

Factors in Infancy and Childhood Related to Reduced Lung Function in Asthmatic Children: A Birth Cohort Study (BAMSE)

Jenny Hallberg, PhD,^{1,2,31,2,3*} Martin Anderson, MD, PhD,^{1,41,4}
Magnus Wickman, MD, PhD,^{2,3,52,3,5} and Magnus Svartengren, MD, PhD^{1,61,6}

Summary. Changes in lung function due to childhood asthma have been reported to occur before school age, and to persist throughout life. The aim was to assess the relationship between aspects of lung function and asthma over time in 4,089 children participating in the large population-based birth cohort BAMSE. Questionnaires were administered at 1, 2, 4, and 8 years of age. At 4 and 8 years, children were invited to a clinical examination, in which 2,965 and 2,630 children participated, respectively. The examinations included blood sampling for evaluation of sensitization to airway allergens ($n = 2,053$), peak expiratory flow (PEF) measurements at 4 and 8 years ($n = 1,957$), and forced expiratory flows ($n = 2,455$) at 8 years. Asthma onset before the age of 4 years, but no thereafter, was at 8 years associated with impaired spirometric flows. This was seen irrespective of symptom presence after the age of 4. Reduced PEF growth between the age of 4 and 8 was seen only for the group of children with early onset transient asthma, while an association between sensitization and lung function was only seen in the late-onset asthma group. In conclusion, school children with asthma have reductions of spirometric flows when categorized as persistent or transient early onset asthma, even if this latter group of children is completely symptom-free at school age. **Pediatr Pulmonol.** 2010; 45:341–348. © 2010 Wiley-Liss, Inc.

Key words: childhood asthma; lung function; persistent asthma; transient asthma; sensitization.

INTRODUCTION

It is now generally accepted that a number of distinct phenotypes of childhood asthma exist, and that some of these are more strongly associated with impaired lung function than others.^{1–5} The timing of this asthma associated impact on lung function has been suggested to take place already before school age, and there is

also evidence of tracking of lung function from birth or childhood into adolescent or adult life,^{6–8} possibly generating a population that is at risk of relapse of asthma or other lung diseases such as COPD.⁹ These conclusions are primarily drawn from longitudinal birth cohort studies, where the most prominently studied measures of lung function are those related to flow impairments.

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

¹Division of Occupational Medicine, Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden.

²Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden.

³Department of Pediatrics, Sachs' Children's Hospital, Stockholm, Sweden.

⁴Unit of Respiratory and Allergic Diseases, Department of Internal Medicine, Södersjukhuset, Stockholm, Sweden.

⁵Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

⁶Department of Occupational and Environmental Health, Stockholm County Council, Stockholm, Sweden.

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*Correspondence to: Jenny Hallberg, PhD, Department of Pediatrics, Sachs' Children's Hospital, SE-171 76 Stockholm, Sweden.
E-mail: jenny.hallberg@sodersjukhuset.se

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At the 4-year follow-up of the BAMSE study,¹⁰ we showed that peak expiratory flow (PEF) was impaired in children with asthma in the first 2 years of life (but not in those who had an asthma debut after the age of 2) compared to children who never had asthma. This effect was particularly pronounced in girls. The current study is an 8-year follow-up of the same population, using more elaborate methods to measure lung function.

The aim of this study was to assess the relationship between different aspects of lung function/lung function growth and asthma phenotypes in a population-based birth cohort (BAMSE) of 4,089 children.

MATERIALS AND METHODS

Study Subjects

Between 1994 and 1996, 4,089 newborn children in the Stockholm region were included in a prospective study, BAMSE.^{11,12} Questionnaires on respiratory symptoms including symptoms of asthma, current asthma medication, and doctor's diagnosis of asthma were mailed to the parents when the children were 1, 2, 4, and 8 years old, with response rates of 96%, 94%, 92%, and 84%, respectively. At 4 and 8 years, children were invited to a clinical examination including lung function testing, in which 2,965 and 2,630 children participated, respectively.

Measurement of Lung Function

Peak expiratory flow was measured at both 4 and 8 years of age, using the same normal-range Ferraris Peak Flow Meter[®] (Ferraris Medical Limited, London, UK) at both occasions. The highest obtained PEF value from several successive attempts was used for analysis, provided that the child's effort was coded as being maximal by the test leader, and that the two highest readings were reproducible (within 15% of each other).

Maximum expiratory flow volume (MEFV) tests were performed at the 8-year follow-up, using a spirometer (2200 Pulmonary Function Laboratory; Sensormedics, Anaheim, CA, USA). All children performed several MEFV measurements sitting, using a nose clip. The highest values of forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV₁), and forced expiratory volume in 0.5 sec (FEV_{0.5}) were extracted and used from analysis, provided that the child's effort was coded as being maximal by the test leader, the MEFV curve passed visual quality inspection, and that the two highest readings were reproducible according to ATS/ERS criteria.¹³

Measurements of Specific IgE Antibodies

Blood samples were taken at the age of 4 and 8. At both occasions, allergen-specific IgE antibodies were measured against a mix of common inhalant allergens (birch pollen, timothy grass pollen, mugwort pollen, house-dust

mite, mould, and cat, dog, and horse dander) using the Pharmacia CAP System[™] (Phadia AB, Uppsala, Sweden) in a certified laboratory (the Unit of Clinical Immunology and Allergy, Department of Medicine, Karolinska University Hospital). An IgE value greater than 0.35 kU/L was regarded as positive. Positive tests were further analyzed for allergen-specific IgE antibodies to the allergens listed above in groups of perennial (cat, dog, horse dander, and mite) and seasonal allergens (mould, birch, timothy, and mugwort).

Definition of Asthma Groups

Based on answers from the questionnaire, the children were defined as being either asthmatic or non-asthmatic at the age of 2, 4, and 8 years. Asthma at 2 years of age was defined as >3 episodes of wheezing between birth and 2 years of age, combined either with inhaled steroids or signs of hyper-reactivity (wheezing or severe coughing at exaltation and cold weather, or disturbing cough at night) without ongoing cold. At 4 and 8 years of age, asthma was defined as >3 episodes of wheezing over the last year, or 1 episode if the child had been given inhaled steroids.^{12,14} Transient asthma was defined as asthma in the first 4 years, but not at 8 years, persistent asthma as asthma in the first 4 years and at 8 years, and late-onset asthma (representing incident cases after the age of 4) as asthma at 8 years, but not during the first 4 years.

Statistical Analysis

Groups of children were compared by *t*-test regarding height and weight. Corresponding comparisons for parental heredity, the mother's smoking habits during pregnancy, and socioeconomic index were made by chi-squared test.

The association between asthma groups and lung function variables were assessed by multiple linear regressions. When appropriate, lung function variables were adjusted for age, height, and sex. The residuals were plotted and visually inspected. Socioeconomic status, sensitization status, and maternal smoking during pregnancy (assessed as binary variables) were evaluated as possible confounders, but were not found to be independently correlated with the outcome. The variables were evaluated as potential effect modifiers for the relationship between lung function and asthma group by introducing an interaction term in the model. Children were categorized as sensitized if levels over the threshold value were seen in blood samples from either 4 or 8 years of age for all, seasonal or perennial allergens. For all analyses including sensitization data, the reference group (no sensitization) consisted of children without any sensitization both at 4 and 8 years. To avoid loss of power due to exclusion of subjects, the maximal number of children available for each lung function variable was used

in the analysis. *P*-values of <0.05 were considered statistically significant. Analyses were performed with the Stata 9.2 software package (StataCorp LP, College Station, TX).

The study was approved by the Ethical Committee of Karolinska Institutet, Stockholm, Sweden. Parents were informed orally and by written information at Baby Health Clinics when the children were 2 months of age by a nurse not participating in the study. When parents gave mutual consent to participate, the baby's personal number was sent to the BAMSE office. With the help of our national personal number register we were able to identify the mother and her address. The parents were invited to participate by returning a posted questionnaire.

RESULTS

Study Sample

Of the 4,089 children of the original cohort, 2,498 (61%) could be classified having or not having asthma and participated in the lung function testing at 8 years of age. The corresponding number for those who participated at both 4 and 8 years was 2,297 (56%). Blood samples for evaluation of sensitization at 4 and/or 8 years were available for 2,053 (82%) of the 2,498 participating at 8, and 2,010 (88%) of those participating at both 4 and 8. A detailed description of the number of children with acceptable lung function measures are presented in E-Table 1. Characteristics of participating and non-participating children are presented in E-Table 2 in the online supplement. In brief, participating children were more likely to have asthma and have a high socioeconomic index, compared to non-participating children.

Prevalence of Asthma

Four hundred six (16%) of the participating children reported enough symptoms to fulfill the criteria of asthma

at any time point during the first 8 years of life (Table 1). Compared with the never asthma group, maternal smoking during pregnancy was more common in those with transient asthma, whereas sensitization and parental allergy were associated to persistent or late-onset asthma. Children with high socioeconomic index were under-represented in the persistent asthma group.

Asthma and Lung Function Measurements at 8 Years of Age

As shown in Table 2 and Figure 1, onset of asthma between birth and the age of 4 (the transient and persistent asthma groups) was associated with impaired PEF, FEV₁, and FEV_{0.5} measured at the age of 8, irrespective of whether or not the symptoms persisted beyond the age of 4. There were no significant effects of asthma on FVC.

Children with asthma during the first 2 years of life, but not thereafter, also presented with significantly lower PEF, as well as low FEV_{0.5} at 8 years, compared to children who never had asthma (PEF at 8 years coeff. -12.4 L/min $P=0.001$; FEV_{0.5} at 8 years coeff. -45.7 ml $P=0.024$), but did not differ significantly in FVC or FEV₁ (data not shown).

Asthma and PEF Growth

The growth of PEF between the age of 4 and 8, adjusted for change in height and age, was significantly lower for the group of children with transient asthma, but not for the group of persistent or late onset of asthma (Table 3). Although the children in the transient asthma group did no longer fulfill our criterion of asthma, they were not necessarily completely symptom-free between the ages of 4 and 8; when comparing symptoms during the last 12 months between all the children of the transient group and those of the group that never had asthma, the former group of children more often had 1–3 episodes of wheeze

TABLE 1—Characteristics of Children With Asthma Data 0–8 Years Who Participated in the Clinical Examination at 8 Years

	Never asthma	Transient asthma (0–4 years)	Late-onset asthma (4–8 years)	Persistent asthma (0–8 years)
No. of children (% of tot.)	2,092 (83.8)	220 (8.8)	79 (3.2)	107 (4.3)
Female sex (%)	1,064 (50.9)	81 (36.8)**	35 (44.3)	42 (39.3)
Mean age in years (min.–max.)	8.3 (7.3–10.2)	8.3 (7.3–9.4)	8.4 (7.4–10.4)	8.4 (7.3–9.4)
Mean height in cm (min.–max.)	132.1 (114.2–156)	132.8 (116.0–157)	133.5 (118.5–150.8)*	131.0 (116.0–148.0)
Sensitization at 4 or 8 years n/N (%)	473/1,704 (27.8)	60/187 (32.1)	50/70 (71.4)***	56/92 (60.9)***
Parental atopy in Q ₀ n/N (%)	613/2,077 (29.5)	78/218 (35.8)	36/78 (46.2)**	57/104 (54.8)***
Maternal atopy in Q ₀ n/N (%)	320/1,072 (15.4)	44/218 (20.2)	25/77 (32.5)***	32/104 (30.8)***
Paternal atopy in Q ₀ n/N (%)	345/2,072 (16.7)	41/218 (18.8)	16/77 (20.8)	36/104 (34.6)***
Maternal smoking at pregnancy n/N (%)	224/2,087 (10.7)	46/220 (20.9)***	7/79 (8.9)	20/107 (18.7)
High socioeconomic index n/N (%)	1,772/2,087 (84.91)	181/220 (82.3)	64/79 (81.0)	82/107 (76.6)*

Q₀ = questionnaire at age 0 year.

* $P < 0.05$ compared to never asthma group.

** $P < 0.01$ compared to never asthma group.

*** $P < 0.001$ compared to never asthma group.

TABLE 2—Difference in Adjusted Mean Lung Function Values and 95% CI at 8 Years of Age Between Never Asthma and Asthma Groups

	Coef. (95% CI)			
	Δ FVC (ml) ¹	Δ FEV ₁ (ml) ¹	Δ FEV _{0.5} (ml) ¹	Δ FEV ₁ /FVC in %
Never asthma	Referent	Referent	Referent	Referent
Transient	6.0 (–29.2; 41.2)	–33.8 (–64.5; –3.2)*	–44.4 (–72.0; –16.8)**	–2.8 (–4.0; –1.6)***
Late onset	26.6 (–28.0; 81.2)	4.8 (–42.7; 52.3)	4.0 (–38.9; 46.8)	–1.0 (–2.9; 0.8)
Persistent	6.6 (–39.6; 52.9)	–43.6 (–83.9; –3.3)*	–53.5 (–89.8; –17.2)**	–2.6 (–4.2; –1.1)**
				Referent
				–13.5 (–18.7; –8.3)***
				6.5 (–1.8; 14.8)
				–12.1 (–19.2; –4.8)**

¹ Adjusted for sex, age, and height at lung function investigation.* $P < 0.05$ compared to never asthma group.** $P < 0.01$ compared to never asthma group.*** $P < 0.001$ compared to never asthma group.

(26% vs 5%, $P < 0.001$), sleep-disturbing wheeze or cough (30% vs 17%, $P < 0.001$), or any asthma-related treatment at the age of 8 years (18% vs 5%, $P < 0.001$). Excluding all children with any kind of respiratory symptom or asthma treatment after the age of 4 from the transient group leaves only 139 out of 220 individuals, but does not remove the negative effect seen for FEV_{0.5} or PEF at 8 years (FEV_{0.5} –60.4, $P < 0.01$; PEF at 8 years –9.5, $P < 0.05$). PEF growth between 4 and 8 years, however, was no longer significantly lower than in the no-asthma group of children ($P > 0.01$).

Asthma and Lung Function Measurements: Interactions With Sex and Sensitization to Inhaled Allergens

There were no significant interactions between asthma group and sex with regard to effect on lung function, although there was a tendency for girls to have lower FEV_{0.5} than boys in the late-onset asthma group (data not shown).

When testing for interactions between asthma group and sensitization to the inhaled allergens tested, an effect was seen only for the group of children with late-onset asthma, where those without sensitization had markedly higher values of FVC, FEV₁, and FEV_{0.5} (Fig. 2 and Table 4). In all other groups, there were no differences between sensitized and non-sensitized children in relation to lung function. Similar results emerged from separate analyses on interactions between asthma group and perennial allergens (positive test to cat, dog, horse dander, or mite) or seasonal allergens (positive test to pollens or mould) compared to individuals with no sensitization to all allergens tested (E-Tables 3 and 4 in the online supplement).

DISCUSSION

In this study of a prospective longitudinal birth cohort, we investigated the relationship between lung function and different phenotypes of asthma. We found that regardless of sensitization status and presence of current symptoms, early age at onset was a predictor of impaired spirometric flows at the age of 8. We could also show that PEF growth was not different from children without asthma, using a strict definition for transient asthma, that is, children fulfilling the definition of asthma up to the age of 4 years, but without symptoms of wheeze or asthma thereafter. Our main findings emphasizes the importance of the first years of life for certain aspects of lung function development, and the lack of effect of sensitization to inhalant allergens on lung function in children with early onset asthma.

A minority of the children with early onset symptoms in the BAMSE cohort continued to have asthma at school age, indicating a benign disease prognosis for this group.

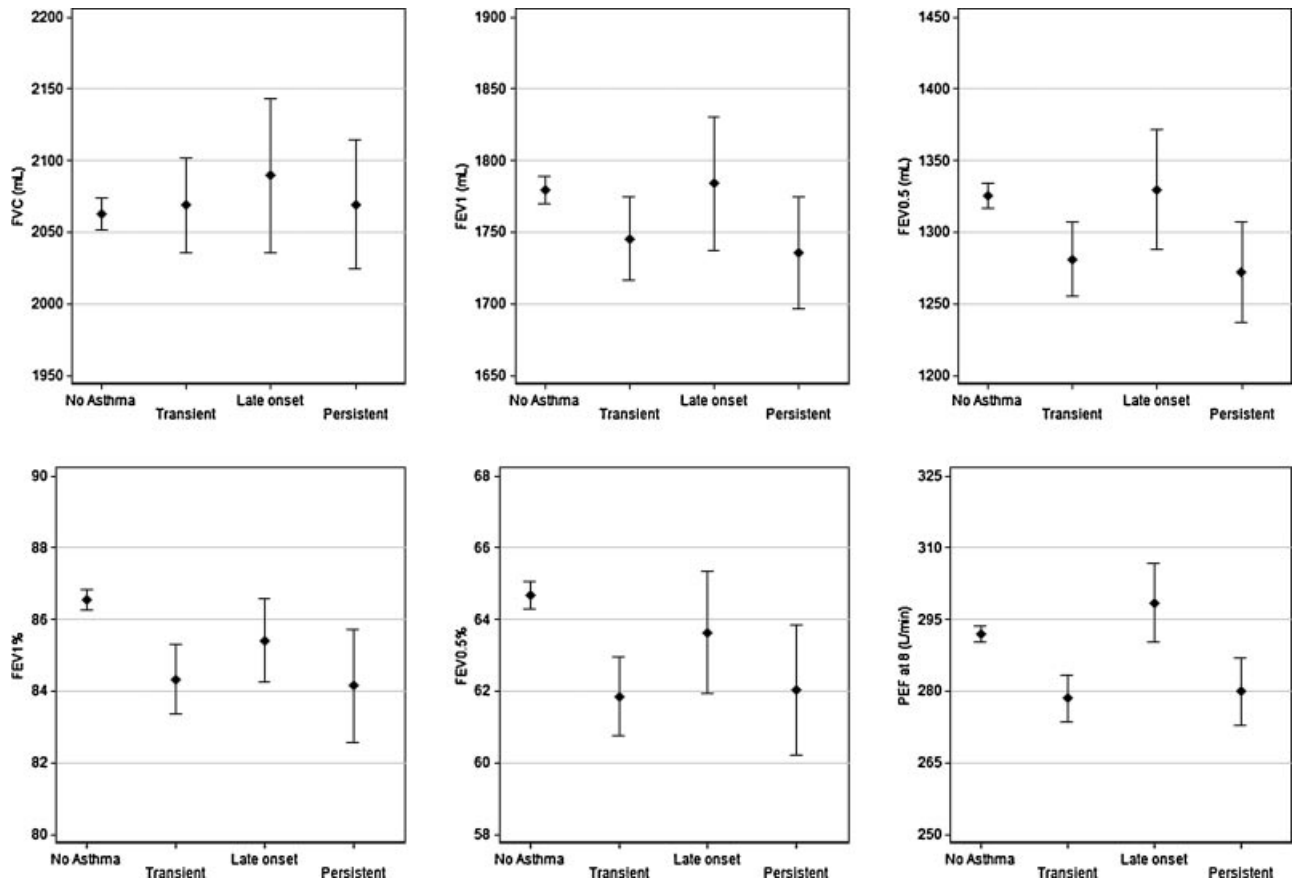


Fig. 1. Adjusted mean lung function values and 95% CI at age 8: no asthma and asthma groups.

However, symptom onset in the first 4 years of life was associated with impaired spirometric flows at the age of 8, regardless of asthma persistency, and, we were also able to show that similar impairments on lung function could be seen for children who fulfilled the asthma criterion only in the first 2 years of life. Further, the association between early onset asthma and low lung function, measured as PEF, was present already at 4 years of age, and that no further impairment could be seen up to the age of 8 (given that no symptoms were allowed after the age of 4 in the transient asthma group). This

confirms and extends the results seen in slightly older children and adults, pointing further to the importance of the very first years of life for the described aspects of lung function development and subsequent tracking.^{4,6–8,15} It is plausible that level of lung function determined congenitally will cause a child to wheeze or not wheeze in the first years of life. Even though children are “phenotyped” here by age at symptoms, age is likely to be a proxy for other factors, such as early wheeze due to congenitally smaller airway, or late-onset wheeze that is related to atopy.

TABLE 3— Difference in Adjusted Mean PEF at 4 Years and PEF Growth Between 4 and 8 Years at Age 4 Between No Asthma and Asthma Groups

	Mean PEF at 4 years ¹ (L/min)	ΔPEF at 4 years ² (L/min)	95% CI	Mean PEF growth ¹ (L/min)	ΔPEF growth ³ (L/min)	95% CI
Never asthma	169.2	Referent	—	123.5	Referent	—
Transient	164.5	−7.3	−11.4; −3.1	118.7	−5.8	−11.3; −0.3
Late onset	177.5	6.3	−0.5; 13.0	126.0	0.2	−8.8; 9.1
Persistent	158.2	−10.6	−16.3; −5.0	120.3	−2.4	−9.9; 5.1

¹Mean PEF and PEF growth values, unadjusted.

²Difference in PEF adjusted for sex, age, and height at the 4-year investigation.

³Difference in PEF growth adjusted for sex, age growth, and height growth between the age of 4 and 8 years.

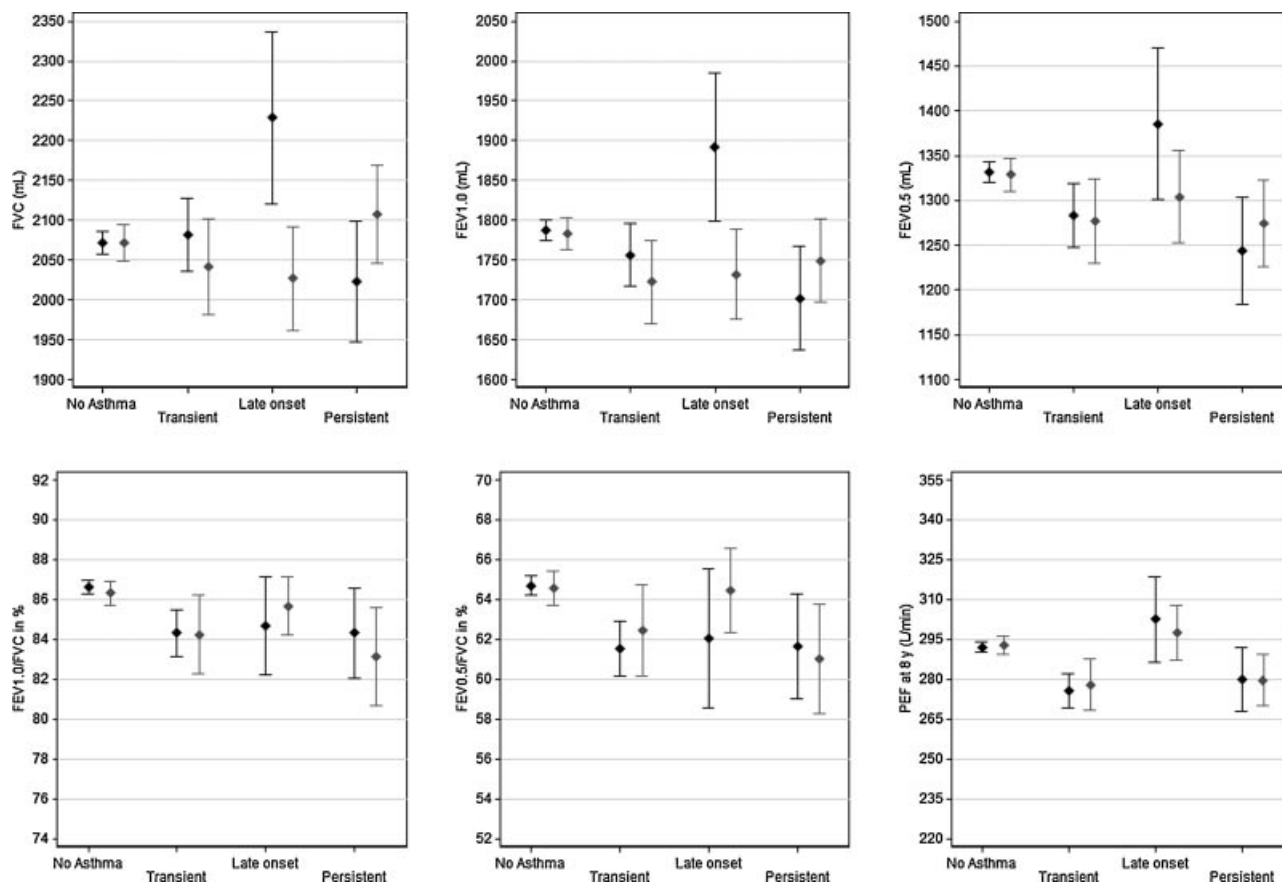


Fig. 2. Estimated mean lung function values and 95% confidence intervals for sensitized and not sensitized children in groups of asthma or no asthma. “Black”—not sensitized; “gray”—sensitized.

Sensitization to inhalant allergens was particularly common in groups with current symptoms, that is the persistent and late-onset asthma groups. As the level of lung function was compared between children with and without sensitization within each asthma group, an effect of sensitization on lung function was only seen in the late asthma group. Children without sensitization exhibited larger FVC, FEV₁, and FEV_{0.5} than expected, while the same parameters were reduced in children with sensitization, FEV₁/FVC in % and FEV_{0.5}/FVC in % were however not significantly changed, indicating a non-obstructive pattern. The mechanism of this is not clear. The results did not differ between sensitization to seasonal or perennial allergens, in contrast to the results from the MAS cohort recently presented by Illi et al.,⁵ where lung function was diminished at 7–13 years of age in children with wheeze at school age (5–7 years), but only in association with early sensitization to perennial allergens, although differences in design between that study and ours preclude an exact comparison.

From the 4-year follow-up of the current study,¹⁰ we reported that the impact of asthma on PEF was larger in girls than in boys. Although there was a tendency for girls

to have lower adjusted lung function values also in the 8-year follow-up (data not shown), we could not show any significant differences between boys and girls. It should be noted that the groups were compiled differently between the previous paper and the current, and it is possible that the sex differences are specifically related to asthma onset before the age of 2, which was not a scope of this paper.

Some quality aspects deserve attention. The BAMSE study is a large birth cohort that has experienced relatively little loss to follow-up over time.¹¹ Even so, of the 4,089 children originally recruited, data on asthma symptoms from all four questionnaires, IgE testing, and at least one acceptable lung function measure at the age of 8 was present in 50%. However, participants and non-participants in this paper were similar regarding background characteristics, as shown in the online Appendix. As expected, subjects who experienced asthma symptoms were more likely to participate in clinical testing. However, as lung function data were compared between groups of children with or without asthma, it is unlikely that this selection should explain the findings of the current paper, findings which we therefore suggest could be applied to the general population.

TABLE 4—Effect of Sensitization on Lung Function Measures in No Asthma and Asthma Groups

	Not sensitized		Sensitized		<i>P</i> int. ¹
	Coefficient	95% CI	Coefficient	95% CI	
ΔFVC (ml) ²					
Never asthma	Referent		0.1	−27.1; 27.2	
Transient	9.9	−38.1; 57.9	−29.6	−94.0; 34.9	0.334
Late onset	157.5	48.8; 266.2	−44.4	−113.3; 24.5	0.002
Persistent	−47.7	−124.9; 29.6	36.0	−29.2; 101.1	0.104
ΔFEV_1 (ml) ²					
Never asthma	Referent		−3.8	−27.3; 19.6	
Transient	−30.8	−72.3; 10.8	−61.0	−116.7; −5.2	0.393
Late onset	105.0	10.9; 199.0	−51.2	−110.8; −8.5	0.006
Persistent	−85.2	−152.0; −18.4	−34.0	−90.3; 22.4	0.250
$\Delta FEV_{0.5}$ (ml) ²					
Never asthma	Referent		−3.2	−24.5; 18.1	
Transient	−48.7	−86.4; −11.0	−51.4	−102.1; −0.8	0.933
Late onset	53.5	−31.9; 138.9	−24.4	−78.5; 29.8	0.131
Persistent	−88.2	−148.9; −27.6	−54.1	−105.3; −3.0	0.399
$\Delta FEV_1/FVC$ (%)					
Never asthma	Referent		−0.3	−1.0; 0.4	
Transient	−2.3	−3.6; −1.0	−2.1	−3.8; −0.4	0.822
Late onset	−1.9	−4.8; 0.9	−0.6	−2.5; 1.2	0.456
Persistent	−2.3	−4.4; −0.3	−3.2	−4.9; −1.5	0.526
$\Delta FEV_{0.5}/FVC$ (%)					
Never asthma	Referent		−0.1	−1.1; 0.8	
Transient	−3.2	−4.8; −1.5	−2.1	−4.3; 0.1	0.453
Late onset	−2.7	−6.4; 1.1	−0.1	−2.5; −2.3	0.258
Persistent	−3.1	−5.7; −0.4	−3.6	−5.8; −1.3	0.777
ΔPEF_8 (L/min) ²					
Never asthma	Referent		0.9	−3.2; 4.9	
Transient	−16.4	−23.3; −9.6	−15.0	−25.1; −4.9	0.819
Late onset	10.4	−5.9; 26.7	4.4	−6.4; 15.3	0.551
Persistent	−12.3	−24.5; −0.1	−13.4	−23.6; −3.1	0.896

¹Interaction term between sensitization and asthma group.²Adjusted for sex, age, and height at lung function investigation.

The definitions of asthma used in this paper has been used in several other publications of the BAMSE project and are based on the ISAAC definition with an amendment of Swedish treatment traditions of asthma.^{14,15,16} This definition differs from those of other large cohorts,^{2,5,8,17} where main outcomes have been single parent reported or doctor confirmed wheeze episodes. This is likely to be the explanation to why the proportion of, for example, transient asthma is lower in the current study compared to others. Another explanation could be that we only allowed wheeze without a concurrent cold to be used in the criteria in the first years, in an attempt to exclude children who have “noisy breathing” at infection due to their smallness. However, the risk of a type 1 statistical error associated with small numbers should be acknowledged. Also lung function variables reported vary between studies, depending on the choice of method to measure lung function and the age of the children examined, which can make comparison of results between studies difficult. $FEV_{0.5}$ is an interesting index because it can be measured in both very young and older children and may, therefore,

be tracked through age. However, $FEV_{0.5}$ physiological determinant might be different with age. The use of a rather rough spirometric measure such as PEF can be discussed. The difference in PEF was small, not clinically significant and may even be within the repeatability of the measurement. It was, however, specifically chosen as a relatively simple and practicable method in a large epidemiological setting in 4-year-old children. Further, it should be emphasized that measurement of PEF in our study has not been used as a tool for diagnosis or diagnostic criterion, but to compare the effect on airflow between groups. The relatively higher flow values seen for the late-onset asthma group, compared to the never asthma group, could possibly be a result of the former group having had the possibility of practicing their technical skills at lung function testing. This could however not explain the effect of sensitization in this group, as the training effect is expected to impact on both sensitized and non-sensitized children. Greater lung function values in asthmatic children would, however, result in smaller differences between them

and the group who were never asthmatic, suggesting that differences between the asthmatic and the never-asthmatic groups are in fact even larger than shown here. Post-bronchodilation lung function, that in theory could have been performed to assess reversibility within the groups, requires considerably more time for testing, and was therefore not possible to perform within the limitations of the present study. Last but not least, the children of the persistent asthma group were somewhat shorter than their healthy peers, which was not found among these with transient or late onset of asthma. Assuming that lower height is associated with asthma, adjustment of lung function values for height may result in an overestimation of values for this group. This would rather result in a dilution of the differences seen between the persistent asthmatic groups and never asthmatic children.

What are the possible explanations for current observations in this study? Together with the results of others, it seems clear that spirometric flow impairments in children with early onset of wheezing disorder are manifested already before school age. It is unclear whether symptoms of asthma reflect existing changes in lung function or whether they lead to changes, but it is likely that in at least in a subgroup of children, early onset symptoms could be a result of congenitally smaller airways.^{2,17} This stresses the need for very early lung function assessment in prospective studies of infants and young children. As the child and its airways grow, symptoms may become less frequent. Possibly, given that symptoms precede impairment of lung function, the lack of effect on lung function in the late-onset asthma group could be solely due to too little time having passed between onset of symptoms and the clinical examination, although this is not supported by birth cohorts with a longer follow-up span.^{6,7} Even if sensitization is not associated with lung function reductions, the high proportion of sensitization among children with late-onset and persistent asthma groups suggests that sensitization to inhalant allergens, which in turn increases the risk of inflammation in the bronchi, could act as a promotor for symptoms after the age of 4, as previously suggested.²

In conclusion, 8-year-old children with asthma have reductions of spirometric flows when categorized as persistent or early onset but transient asthma, even if this latter group of children is completely symptom-free at school age.

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Factors in infancy and childhood related to reduced lung function in asthmatic children: a birth cohort study (BAMSE).

Jenny Hallberg, PhD^{1,2,3}, Martin Anderson MD, PhD^{1,4}, Magnus Wickman MD, PhD^{2,5,3}, and Magnus Svartengren MD, PhD^{1,6}

¹ Division of Occupational Medicine, Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden, ²Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden, ³ Department of Pediatrics, Sachs' Children's Hospital, Stockholm, Sweden, ⁴Unit of Respiratory and Allergic diseases, Department of Internal Medicine, Södersjukhuset, Stockholm, Sweden, ⁵Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
⁶Department of Occupational and Environmental Health, Stockholm County Council, Stockholm, Sweden.

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Corresponding author:

Jenny Hallberg

Department of Pediatrics, Sachs' Children's Hospital

SE-171 76 Stockholm, Sweden

Telephone: +46 8 616 4101

FAX: +46 8 616 4007

E-mail: jenny.hallberg@sodersjukhuset.se

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SUMMARY

Changes in lung function due to childhood asthma have been reported to occur before school age, and to persist throughout life.

The aim was to assess the relationship between aspects of lung function and asthma over time in 4089 children participating in the large population-based birth cohort BAMSE.

Questionnaires were administered at 1, 2, 4, and 8 years of age. At 4 and 8 years, children were invited to a clinical examination, in which 2,965 and 2,630 children participated, respectively. The examinations included blood sampling for evaluation of sensitization to airway allergens (n=2053), peak expiratory flow (PEF) measurements at 4 and 8 years (n=1957), and forced expiratory flows (n=2455) at 8 years.

Asthma onset before the age of 4 years, but no thereafter, was at 8 years associated with impaired spirometric flows. This was seen irrespective of symptom presence after the age of 4. Reduced PEF growth between the age of 4 and 8 was seen only for the group of children with early onset transient asthma, while an association between sensitization and lung function was only seen in the late onset asthma group.

In conclusion, school children with asthma have reductions of spirometric flows when categorized as persistent or transient early onset asthma, even if this latter group of children is completely symptoms free at school age.

INTRODUCTION

It is now generally accepted that a number of distinct phenotypes of childhood asthma exist, and that some of these are more strongly associated with impaired lung function than others (1-5). The timing of this asthma associated impact on lung function has been suggested to take place already before school age, and there is also evidence of tracking of lung function from birth or childhood into adolescent or adult life (6-8), possibly generating a population that is at risk of relapse of asthma or other lung diseases such as COPD (9). These conclusions are primarily drawn from longitudinal birth cohort studies, where the most prominently studied measures of lung function are those related to flow impairments.

At the four year follow-up of the BAMSE study (10), we showed that peak expiratory flow (PEF) was impaired in children with asthma in the two first years of life (but not in those who had an asthma debut after the age of 2) compared to children who never had asthma. This effect was particularly pronounced in girls. The current study is an eight year follow-up of the same population, using more elaborate methods to measure lung function.

The aim of this study was to assess the relationship between different aspects of lung function/lung function growth and asthma phenotypes in a population-based birth cohort (BAMSE) of 4,089 children.

MATERIAL AND METHODS

Study subjects

Between 1994 and 1996, 4,089 newborn children in the Stockholm region were included in a prospective study, BAMSE (11,12). Questionnaires on respiratory symptoms including symptoms of asthma, current asthma medication, and doctor's diagnosis of asthma were mailed to the parents when the children were one, two, four and eight years old, with response rates of 96, 94, 92, and 84%, respectively. At four and eight years, children were invited to a clinical examination including lung function testing, in which 2,965 and 2,630 children participated, respectively.

Measurement of lung function

Peak expiratory flow (PEF) was measured at both 4 and 8 years of age, using the same normal-range Ferraris Peak Flow Meter® (Ferraris Medical Limited, UK) at both occasions. The highest obtained PEF value from several successive attempts was used for analysis, provided that the child's effort was coded as being maximal by the test leader, and that the two highest readings were reproducible (within 15% of each other).

Maximum expiratory flow volume (MEFV) tests were performed at the eight year follow up, using a spirometer (2200 Pulmonary Function Laboratory; Sensormedics, Anaheim, CA, USA). All children performed several MEFV measurements sitting, using a nose clip. The highest values of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and forced expiratory volume in 0.5 seconds ($FEV_{0.5}$) were extracted and used from analysis, provided that the child's effort was coded as being maximal by the test leader, the MEFV curve passed visual quality inspection, and that the two highest readings were reproducible according to ATS/ERS criteria [13].

Measurements of specific IgE antibodies

Blood samples were taken at the age of four and eight. At both occasions, allergen-specific IgE-antibodies were measured against a mix of common inhalant allergens (birch pollen, timothy grass pollen, mugwort pollen, house-dust mite, mould, and cat, dog, and horse dander) using the Pharmacia CAP System™ (Phadia AB, Uppsala, Sweden) in a certified laboratory (the Unit of Clinical Immunology and Allergy, Department of Medicine, Karolinska University Hospital). An IgE value greater than 0.35 kU/L was regarded as positive. Positive tests were further analyzed for allergen-specific IgE antibodies to the allergens listed above in groups of perennial (cat, dog, horse dander, and mite) and seasonal allergens (mould, birch, timothy, and mugwort).

Definition of asthma groups

Based on answers from the questionnaire, the children were defined as being either asthmatic or non-asthmatic at the age of two, four and eight years. Asthma at two years of age was defined as > 3 episodes of wheezing between birth and 2 years of age, combined either with inhaled steroids or signs of hyper-reactivity (wheezing or severe coughing at exaltation and cold weather, or disturbing cough at night) without ongoing cold. At four and eight years of age, asthma was defined as > 3 episodes of wheezing over the last year, or 1 episode if the child had been given inhaled steroids (12,13). Transient asthma was defined as asthma in the first four years, but not at eight years, persistent asthma as asthma in the first four years and at eight years, and late-onset asthma (representing incident cases after the age of four) as asthma at eight years, but not during the first four years.

Statistical analysis

Groups of children were compared by t-test regarding height and weight. Corresponding comparisons for parental heredity, the mother's smoking habits during pregnancy, and socioeconomic index were made by chi-2-tests.

The association between asthma groups and lung function variables were assessed by multiple linear regressions. When appropriate, lung function variables were adjusted for age, height and sex. The residuals were plotted and visually inspected. Socioeconomic status, sensitization status and maternal smoking during pregnancy (assessed as binary variables) were evaluated as possible confounders but were not found to be independently correlated with the outcome. The variables were evaluated as potential effect modifiers for the relationship between lung function and asthma group by introducing an interaction term in the model. Children were categorized as sensitized if levels over the threshold value were seen in blood samples from either four or eight years of age for all, seasonal or perennial allergens. For all analyses including sensitization data, the reference group (no sensitisation) consisted of children without any sensitisation both at four and eight years. To avoid loss of power due to exclusion of subjects, the maximal number of children available for each lung function variable was used in the analysis. P-values of < 0.05 were considered statistically significant. Analyses were performed with the Stata 9.2 software package (StataCorp LP, College Station, TX, USA).

The study was approved by the ethical committee of Karolinska Institutet, Stockholm, Sweden. Parents were informed orally and by written information at baby health clinics when the children were 2 months of age by a nurse not participating in the study. When parents gave mutual consent to participate, the baby's personal number was sent to the BAMSE office. With the help of our national personal number register we were able to identify the mother and her address. The parents were invited to participate by returning a posted questionnaire.

RESULTS

Study sample

Of the 4,089 children of the original cohort, 2,498(61%) could be classified having or not having asthma and participated in the lung function testing at eight years of age. The corresponding number for those who participated at both four and eight years was 2297(56%). Blood samples for evaluation of sensitization at four and/or eight years were available for 2053(82%) of the 2,498 participating at eight, and 2010(88%) of those participating at both four and eight. A detailed description of the number of children with acceptable lung function measures are presented in E-table 1. Characteristics of participating and non-participating children are presented in E-table 2 in the online supplement. In brief, participating children were more likely to have asthma and have a high socioeconomic index, compared to non-participating children.

Prevalence of asthma

Four hundred six (16%) of the participating children reported enough symptoms to fulfil the criteria of asthma at any time point during the first 8 years of life (table 1). Compared with the never asthma group, maternal smoking during pregnancy was more common in those with transient asthma, whereas sensitisation and parental allergy were associated to persistent or late onset asthma. Children with high socioeconomic index were underrepresented in the persistent asthma group.

Asthma and lung function measurements at eight years of age

As shown in table 2 and figure 1, onset of asthma between birth and the age of four (the transient and persistent asthma groups) was associated with impaired PEF, FEV₁, and FEV_{0.5} measured at

the age of eight, irrespective of whether or not the symptoms persisted beyond the age of four. There were no significant effects of asthma on FVC.

Children with asthma during the first two years of life, but not thereafter, also presented with significantly lower PEF, as well as low FEV_{0.5} at eight years, compared to children who never had asthma (PEF at eight years coeff. -12.4 L/min p=0.001; FEV_{0.5} at eight years coeff. -45.7 mL p=0.024), but did not differ significantly in FVC or FEV₁ (data not shown).

Asthma and PEF growth

The growth of PEF between the age of four and eight, adjusted for change in height and age, was significantly lower for the group of children with transient asthma, but not for the group of persistent or late onset of asthma (table 3). Although the children in the transient asthma group did not longer fulfilled our criterion of asthma, they were not necessarily completely symptom-free between the ages of four and eight; when comparing symptoms during the last 12 months between all the children of the transient group and those of the group that never had asthma, the former group of children, more often had 1–3 episodes of wheeze (26% vs. 5%, p < 0.001), sleep-disturbing wheeze or cough (30% vs. 17%, p < 0.001), or any asthma-related treatment at the age of eight years (18% vs. 5%, p < 0.001). Excluding all children with any kind of respiratory symptom or asthma treatment after the age of four from the transient group leaves only 139 out of 220 individuals, but does not remove the negative effect seen for FEV_{0.5} or PEF at eight years (FEV_{0.5} -60.4, p<0.01; PEF at eight years -9.5, p<0.05). PEF growth between four and eight years, however, was no longer significantly lower than in the no-asthma group of children (p>0.01).

Asthma with lung function measurements: interactions with sex and sensitization to inhaled allergens

There were no significant interactions between asthma group and sex with regard to effect on lung function, although there was a tendency for girls to have lower FEV_{0.5} than boys in the late-onset asthma group (data not shown).

When testing for interactions between asthma group and sensitization to the inhaled allergens tested, an effect was seen only for the group of children with late-onset asthma, where those without sensitization had markedly higher values of FVC, FEV₁ and FEV_{0.5} (figure 2 and table 4). In all other groups, there were no differences between sensitized and non-sensitized children in relation to lung function. Similar results emerged from separate analyses on interactions between asthma group and perennial allergens (positive test to cat, dog, horse dander, or mite) or seasonal allergens (positive test to pollens or mould) compared to individuals with no sensitization to all allergens tested (E-tables 3 and 4 in the online supplement).

DISCUSSION

In this study of a prospective longitudinal birth cohort, we investigated the relationship between lung function and different phenotypes of asthma. We found that regardless of sensitization status and presence of current symptoms, early age at onset was a predictor of impaired spirometric flows at the age of eight. We could also show that PEF growth was not different from children with and without asthma, using a strict definition for transient asthma, i.e. children fulfilling the definition of asthma up to the age of four years, but without symptoms of wheeze or asthma thereafter. Our main findings emphasize the importance of the first years of life for certain aspects of lung function development, and the lack of effect of sensitisation to inhalant allergens and reduced lung function seen in children with early onset asthma.

A minority of the children with early onset symptoms in the BAMSE cohort continued to have asthma at school age, indicating a benign disease prognosis for this group. However, symptom onset in the first four years of life was associated with impaired spirometric flows at the age of eight, regardless of asthma persistency, and, we were also able to show that similar impairments on lung function could be seen for children who fulfilled the asthma criterion only in the first two years of life. Further, the association between early onset asthma and low lung function, measured as PEF, was present already at four years of age, and that no further impairment could be seen up to the age of eight (given that no symptoms were allowed after the age of 4 in the transient asthma group). This confirms and extends the results seen in slightly older children and adults, pointing further to the importance of the very first years of life for the described aspects of lung function development and subsequent tracking (4,6-8,15). It is plausible that level of lung function determined congenitally will cause a child to wheeze or not wheeze in the first years of life. Even though children are “phenotyped” here by age at symptoms, age is likely to be a proxy for other

factors, such as early wheeze due to congenitally smaller airway, or late onset wheeze that is related to atopy.

Sensitization to inhalant allergens was particularly common in groups with current symptoms, i.e. the persistent and late onset asthma groups. As the level of lung function was compared between children with and without sensitization within each asthma group, an effect of sensitization on lung function was only seen in the late asthma group. Children without sensitization exhibited larger FVC, FEV₁ and FEV_{0.5} than expected, while the same parameters were reduced in children with sensitization, FEV₁/FVC in % and FEV_{0.5}/FVC in % were however not significantly changed, indicating a non-obstructive pattern. The mechanism of this is not clear. The results did not differ between sensitization to seasonal or perennial allergens, in contrast to the results from the MAS cohort recently presented by Illi et al. (5), where lung function was diminished at 7–13 years of age in children with wheeze at school age (5–7 yrs), but only in association with early sensitization to perennial allergens, although differences in design between that study and ours preclude an exact comparison.

From the four year follow up of the current study (10), we reported that the impact of asthma on PEF was larger in girls than in boys. Although there was a tendency for girls to have lower adjusted lung function values also in the eight year follow up (data not shown) we could not show any significant differences between boys and girls. It should be noted that the groups were compiled differently between the previous paper and the current, and it is possible that the sex differences are specifically related to asthma onset before the age of two, which was not a scope of this paper.

Some quality aspects deserve attention. The BAMSE study is a large birth cohort that has experienced relatively little loss to follow up over time (11). Even so, of the 4,089 children originally recruited, data on asthma symptoms from all four questionnaires, IgE testing, and at least one acceptable lung function measure at the age of eight was present in 50%. However, participants and non-participants in this paper were similar regarding background characteristics, as shown in the online appendix. As expected, subjects who experienced asthma symptoms were more likely to participate in clinical testing. However, as lung function data was compared between groups of children with or without asthma, it is unlikely that this selection should explain the findings of the current paper, findings which we therefore suggest could be applied to the general population.

The definitions of asthma used in this paper has been used in several other publications of the BAMSE project and are based on the ISAAC definition with an amendment of Swedish treatment traditions of asthma (14,16,17). This definition differs from those of other large cohorts (2,5,8,15), where main outcomes have been single parent reported or doctor confirmed wheeze episodes. This is likely to be the explanation to why the proportion of e.g. transient asthma is lower in the current study compared to others. Another explanation could be that we only allowed wheeze without a concurrent cold to be used in the criteria in the first years, in an attempt to exclude children who have “noisy breathing” at infection due to their smallness. However, the risk of a type 1 statistical error associated with small numbers should be acknowledged. Also lung function variables reported vary between studies, depending on the choice of method to measure lung function and the age of the children examined, which can make comparison of results between studies difficult. FEV0.5 is an interesting index because it can be measured in both very young and older children and may, therefore, be tracked through age. However, FEV0.5 physiological determinant might be different with age. The use of a rather rough spirometric measure such as PEF can be discussed.

The difference in PEF was small, not clinically significant and may even be within the repeatability of the measurement. It was, however, specifically chosen as a relatively simple and practicable method in a large epidemiological setting in 4 year old children. Further, it should be emphasized that measurement of PEF in our study has not been used as a tool for diagnosis or diagnostic criterion, but to compare the effect on airflow between groups. The relatively higher flow values seen for the late onset asthma group, compared to the never asthma group, could possibly be a result of the former group having had the possibility of practicing their technical skills at lung function testing. This could however not explain the effect of sensitization in this group, as the training effect is expected to impact on both sensitized and non sensitized children. Greater lung function values in asthmatic children would, however, result in smaller differences between them and the group who were never asthmatic, suggesting that differences between the asthmatic and the never-asthmatic groups are in fact even larger than shown here. Post-bronchodilation lung function, that in theory could have been performed to assess reversibility within the groups, requires considerably more time for testing, and was therefore not possible to perform within the limitations of the present study. Last but not least, the children of the persistent asthma group were somewhat shorter than their healthy peers which was not found among these with transient or late onset of asthma. Assuming that lower height is associated with asthma, and by adjustment of lung function values for height, this may result in an overestimation of values for this group. This would rather result in a dilution of the differences seen between the persistent asthmatic groups and never asthmatic children.

What are the possible explanations for current observations in this study? Together with the results of others, it seems clear that spirometric flow impairments in children with early onset of wheezing disorder are manifested already before school age. It is unclear whether symptoms of asthma reflect existing changes in lung function or whether they lead to changes, but it is likely

that in at least in a subgroup of children, early onset symptoms could be a result of congenitally smaller airways (2, 15). This stresses the need for very early lung function assessment in prospective studies of infants and young children. As the child and its airways grow, symptoms may become less frequent. Possibly, given that symptoms precede impairment of lung function, the lack of effect on lung function in the late onset asthma group could be solely due to too little time having passed between onset of symptoms and the clinical examination, although this is not supported by birth cohorts with a longer follow-up span (6-7). Even if sensitization is not associated with lung function reductions, the high proportion of sensitization among children with late onset and persistent asthma groups suggests that sensitisation to inhalant allergens, which in turn increases the risk of inflammation in the bronchi, could act as a promotor for symptoms after the age of 4, as previously suggested (2).

In conclusion, 8 year old children with asthma have reductions of spirometric flows when categorized as persistent or early onset but transient asthma, even if this latter group of children is completely symptom free at school age.

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**Factors in infancy and childhood related to reduced lung function in
asthmatic children: a birth cohort study (BAMSE).**

Jenny Hallberg, Martin Anderson, Magnus Wickman and Magnus Svartengren

"Online Data Supplement"

Results

Characteristics of participating children

Of the children 2630 who participated in the clinical testing at 8 yrs, 132 were excluded due to incomplete key questionnaire data. Of the remaining 2,498 children, 5 refused MEFV testing and 38 could not be examined due to equipment malfunction. Only one child refused PEF measurements. To be able to evaluate the effect of asthma on lung function growth between 4 and 8 years of age, children had to have attended both clinical follow-ups and to have performed acceptable PEF tests, which left 1,957 children eligible for analysis.

E-table 2 shows the characteristics of participating and non-participating children at the clinical testing at 4 and/or 8. Children who only participated at 4 did not differ in PEF at 4 from those who participated both at 4 and 8 (coeff 0.92, 95% CI -1.81,3.6).

Children who performed technically acceptable PEF at the 4- and 8-year measurements were not significantly different in height, history of asthma, smoking status of their mother during pregnancy, or socioeconomic index compared to those who did not succeed; for MEFV tests, the children who succeeded were taller and more likely to have a history of asthma (data not shown).

E-table 1. Acceptable lung function measures at 8 years of age.

	Never asthma	Transient asthma (0–4 yrs)	Late onset asthma (4–8 yrs)	Persistent asthma (0–8 yrs)
Acceptable PEF at 8 (%)	97.5	96.8	97.5	99.1
Acceptable MEFV ^a (%)	69.8	74.1	79.5	82.2**

*Excluding those who had missing data due to equipment malfunction. * $p < 0.05$ compared to never asthma group, ** $p < 0.01$ compared to never asthma group, *** $p < 0.001$ compared to never asthma group*

E-table 2. Characteristics of children who did/did not participate in the clinical testing at age 4 and/or 8 yrs.

	Participated at 4 and 8 yrs	Participated at 4, but not 8 yrs	No participation in clinical examinations
Asthma 0-2 yrs n/N(%)	210/2315 (9.1)	64/570 (11.2)	45/692 (6.5)*
Asthma at 4 yrs n/N(%)	177/2358 (7.5)	54/586 (9.2)	13/564 (2.3)***
Asthma at 8 yrs n/N(%)	169/2194 (7.2)	19/387 (4.7)	8/382 (2.1)***
Maternal smoking, pregnancy n/N(%)	287/2366 (12.1)	94/589 (16.0)*	118/880 (13.4)
High socioeconomic index n/N(%)	1995/1359 (84.6)	451/585 (77.1)***	682/874 (78.0)***

** $p < 0.05$ compared to "Participated at 4 and 8 yrs", ** $p < 0.01$ compared to "Participated at 4 and 8 yrs", *** $p < 0.001$ compared to "Participated at 4 and 8 yrs".*

E-table 3. Difference in adjusted mean lung function between no asthma and asthma groups, stratified on children with sensitization to seasonal inhalant allergens at 4 or 8, compared to never sensitized children.

$\Delta FVC(mL)^b$							
	Not sensitized			Sensitized			P int. ^a
	n	Coefficient	95% CI	n	Coefficient	95% CI	
Never asthma	845	Referent.		257	-0.4	-30.3; 29.5	
Transient	83	10.6	-37.5; 58.7	37	-60.4	-133.8; 12.9	0.112
Late onset	15	158.1	49.2; 267.0	35	-52.7	-127.9; 22.5	0.002
Persistent	30	-47.3	-124.6; 30.1	43	45.9	-23.0; 114.8	0.111
$\Delta FEV1(mL)^b$							
	Not sensitized			Sensitized			P int. ^a
	n	Coefficient	95% CI	n	Coefficient	95% CI	
Never asthma	845	Referent.		257	-5.5	-31.4; 20.4	
Transient	83	-29.9	-71.5; 11.8	37	-67.5	-131.0; -4.0	0.330
Late onset	15	106.3	11.9; 200.6	35	-51.6	-116.7; 13.6	0.007
Persistent	30	-84.8	-151.7; -17.8	43	-30.7	-90.4; 29.0	0.237
$\Delta FEV_{0.5}(mL)^b$							
	Not sensitized			Sensitized			P int. ^a
	n	Coefficient	95% CI	n	Coefficient	95% CI	
Never asthma	845	Referent.		257	-5.4	-28.9; 18.1	
Transient	83	-48.1	-86.0; -10.3	37	-41.5	-99.2; 16.1	0.850
Late onset	15	54.7	-30.9; 140.3	35	-26.6	-85.7; 32.5	0.125
Persistent	30	-88.1	-148.9; -27.2	43	-48.9	-103.1; 5.3	0.345
FEV ₁ /FVC in %							

	Not sensitized			Sensitized			P int. ^a
	n	Coefficient	95% CI	n	Coefficient	95% CI	
Never asthma	845	Referent		257	-0.34	-1.13; 0.45	
Transient	83	-2.31	-3.59; -1.03	37	-1.09	-3.04; 0.86	0.305
Late onset	15	-1.94	-4.83; 0.96	35	-0.39	-2.39; 1.62	0.387
Persistent	30	-2.31	-3.38; -0.25	43	-3.47	-5.29; -1.64	0.413

FEV_{0.5}/FVC in %

	Not sensitized			Sensitized			P int. ^a
	n	Coefficient	95% CI	n	Coefficient	95% CI	
Never asthma	845	Referent		257	-0.09	-1.11; 0.93	
Transient	83	-3.16	-4.81; -1.51	37	-0.71	-3.23; 1.81	0.111
Late onset	15	-2.65	-6.38; 1.08	35	-0.15	-2.73; 2.43	0.280
Persistent	30	-3.05	-5.71; -0.39	43	-3.64	-6.00; -1.28	0.746

ΔPEF8(L/min) ^b

	Not sensitized			Sensitized			P int. ^a
	n	Coefficient	95% CI	n	Coefficient	95% CI	
Never asthma	1203	Referent.		363	1.1	-3.2; 5.5	
Transient	123	-16.3	-23.1; -9.5	46	-13.8	-25.1; -2.6	0. 712
Late onset	20	10.5	-5.8; 26.7	42	7.2	-4.5; 18.9	0. 749
Persistent	36	-12.3	-24.4; -0.1	51	-10.8	-21.6; -0.0	0. 862

^a Interaction term between sensitization and asthma group. ^b Adjusted for sex, age and height at lung function investigation. Children were categorized as sensitized if levels over the threshold value were seen in blood samples from either four or eight years of age for all, seasonal or perennial allergens. For all analyses including sensitization data, the reference group (no sensitisation) consisted of children without any sensitisation both at four and eight years.

E-table 4. Difference in adjusted mean lung function between no asthma and asthma groups, stratified on children with sensitization to perennial inhalant allergens at 4 or 8, compared to never sensitized children.

$\Delta FVC(mL)^b$							
	Not sensitized			Sensitized			P int. ^a
	n	Coefficient	95% CI	n	Coefficient	95% CI	
Never asthma	845	Referent.		210	-4.9	-37.4; 27.5	
Transient	83	11.3	-37.0; 59.7	33	-21.6	-100.1; 56.9	0.483
Late onset	15	159.1	49.6; 268.5	35	-55.5	-132.0; 21.0	0.002
Persistent	30	-47.0	-124.7; 30.8	43	52.5	-18.0; 123.0	0.063

$\Delta FEV1(mL)^b$							
	Not sensitized			Sensitized			P int. ^a
	n	Coefficient	95% CI	n	Coefficient	95% CI	
Never asthma	845	Referent.		210	-8.1	-36.2; 20.0	
Transient	83	-29.6	-71.5; 12.3	33	-64.8	-132.8; 3.2	0.386
Late onset	15	106.4	11.6; 201.2	35	-59.2	-125.5; 7.0	0.005
Persistent	30	-84.6	-152.0; -17.3	43	-25.8	-86.9; 35.2	0.204

$\Delta FEV_{0.5}(mL)^b$							
	Not sensitized			Sensitized			P int. ^a
	n	Coefficient	95% CI	n	Coefficient	95% CI	
Never asthma	845	Referent.		210	-3.9	-29.5; 21.7	
Transient	83	-47.8	-85.9; -9.7	33	-66.8	-128.7; -5.0	0.607
Late onset	15	54.7	-31.6; 141.0	35	-36.9	-97.2; 23.4	0.088
Persistent	30	-87.8	-149.1; -26.5	43	-54.1	-109.7; 1.5	0.423

FEV ₁ /FVC in %							
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	Not sensitized			Sensitized			P int. ^a
	n	Coefficient	95% CI	n	Coefficient	95% CI	
Never asthma	845	Referent		210	-0.35	-1.21; 0.51	
Transient	83	-2.31	-3.60; -1.03	33	-2.52	-4.46; -0.43	0.867
Late onset	15	-1.94	-4.84; 0.97	35	-0.49	-2.53; 1.55	0.426
Persistent	30	-1.32	-4.39; -0.24	43	-3.36	-5.23; -1.49	0.463

FEV_{0.5}/FVC in %

	Not sensitized			Sensitized			P int. ^a
	n	Coefficient	95% CI	n	Coefficient	95% CI	
Never asthma	845	Referent		210	-0.09	-1.19; 1.02	
Transient	83	-3.16	-4.81; -1.51	33	-2.95	-5.63; -0.26	0.895
Late onset	15	-2.65	-6.38; 1.08	35	-0.24	-2.86; 2.38	0.300
Persistent	30	-3.05	-5.71; -0.39	43	-3.85	-6.25; -1.45	0.664

ΔPEF8(L/min) ^b

	Not sensitized			Sensitized			P int. ^a
	n	Coefficient	95% CI	n	Coefficient	95% CI	
Never asthma	1203	Referent.		288	0.6	-4.2; 5.4	
Transient	123	-16.4	-23.3; -9.5	41	-19.6	-31.7; -7.6	0.647
Late onset	20	10.3	-6.0; 26.6	40	3.5	-8.7; 15.7	0.516
Persistent	36	-12.3	-24.5; -0.0	50	-13.3	-24.4; -2.2	0.904

^a Interaction term between sensitization and asthma group. ^b Adjusted for sex, age and height at lung function investigation. Children were categorized as sensitized if levels over the threshold value were seen in blood samples from either four or eight years of age for all, seasonal or perennial allergens. For all analyses including sensitization data, the reference group (no sensitisation) consisted of children without any sensitisation both at four and eight years.

Figure legends

Figure 1. Adjusted mean lung function values and 95% CI at age eight between no asthma and asthma groups.

Figure 2. Estimated mean lung function values and 95% confidence intervals for sensitized and not sensitized children in groups of asthma or no asthma. “Black” - not sensitized, “grey” - sensitized.

Table 1. Characteristics of children with asthma data 0–8 yrs who participated in the clinical examination at 8 years.

	Never asthma	Transient asthma (0–4 yrs)	Late onset asthma (4–8 yrs)	Persistent asthma (0–8 yrs)
No. of children (% of tot.)	2,092(83,8)	220 (8,8)	79 (3,2)	107 (4,3)
Female sex (%)	1,064 (50.9)	81 (36.8)***	35 (44.3)	42 (39.3)
Mean age in yrs (min-max)	8.3 (7.3–10.2)	8.3 (7.3–9.4)	8.4 (7.4–10.4)	8.4 (7.3–9.4)
Mean height in cm (min-max)	132.1 (114.2–156)	132.8 (116.0–157)	133.5 (118.5– 150.8)*	131.0 (116.0–148.0)
Sensitization at 4 or 8 y n/N(%)	473/1704 (27.8)	60/187 (32.1)	50/70 (71.4)***	56/92 (60.9)***
Parental atopy in Q0 n/N(%)	613/2077 (29.5)	78/218 (35.8)	36/78 (46.2)**	57/104 (54.8)***
Maternal atopy in Q0 n/N(%)	320/1072 (15.4)	44/218 (20.2)	25/77 (32.5)***	32/104 (30.8)***
Paternal atopy in Q0 n/N(%)	345/2072 (16.7)	41/218 (18.8)	16/77 (20.8)	36/104 (34.6)***
Maternal smoking at pregnancy n/N(%)	224/2087 (10.7)	46/220 (20.9)***	7/79 (8.9)	20/107 (18.7)
High socioeconomic index n/N(%)	1772/2087 (84.91)	181/220 (82.3)	64/79 (81.0)	82/107 (76.6)*

*Q0 = questionnaire at age 0 yrs. * $p < 0.05$ compared to never asthma group, ** $p < 0.01$ compared to never asthma group,*

**** $p < 0.001$ compared to never asthma group*

Table 2. Difference in adjusted mean lung function values and 95% CI at 8 yrs of age between never asthma and asthma groups.

	Δ FVC(mL) ^a	Δ FEV ₁ (mL) ^a	Δ FEV _{0.5} (mL) ^a	Δ FEV ₁ /FVC in %	Δ FEV ₅ /FVC in %	Δ PEF(L/min) ^a
	Coef.(95%CI)	Coef.(95%CI)	Coef.(95%CI)	Coef.(95%CI)	Coef.(95%CI)	Coef.(95%CI)
Never asthma	Referent	Referent	Referent	Referent	Referent	Referent
Transient	6.0(-29.2; 41.2)	-33.8(-64.5; -3.2) *	-44.4(-72.0; -16.8)**	-2.2(-3.2; -1.3)***	-2.8(-4.0; -1.6)***	-13.5(-18.7; -8.3)***
Late onset	26.6(-28.0; 81.2)	4.8(-42.7; 52.3)	4.0(-38.9; 46.8)	-1.1(-2.6; 0.3)	-1.0(-2.9; 0.8)	6.5(-1.8; 14.8)
Persistent	6.6(-39.6; 52.9)	-43.6(-83.9; -3.3)*	-53.5(-89.8; -17.2)**	-2.4(-3.6; -1.2)***	-2.6(-4.2; -1.1)**	-12.1(-19.2; -4.8)**

^aAdjusted for sex, age and height at lung function investigation.

* $p < 0.05$ compared to never asthma group, ** $p < 0.01$ compared to never asthma group, *** $p < 0.001$ compared to never asthma group

Table 3. Difference in adjusted mean PEF at 4 years and PEF growth between 4 and 8 years at age four between no asthma and asthma groups.

	Mean PEF at 4 yrs ^a	ΔPEF at 4 yrs ^b	95% CI	Mean PEF growth ^a	ΔPEF growth ^c	95% CI
	(L/min)	(L/min)		(L/min)	(L/min)	
Never asthma	169.2	Referent	-	123.5	Referent	-
Transient	164.5	-7.3	-11.4; -3.1	118.7	-5.8	-11.3; -0.3
Late onset	177.5	6.3	-0.5; 13.0	126.0	0.2	-8.8; 9.1
Persistent	158.2	-10.6	-16.3; -5.0	120.3	-2.4	-9.9; 5.1

^aMean PEF and PEF growth values, unadjusted.

^bDifference in PEF adjusted for sex, age and height at the 4 year investigation.

^cDifference in PEF growth adjusted for sex, age growth and height growth between the age of 4 and 8 years.

Table 4. Effect of sensitization on lung function measures in no asthma and asthma groups.

$\Delta FVC(mL)^b$					
	Not sensitized		Sensitized		p int. ^a
	Coefficient	95% CI	Coefficient	95% CI	
Never asthma	Referent		0.1	-27.1; 27.2	
Transient	9.9	-38.1; 57.9	-29.6	-94.0; 34.9	0.334
Late onset	157.5	48.8; 266.2	-44.4	-113.3; 24.5	0.002
Persistent	-47.7	-124.9; 29.6	36.0	-29.2; 101.1	0.104
$\Delta FEV_1(mL)^b$					
	Not sensitized		Sensitized		p int. ^a
	Coefficient	95% CI	Coefficient	95% CI	
Never asthma	Referent		-3.8	-27.3; 19.6	
Transient	-30.8	-72.3; 10.8	-61.0	-116.7; -5.2	0.393
Late onset	105.0	10.9; 199.0	-51.2	-110.8; -8.5	0.006
Persistent	-85.2	-152.0; -18.4	-34.0	-90.3; 22.4	0.250
$\Delta FEV_{0.5}(mL)^b$					
	Not sensitized		Sensitized		p int. ^a
	Coefficient	95% CI	Coefficient	95% CI	
Never asthma	Referent		-3.2	-24.5; 18.1	
Transient	-48.7	-86.4; -11.0	-51.4	-102.1; -0.8	0.933
Late onset	53.5	-31.9; 138.9	-24.4	-78.5; 29.8	0.131
Persistent	-88.2	-148.9; -27.6	-54.1	-105.3; -3.0	0.399
$\Delta FEV_1/FVC$ in %					
	Not sensitized		Sensitized		p int. ^a
	Coefficient	95% CI	Coefficient	95% CI	
Never asthma	Referent		-0.3	-1.0; 0.4	
Transient	-2.3	-3.6; -1.0	-2.1	-3.8; -0.4	0.822

Late onset	-1.9	-4.8; 0.9	-0.6	-2.5; 1.2	0.456
Persistent	-2.3	-4.4; -0.3	-3.2	-4.9; -1.5	0.526

$\Delta FEV_{0.5}/FVC$ in %

	Not sensitized		Sensitized		p int. ^a
	Coefficient	95% CI	Coefficient	95% CI	
Never asthma	Referent		-0.1	-1.1; 0.8	
Transient	-3.2	-4.8; -1.5	-2.1	-4.3; 0.1	0.453
Late onset	-2.7	-6.4; 1.1	-0.1	-2.5; -2.3	0.258
Persistent	-3.1	-5.7; -0.4	-3.6	-5.8; -1.3	0.777

$\Delta PEF_8(L/min)$ ^b

	Not sensitized		Sensitized		p int. ^a
	Coefficient	95% CI	Coefficient	95% CI	
Never asthma	Referent		0.9	-3.2; 4.9	
Transient	-16.4	-23.3; -9.6	-15.0	-25.1; -4.9	0.819
Late onset	10.4	-5.9; 26.7	4.4	-6.4; 15.3	0.551
Persistent	-12.3	-24.5; -0.1	-13.4	-23.6; -3.1	0.896

^a Interaction term between sensitization and asthma group.

^b Adjusted for sex, age and height at lung function investigation.