

Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study



Sabina Illi, Erika von Mutius, Susanne Lau, Bodo Niggemann, Christoph Grüber, Ulrich Wahn, on behalf of the Multicentre Allergy Study (MAS) group*

Summary

Background Reduced lung function is a feature of chronic asthma, which becomes apparent at school age. Unknown factors between birth and school age determine the progressive loss of pulmonary function in children with persistent asthma. We investigated the role of allergic sensitisation and allergen exposure early in life.

Methods The German Multicentre Allergy Study followed 1314 children from birth to 13 years of age. We regularly interviewed parents about their child's asthma and measured IgE levels. Allergen exposure was assessed at age 6 months, 18 months, and at 3, 4, and 5 years; lung function was assessed at 7, 10, and 13 years; post-bronchodilator response at 10 and 13 years; and a bronchial histamine challenge was done at 7 years.

Results 90% of children with wheeze but no atopy lost their symptoms at school age and retained normal lung function at puberty. By contrast, sensitisation to perennial allergens (eg, house dust mite, cat and dog hair) developing in the first 3 years of life was associated with a loss of lung function at school age. Concomitant exposure to high levels of perennial allergens early in life aggravated this process: forced expiratory volume in 1 s (FEV₁) to forced vital capacity (FVC) ratio was 87·4 (SD 7·4) for those sensitised and with high exposure compared with 92·6 (6·0) for those not sensitised, $p < 0·0001$; and maximal expiratory flow at 50% (MEF₅₀) 86·4 (25·1) for sensitised and with high exposure compared with 101·5 (23·2; $p = 0·0031$) for those not sensitised. Such exposure also enhanced the development of airway hyper-responsiveness in sensitised children with wheeze. Sensitisation and exposure later in life had much weaker effects and sensitisation to seasonal allergens did not play a part.

Interpretation The chronic course of asthma characterised by airway hyper-responsiveness and impairment of lung function at school age is determined by continuing allergic airway inflammation beginning in the first 3 years of life. However, children with a non-atopic wheezing phenotype lose their symptoms over school age and retain normal lung function at puberty.

Introduction

Morbidity from chronic asthma is very high in the western world. The estimated costs for the management of childhood asthma in the European Union are €3000 million.¹ Chronic asthma is characterised by repeated attacks of airway obstruction and intermittent symptoms of increased airway responsiveness to triggering factors such as exercise, allergen exposure, and viral infections. Airway inflammation and airway remodelling have been suggested as underlying mechanisms of this condition. Reduced lung function is a feature of asthma, and asthma management guidelines aim to achieve near-normal lung function in affected patients.²

In prospective studies of children at risk of asthma from birth onwards, a fall in pre-bronchodilator lung function becomes apparent around school age.³ No further progression of lung function impairment up to adolescence and adult age has been identified.^{3–5} Lung function in asthmatic people is subnormal but develops at the same rate as in asymptomatic individuals. Unknown factors between birth and school age determine the progressive loss of pulmonary function in children with asthma.

We investigated the role of allergic sensitisation and allergen exposure early in life for the course of asthma

and the development of lung function from birth to school age and puberty in the prospective German Multicentre Allergy Study (MAS).

Methods

Patients

The MAS, a birth cohort, recruited 1314 healthy mature infants born in 1990 in five German cities. A detailed description of the sampling scheme and the study participants is given elsewhere.⁶ 499 newborns with risk factors for atopy (raised cord blood IgE $\geq 0·9$ kU/L) or at least two atopic family members, or both) and 815 newborns with none of these risk factors were included in the cohort. All children were followed-up at ages 1, 3, 6, 12, 18, and 24 months and from then on yearly within 4 weeks of the child's birthday up to the age of 13 years. The study was approved by the local ethics committee. Each child's parents gave written informed consent at the time of enrolment.

Procedures

At each follow-up visit, parents gave structured interviews to a study physician or completed postal questionnaires (at age 8, 9, 11, and 12 years). The main topics of these interviews were asthmatic and atopic

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*Additional members listed at end of report

Department of Pediatric Pneumology and Immunology, Charité-Universitätsmedizin Berlin, Germany (S Illi PhD, S Lau MD, B Niggemann MD, C Grüber MD, U Wahn MD); and University Children's Hospital, Munich, Germany (S Illi, E von Mutius MD)

Correspondence to: Dr Sabina Illi, Dr von Haunersches Kinderspital, Lindwurmstr 4, 80337 Munich, Germany
sabina.illi@med.uni-muenchen.de

symptoms and disease; questions on diet, development, and psychological aspects were also included. From age 5 years onwards, questions relating to wheeze corresponded to the International Study of Asthma and Allergies in Childhood (ISAAC) core questions.

Early wheeze was defined as any parent-reported wheezing in the first 3 years of life. In children who participated in at least two of three follow-ups at age 5, 6, or 7 years, wheezing at school age was defined as wheeze in the past 12 months at any of these follow-ups. Lower respiratory tract infections in the first 3 years of life were defined on the basis of parental reporting of symptoms and diagnoses.⁷ Furthermore, the use of medication was assessed at every follow-up.

Serum samples were obtained from the children at 1, 2, 3, 5, 6, 7, and 10 years of age. Specific IgE antibodies to food allergens (cow's milk, egg white, soy bean, wheat) and inhalant allergens (house dust mites *Dermatophagoides pteronyssinus*, cat dander, mixed grass, birch pollen, and dog dander from age 3 years on) were determined with ImmunoCAP (Phadia, Freiburg, Germany). Sensitisation was defined as specific IgE level of 0.35 kU/L or more. Early sensitisation was defined as any sensitisation at age 3 years or younger. In children who participated in at least one out of three blood samplings at age 5, 6, or 7 years, wheezing at school age was stratified into non-atopic and atopic wheeze according to the results of blood testing (0 vs ≥ 1 sensitisation). Perennial sensitisation was defined as detectable IgE antibodies towards house dust mite, cat and dog dander, the latter from age 3 years on, whereas sensitisation to grass and birch pollen was defined as seasonal sensitisation.

At the ages of 6 and 18 months and 3, 4, and 5 years, Der p 1, Der f 1, and Fel d 1 allergens were extracted from dust samples collected by parents from the carpet and analysed with a sandwich ELISA (ALK, Copenhagen, Denmark).^{8,9} High level of exposure to a specific allergen at a specific age was defined as a measured value above the third quartile of the respective distribution in the total population.⁹

At the ages of 7, 10, and 13 years, lung function was measured in 800, 638, and 680 children, respectively, with a bodyplethysmograph (Master-Lab, E Jaeger, Würzburg, Germany). β -2-agonists were withdrawn at least 12 h and sodium cromoglycate 48 h before testing. The indices of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), maximal expiratory flow at 75% (MEF₇₅), maximal expiratory flow at 50% (MEF₅₀), and maximal expiratory flow at 25% (MEF₂₅) were expressed as percentage predicted by internal reference values. Results remained essentially unchanged when converting lung function indices to height-adjusted Z scores (Z scores have a mean of 0 and an SD of 1 and describe each child's position relative to that of other individuals in the distribution, data not shown). We also calculated the FEV₁ to FVC ratio. After the assessment of baseline lung function at the ages of 10 and 13 years, two puffs of albuterol from a metered

dose inhaler, as recommended,² were given to 612 and 547 children, respectively, via a spacer and spirometry was repeated 15 minutes after inhalation.

At the age of 7 years, a bronchial challenge was done in 647 of the 800 children whose lung function had been tested, starting with 0.5 mg/mL up to 8.0 mg/mL histamine according to a standard procedure.¹⁰ The 90th percentile of the distribution of the histamine concentration causing a 20% fall in FEV₁ (PC₂₀FEV₁) in a healthy subsample was 0.85 mg/mL. Airway hyper-responsiveness was defined as a PC₂₀FEV₁ less than this value. The results did not change significantly after use of the log-transformed dose-response slope as continuous outcome (data not shown).

Statistical analyses

χ^2 tests were used to compare prevalences between groups, in case of small expected cell counts, Fisher's exact test was used instead. The Mantel-Haenszel χ^2 test for trend was used for analysing trends over categories. Cross-sectional differences in lung function between groups were assessed by *t* tests. In case of more than two groups, Bonferroni correction for multiple testing was applied to the *p* values.

For the combined analysis of sensitisation, and exposure to the sensitising allergen, children were divided into three groups: those sensitised to cat dander or mites and concurrently exposed to high levels of the respective allergen; sensitised to cat dander or mites but not concurrently exposed to high levels of the respective allergen; not sensitised to either allergen. Since data for sensitisation and exposure were not always assessed at the same follow-up, the following time points were paired to meet our definitions: sensitisation at age 1 year and exposure at age 6 months, sensitisation at age 2 years and exposure at age 18 months, sensitisation and exposure at age 3 years, and sensitisation and exposure at age 5 years. The variables for cat dander and house dust mite allergen sensitisation and exposure had similar effects on lung function, allowing us to pool the data. Dog dander sensitisation and exposure was not included in this combined analysis, since such sensitisation was not assessed before the age of 3 years and exposure was only assessed via questionnaire (whether or not the family had a dog) and not on the basis of measurements of allergen levels.

The analysis of factors influencing airway hyper-responsiveness was done with univariate and multivariate stepwise logistic regression analysis; for the multivariate stepwise analysis, study centre, parental atopy, and current asthma medication were forced into the model as potential confounders.

To adjust for repeated measures data, factors influencing lung function over time (ie, at ages 7, 10, and 13 years) were analysed with generalised linear mixed models,¹¹ as implemented in the MIXED procedure in SAS. The covariance structure for the lung function data

was specified with an unstructured model, which provided the best fit for the data after testing other covariance matrices. Multivariate models were adjusted for study centre, maternal smoking in pregnancy, and parental atopy as fixed covariates; current asthma medication and current wheeze were included as time-dependent covariates. Age at time of spirometry was included as time-dependent covariate if significant.

The maximum number of individuals was used for all analyses, resulting in varying sample sizes. SAS software (versions 8.02 and 9.1) was used for all statistical analyses.

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, and data interpretation, or writing of the report, or in the decision to submit the paper for publication. The corresponding author had full access to all the study data and had final responsibility for the decision to submit for publication.

Results

Of the 1314 enrolled children, 971 (73.9%) and 759 (57.8%) had information on wheezing at school age (5–7 years)

and at age 13 years, respectively. Participation rates for blood sampling at the respective time points were slightly lower. To assess potential participation bias we analysed the number of attended follow-ups per child—ie, we tested whether some children participated in more follow-ups than other children based on data collected at birth. Of the 1314 children included in the MAS at birth, 52 attended only one follow-up and 454 attended the maximum number of 17 follow-ups. Children who have an atopic parent ($p<0.0001$ for trend), whose parents have a high level education ($p<0.0001$ for trend), or whose mothers did not smoke while pregnant ($p<0.0001$ for trend) were significantly more likely to attend follow-up than children without these characteristics. Webtable 1 provides a detailed description of the cohort.

At 7 years of age, indices of baseline lung function were significantly lower in children with wheeze compared with those without wheeze (eg, MEF_{50} : 92.4 [SD 22.3] vs 102.2 [23.4], $p<0.0001$; webfigure). This significant difference was more pronounced for measures of small airway calibre (MEF_{50} , MEF_{25}) than for the FEV_1 . Thereafter, differences in baseline lung function did not change. In other words, lung function tracked along values set at age 7, until ages 10 and 13 years.

See Online for webtable 1

See Online for webfigure

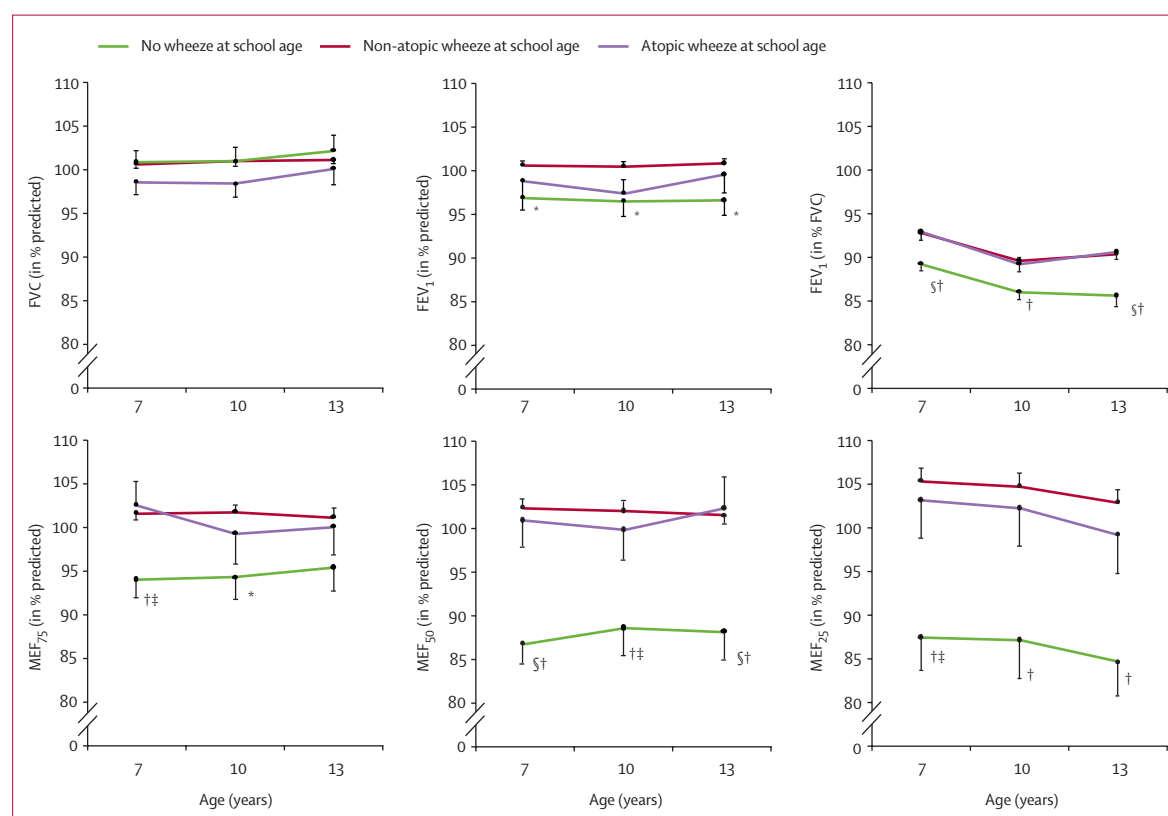


Figure 1: Lung function at ages 7, 10, and 13 years, stratified for wheezing (atopic and non-atopic) at school age (5–7 years)

Of the 793 children with no wheeze at school age, 645, 512, and 545 had measurements of lung function data at ages 7, 10, and 13 years, respectively; of the 59 children with non-atopic wheeze, 53, 38, and 38 had such measurements at ages 7, 10, and 13 years, respectively; of the 94 children with atopic wheeze 86, 63, and 70 had such measurements at ages 7, 10, and 13 years, respectively. Error bars are SE. * $p<0.05$ /† $p<0.01$ for difference between atopic wheeze and no wheeze; ‡ $p<0.05$ /§ $p<0.01$ for difference between atopic wheeze and non-atopic wheeze.

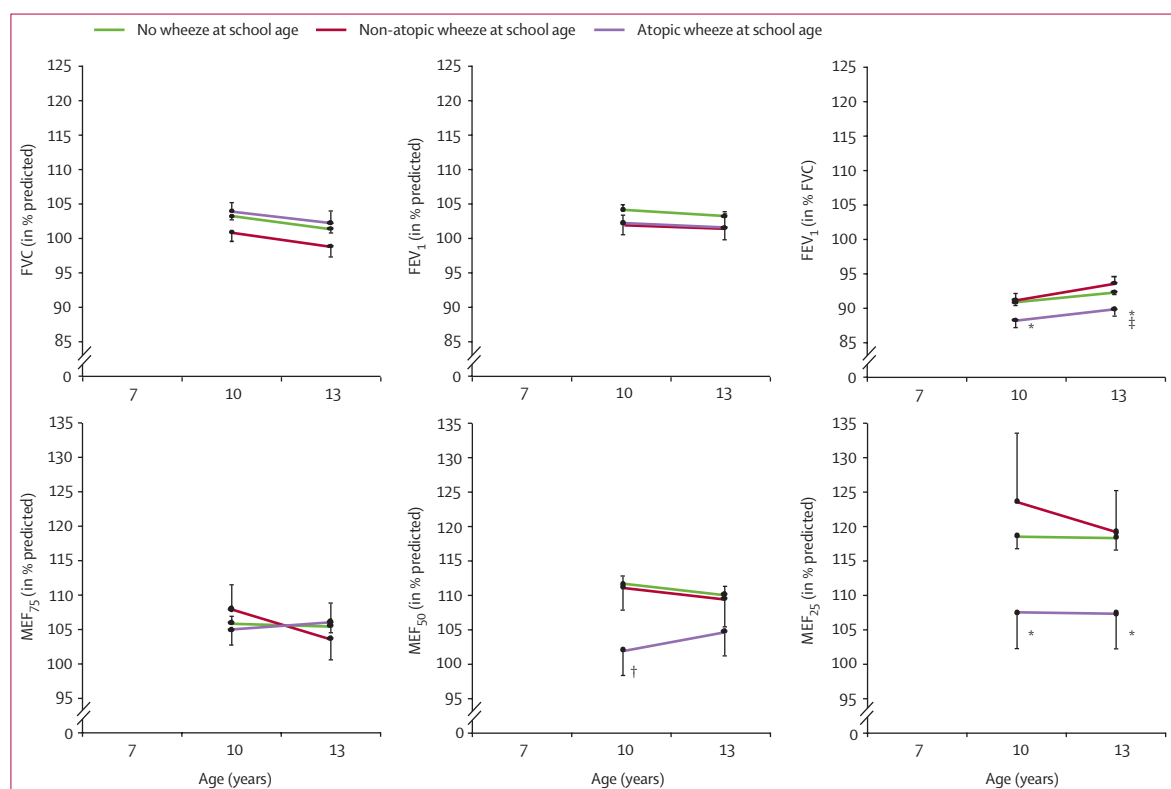


Figure 2: Post-bronchodilator lung function at ages 10 and 13 years, stratified for wheezing at school age (5-7 years)

Of the 793 children with no wheeze at school age, 487 and 438 had measurements of post-bronchodilator lung function at ages 10 and 13 years, respectively; of the 59 children with non-atopic wheeze, 37 and 32 had such measurements at ages 10 and 13 years, respectively; of the 94 children with atopic wheeze, 63 and 53 had such measurements at ages 10 and 13 years, respectively. Error bars are SE. * $p < 0.05$; † $p < 0.01$ for difference between atopic wheeze and no wheeze; ‡ $p < 0.05$ for difference between atopic wheeze and non-atopic wheeze.

The course of lung function from age 7 to 13 differed significantly between atopic and non-atopic wheezers. The impairment in all indices was seen among the atopic but not the non-atopic wheezers (eg, MEF₅₀ age 7 years:

86.6 [SD 21.7] vs 100.7 [21.5], $p = 0.0016$; figure 1). The impairment in lung function was still significant after bronchodilator administration, though on a lower level (figure 2). No effect of atopy on lung function was seen for non-wheezing children (data not shown).

We then investigated whether the occurrence of symptoms differed between the atopic and non-atopic wheezing phenotype up to and beyond school age. The frequency of wheezing episodes from birth up to the age of 5 years was equivalent for children with atopic and non-atopic wheeze, respectively (figure 3). Early onset of wheeze and repeated episodes of wheeze before age 3 years were also not significantly different between groups (webtable 1). In turn, non-atopic wheezers showed higher rates of recurrent lower respiratory tract illnesses early in life compared with atopic wheezers ($n = 37$ [62.7%] vs 40 [42.5%], $p = 0.0152$). At school age, the severity of asthma symptoms was higher among the atopic group as assessed by the frequency of wheezing episodes in the last year (≥ 4 episodes 22 [23.7%] vs 5 [8.9%], $p = 0.0238$), the rate of exercise-induced symptoms (30 [32.3%] vs 8 [14.3%], $p = 0.0148$) and the proportion of children with airway hyper-responsiveness (36 [57.1%] vs 9 [19.6%], $p < 0.0001$) compared with non-atopic wheezers.

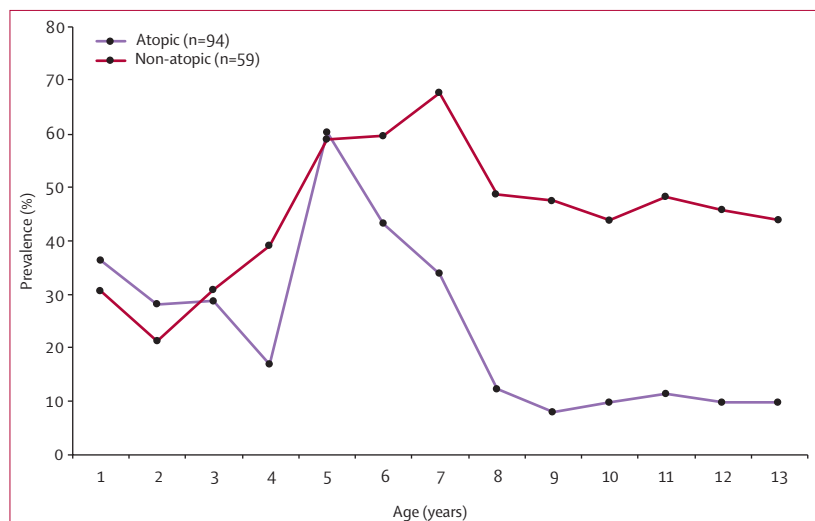


Figure 3: Prevalence of current wheeze from birth to age 13 years in children with any wheezing episode at school age (5-7 years), stratified for atopy at school age

Of the 178 children with wheeze at school age, 153 had measurements of IgE at school age.

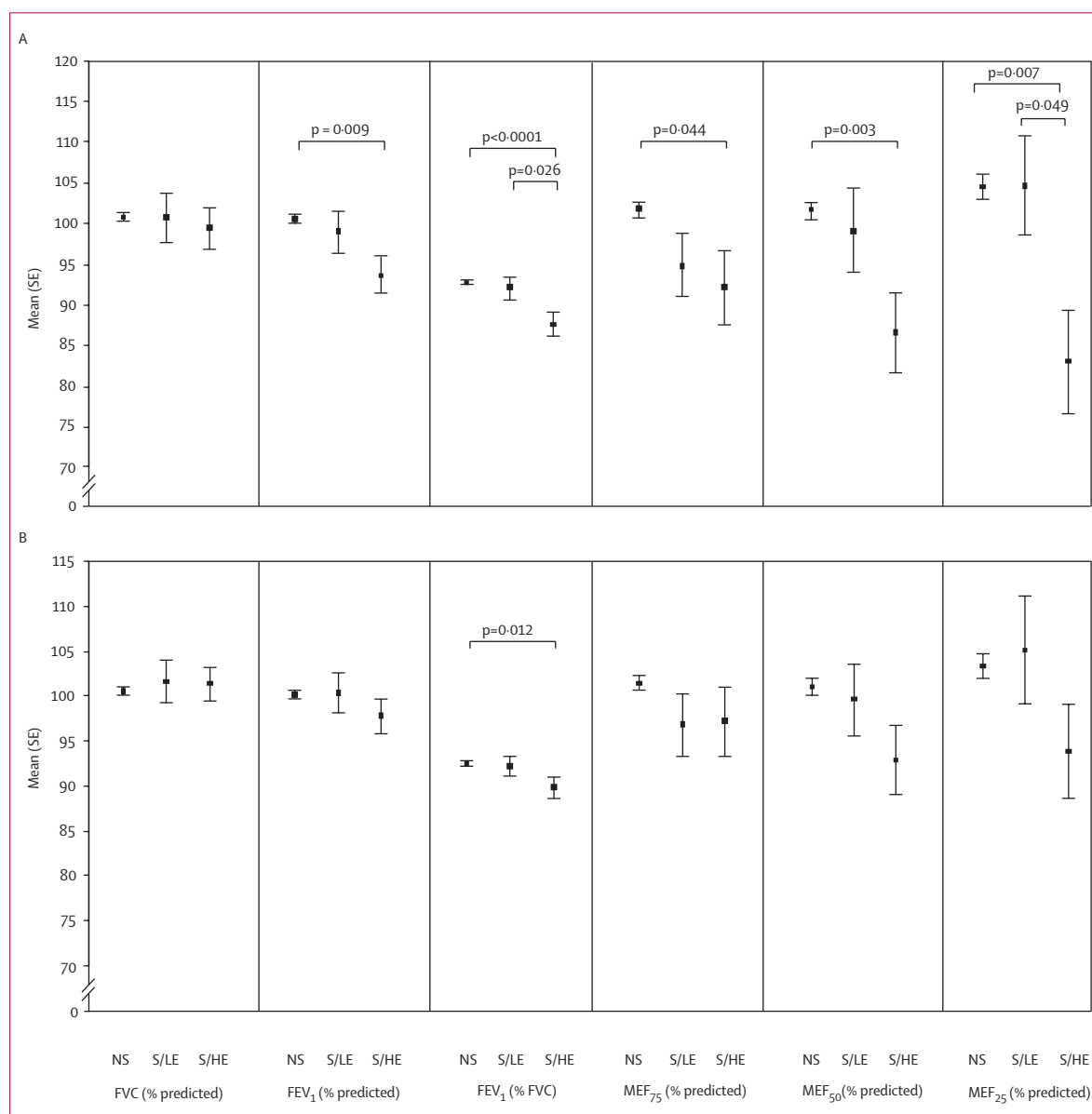


Figure 4: Effect of allergen sensitisation and exposure at ≤3 years (A) and ≤5 years (B) on lung function at age 7 years

NS=Not sensitised to dust mites or cat dander (≤age 3 years [n=647]; ≤age 5 years [n=642]). S/LE=Sensitised to dust mites or cat dander and low exposure to these allergens (≤age 3 years [n=22]; ≤age 5 years [n=42]). S/HE=Sensitised to dust mites or cat dander and high exposure to these allergen (≤age 3 years [n=27]; ≤age 5 years [n=46]). Quartiles of allergen exposure were calculated across the whole population. Since exposure to house dust mites and cats significantly increased the risk of sensitisation towards these allergens,⁹ more children sensitised to perennial allergens were found in the highest quartile of allergen exposure.

By contrast, after age 5 years the course of wheezing differed markedly between groups (figure 3). Whereas in non-atopic wheezers the prevalence of current symptoms diminished substantially in subsequent years, among the atopic wheezers the prevalence of current symptoms first increased and then remained stable over the following years. 37 (90.2%) non-atopic wheezers had a remission of symptoms at age 13 years, compared with 41 (56.2%) for atopic wheezers (p=0.0002).

Early sensitisation to perennial allergens significantly affected lung function at school age, whereas later

sensitisation to these allergens had a less pronounced effect (webtable 2). By contrast, sensitisation to seasonal allergens and early sensitisation to food allergens had no significant effect on lung function at ages 7, 10, and 13 years.

Lung function was significantly reduced in children sensitised to perennial allergens early in life and exposed to high levels of the respective allergens in the first 3 years of life, compared with non-sensitised, and sensitised but less exposed, children (eg, MEF₅₀ 86.4 [SD 25.1] vs 101.5 [23.2], p=0.0031 for sensitised and

See Online for webtable 2

	Wheezers			Non-wheezers		
	n/N	OR (95% CI)	p	n/N	OR (95% CI)	p
Univariate analysis						
Current perennial sensitisation (age 7 years)	39/102	5.71 (2.38–13.70)	<0.0001	78/439	4.22 (2.25–7.91)	<0.0001
Current seasonal sensitisation (age 7 years)	43/102	2.84 (1.25–6.47)	0.013	94/441	2.10 (1.11–3.97)	0.022
At least 3 years with wheeze until age 7 years	56/116	2.69 (1.26–5.77)	0.011	9/527	2.41 (0.49–11.87)	0.281
At least four episodes of wheeze in the previous 12 months at age 7 years	19/115	2.29 (0.84–6.23)	0.104	..	..	..
Early perennial sensitisation (≤age 3 years)	17/106	15.52 (3.32–72.42)	0.0005	35/477	0.77 (0.23–2.61)	0.674
Early seasonal sensitisation (≤age 3 years)	22/107	2.52 (0.97–6.56)	0.059	57/478	1.69 (0.78–3.69)	0.186
Early wheeze (≤age 3 years)	56/105	1.96 (0.88–4.38)	0.099	125/468	1.08 (0.56–2.07)	0.827
Parental history of atopy or asthma	76/116	3.63 (1.52–8.65)	0.004	273/526	0.88 (0.51–1.53)	0.657
Maternal smoking in pregnancy	28/107	1.47 (0.62–3.49)	0.384	102/493	0.84 (0.41–1.72)	0.627
Current smoke exposure at home (age 7 years)	41/115	1.14 (0.54–2.39)	0.736	223/524	1.24 (0.72–2.16)	0.437
High exposure to any perennial allergen (≤age 3 years)	57/108	2.11 (0.96–4.64)	0.063	301/500	0.87 (0.49–1.52)	0.620
Sensitisation and exposure status (≤age 3 years)						
Not sensitised*	90/103	1.00 (..)	..	445/473	1.00 (..)	..
Sensitised/low exposure†	4/103	6.31 (0.63–63.32)	0.077	16/473	0.54 (0.07–4.17)	0.554
Sensitised/high exposure‡	9/103	39.61§ (2.23–703.86)	<0.0001	12/473	1.62 (0.34–7.59)	0.543
Multivariate stepwise analysis¶						
Current perennial sensitisation (age 7 years)	36/94	3.29 (0.95–11.36)	0.059	78/439	4.39 (2.32–8.30)	<0.0001
Early perennial sensitisation (≤age 3 years)	15/94	8.63 (1.07–69.74)	0.043	..	.. (..)	..

*Not sensitised to dustmites or cat dander ≤age 3 years; †Sensitised to dust mites or cat dander but low exposure to the respective allergen ≤age 3 years; ‡Sensitised to dust mites or cat dander and high exposure to the respective allergen ≤age 3 years. §This estimate is based on a correction of 0.5 in every cell of the respective table due to a zero cell (0 of 9 sensitised and exposed wheezers had no airway hyper-responsiveness); ¶Adjusted for study centre, parental atopy, and current asthma medication.

Table 1: Predictors of airway hyper-responsiveness at age 7 years, stratified for wheezing at school age (5–7 years)

	FEV ₁ (% FVC)†		FEV ₁ (% pred)		MEF ₇₅ (% pred)		MEF ₅₀ (% pred)		MEF ₂₅ (% pred)	
	beta (SE)	p	beta (SE)	p	beta (SE)	p	beta (SE)	p	beta (SE)	p
Model 1										
Perennial sensitisation (≤age 3 years)	-2.51 (0.69)	<0.001	-3.51 (1.32)	0.008	-3.28 (2.18)	0.134	-6.93 (2.63)	0.009	-9.63 (3.59)	0.008
Model 2										
Perennial sensitisation (≤age 3 years)	-1.74 (0.77)	0.025	-0.97 (1.49)	0.513	-0.36 (2.45)	0.883	-1.48 (2.95)	0.616	-3.27 (4.00)	0.414
Airway hyper-responsiveness (age 7 years)	-2.21 (0.60)	0.0003	-4.46 (1.17)	0.0002	-7.49 (1.92)	<0.0001	-13.03 (2.30)	<0.0001	-15.65 (3.12)	<0.0001

*Adjusted for study centre, parental atopy, and maternal smoking in pregnancy as fixed covariates and current wheeze and current use of asthma medication as time-dependent covariates. †Additionally adjusted for age at spirometry (years) as time-dependent covariate.

Table 2: Predictors of lung function at ages 7, 10, and 13 years from repeated measure analysis with mixed linear models*

high exposure vs not sensitised; figure 4). Sensitisation and exposure up to age 5 years had less pronounced effects. No effect of allergen exposure on lung function was seen in non-sensitised children (data not shown).

Several factors relating to sensitisation, allergen exposure, duration, and severity of the illness as well as to a family history of asthma and atopy were associated with airway hyper-responsiveness at school age in wheezing and non-wheezing children (table 1). In wheezy children only two factors were significant in a stepwise multivariate logistic regression model—early (adjusted OR 8.63, 95% CI 1.07–69.74) and current perennial

sensitisation (3.29, 0.95–11.36), which were independent determinants of airway hyper-responsiveness in these children.

We investigated the independent effects of sensitisation and airway hyper-responsiveness on baseline lung function at ages 7, 10, and 13 years in a multivariate regression model adjusting for current wheeze, study site, parental smoking at birth, parental atopy, and asthma medication (table 2). Perennial sensitisation before age 3 years was a significant risk factor for all parameters of pulmonary function, except the MEF₇₅. When including airway hyper-responsiveness into the

model, early perennial sensitisation was no longer significant, but airway hyper-responsiveness became a significant predictor. This finding suggests that airway hyper-responsiveness is the intermediate step in the causal pathway relating early-life sensitisation to perennial allergens to decrements in baseline lung function at school age. This notion is supported by the partial improvement of baseline lung function after bronchodilator administration (figure 2).

Discussion

Children with repeated wheeze over the first 5 years of life who do not develop atopic sensitisation lose their symptoms during school age and retain normal lung function at puberty. By contrast, children with repeated wheeze in the first 5 years who also become sensitised to perennial allergens are prone to a chronic course of asthma characterised by more severe symptoms, presence of airway hyper-responsiveness, and decrements in baseline and post-bronchodilator lung function. Increased exposure to perennial allergens early in life contributes to the chronicity of asthma.

Sensitisation to house dust mites, and cat and dog dander were judged to be perennial sensitisation. In Germany, the prevalence of sensitisation to cockroach and alternaria has been estimated to be low (4.2% and 0.7%, respectively)^{12,13} and is therefore unlikely to contribute much to perennial allergic sensitisation in Germany. Furthermore, no significant effect of cockroach sensitisation on baseline lung function, airway responsiveness, and a doctor's diagnosis of asthma at school age has been found in Germany.¹²

In the first years of life, IgE-antibody responses are first directed towards food allergens, later towards indoor and outdoor allergens.¹⁴ Therefore, early perennial sensitisation might merely be an indicator of atopic sensitisation developing early in life. However, the lack of association between early food sensitisation and loss of lung function at ages 7, 10, or 13 years, as well as the interaction between perennial sensitisation and exposure to those specific allergens strongly argues against a surrogate association. Early start of sensitisation might furthermore be a proxy for longer duration of sensitisation. However, there were no significant effects of perennial sensitisation occurring between ages 3 and 6 years on lung function at age 10 years.

Therefore, the timing of the process seems of importance: the harmful effect of indoor allergen exposure interacting with sensitisation towards these allergens was most pronounced for the first 3 years of life. Adaptive immunity in children matures over the first 6 years of life, but the most important steps towards the development of mature systemic immune responses are taken in the first 1–2 years of life.¹⁵ Very little is known about the maturation of normal immune responses in the airway mucosa and the aberrant development of allergic airway inflammation early in life. In adults, airway inflammation has been

strongly linked to remodelling of the airway structure with eosinophilic inflammation and thickening of the reticular basement membrane. A study in symptomatic infants aged 3–26 months with reversible airflow obstruction has shown no reticular basement membrane thickening and eosinophilic inflammation even in the presence of atopy.¹⁶

These findings, taken together with the data presented here, suggest that it is the subsequent chronic exposure in susceptible, allergic children that results in alterations of airway function at school age. The significant loss in the post-bronchodilator FEV₁/FVC ratio could support a notion of airway remodelling, but no objective measurement of reticular basement membrane can be done in a population-based study. Although we cannot exclude with certainty the suggestion that a higher bronchodilator dose might have further improved lung function, airway remodelling is a likely explanation since it has been documented in children with chronic asthma.¹⁷ This process also included small airways because the loss of lung function in atopic individuals was most pronounced for mid-expiratory flows at low levels of FVC. In the Manchester birth cohort, children persistently wheezing from age 1 to 5 years already had poorer lung function at age 3 years.¹⁸ The combination of sensitisation to indoor allergens and exposure to the sensitising allergens also determined the level of lung function at age 3 years in this cohort.¹⁹

The term wheezy bronchitis is used to describe children with episodes of wheeze triggered by viral infections to distinguish these patients from asthmatic children whose symptoms are triggered by several other factors such as allergen exposure, irritant exposures, and exercise.²⁰ Notably, in the long-term prospective study in Melbourne that followed-up children diagnosed with wheezy bronchitis at age 7 years to mid-adult age, pulmonary function remained normal throughout the study period.⁵ Although the investigators in Australia did not test the cohort for allergies, it seems likely that their group of children with wheezy bronchitis represents the non-atopic asthma phenotype described here. In the MAS cohort, non-atopic wheeze was highly prevalent since more than a third (38.6%) of all wheezers at age 5–7 years did not have detectable serum IgE antibodies. The frequency of wheeze episodes in the first years of life was as high as in the atopic wheezers (figure 3). Therefore, morbidity of the non-atopic phenotype is significant in infant and toddler years, but limited as the remission rate over puberty was high and normal lung function was retained.

If processes resulting in chronic airway inflammation and remodelling do start early in life, then the management of infants and toddlers with wheeze should be re-assessed.²¹ Selective eradication of the ubiquitous allergen exposure might not be achievable. In fact, drastic reduction of house dust mites has resulted in an increased rather than decreased risk of atopy,²² possibly through the concomitant

eradication of other protective environmental exposures. Less radical reductions of allergen levels by using dust mite impermeable mattress covers have also failed to prevent asthma.²³ The best treatment strategies for these children are still unclear. Inhaled corticosteroids after school age do not strongly affect baseline lung function, although symptoms and airway hyper-responsiveness can be well controlled.²⁴ This lack of efficacy on pulmonary function could be attributable to a delayed onset of treatment,^{25,26} or to the inability of corticosteroids to sufficiently suppress the allergic immune responses that amplify airway inflammation. Some investigators have cast doubt on the ability of inhaled steroids to alter the natural course of wheezing illnesses early in life.^{27,28} However, in none of the trials were findings stratified for atopic and non-atopic wheezers. Therefore, clinical studies investigating the effect of an early onset of continuous treatment with inhaled corticosteroids up to school age in atopic wheezy infants and toddlers are needed to assess their potential for the secondary prevention of airway remodelling and loss of lung function until that age. Given the good prognosis for non-atopic wheezing children, the need for these individuals to continue to take inhaled corticosteroids on a regular basis should be re-assessed.

Contributors

S Illi analysed the data and participated in drafting the manuscript. E von Mutius contributed to the analysis and interpretation of data and drafting of the manuscript. S Lau, B Niggemann, and C Grüber planned the MAS and undertook the clinical part of the MAS. S Lau supervised measurements of serum IgE and indoor allergen exposure. B Niggemann was responsible for lung function testing and bronchial challenge. U Wahn is the coordinator and principal investigator of the MAS.

Conflict of interest statement

We declare that we have no conflict of interest.

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