

ORIGINAL ARTICLE

Infant wheeze, comorbidities and school age asthma

Åsa Neuman^{1,2}, Anna Bergström¹, Per Gustafsson³, Per Thunqvist^{4,5}, Niklas Andersson^{1,6}, Lennart Nordvall², Inger Kull^{4,5} & Magnus Wickman^{1,4}

¹Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; ²Department of Women's and Children's Health, Uppsala University Hospital, Uppsala, Sweden; ³Department of Paediatrics, Central Hospital, Skövde, Sweden; ⁴Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden; ⁵Sachs' Children's Hospital, Södersjukhuset, Stockholm, Sweden; ⁶Centre for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden

To cite this article: Neuman Å, Bergström A, Gustafsson P, Thunqvist P, Andersson N, Nordvall L, Kull I, Wickman M. Infant wheeze, comorbidities and school age asthma. *Pediatr Allergy Immunol* 2014; **00**.

Keywords

Barn/Children, Allergy and Milieu in Stockholm, an Epidemiologic study; birth cohort; child; gastroesophageal reflux disease; prediction

Correspondence

Åsa Neuman, Institute of Environmental Medicine, Karolinska Institutet, P.O. Box 210, SE-171 77 Stockholm, Sweden
E-mail: asa.neuman@ki.se

Accepted for publication 17 March 2014

DOI:10.1111/pai.12223

Abstract

Background: Factors associated with early onset of wheeze have been described, but there is limited knowledge on which of these infant wheezers who will have developed asthma in school age. The aim was to identify clinical risk factors for asthma in the 8-yr-old children that wheezed during infancy in a population-based setting.

Methods: Three thousand two hundred and fifty-one children from a population-based birth cohort followed prospectively from infancy until age 8 yr were included in the study. Data were analyzed using multivariate logistic regression analysis.

Results: Parents reported any wheeze episode before age 2 yr in 823 subjects (25%). Infant wheezers had an almost fourfold risk of asthma at age 8 [adjusted odds ratio (aOR) 3.68, 95% CI 2.74–4.96], equivalent to an asthma prevalence of 14% compared with 4% among non-wheezers ($p < 0.001$). After adjustments for sex, exposure to tobacco smoke and indoor dampness/mould, allergic heredity (aOR 1.53, 95% CI 1.02–2.30), increased frequency of wheeze (aOR 3.41, 95% CI 2.09–5.56 for children with ≥ 3 episodes compared with ≤ 2 episodes during the first 2 yr of life), infant eczema (aOR 2.31, 95% CI 1.52–3.49), and recurrent abdominal pain (aOR 2.33, 95% CI 1.30–4.16) remained risk factors for school age asthma in the infant wheezing group.

Conclusions: Among infant wheezers, allergic heredity, increased severity of wheeze, infant eczema, and recurrent abdominal pain were independent risk factors for asthma at age 8 yr. Among children with three or four of these risk factors, 38% had asthma at school age.

Wheeze is a common disorder with peak incidence during infancy. In several epidemiologic studies, the reported prevalence of infant wheeze has been around 25% (1–3). Early wheezing illnesses vary in clinical presentation and disease course (4). It is currently believed that infants and pre-school children with persistent or multiple-trigger wheeze more often have airways characterized by chronic allergic inflammation typical of asthma (5–7).

Risk factors have been described for early onset of wheeze (1, 3, 8–12), and children with infantile eczema have an increased risk of asthma later in childhood (13). Recurrent abdominal pain has been found to be associated with wheeze or asthma or associated with an increased risk of developing asthma (14–18), but this was not confirmed in a prospective study (19).

Characteristics of early onset of wheeze and wheeze-related symptoms in relation to asthma development have been studied in order to understand the transition of wheeze into asthma in school children (4, 20, 21). So far, the clinical value has been limited (22). The aim of the present study was to identify clinical risk factors for asthma in 8-yr-old children with infant wheeze in a population-based setting.

Methods

Study design

Barn/Children, Allergy and Milieu in Stockholm, an Epidemiological study (BAMSE) is a population-based birth cohort consisting of 4089 children born between 1994 and 1996 in

Stockholm, Sweden. Data on allergic heredity and various baseline characteristics were obtained through parental questionnaires when the children were 2 months old (median age). This has previously been described in detail (23).

Questionnaires focusing on key exposures and symptoms related to allergic disease were answered by the parents through postal questionnaires when the children were 1, 2, 4, and 8 yr of age. At the 8-yr follow-up, 84% of the children remained in the study. Approval was obtained from the Ethics Committee of Karolinska Institutet, Stockholm. Informed consent was obtained from all parents.

Definitions of baseline characteristics, infant wheeze, comorbidity, and health outcomes

The definitions for baseline characteristics and early comorbidity are described in Table S1. *Infant wheeze* was defined as having at least one episode of wheezing or whistling breathing sounds during the 2 first years of life. *Asthma at age 8 yr* was defined as at least four episodes of wheeze in the last 12 months or at least one episode of wheeze during the same time period in combination with occasional or regular treatment with inhaled glucocorticosteroids (24). *Sensitization to food at age 4 yr* was assessed using blood samples screened with fx5[®], a specific IgE (Immunoglobulin E) test containing a mix of common food allergens: cow's milk, egg white, soy bean, peanut, cod fish, and wheat (ImmunoCAP[™], Phadia AB, Uppsala, Sweden). Sera with a positive test in fx5[®] were defined as IgE antibody levels ≥ 0.35 kU_A/L (kilo unit antibodies per liter).

Statistical analyses

Exact binomial confidence intervals were calculated for all proportions. Early symptoms and baseline characteristics that might influence asthma development and occurrence of infant wheeze were tested between the group of children originally enrolled and the group included in the study to detect differences as regards sex, heredity, breast feeding duration, parental socio-economic status, pre-term delivery, tobacco smoke exposure, and early allergic symptoms. This was done by comparing proportions with 95% confidence intervals. Non-overlapping confidence intervals were considered significantly different. Proportional Venn diagrams were calculated for asthma, eczema, and allergic rhinitis at age 8 yr for infant wheezers and non-wheezers, respectively, as well as for markers of increased wheeze severity. The chi-square test was used for detecting significant differences in disease prevalence between wheezers and non-wheezers and for the assessment of potential confounders to recurrent abdominal pain.

Associations between sex, heredity, characteristics of infant wheeze, early comorbidity, and asthma at age 8 yr for the infant wheezers were analyzed using logistic regression. The results are expressed as adjusted odds ratios (aOR) with 95% confidence intervals (CI). Besides from prior knowledge, confounders were chosen by testing several covariates in the regression model. Covariates resulting in a 5% OR change or more were considered confounders. The multivariate

regression model (*model 1*) included adjustments for sex, heredity, exposure at home to dampness or mould, maternal age, and exposure to tobacco smoke.

Further, confounders in combination with infant eczema, recurrent abdominal pain, and variables related to abdominal pain were tested in a second multivariate regression model (*model 2*).

To be included in this study, we required participation at the 1-, 2-, and 8-yr follow-ups and information on symptoms related to wheeze, eczema, and rhinorrhea at 1 and 2 yr of age and on asthma at age 8 yr. These criteria were met by 3251 children. All statistical analyses were performed using the STATA Statistical Software, version 11, (College Station, TX, USA).

Results

Among the 3251 children included in our analyses, wheeze ever during the 2 first years of life was reported in 823 children (25%), hereafter called infant wheezers. Male sex, heredity, young maternal age at delivery, allergic comorbidity as well as exposure to dampness, mold, or tobacco smoke were more common in the infant wheezing group (Table 1). Fig. 1 shows the prevalence of allergic disease at age 8 yr among children with and without infant wheeze. Among the infant wheezers, 14% ($n = 116$) had asthma at age 8 yr compared with 4% ($n = 90$) for the infant non-wheezers ($p < 0.001$), equivalent to an almost fourfold risk of asthma (aOR 3.68, 95% CI 2.74–4.96). Moreover, 33% of the infant wheezers had any of asthma, rhinitis, or eczema at age 8 yr, compared with 22% for the non-wheezers, ($p < 0.001$).

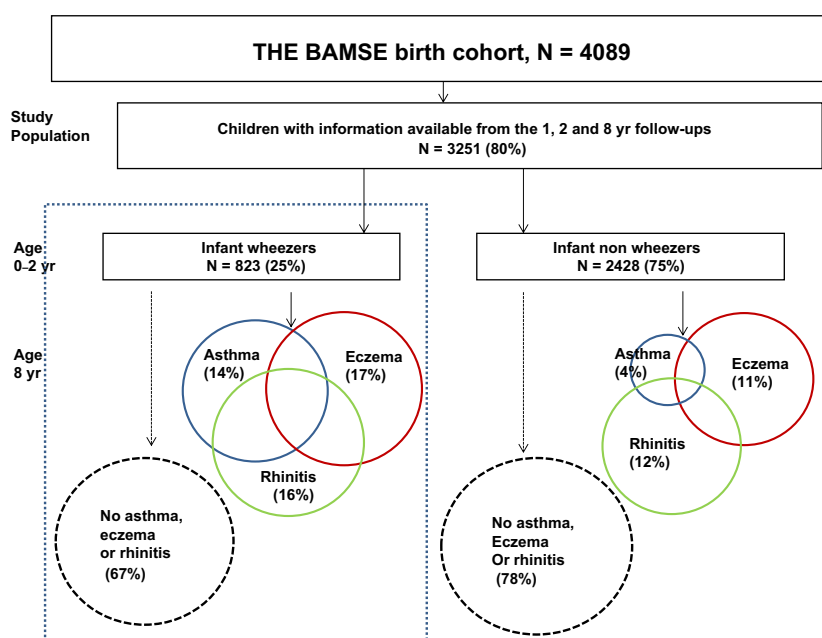
As we aimed at studying clinical risk factors for transition of wheeze into asthma, the following analyses are limited to the 823 children with infant wheeze. The association between sex, heredity, characteristics of infant wheeze, and early comorbidity in relation to asthma at the age of 8 yr among children with infant wheeze expressed as adjusted odds ratios with 95% confidence intervals is shown in Table 2. No sex difference was seen for the risk of asthma in the infant wheezers (aOR 1.10, 95% CI 0.73–1.67 for boys compared to girls). Allergic heredity increased the risk of asthma at age 8 yr (aOR 1.53, 95% CI 1.02–2.30).

Wheeze persistency, number of wheeze episodes, and use of inhaled steroids were associated with increased odds ratios (aOR 5.11, 95% CI 2.51–10.41, aOR 3.41, 95% CI 2.09–5.56, and aOR 3.42, 95% CI 2.20–5.32), respectively. These characteristics of infant wheeze, describing increased severity of wheeze, were largely overlapping (Fig. 2). The cutoff for increased severity of wheeze was set at three episodes because this was the median of wheezing episodes during the first 2 yr of life.

Infant eczema was associated with an increased risk of asthma (aOR 2.31, 95% CI 1.52–3.49), while infant rhinorrhea was not (aOR 1.32, 95% CI 0.75–2.34). Cough was common in the entire group of infant wheezers (almost 96% presented with some kind of cough), and as a consequence cough did not significantly increase the risk of asthma. Moreover, recurrent abdominal pain between 6 months and 2 yr also increased the

Table 1 Distribution of baseline characteristics and parental reported symptoms during the first 2 yr of life in relation to infant wheezing, (N = 3251)

	Infant wheezers		Infant non-wheezers		p-Value
	N = 823		N = 2428		
	n	% (95% CI)	n	% (95% CI)	
Baseline characteristics					
Sex (boy)	482	58.6 (55.1–62.0)	1163	47.9 (45.9–49.9)	<0.001
Allergic heredity	302	37.3 (33.9–40.7)	676	28.0 (26.2–29.8)	<0.001
Maternal age at delivery ≤25 yr	83	10.1 (8.1–12.3)	147	6.1 (5.1–7.1)	<0.001
Home dampness or mould	91	11.1 (9.0–13.4)	167	6.9 (5.9–8.0)	<0.001
Tobacco smoke exposure	128	15.6 (13.2–18.3)	276	11.4 (10.1–12.7)	0.002
Parental reported symptoms during the first 2 yr of life					
Infant eczema	249	30.3 (27.1–33.5)	572	23.6 (21.9–25.3)	<0.001
Infant rhinorrhea	97	11.8 (9.7–14.2)	134	5.5 (4.6–6.5)	<0.001
Use of inhaled steroids	151	18.3 (15.8–21.2)	20	0.8 (0.5–1.3)	<0.001
Croup-like cough	368	44.7 (41.3–48.2)	329	13.6 (12.2–15.0)	<0.001
Night cough	748	91.1 (88.9–93.0)	1677	69.2 (67.3–71.0)	<0.001
Cough during activity	543	66.2 (62.9–69.4)	967	39.8 (37.9–41.8)	<0.001
Food hypersensitivity	165	20.6 (17.9–23.6)	319	13.4 (12.1–14.9)	<0.001
Acute media otitis	453	55.2 (51.7–58.6)	1050	43.5 (41.5–45.5)	<0.001
Recurrent abdominal pain	77	9.4 (7.5–11.6)	127	5.2 (4.4–6.2)	<0.001

**Figure 1** Subjects of the BAMSE birth cohort included in the study population and outcome of asthma, rhinitis, and eczema at age 8 yr. Venn diagrams are proportional for the allergic diseases at age 8 yr.

risk of asthma among the infant wheezers (aOR 2.33, 95% CI 1.30–4.16).

To identify potential confounders that might explain the observed association between recurrent abdominal pain and asthma, we examined the distribution of recurrent abdominal pain in relation to these potential confounding factors among the infant wheezers (Table S2). Recurrent abdominal pain between age 6 months and 2 yr was more common among infant wheezers with a doctor's diagnosis of food allergy, food hypersensitivity, diarrhea, and symptoms at ingestion of cows'

milk or wheat before age 2 yr ($p < 0.05$). In addition, recurrent abdominal pain was more common among the wheezers who were exposed to parental tobacco smoking ($p = 0.018$). In a subgroup analyses of the 617 infant wheezers with available information on sensitization to common food allergens at age 4 yr, comparable prevalence of recurrent abdominal pain was observed in children with and without sensitization ($p = 0.89$).

The association between recurrent abdominal pain and factors associated with recurrent abdominal pain in relation

Table 2 Associations between sex, allergic heredity, characteristics of infant wheeze, and early comorbidity in relation to asthma at age 8 yr among children with infant wheeze, (N = 823)

	Asthma at age 8 yr			
	N	n	%	aOR (95% CI)*
Total	823	116	14.1	
Sex†				
Girl	341	46	13.5	1.00 (reference)
Boy	482	70	14.5	1.10 (0.73–1.67)
Allergic heredity‡				
No	508	59	11.6	1.00 (reference)
Yes	302	54	17.9	1.53 (1.02–2.30)
Wheeze persistency				
1st year of life only	218	11	5.0	1.00 (reference)
2nd year only	353	51	14.4	3.43 (1.69–6.96)
Both years	249	53	21.3	5.11 (2.51–10.41)
Wheeze episodes				
≤2 episodes	354	24	6.8	1.00 (reference)
≥3 episodes	469	92	19.6	3.41 (2.09–5.56)
Use of inhaled steroids				
No	672	70	10.4	1.00 (reference)
Yes	151	46	30.5	3.42 (2.20–5.32)
Infant eczema				
No	574	62	10.8	1.00 (reference)
Yes	249	54	21.7	2.31 (1.52–3.49)
Infant rhinorrhea				
No	726	98	13.5	1.00 (reference)
Yes	97	18	18.6	1.32 (0.75–2.34)
Croup-like cough				
No	455	54	11.9	1.00 (reference)
Yes	368	62	16.9	1.45 (0.96–2.18)
Night cough				
No	73	12	16.4	1.00 (reference)
Yes	748	103	13.8	0.73 (0.38–1.43)
Cough during activity				
No	277	29	10.5	1.00 (reference)
Yes	543	87	16.0	1.53 (0.97–2.44)
Acute media otitis				
No	368	48	13.0	1.00 (reference)
Yes	453	67	14.8	1.07 (0.71–1.61)
Recurrent abdominal pain				
No	744	97	13.0	1.00 (reference)
Yes	77	19	24.7	2.33 (1.30–4.16)

aOR, adjusted odds ratio; CI, confidence interval.

*Adjustment made for sex, heredity, dampness or mold at home, tobacco smoke exposure, and maternal age.

†Adjustment made for all potential confounders besides sex.

‡Adjustment made for all potential confounders besides heredity.

to asthma at age 8 yr among wheezy infants is shown in Table 3. Multivariate analyses adjusting for sex, heredity, dampness or mold at home, tobacco smoke exposure, and maternal age (*Model 1*) showed increased odds of asthma at 8 yr for food allergy-related factors such as a doctor's diagnosis of food allergy (aOR 2.66, 95% CI 1.52–4.63), infant eczema (aOR 2.30, 95% CI 1.52–3.48), food hypersensitivity (aOR

1.92, 95% CI 1.22–3.02), symptoms at ingestion of hens' egg (aOR 2.40, 95% CI 1.15–5.00), or wheat (aOR 3.15, 95% CI 1.08–9.21). When we additionally adjusted the analyses for these abdominal-pain-related factors (*Model 2*), this mutual adjustment resulted in loss of significance for the majority of them. However, significant associations remained for recurrent abdominal pain (aOR 2.31, 95% CI 1.20–4.47) and infant eczema (aOR 1.99, 95% CI 1.24–3.20). Thus, among infant wheezers, heredity, increased severity of wheeze, infant eczema, and recurrent abdominal pain seemed to be independent risk factors for asthma at age 8 yr.

To assess potential risk differences for asthma depending on number of risk factors in the infant wheezers, we combined the independent risk factors into four groups (Table 4). In the group with three or four risk factors (n = 92), 32 (38%) had asthma at age 8. This is to be compared with the infant wheezers without heredity, eczema or recurrent abdominal pain, and only mild wheeze (n = 151) out of whom only 11 (7%) had asthma at school age. For the 'intermediate risk' group with one (n = 329) or two (n = 236) risk factors, the proportion of children with asthma at age 8 yr was 9% and 16%, respectively.

Discussion

In this large prospective, population-based birth cohort including 3251 Swedish children followed over the first 8 yr of life, 25% (n = 823) wheezed before the age of 2 yr. These children had an almost fourfold risk of asthma at age 8 yr compared with non-wheezers. We identified four independent clinical risk factors among the infant wheezers for having asthma at age 8 yr. These were heredity, increased severity of wheeze, infant eczema, and recurrent abdominal pain. In the group of infant wheezers with three or four of these risk factors, 38% suffered from asthma at age 8 yr, compared with 7% in the group with none of these risk factors.

The major strengths of this study are the population-based study design with a large unselected group of children, the high participation rate, as well as the limited loss to follow-up, rendering high generalizability. Information on various baseline characteristics was collected before symptom development. Outcome and exposure assessment was detailed. Moreover, we had a sufficient number of children with infant wheeze to allow for analysis of persistency of disease up to age 8 yr.

Misclassification of symptoms and exposures is a potential limitation because all information was based on parental reported questionnaires. However, the wheeze definition was in accordance with the ISAAC study criteria (25) and the eczema definition a validated, although slightly different, version of the UK working party's definition (26). Recurrent abdominal pain between age 6 and 24 months was reported solely as presence or absence. It would have been of benefit to have information on symptom frequency. Misinterpretation of discomfort at wheeze as abdominal pain by parents cannot be completely ruled out. Irrespective of this, abdominal pain of the infant as perceived by the parents is nevertheless a risk marker for asthma at 8 yr. Yearly follow-ups during the first 2 yr of life minimize misclassification of symptoms. Asthma at age 8 yr

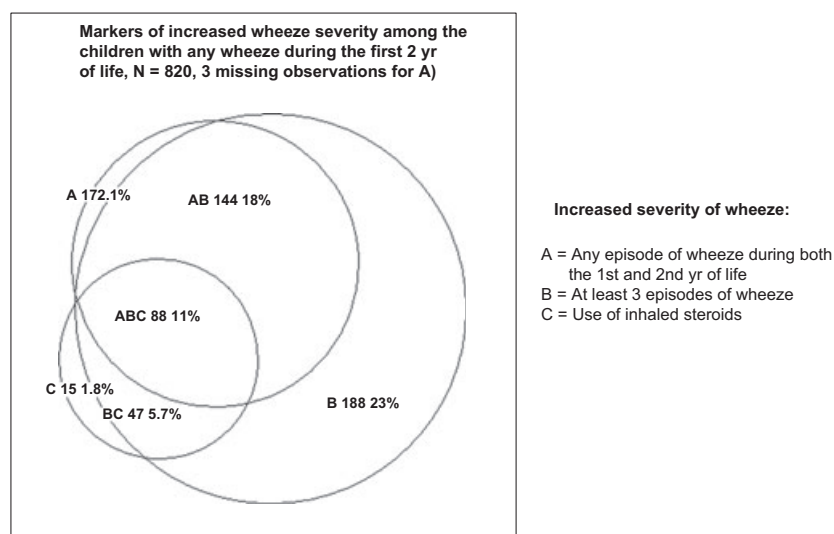


Figure 2 The infant wheezers up to 2 yr of age, of whom 249 had persistent wheeze (A), 467 had at least three wheeze episodes (B), and 150 had used inhaled steroids (C). Venn diagrams are proportional.

was assessed using a definition of asthma where wheeze symptoms and asthma medication were combined (27, 28).

Albeit a large population sample, some subgroup sizes were small, rendering some statistical uncertainty. The IgE antibody levels were assessed at a later time point than the early symptoms. A positive fx5[®] at 4 yr still might reflect food sensitization at age 2 yr because IgE antibody levels are elevated after clinical tolerance has occurred. In addition, detailed data on symptoms after ingestion of common food allergens were available at ages 1 and 2 yr enabling assessment and adjustment for suspected food hypersensitivity.

About 25% of the children wheezed at least once during their first 2 yr of life which is in line with previous studies (1, 2, 29, 30). The higher prevalence of infant wheeze in boys shown previously (1, 29) was confirmed. Among the infant wheezers, 14% had asthma at age 8 yr which is comparable to previous studies (4, 20). Male sex remained a risk factor for wheeze or bronchial hyper-reactivity in school age among infant wheezers in two European birth cohorts (31, 32). However, we observed no sex difference in relation to asthma progression in this study. Possible explanations for this might be different inclusion criteria or timing of outcome assessment.

Allergic heredity, increased severity of wheeze, infant eczema, and recurrent abdominal pain independently increased the risk of asthma in school age among children with infant wheeze. An association between heredity, wheeze severity characteristics, and comorbidity of eczema and asthma development has been shown by others (4, 33, 34). Additionally, rhinitis in infancy has been associated with both increased and decreased risk of asthma in school age among infant wheezers (12, 34, 35). We saw no such association. The observed association between recurrent abdominal pain in infancy and later asthma among infant wheezers has been sparsely reported (18), possibly due to lack of information on early abdominal

pain in previous cohorts focusing on asthma. In a large prospective study, infantile colic did not increase the risk of school age asthma (19), whereas it was reported as strong risk factor for asthma in pre-school age in a smaller study, where information on infantile colic was collected from clinical records (17). In another birth cohort study, early recurrent abdominal pain was associated with an increased risk of asthma in pre-school age, but not in school age (14).

As abdominal pain could be caused by food hypersensitivity and food allergy, we explored how potential confounders related to food hypersensitivity and food allergy affected the association between recurrent abdominal pain in infancy and asthma at age 8 yr among the infant wheezers. Interestingly, recurrent abdominal pain remained a significant and independent risk factor, indicating that food hypersensitivity or allergy *per se* might not be a risk factor for asthma in school age among the wheezers. Moreover, no significant associations were found between recurrent abdominal pain and specific IgE antibodies to common food allergens at age 4 yr. However, we cannot exclude that other factors may confound the relation between recurrent abdominal pain in infancy and asthma in school age. For example, infantile colic has been associated with several underlying causes and related to allergic disease (17). Some studies have reported reduced abdominal symptoms after elimination of cows' milk from the mother's diet. Cows' milk consumption in children has also been associated with constipation (36), a symptom with a prevalence of 1–30% in the pediatric population (36, 37) that might be reported as recurrent abdominal pain. Gastroesophageal reflux disease (GERD) has been associated with abdominal pain (38), and a higher prevalence of GERD has been shown among children with asthma compared with non-asthmatics (39). As we lacked information on constipation and GERD, the association between these potential abdominal pain confounders and school age asthma could not be evaluated. We suggest that

Table 3 Association between recurrent abdominal pain and factors associated with recurrent abdominal pain during the first 2 yr of life in relation to asthma at age 8 yr among children with infant wheeze. Results expressed as adjusted odds ratios with 95% confidence intervals, (N = 823)

Asthma at age 8 yr					
	N	n	%	Model 1 aOR (95% CI)*	Model 2 aOR (95% CI)†
Recurrent abdominal pain					
No	744	97	13.0	1.00 (reference)	1.00 (reference)
Yes	77	19	24.7	2.33 (1.30–4.16)	2.31 (1.21–4.43)
A doctor's diagnosis of food allergy					
No	741	94	12.7	1.00 (reference)	1.00 (reference)
Yes	81	22	27.2	2.66 (1.52–4.63)	1.89 (0.87–4.12)
Infant eczema					
No	574	62	10.8	1.00 (reference)	1.00 (reference)
Yes	249	54	21.7	2.31 (1.52–3.49)	2.03 (1.28–3.21)
Food hypersensitivity					
No	635	77	12.1	1.00 (reference)	1.00 (reference)
Yes	165	36	21.8	1.93 (1.22–3.04)	1.33 (0.69–2.58)
Symptoms at ingestion of cows' milk					
No	746	100	13.4	1.00 (reference)	1.00 (reference)
Yes	77	16	20.8	1.65 (0.90–3.03)	0.61 (0.26–1.43)
Symptoms at ingestion of wheat					
No	807	110	13.6	1.00 (reference)	1.00 (reference)
Yes	16	6	37.5	3.15 (1.08–9.20)	2.26 (0.66–7.69)
Diarrhea					
No	608	88	14.5	1.00 (reference)	1.00 (reference)
Yes	214	28	13.1	0.81 (0.50–1.30)	0.57 (0.34–0.97)

aOR, adjusted odds ratio; CI, confidence interval.

*Model 1: Adjustment made for sex, heredity, dampness or mold at home, tobacco smoke exposure, and maternal age.

†Model 2: Besides adjustment as in model a, each multivariate logistic regression model consists of recurrent abdominal pain, doctor's diagnosis of food allergy, infant eczema, food hypersensitivity, symptoms at ingestion of cows' milk and wheat, and diarrhea.

future research with focus on asthma progression should assess prevalence, severity, and frequency of early gastrointestinal symptoms and GERD.

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Table 4 Combination of the four independent infant risk factors: allergic heredity, increased severity of wheeze (≥ 3 episodes of wheeze), infant eczema, recurrent abdominal pain, and risk of asthma at age 8 yr (N = 823)

Infant risk factor	N	n	% (95% CI)	aOR (95% CI)*
Wheeze <3 episodes	151	11	7.3 (3.7–12.7)	1.00 (reference)
One risk factor	329	29	8.8 (6.0–12.4)	1.24 (0.60–2.57)
Two risk factors	236	38	16.1 (11.6–21.4)	2.42 (1.19–4.92)
Three or four risk factors	92	35	38.0 (28.1–48.8)	7.70 (3.62–13.68)

aOR, adjusted odds ratio; CI, confidence interval.

*Adjustment made for sex, dampness or mold at home, tobacco smoke exposure, and maternal age.

In summary, in this prospective, population-based birth cohort, 14% of the infant wheezers had developed asthma at age 8, which is equivalent to an almost fourfold risk compared with non-wheezers. There was an augmented risk of asthma progression in infant wheezers with allergic heredity, increased severity of wheeze combined with eczema or recurrent abdominal pain. Among wheezing children with three or four of these risk factors, 38% had asthma at age 8 yr.

Acknowledgments

The authors thank the participating BAMSE cohort children and families and the BAMSE study team, in particular our data base managers Eva Hallner and André Lauber. The study was financially supported by The Swedish Research Council, the Swedish Heart and Lung Foundation, the County Council of Stockholm, and the foundation of 'Frimurarna Barnhuset'.

Conflict of interest

No author has any conflict of interest to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Definitions of the baseline characteristics and comorbidities investigated during the 2 first years of life.

Table S2. Distribution of potential confounders in relation to recurrent abdominal pain in the infant wheezers.

Supporting Information for online publication

Neuman et al; Heredity, severity of wheeze, eczema and abdominal pain in relation to asthma at eight years among infant wheezers

Table S1. Definitions of the baseline characteristics and comorbidities investigated during the 2 first years of life.

Baseline characteristic or comorbidity	Definition
Allergic heredity*	Mother and/or father with a doctor's diagnosis of asthma and asthma medication and/or a doctor's diagnosis of hay fever in combination with furred pets- and/or pollen allergy at baseline
Maternal age*	Mother's age 25 years or less at delivery
Home dampness or mould*	Current or past smell of mould and visible mould in the home in the last year and/or known dampness damage in the home and building construction or visible condensation on the inner surface of the windows combined with known dampness damage in the building construction
Tobacco smoke exposure*	Mother smoked at least one cigarette daily at 2 months of age of the child and/or at any point of time during pregnancy
White collar worker*	At least one parent being a white collar worker
Wheeze persistency†	Wheezing age 0 to 1 years only, age 1 to 2 years only or during both years
Wheeze episodes†	Wheeze less than 3 times or at least 3 times
Use of steroid inhalants†	Prescribed corticosteroid inhalants due to symptoms of wheezing and whistling breathing sounds or forced or heavy breathing
Infant eczema†	Dry skin and itchy rash with duration of 2 weeks or more and typical localisation (face or arm/leg extension surfaces or arm/leg flexures or wrist/ankle flexures) and/or a doctor's diagnosis of eczema
Infant rhinorrhoea†	Runny or blocked nose with duration of at least 2 months during the last 12 months
Croup-like cough†	Breathing difficulties combined with barking cough
Nocturnal cough†	Troublesome cough at night
Cough during activity†	Cough during play, laughter or while being outdoors
Acute media otitis†	Otitis or otosuppurative symptoms treated with antibiotics
Recurrent abdominal pain†	Recurrent episodes of abdominal pain after the age of 6 months
Food hypersensitivity†	At least one symptom related to ingestion of at least one certain food: asthma, itchy eyes and/or runny nose, facial oedema, urticaria, eczema or vomiting/diarrhoea
Symptoms at ingestion of cows' milk/hens' egg/wheat†	Symptoms related to ingestion of hens' egg/cows' milk/wheat: asthma, itchy eyes and/or runny nose, facial oedema, urticaria, eczema or vomiting/diarrhoea
Diarrhoea†	Recurrent or long-term episodes of diarrhoea
Use of antibiotics†	Having received antibiotics for any reason

*Information collected at baseline (median age 2 months).

†Information collected at age 1 and 2 years.

Table S2. Distribution of potential confounders in relation to recurrent abdominal pain in the infant wheezers, (N=823)

		N	n	%	p-value
Recurrent abdominal pain		821	77	9.4	-
Potential confounder					
Sex	Girl	341	36	10.6	0.329
	Boy	480	41	8.5	
Allergic heredity	No	507	43	8.5	0.243
	Yes	301	33	10.6	
Doctor's diagnosis of food allergy	No	740	62	8.4	0.003
	Yes	81	15	18.5	
Infant eczema	No	572	49	8.6	0.226
	Yes	249	28	11.2	
Use of steroid inhalants	No	670	60	9.0	0.381
	Yes	151	17	11.3	
Acute media otitis	No	368	28	7.6	0.112
	Yes	451	49	10.9	
Use of antibiotics	No	150	13	8.7	0.733
	Yes	669	64	9.6	
Food hypersensitivity	No	635	42	6.6	0.000
	Yes	164	34	20.7	
Pneumonia	No	698	67	9.6	0.624
	Yes	122	10	8.2	
Diarrhoea	No	607	35	5.8	0.000
	Yes	214	42	16.9	
Exclusive breast feeding $\geq$ 4 months	No	185	18	9.7	0.857
	Yes	635	59	9.3	
Maternal age $\leq$ 25 years at delivery	No	738	71	9.6	0.479
	Yes	83	6	7.2	
White collar worker	No	147	20	13.6	0.053
	Yes	673	57	8.5	
Tobacco smoke exposure	No	691	57	8.2	0.018
	Yes	128	19	14.8	
Preterm delivery	No	759	72	9.5	0.712
	Yes	62	5	8.1	
Symptoms at ingestion of cows' milk	No	744	56	7.5	0.000
	Yes	77	21	27.3	
Symptoms at ingestion of hens' egg	No	771	69	8.9	0.108
	Yes	43	7	16.3	
Symptoms at ingestion of wheat	No	805	70	8.7	0.000
	Yes	16	7	43.7	
Fx5 positive at age 4 years	No	506	43	8.5	0.893
	Yes	111	9	8.1	