Early patterns of wheezing in asthmatic and nonasthmatic children

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ABSTRACT The aim of this study was to describe the time patterns of wheezing in both asthmatic and nonasthmatic children during the first 36 months of life, and to determine whether there are asthma-related breakpoints in the incidence of wheezing.

Data from a historical cohort of children followed from birth to 6 years (SLAM cohort) were used. Wheezing episodes until 36 months and asthma at 6 years were both recorded by a doctor. Monthly mean incidence rate of wheezing and rate ratio were calculated. Joinpoint regression models were built to identify breakpoints in the risk of wheeze.

Complete information was available for 3739 children. Wheezing in the first 36 months was more frequent in asthmatic than in nonasthmatic children (rate ratio 2.62, 95% CI 1.81–3.78). Differences were appreciable within the first months and increased steadily thereafter because of a persistently high rate in asthmatic children. No breakpoint in the rate ratio could be identified. Asthmatic children exhibited a one-phase curve of incidence and nonasthmatic children exhibited a two-phase curve. However, children with allergic asthma also displayed a two-phase curve.

There is no identifiable breakpoint during the first 36 months of life at which the incidence of wheezing in asthmatic children begins to stand out.

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Increased wheezing in asthmatic children from birth; different progression patterns for allergic and nonallergic asthma http://ow.ly/lo9Yk

This article has supplementary material available from www.erj.ersjournals.com

Received: Sept 18 2012 | Accepted after revision: Dec 23 2012 | First published online: Jan 24 2013

Support statement: This study was funded by the Fundación Ernesto Sánchez Villares (project 2011/03).

Conflict of interest: None declared.

Introduction

Approximately 40–50% of infants have at least one wheezing episode in their first year of life, and these episodes are frequently repeated thereafter [1]. Wheeze is also one of the cardinal manifestations of asthma, and the relationship between infant wheeze and persistent asthma has attracted significant interest. The current knowledge of the natural history of infant wheezing comes from a set of large studies that analysed both the timeline of this disease and its association with persistent asthma symptoms in schoolchildren. The Tucson Children's Respiratory Study classified wheezing in the first 3 years as either transient or persistent, depending on the absence or presence of symptoms at 6 years of age [2]. The Avon Longitudinal Study of Parents and Children (ALSPAC) has recently added complexity to this issue through the identification of new disease patterns [3]. Based on these and other studies, it may be said that many wheezing infants have only a transient type of disease; however, up to 40% of them will have asthma symptoms during school years. There have been advances in the development of methods to predict the risk of asthma in young children with wheeze, and asthma predictive indexes have been devised and tested [4].

An under-studied aspect of asthma is whether early wheezing history is different in children with asthma compared with children without asthma. It has been suggested that there is no association between asthma and wheeze in children <1 year of age, but it is unclear when that association does appear [5]. It is possible that some turning points do exist at which the incidences of wheeze in asthmatic and nonasthmatic children diverge. The British Guideline on the Management of Asthma suggests that there is a breakpoint at ~2 years of age [6]. However, there is a lack of evidence supporting that statement.

The aims of this study are as follows: to describe the different time patterns of wheezing in both asthmatic and nonasthmatic children throughout the first 36 months of life and to determine whether there is any clear turning point in the incidence of asthmatic wheezing.

Population and methods

Population and setting

The SLAM (Sibilancias en Lactante y Asma en el Mayor (Infant Wheezing and Later Asthma)) study utilised data from a historical cohort composed of all 6-year-old children born between 2002 and 2004, in a population covered by 29 primary healthcare practices in Asturias, a northern Spanish region with both a warm, temperate, humid climate and a high asthma prevalence, estimated to be 11.5% at 6–7 years and 15.3% at 13–14 years in 2002 [7]. Participating centres were primary healthcare practices, both urban and rural, that provided public healthcare, the only health insurance system for ~87% of the paediatric population of Spain in 2006 (National Health Survey data http://pestadistico.inteligenciadegestion.msssi.es/ArbolNodos.aspx). Depending on their place of residence, children were assigned at birth to a primary health centre where a paediatrician acted as the primary care physician for children aged <14 years. All children attended a scheduled visit at 6 years, when a review of health problems, vaccination and other preventive care were provided by the attending paediatrician.

Children with specific diseases related to chronic or recurrent respiratory problems were excluded. A detailed list of specified exclusion criteria is included in online supplementary table S1. Incomplete follow-up was noted if a child was not assigned to the study centre at birth. These were children who had either changed residency or been born abroad.

Information about wheeze and asthma

The clinical records of all the children were reviewed for wheezing episodes in the first 36 months of life. The review focused on every note included in both the paper and electronic clinical records (since 2001, all primary healthcare practices in Asturias have used the same electronic clinical recording system), as well as the reports of both hospitalisations and emergency room visits, which are routinely documented in clinical records.

A wheezing episode was defined as any respiratory disease in which a physician recorded that wheeze was auscultated on physical examination. The date of detection of wheeze was taken as the date of the episode, and 1 month was required as a minimum elapsed time between distinct episodes [8].

Clinical records were also used to identify active asthma at 6 years, defined as the occurrence in the previous 12 months of both symptoms attributed to asthma by a paediatrician and the reception of at least one antiasthmatic drug prescription.

Allergy tests for airborne allergens (either skin prick tests or serum-specific IgE determinations) were frequently, but not constantly, performed as a part of the health care of asthmatic children, and the results were recorded as either positive or negative in the clinical records. The age at which they were carried out, as well as the type and the number of tested allergens could vary according to clinical needs, but dust mite sensitisation was always included for testing because it is the allergen most commonly associated with

asthma in Asturias. Asthma was classified as either allergic or nonallergic based on a positive or negative test to any airborne allergen.

Analysis

All wheezing episodes between birth and 36 months of age were identified, and the mean monthly incidence rates per 1000 children were calculated and assigned to the midpoint of each monthly interval. Incidence rate ratios between asthmatic and nonasthmatic children, as well as their 95% Wald confidence intervals, were also calculated. The seasonality of wheezing was evaluated by plotting the incidence rate for each calendar month. The seasonal variability was calculated by the coefficient of variation of the 3-year mean of the incidence rate in each calendar month, and between-group differences in coefficient of variation were analysed statistically [9].

Changes in both incidence rate and rate ratio throughout the first 36 months of life were analysed by joinpoint regression models, looking for breakpoints in the trends. Regression models were constructed using the Joinpoint Regression Program software from the US National Cancer Institute [10]. Linear models were constructed for incidence rate, and log-linear models were constructed for rate ratio, with the midpoint of every month of age as the independent variable. The models were constructed by a grid-search method, and models with between zero and five joinpoints were tested. The selection of the best model was made by a permutation test, with a global signification level of 0.05 following Bonferroni correction for repeated tests [11]. Further details on regression model building, selection and fit are provided in the online supplementary material. Other comparisons were made by Chi-squared tests for tabulated data and by Mann–Whitney nonparametric tests for non-normally distributed numerical data.

Ethics

The study protocol was approved by the regional clinical research ethics committee of the Principado de Asturias (number 03/2011).

Results

Sample

Out of a cohort of 4765 6-year-old children, 36 (0.8%) had one of the exclusion criteria (detailed in online supplementary table S1) and 990 children (20.8%) had an incomplete follow-up. There were no differences in sex, year of birth or birthweight between children with and without complete follow-up. The analysis utilised the complete data collected from 3739 children (51.2% male).

There were 1704 children (45.6%) with at least one wheezing episode in the first 36 months of life. Active asthma at 6 years of age was identified in 573 (15.3%) children, 359 (62.7%) of whom underwent allergy tests, with 228 (63.5%) children being sensitised; house dust mites were the most frequently involved allergen (94.7%). A flow diagram of the follow-up and classification of the children is provided in the online supplementary material.

Wheezing in the first 36 months was more common in asthmatic than in nonasthmatic children (73.6% *versus* 40.5%, $p<0.001$), without significant differences between allergic and nonallergic asthma (75.4% *versus* 77.1%, $p=0.798$). The first episode of wheeze in nonasthmatic children occurred at a median (interquartile range) age of 8.8 (5.4–18.2) months, and in asthmatic children at 9.9 (5.2–21.5) months ($p=0.047$). Children with nonallergic asthma had their first episode at a significantly earlier age than children with allergic asthma (9.0 (4.9–18.7) months *versus* 12.0 (6.5– 26.1) months, $p=0.005$).

Incidence of wheezing

The mean monthly incidence rates of wheezing in the first 36 months of life were 27.84 episodes per 1000 children without asthma and 72.86 per 1000 children with asthma, with a rate ratio of 2.62 (95% CI 1.81–3.78). The monthly incidence rate throughout the first 36 months are shown in figure 1, and the tabulated incidence rate and rate ratio data are presented in online supplementary table S2. Asthmatic children had a significantly higher risk of wheezing beginning at the third month of age, increasing steadily throughout the first 36 months. While the incidence rate among children without asthma demonstrated a smooth decrease following a peak, asthmatic children continued to have an elevated incidence rate throughout the first 3 years of life. The mean monthly incidence rates were lower in allergic asthma than in nonallergic asthma, with 70.42 and 86.30 episodes per 1000, respectively, and a rate ratio of 0.82 (95% CI 0.38–1.75). The related figures and tables are presented in online supplementary table S3 and figure S2.

Seasonality

Figure 2 shows incidence rates for each calendar month (tabulated data in online supplementary table S4). Seasonality, with a lower incidence rate during summer, was evident in both asthmatic and nonasthmatic

DOI: 10.1183/09031936.00148712

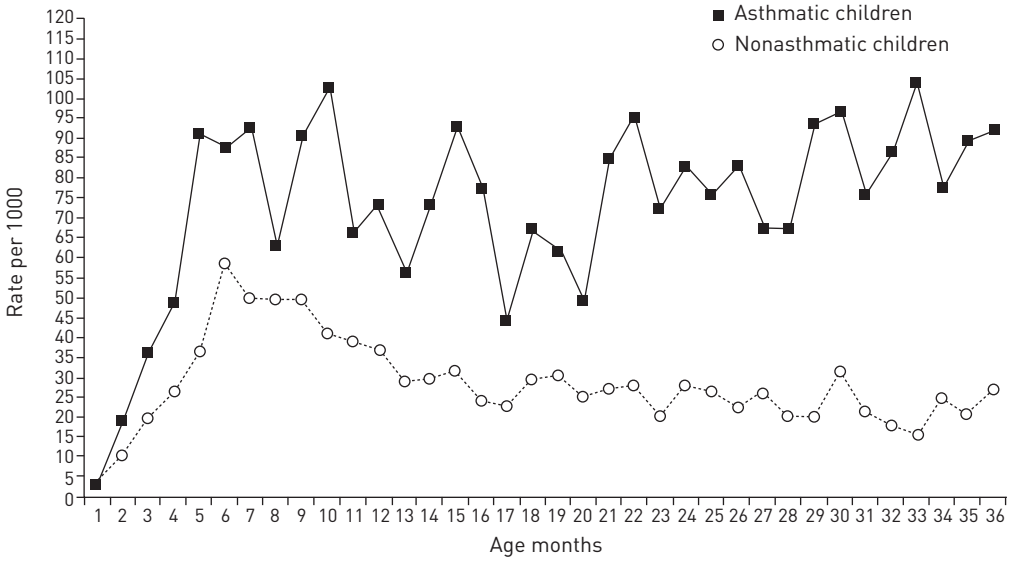

FIGURE 1 Mean monthly incidence rates (per 1000) of wheeze in asthmatic and nonasthmatic children from birth to 36 months of age.

children, but yearly changes were different. Each consecutive year, the incidence rate in nonasthmatic children reduced in winter and spring (December–June), whereas asthmatic children maintained the same elevated incidence rate in winter and spring but increased it in summer (July–September). As a result, seasonality was higher in nonasthmatic than in asthmatic children (coefficient of variation 46.7% and 37.0%, respectively; $p<0.001$). Seasonality was present in children with both allergic and nonallergic asthma, and was slightly greater in allergic asthma (coefficient of variation 43.1% and 37.9%, respectively; $p=0.083$). See online supplementary figure S3.

Joinpoint regression

Details regarding the selection of the best models are included in online supplementary tables S5–S8 of the online depository. Regression lines are shown in figure 3, and table 1 demonstrates the regression parameters. Clear turning points in the incidence rate throughout the first 36 months were identified. In nonasthmatic children, the incidence rate rose quickly to a peak at 5.5 months (95% CI 4.5–7.5), then it quickly dropped to a second joinpoint at 15.5 months (95% CI 10.5–18.5). Thereafter, the decrease

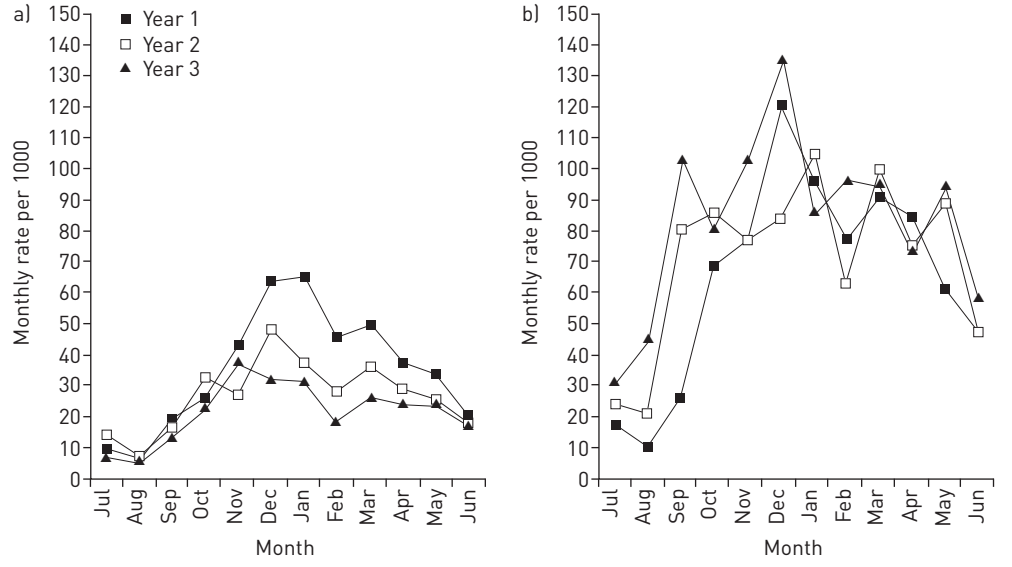

FIGURE 2 Monthly incidence rates of wheeze in a) nonasthmatic and b) asthmatic children, normalised for calendar month, in the first, second and third years of age.

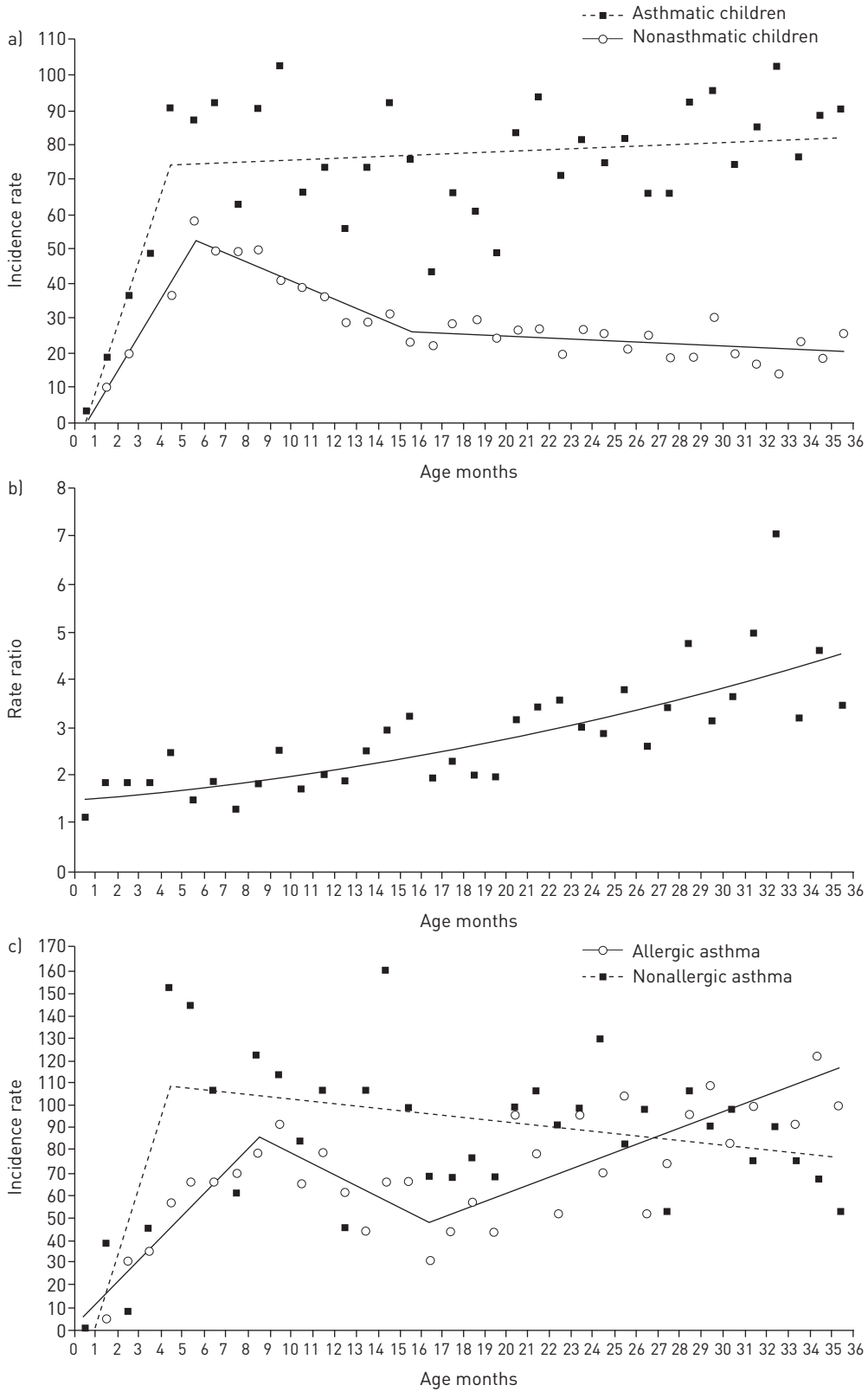

FIGURE 3 Incidence of wheeze in the first 36 months and joinpoint regression lines. a) Children with and without asthma at 6 years; b) rate ratio of asthmatic over nonasthmatic children; c) children with allergic and nonallergic asthma at 6 years.

DOI: 10.1183/09031936.00148712

TABLE 1 Parameters of the final regression models

	R^2	Parameter estimate	p-value	Number of joinpoints	Joinpoint location estimate months
Incidence rate#					
Asthmatic children	0.608			1	4.5 (2.5–6.5)
Intercept 1		-8.20 (-37.43–21.03)	0.586		
Intercept 2		73.40 (60.59–86.21)	<0.001		
Slope 1¶		18.38 (5.63–31.14)	0.008		
Slope 2¶		0.25 (-0.32–0.82)	0.398		
Nonasthmatic children	0.898			2	5.5 (4.5–7.5) 15.5 (10.5–18.5)
Intercept 1		-5.69 (-11.99–0.62)	0.088		
Intercept 2		67.16 (57.47–76.85)	<0.001		
Intercept 3		30.56 (23.39–37.73)	<0.001		
Slope 1¶		10.60 (8.41–12.80)	<0.001		
Slope 2¶		-2.64 (-3.54– -1.75)	<0.001		
Slope 3¶		-0.28 (-0.55– -0.01)	0.050		
Rate ratio+	0.691			0	
Intercept 1		1.47 (1.27–1.71)	<0.001		
Slope 1§		3.23 (2.50–3.97)	<0.001		
Incidence rate#					
Allergic asthma	0.742			2	8.5 (3.5–12.5) 16.5 (10.5–23.5)
Intercept 1		-0.66 (-24.42–23.10)	0.957		
Intercept 2		126.55 (46.65–206.45)	0.004		
Intercept 3		-12.44 (-50.29–25.42)	0.525		
Slope 1¶		10.21 (5.06–15.36)	0.001		
Slope 2¶		-4.76 (-11.07–1.55)	0.151		
Slope 3¶		3.67 (2.27–5.07)	<0.001		
Nonallergic asthma	0.461			1	4.5 (3.5–6.5)
Intercept 1		-27.92 (-78.16–22.32)	0.284		
Intercept 2		113.02 (91.00–135.04)	<0.001		
Slope 1¶		30.32 (8.39–52.25)	0.011		
Slope 2¶		-1.00 (-1.99–-0.02)	0.055		

Data are presented as estimate (95% CI), unless otherwise stated. #: monthly incidence rate of wheezing episodes per 1000; ¶: mean monthly change in incidence rate per 1000; +: log-linear model; §: mean monthly change in rate ratio (%).

continued at a slower pace. Asthmatic children also demonstrated a very quick rise of the incidence rate to a peak at 4.5 months (95% CI 2.5–6.5), but thereafter the incidence rate remained almost unchanged (nonsignificant regression slope), without any new identifiable joinpoint. The regression model for the rate ratio demonstrated a significant intercept at a log-value equivalent to a rate ratio of 1.47 (95% CI 1.27–1.71), corresponding to an elevated risk of wheezing in asthmatic children since birth. There were no identifiable joinpoints in the model, with a steady 3.2% rise in the rate ratio each month.

The model for allergic asthma had some similarities to that used for nonasthmatic children, as it also exhibited two joinpoints. The first occurred at 8.5 months (95% CI 3.5–12.5), and the second at 16.5 months (95% CI 10.5–23.5). The change at this second point was towards a rapid increase in incidence rate, thus demonstrating a two-phase pattern. Children with nonallergic asthma had only one joinpoint, located at 4.5 months (95% CI 3.5–6.5).

Discussion

Key findings

Children with active asthma at 6 years of age have an increased risk (risk ratio) of wheezing within the first months of life, a risk that increases constantly thereafter. Following an early peak, there is no identifiable subsequent age breakpoint at which a change in the incidence of asthma-related wheezing occurs, and the gradual increase in the rate ratio is due to the gradual decrease of the incidence ratio in nonasthmatic children.

Children with allergic asthma have an incidence ratio with an obvious two-phase curve, with the first phase resembling the one observed in children without asthma, and the second phase beginning at the middle of

the second year, when the incidence ratio changes towards a new rise. However, children with nonallergic asthma demonstrate a single-phase pattern with a persistently high incidence ratio.

Limitations and strengths

Limitations of the study are primarily due to its historical nature and the risk of missing or unrecorded episodes, leading to an underestimation of incidence. However, the cumulative incidence of 45.6% in the first 3 years was close to that previously reported (*e.g.* 43.5% in the Leicester Respiratory Cohort) [12]. Wheezing episodes can be missed if families are reluctant to consult because of familiarity with respiratory symptoms, cultural or ideological traits, a preference to consult in private practices or other reasons. We did not contrast the recorded data with parental reports, because their memory of events that occurred years ago would be a very biased source of information. Readiness to consult can decrease as the child grows up. Were this the case, the true incidence rate in nonasthmatic children would be rather constant after the early peak instead of showing the smooth reduction found in the regression model. Moreover, the true incidence rate in asthmatic children would display a continuous increase after the early peak. In addition, if the rate of missing episodes had been different between asthmatic and nonasthmatic children, the estimated rate ratio would be biased towards an unpredictable direction, as both higher and lower consultation thresholds in asthmatic children could be theoretically claimed. What is not expected is a brisk change in the rate of missing episodes at a given age, so the incidence joinpoints are likely to be due to true changes in incidence. It is also unlikely that abrupt changes occur in the differential risk of missing a wheezing episode between asthmatic and nonasthmatic children, so the absence of any joinpoint in the rate ratio should not be attributed to a bias caused by missing episodes.

Additionally, the classification of both allergic and nonallergic asthma was derived from different techniques, applied at different ages and not universally performed in asthmatic children. Allergy testing was performed in 62.7% of asthmatic children, a figure that compares well with prospective cohorts in which scheduled allergy tests were performed only in between 50 and 80% of the cohort [2, 13, 14]. However, had all children undergone allergic tests at six years, some non-allergic asthmatics could have been considered as having allergic asthma, as sensitisation to inhalant allergens increases with age. Nevertheless, not too much misclassification seems to have happened as the percentage of asthmatic children with allergic asthma (63.5%) was not lower than the one found in other studies [15, 16]. Another limitation of the study is the absence of some data, which may help a more subtle interpretation: family allergy risk, smoke exposure and other risk factors. The decision to not include these factors in the analysis was made based on the historical design of the study, as both the quality of and the completeness of those data in the clinical records were irregular, and their use posed a significant risk of bias.

This study has four noteworthy strengths. First, data were obtained prospectively, as wheezing episodes occurred, and wheeze was confirmed by a physician. This contrasts with studies in which information regarding wheeze was retrospectively obtained *via* parents' responses to questionnaires. Studies have shown that those answers are not reliable [17]. Secondly, we established a clear criterion to separate each episode from the next, thus avoiding a false multiplication of episodes. Thirdly, the date of each episode could be precisely established, allowing for a high-resolution month-to-month analysis. Fourthly, the sample size is relatively large, as compared to questionnaire-based prospective birth cohort studies, and the rate of losses is quite small [2, 3, 13, 14, 18–20].

Interpretation

Three main conclusions can be derived from the results of the study. First, asthmatic and nonasthmatic children exhibit differences beginning at birth that determine a disparate risk and course of wheezing in the early months of life. What distinguishes children who will have asthma from those who will not have asthma is a multitude of factors. There are heterogeneous gene polymorphisms involved in inflammatory responses that are related to both childhood asthma and respiratory symptoms in infancy [21, 22]. However, any genetic susceptibility should exert a very early phenotypic effect, causing a different pattern of wheeze beginning almost at birth. Changes in inflammatory regulation could facilitate viral infections, leading to an increased early incidence of wheeze, as viral diseases have been found to be related to persistent wheeze and asthma [23]. Differences exist before the onset of any viral disease, however. Studies have highlighted the relationship between the presence of both airflow limitation and airway reactivity at birth and the development of both virus-related wheeze in the first year of life and asthma in schoolchildren [24–27]. Prenatal factors related to a reduction in neonatal airflow, such as *in utero* smoke exposure, may also have a genetic basis [28].

Secondly, it is difficult to establish a unique age cut-off at which the incidence rate of wheeze in asthmatic children becomes higher than in nonasthmatic children. Early identification of asthma in a wheezing infant is difficult, and although predictive indexes have been developed, they lack sensitivity [4]. Therefore, there is

DOI: 10.1183/09031936.00148712

still a need for more precise predictive clues, and age may be one of them. The British Guideline on the Management of Asthma [6] declares that there is a breakpoint at approximately 2 years of age. The data of the SLAM cohort do not support this statement, however. Certainly, there is an age-dependent relative risk of infant wheezing in children with asthma, but it is continuous; therefore, it is not possible to establish a unique breakpoint that abruptly separates them from nonasthmatic children.

Third, the differences between allergic and nonallergic asthma deserve careful interpretation. Asthma is a clinical manifestation of heterogeneous diseases, some of which are related to allergic sensitisation [29]. The two-phase curve of the incidence rate in allergic asthma is remarkable. There is a lack of recognition in the literature of the nonexclusivity of wheezing phenotypes and of the possibility that children have two separate but sequential diseases. The first part of the curve resembles that of nonasthmatic children, and it may be interpreted as a manifestation of the same mechanisms that cause wheeze in nonasthmatic children. The later rise in prevalence may be explained as the effect of increasing prevalence of sensitisation to airborne allergens, a prevalence that is known to increase in the second and third years [30]. This later rise in prevalence may also be associated with the intermediate-onset phenotype in the ALSPAC study [3]. As we had no reliable data regarding the age of sensitisation, we could not examine whether the incidence of wheeze and the prevalence of sensitisation matched in the SLAM cohort. Children with nonallergic asthma have a single-phase curve with a persistently high incidence, so they should have a powerful, nonallergic predisposition to wheeze that should be present at birth, given their extremely rapid and early rise in the incidence rate. As discussed above, reduced neonatal airflow may be an explanation.

In conclusion, this study determined that asthmatic children have a greater risk of wheezing beginning almost at birth and that there are different patterns of progression for allergic and nonallergic asthma. These early differences must encourage the search for early clues to an asthma diagnosis.

Acknowledgements

The SLAM Study Group members are as follows. Á. Cobo Ruisánchez, I. Pérez Candás, E. Díaz Estrada, B. Yáñez Meana, Á. García Merino, A. Arranz Velasco, I. Carvajal Urueña, B. Domínguez Aurrecoechea, C. Ruano Fajardo, M. Fernández Francés, M.L. García Balbuena, A. Pérez Vaquero, R. Buznego Sánchez, L. Merino Ramos, L.M. Alonso Bernardo, M. Coto Fuente, M. Moreno Sierra, R. Rodríguez Posada, F. Nuño Martín, F. Fernández López, M.Á. Ordóñez Alonso, A. Alonso Álvarez, M. García Adaro, L.M. Fernández Cuesta, Z. García Amorín, F. González Rodríguez, A. Aladro Antuña, I. Carballo Castillo, C. Castañón Rodríguez and Á. Costales Álvarez: Regional Health Service, Principado de Asturias, Spain.

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DOI: 10.1183/09031936.00148712