

Frequency of Infections, Atopic Eczema and Asthma outcome in infancy

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INTRODUCTION

Studies of the effect of early life infections and the subsequent prevalence of allergic diseases have produced conflicting results. The so-called "hygiene hypothesis" was formulated on the basis of epidemiological studies of birth order, family size and farming families all of which suggested that reduced exposure to infectious agents led to an increased prevalence of allergy. Subsequent inverse relationships between raised antibodies to specific organisms such as Hepatitis A, Toxoplasma Gondii and Helicobacter Pylori have reinforced this hypothesis. There are also inverse relationships between prevalence of allergy and tuberculin reactivity, exposure to endotoxin in the domestic environment and infection with gut parasites. Conversely, increased use of antibiotics in pregnancy and postnatally has increased allergy risk. However, if rhinovirus the commonest cause of respiratory infections occurs frequently, it is associated with an increased risk of subsequent asthma. Thus recent reviews have concluded that the relationship between hygiene and allergy is not proven and further investigation is required (1,2).

METHODS

Early prevention of asthma in the atopic child (EPAAC) study was designed to test the effect of levocetirizine on the onset of asthma in infants between 1 and 2 years of age with atopic eczema and sensitisation to house dust mite and/or grass pollen. Subsequent follow up over 18 months established who had developed asthma defined as three separate episodes of wheezing and/or nocturnal cough disturbing sleep on three consecutive nights. There was an extensive database generated of a range of demographic variables as well as those related to clinical features at recruitment and follow up which facilitated evaluation of independent and combined influences on the development of asthma in this high risk infant cohort.

STATISTICAL METHODS

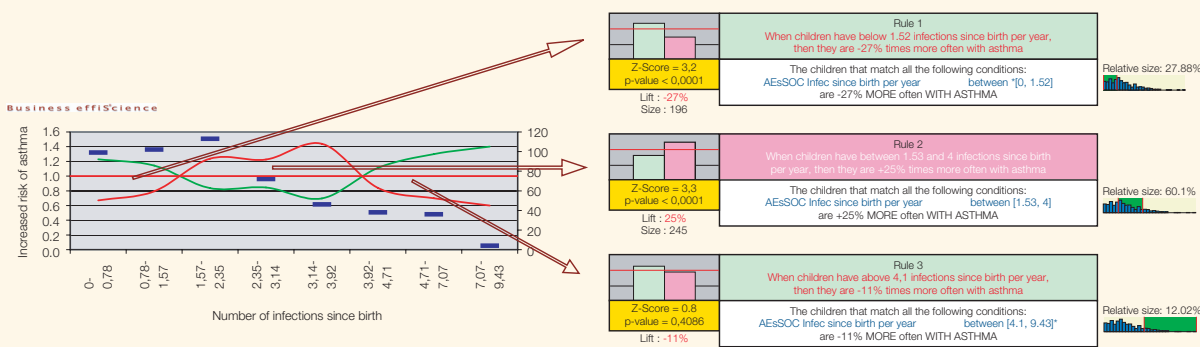
Descriptive statistics were conducted in a standard way. Measurement of association employed Business effiScience unique algorithm. A matrix was computed with candidate factors contrasted with the presence or absence of asthma building what has become known as a hyper cube which is defined as a region where similarities between predictors for simultaneous conditions leads to a hyper density. This facilitates the development of a scientific rule which is expressed as "the patients who match the following conditions are "n" more likely to develop asthma than the remaining population". The rule is defined by the percentage of children who have developed asthma, the ratio of children in this category by comparison with the reference prevalence, the number of children who comply with the rule and a Z score computed in the standard way. This facilitates the detection of associations which might hitherto have not been known, as well as defining the effects of the range of continuous variables that impact on asthma outcome.

RESULTS

510 infants between 1 and 2 years of age with atopic eczema (SCORAD > 10) were recruited and 434 completed 18 months of follow up. 83.3% were sensitised to house dust mite and 33.5% to grass pollen. Many other sensitivities were present with 80.4% being polysensitised. The mean SCORAD was 29.9. There were wide variations in frequency of infection which was recorded retrospectively up to the point of recruitment and prospectively thereafter. 94.3% of children had at least one infection. 40% of the subjects developed asthma over the 18 months follow up. 39.8% on levocetirizine and 40.2% on placebo. It was therefore possible to merge the data for calculation of risk factors for asthma.

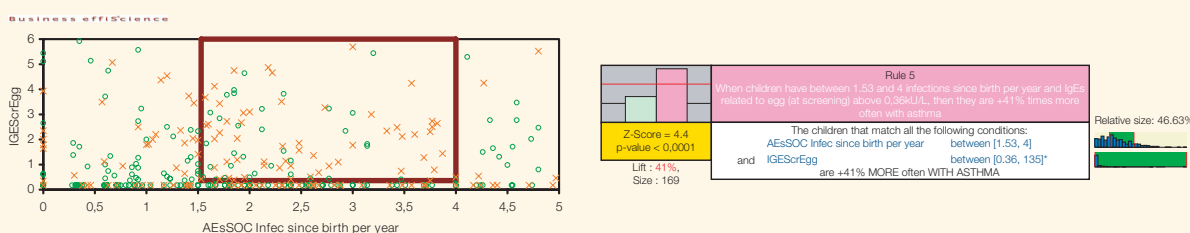
The individual variables that had the greatest impact in increasing the risks of asthma significantly were frequency of infections; sensitisation to foods, milk, egg or peanut; sensitisation to cat, alternaria and tree pollen; and proximity of dwelling to factory as a marker of pollutant exposure.

Low infection frequency since birth ranging between 0 and 1.52 per year reduced the incidence of asthma by 25%. Moderate frequency between 1.53 and 4 per year increased the risk of asthma by 25% and high frequency between 4.1 and 9.43 per year decreased the incidence by 11%. See graph below.



On the left is a graph demonstrating the bell shaped curve of risk of asthma in relation to frequency of infection since birth with very low and high frequencies associated with a lower prevalence of asthma. On the right are the computer generated results indicating Z scores and probability values for very low, moderate, and high frequencies of infection.

The effects of a moderate frequency of infection was enhanced by sensitisation to egg (41%). See graph below.



This shows the increased density (risk) of asthma development (red crosses) in the "hypercube" where egg sensitisation is combined with a moderate frequency of infection on the left and the detailed statistical results on the right.

Rule	Description of the rule	Increase risk of asthma	size	z-score	p-value
N° 1	Infection since birth per year between 0 infection and 1,52	-27%	196	3.2	< 0.0001
N° 2	Infection since birth per year between 1,53 infections and 4	+25%	245	3.3	< 0.0001
N° 3	Infection since birth per year between 4,1 infections and 9,43	-11%	69	0,8	0,4086
N° 4	Combination of "Infection since birth per year between 1,53 infection and 4" and "IGE related to Peanut" between 0,53 and 135 kJ/L	+48%	111	4,2	< 0,0001
N° 5	Combination of "Infection since birth per year between 1,53 infections and 4" and "IGE related to Egg" between 0,36 and 135 kJ/L	+41%	169	4,4	< 0,0001
N° 6	Combination of "Infection since birth per year between 1,53 infections and 4" and "IGE related to Food" between 2,135 and 405 kJ/L	+43%	149	4,4	< 0,0001
N° 7	Combination of "Infection since birth per year between 1,53 infections and 4" and "distance to factory between 0 and 5 km"	+47%	97	3,8	< 0,0001
N° 8	Combination of "Infection since birth per year between 1,53 infections and 4" and "distance to factory between 0 and 5 km" and "IGE related to Egg" between 0,36 and 135 kJ/L and "IGE related to Food" between 2,135 and 405	+77%	54	4,7	< 0,0001

Final rules obtained by combination of run of the algorithm with biological plausibility and clinical value.

DISCUSSION

Frequency of infection per year since birth in relation to the development of asthma by 2 1/2 to 3 1/2 years of age produced a bell shaped curve with both very low and very high frequencies of infections being associated with less asthma. It has recently been estimated that the mean annual number of infections per year in infancy up to two years of age is 3.4 and in the pre-school age children 2.3. However in infancy up to 11 infections per year have been reported as being within the normal range based on the two fold standard deviation from the mean (3). Thus all the reported frequencies in this study would be considered to be within the normal range but nevertheless are associated with significant differences in outcomes in relation to asthma. Very low frequency of infection may be a surrogate marker of an infant with a highly effective TH-1 response which will be associated with a reduced probability of allergic disease evolving into asthma while those with very high frequency of infection have a greater probability of inducing TH-1 responsiveness and thereby reducing the allergic drive. Normal rates of infection in atopically predisposed individuals will not modify outcome. These data may perhaps go some way to explain the discrepancies found in many other studies investigating these associations where actual frequency of infection has not been assessed.

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