gender-specific differences include behavioural aspects next to biomedical differences between the sexes. In young children, behavioural aspects are probably closely linked to those of their parents. Parents can (subconsciously) treat their male and female offsprings differently, because they attribute different images to baby boys and girls. As an example, boys are considered perhaps more active than girls, and a dog present in the house to play and walk with might be regarded as very positive for them. In addition, a baby boy crying after breastfeeding, might be suspected of being hungry, and thus receive extra formula milk more quickly than a baby girl. Intervention protocols to stop the 'allergic march' in young children might therefore be applied differently for boys and girls. When older, boys and girls display different attitudes to their complaints themselves: a recent study showed that teenagers manage asthma in gendered ways with a greater adaptation in girls, incorporating the chronic condition into their social and personal identities more easily (13), perhaps as a result of socialization.

Boys in this intervention population are exclusively breastfed for a statistically significant shorter period than girls, while the present statistical analyses suggest that they might benefit more (see Tables 3 and 4). In the international literature, most studies show that girls are generally breastfed for longer periods than boys (14–17), but also the opposite is found (18, 19). Why this is so, is unknown. Perhaps, boys show signs of a higher caloric need at a younger age, which makes mothers prone to shift from breast to bottle (20). When not breastfed, the boys received bottle-feeding with hypoallergenic formula in most cases in this study. Breastfeeding has been found to be protective against recurrent wheezing early in life, but was sometimes associated with an increased risk of asthma and wheezing over the age of 6 yr (21). The short follow-up period in the present study precludes any conclusions about long-time effects of the interventions. A long-time follow-up study, that will follow the PREVASC-study children for years to come, is already underway.

The higher frequency of developing asthma-like symptoms in boys might be due to an increased susceptibility, which could be reduced by (a longer period of) breastfeeding. Hypoallergenic formula does not seem to compensate (completely) for an early discontinuation of breastfeeding in this respect.

We could not establish other differences in the application of allergy reduction strategy: the frequency of passive smoking, and the presence of dust mites and pets were uniformly distributed over the sexes. Our present preliminary findings, however, indicate that prevention strategies for children with a high risk of developing asthma, should probably take gender into account, and especially stress the importance of breastfeeding boys for a longer period, at least as long as girls, but maybe even longer, thus tackling the behavioural aspect.

We feel that the results in the present study merit further research, exploring the observed gender differences to increase the understanding of the complicated aetiology of asthmatic development in children. It should be noted that recurrent wheezing and shortness of breath in these young children cannot certainly be diagnosed as asthma and moreover, not all that wheezes turn out to be asthma. Therefore, these symptoms are called asthma-like complaints.

In conclusion, it seems that the gender-specific differences that exist in asthma and its prevention, could be based on both behavioural and biological aspects. Girls are longer breastfed than boys, who, according to our observations could possibly benefit even more: in this study, 4 wk of longer breastfeeding reduce shortness of breath and wheezing episodes by 15–19% in boys but not in girls.

Support statement

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Ethics approval

The Ethical Committee of the University of Maastricht (Maastricht, the Netherlands) approved the study.

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