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EARLY PATTERNS OF WHEEZING IN ASTHMATIC AND NON-ASTHMATIC CHILDREN

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ABSTRACT

The aim of this study was to describe the time patterns of wheezing in both asthmatic and non-asthmatic children during the first thirty-six months, 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 six years (SLAM cohort) were used. Wheezing episodes until thirty-six months and asthma at six 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 thirty-six months was more frequent in asthmatic than in non-asthmatic 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 non-asthmatic 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 thirty-six months at which the incidence of wheezing in asthmatic children begins to stand out.

KEYWORDS

Child
Child, Preschool
Infant
Respiratory Sounds

INTRODUCTION

Approximately 40-50% of infants have at least one wheezing episode in their first year of life, and these episodes frequently repeat 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 (TCRS) classified wheezing in the first three years as either transient or persistent depending on the absence or presence of symptoms at six 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 forty percent 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 understudied 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 less than one 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 non-asthmatic children diverge. The British Guideline on the Management of Asthma suggests that there is a breakpoint at approximately two 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 non-asthmatic children throughout the first thirty-six 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) study utilised data from a historical cohort composed of all six year old children born between 2002 and 2004, in a population covered by twenty-nine primary health care 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 health care practices, both urban and rural, that provided public health, the only health insurance system for approximately 87% of the paediatric population of Spain in 2006 (National Health Survey data). 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 under fourteen. All children attended a scheduled visit at six 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 table E1 of the online depository. 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 thirty-six months of life. The review focused on every note included in both the paper and electronic clinical records (since 2001, all primary health care 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 one month was required as a minimum elapsed time between distinct episodes. [8]

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

Allergy tests for air borne allergens (either skin prick tests or serum specific immunoglobulin E 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 non-allergic based on a positive or negative test to any air-borne allergen.

Analysis. All wheezing episodes between birth and thirty-six months of age were identified, and the mean monthly incidence rates per 1000 children (IR) were calculated and assigned to the midpoint of each monthly interval. Incidence rate ratios (RR) between asthmatic and non-asthmatic children, as well as their 95% Wald confidence intervals (CI), were also calculated. The seasonality of wheezing was evaluated by plotting the IR for each calendar month. The seasonal variability was calculated by the coefficient of variation (CV) of the three-year mean of the IR in each calendar month, and between-group differences in CV were statistically analyzed. [9]

Changes in both IR and RR throughout the first thirty-six 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 U.S. National Cancer Institute. [10] Linear models were constructed for IR, and log-linear models were constructed for RR, 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

depository. Other comparisons were made by chi-squared tests for tabulated data and by Mann-Whitney non-parametric 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 six year-old children, 36 (0.8%) had one of the exclusion criteria (detailed in the E1 table in the online depository) 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 thirty-six months of life. Active asthma at six years of age was identified in 573 children (15.3%), 359 of whom (62.7%) underwent allergy tests, with 228 children (63.5%) 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 depository.

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

Incidence of wheezing. The mean monthly incidence rates of wheezing in the first thirty-six 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 (CI=1.81-3.78). The monthly IR throughout the first thirty-six months are shown in figure 1, and the tabulated IR and RR data are presented in table E2 of the online depository. Asthmatic children had a significantly higher risk of wheezing beginning at the third month of age, increasing steadily throughout the first thirty-six months. While the IR among children without asthma demonstrated a smooth decrease following a peak, asthmatic children continued to have an elevated IR throughout the first three years of life. The mean monthly incidence rates were lower in allergic asthma than in non-allergic asthma, with 70.42 and 86.30 episodes per 1000, respectively, and a RR of 0.82 (CI=0.38-1.75). The related figures and tables are presented in table E3 and figure E9 of the online depository.

Seasonality. Figure 2 shows incidence rates for each calendar month (tabulated data in table E4 of the online depository). Seasonality, with a lower IR during summer, was evident in both asthmatic and non-asthmatic children, but yearly changes were different. Each consecutive year, non-asthmatic children reduced their IR in winter and spring (December to June), whereas asthmatic children maintained the

same elevated IR in winter and spring but increased it in summer (July to September). As a result, seasonality was higher in non-asthmatic than in asthmatic children (CV=46.7% and 37.0%, respectively, p<0.001). Seasonality was present in children with both allergic and non-allergic asthma, and was slightly greater in allergic asthma (CV=43.1% and 37.9%, respectively, p=0.083). See figure E10 in the online depository.

Joinpoint regression. Details regarding the selection of the best models are included in tables E5 through E8 of the online depository. Regression lines are shown in figure 3, and table 1 demonstrates the regression parameters. Clear turning points in the IR throughout the first thirty-six months were identified. In non-asthmatic children, the IR rose quickly to a peak at 5.5 months (CI=4.5–7.5), then it quickly dropped to a second joinpoint at 15.5 months (CI=10.5–18.5). Thereafter, the decrease continued at a slower pace. Asthmatic children also demonstrated a very quick rise of the IR to a peak at 4.5 months (CI=2.5–6.5), but thereafter the IR remained almost unchanged (non-significant regression slope), without any new identifiable joinpoint. The regression model for the RR demonstrated a significant intercept at a log-value equivalent to a RR of 1.47 (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 RR each month.

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

Table 1. Parameters of the final regression models.

Model	R^2	Parameter	Parameter estimate (95% CI)	p	Number of joinpoints	Joinpoint location estimate (95% CI)[†]
IR (asthmatic children)	0.608	Intercept 1	-8.20 (-37.43 – 21.03)	0.586	1	4.5 (2.5 – 6.5)
		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		
IR (non-asthmatic children)	0.898	Intercept 1	-5.69 (-11.99 – 0.62)	0.088	2	5.5 (4.5 – 7.5) 15.5 (10.5 – 18.5)
		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[¶] (asthmatic over non asthmatic)	0.691	Intercept 1	1.47 (1.27 – 1.71)	<0.001	0	
		Slope 1[#]	3.23 (2.50 – 3.97)	<0.001		
IR (allergic asthma)	0.742	Intercept 1	-0.66 (-24.42 – 23.10)	0.957	2	8.5 (3.5 – 12.5) 16.5 (10.5 – 23.5)
		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		
IR (non-allergic asthma)	0.461	Intercept 1	-27.92 (-78.16 – 22.32)	0.284	1	4.5 (3.5 – 6.5)
		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		

IR: Monthly incidence rate of wheezing episodes per 1000; CI: confidence interval.
* Mean monthly change in incidence rate per 1000.
[#] Mean monthly change in rate ratio (percent).
[†] Month of age.
[¶] Log-lineal model.

DISCUSSION

Key findings. Children with active asthma at six years of age have an increased risk (RR) 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 RR is due to the gradual decrease of the IR in non-asthmatic children.

Children with allergic asthma have an IR 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 IR changes towards a new rise. However, children with non-allergic asthma demonstrate a single-phase pattern with a persistently high IR.

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 three years was close to the previosuly 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 occurred years ago would be a very biased source of information. The readiness for consultation can get lower as the child grew up . Had been this the case, the true IR in non-asthmatic children would be rather constant after the early peak instead of show the smooth reduction found in the regression model. Moreover, the true IR in asthmatic children would display a continuous increase after the early peak. Also, if the rate of missing episodes had been different between asthmatic and non-asthmatic 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 hardly 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 non-asthmatic children, so the absence of any joinpoint in the rate ratio should not be attributed to a bias caused by missing episodes.

Also, the classification of both allergic and non-allergic 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 sensitization 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] Second, we established a clear criterion to separate each episode from the next, thus avoiding a false multiplication of episodes. Third, the date of each episode could be precisely established, allowing for a high-resolution month-to-month analysis. Fourth, 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 non-asthmatic 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]

Second, it is difficult to establish a unique age cut-off at which IR of wheeze in asthmatic children becomes higher than in non-asthmatic 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 still a need for more precise predictive clues, and age may be one of them. The British Guideline on the Management of Asthma declares that there is a breakpoint at approximately two 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 non-asthmatic children.

Third, the differences between allergic and non-allergic 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 IR in allergic asthma is remarkable. There is a lack of recognition in the literature of the non-exclusivity of wheezing phenotypes and of the possibility that children have two separate but sequential diseases. The first part of the curve resembles that of non-asthmatic children,

and it may be interpreted as a manifestation of the same mechanisms that cause wheeze in non-asthmatic children. The later rise in prevalence may be explained as the effect of increasing prevalence of sensitisation to air-borne 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 non-allergic asthma have a single-phase curve with a persistently high incidence, so they should have a powerful, non-allergic predisposition to wheeze that should be present at birth, given their extremely rapid and early rise in the IR. 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 as soon as birth and that there are different patterns of progression for allergic and non-allergic asthma. These early differences must encourage the search for early clues to an asthma diagnosis.

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FIGURE LEGENDS

Figure 1. Mean monthly incidence rates (per 1000) of wheeze in asthmatic (*closed squares*) and non-asthmatic (*open circles*) children from birth to thirty-six months of age.

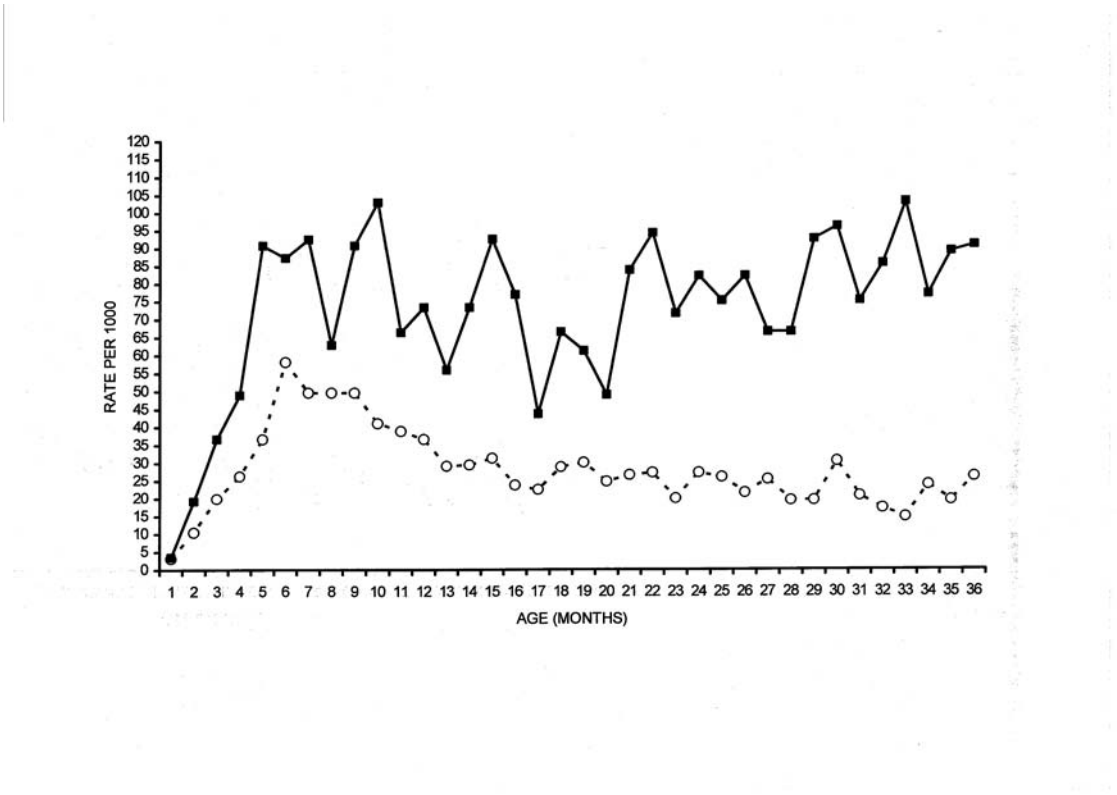


Figure 2. Monthly incidence rates of wheeze in non-asthmatic (*left*) and asthmatic (*right*) children, normalized for calendar month, in the first (*closed squares*), second (*open squares*) and third (*closed triangles*) years of age.

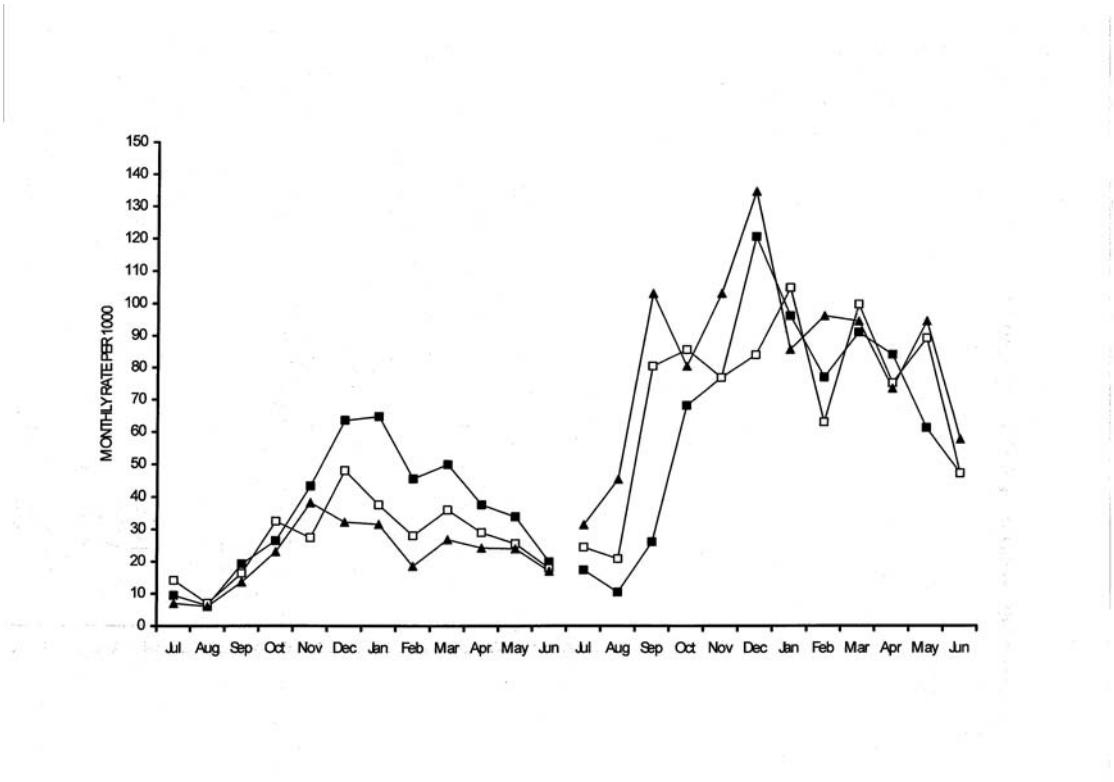
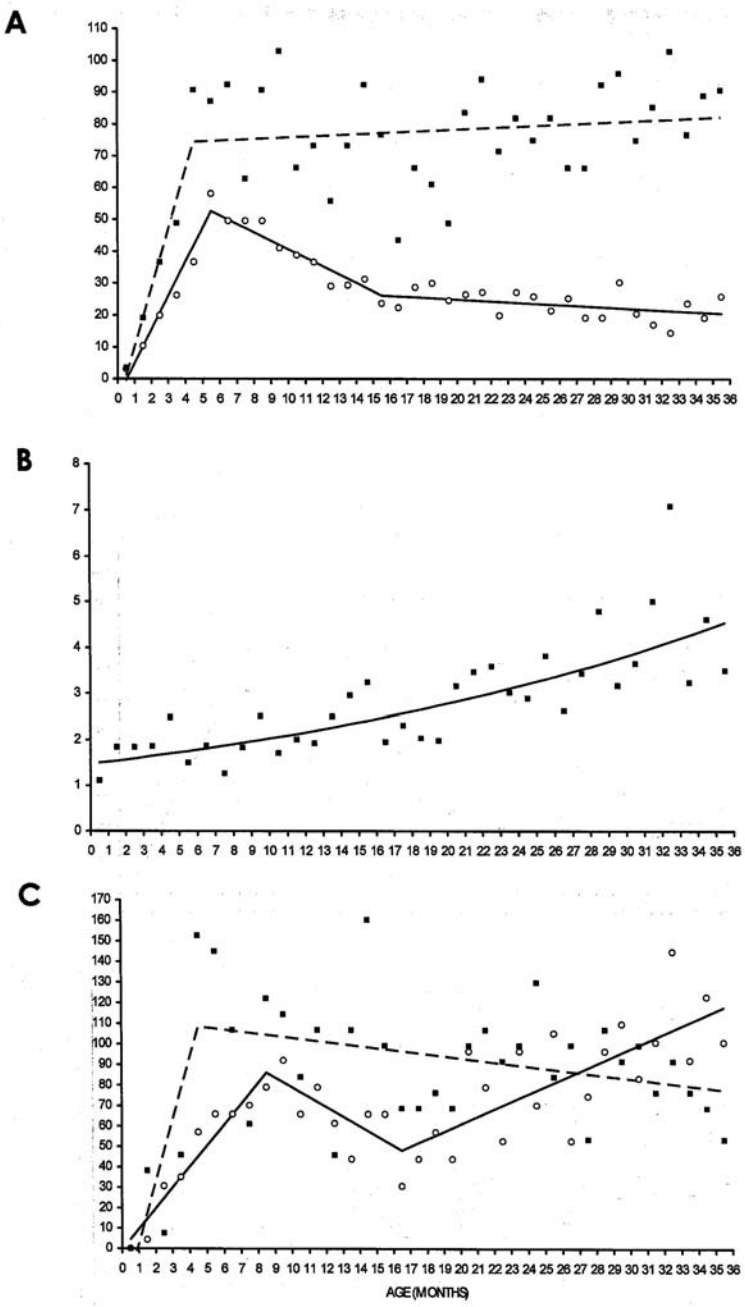


Figure 3. Incidence of wheeze in the first thirty-six months and joinpoint regression lines. A) children with (*closed squares* and *dotted line*) and without (*open circles* and *bold line*) asthma at six years; B) rate ratio of asthmatic over non-asthmatic children; C) children with allergic (*open circles* and *bold line*) and non-allergic (*closed squares* and *dotted line*) asthma at six years.


A
B
C
AGE (MONTHS)