Relationship between early life respiratory illness, family size over time, and the development of asthma and hay fever: a seven year follow up study

Anne-Louise Ponsonby, David Couper, Terence Dwyer, Allan Carmichael, Andrew Kemp

Abstract

Background—The timing and mechanism of the inverse association between increasing sibling number and atopic disease are not yet understood. A study was undertaken to examine how family size at birth predicts early respiratory illness, to report the association between infant respiratory illness and childhood atopic disease, and to determine whether the protective effect of large family size operates during infancy or later childhood.

Methods—A prospective follow up study was carried out on 863 children (78%) of 1111 participants in the Tasmanian Infant Health Survey performed in 1988. In 1988 household size and history of respiratory illness were obtained by parental interview at home (median age 35 days) and later by telephone (median age 85 days). In 1995 asthma, hay fever, and household size were assessed by parental questionnaire in a large cross sectional survey.

Results—In 1988 increasing resident number (per resident) (adjusted odds ratio (AOR) 1.17 (95% CI 1.05 to 1.31)) and resident density (AOR 1.77 (95% CI 1.07 to 2.94)) were related to parental report of an upper respiratory tract infection (URTI) by one month of age. Children with a reported URTI by home interview were more likely to have subsequent asthma (adjusted relative risk (ARR) 1.27 (95% CI 1.05 to 1.53)). The association between lower respiratory tract infection (LRTI) at telephone interview (relative risk (RR) 1.34 (95% CI 1.02 to 1.75) and asthma was reduced after adjustment for family history of asthma (ARR 1.27 (95% CI 0.98 to 1.66)). Antibiotic use by home interview was not associated with subsequent asthma or hay fever. Indicators of family size in 1988 were associated with hay fever but not asthma but, in contrast, resident number in 1995 was inversely associated with asthma (AOR 0.82 (95% CI 0.72 to 0.92) per resident) and hay fever (AOR 0.82 (95% CI 0.71 to 0.96) per resident). Children with no siblings were at risk for current asthma, particularly if symptoms began after the age of four (RR 2.81 (95% CI 1.36 to 5.84)).

Conclusions—The apparent protective effect of large household size and asthma could not be explained by an increase in reported early respiratory illness. The first year of life may not be the most critical time for the protective effect of large household size to be mediated in relation to asthma, but this effect occurred by the seventh year of life.

Keywords: family size; respiratory infection; childhood; asthma; hay fever

Children of large families have an increased risk of early respiratory infection1 and a reduced risk for hay fever2–7 and eczema.8 Asthma rates have been found to be lower in children of larger families in some studies9–10 but not related to older sibling number11 or total sibling number12 in others. Children of large families have also shown reduced skin sensitisation13–15 or lower specific IgE levels16 to common aeroallergens.

In 1989 the finding that the older sibling number rather than younger sibling number was more strongly associated with a lower risk of hay fever in a large cohort led to the proposal that infection in early childhood may protect against atopic disease.15 Later studies have provided some support for the hypothesis that infections may reduce the development of atopy in childhood.15–18 However, parental report of non-specific infection during the first month of life is not associated with a reduction in the incidence of hay fever at age 11–16.17

Allergen exposure in early life may prime for subsequent T cell reactivity. If T cell selection favours the growth of Th helper 1 (Th1) cells, IgA and IgG host responses will be favoured.19 However, if T cell selection favours the production of Th helper 2 (Th2) cells, IgE production will be promoted, increasing the likelihood of atopic disease.19 Repeated bacterial or viral infections might protect against the development of allergic disease by enhancing Th1 responses.19 After repeated restimulation a T cell phenotype becomes dominant, leading to memory T cells that direct immune responses...
to the allergen throughout later life. It is not clear which period of early life is most important for this process. A critical window may occur during the first months of life or a stable state of Th1:Th2 balance may not occur until school age.

**Methods**

**COHORT STUDY**

The cohort study operated from six obstetric hospitals in the state where approximately 93% of births occurred. All infants born within these hospitals were scored to assess the risk of sudden infant death syndrome (SIDS) using a predictive model based on a composite score of maternal age, birth weight, season of birth, sex, duration of second stage of labour, and type of infant feeding (intention to breastfeed or not). Singletons with a score over the cut off were eligible to join the survey; multiple births were automatically eligible. Eligible infants represented approximately one fifth of live births in the state. Infants with severe neonatal disease, major congenital anomalies, those placed for adoption, and those expected to reside outside Tasmania were excluded (n = 15 of 1988 cohort).

Data were obtained by research assistants on three occasions. The first interview was conducted in the hospital on the fourth day of life. The second interview was a home visit arranged for the fifth postnatal week (median age at interview was 35 days). Premature infants (<37 weeks), however, were visited at home at 40 weeks post-conceptional age. At the third interview was conducted by using a linear term in the logistic regression model as well as by grouping sibling size at birth and asthma or hay fever do not approximate the relative risk as the proportion of disease positive subjects is large. However, the associated p values are valid. An assessment of the effect of family size indicators was conducted by using a linear term in the logistic regression model as well as by grouping sibling number into various categories and comparing how they predicted asthma risk in a logistic model. A linear term was retained if the use of dummy variables did not result in an improvement in the likelihood ratio statistic. The respiratory response to exercise was calculated as the post-exercise forced expiratory volume in one second (FEV1) expressed as a percentage of the baseline FEV1, and is described in detail elsewhere. All analyses were performed using SAS version 6.09.

**Definitions**

For this paper a positive history of a cold by home interview is termed an early upper respiratory tract infection (early URTI) and by telephone interview an URTI. Chest infection by telephone interview is termed a lower respiratory tract infection (LRTI). A positive response to the ISAAC question “has your child ever had asthma?” is termed asthma. Current asthma denotes a positive response to both this question and the ISAAC question “has your child had wheezing or whistling in the chest in the past twelve months?” We have previously reported that the probability that a child will demonstrate bronchial hyperresponsiveness (BHR) after exercise is significantly associated with positive responses to these questions. Age of onset refers to the age (in complete years) when the parent reported that episodes of asthma or wheezy breathing began.

**Statistical methods**

The data were first examined using contingency tables and the Mantel-Haenszel χ² test. The relationship between each infant characteristic and early respiratory illness was estimated using logistic regression analysis. The prevalence rates for asthma and hay fever were calculated by history of early respiratory illness with direct calculation of relative risk and adjustment for multiple confounders using a generalised linear model with a log link function and a binomial error distribution. The relationships between infant and child family structure and asthma and hay fever were calculated by multiple logistic regression. This allows a direct comparison of the different effect of family size between the two periods but the odds ratios in table 3 between family size at birth and asthma or hay fever do not approximate the relative risk as the proportion of disease positive subjects is large. However, the associated p values are valid. An assessment of the effect of family size indicators was conducted by using a linear term in the logistic regression model as well as by grouping sibling number into various categories and comparing how they predicted asthma risk in a logistic model. A linear term was retained if the use of dummy variables did not result in an improvement in the likelihood ratio statistic. The respiratory response to exercise was calculated as the post-exercise forced expiratory volume in one second (FEV1) expressed as a percentage of the baseline FEV1, and is described in detail elsewhere. All analyses were performed using SAS version 6.09.

**Results**

**Disease rates**

The proportion of children with asthma ever was 32.4% (280/863). The prevalence of hay
Table 1  Factors associated with parental report of early respiratory illness in 1988

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted* odds ratio (95% CI) for URTI at home interview</th>
<th>Adjusted* odds ratio (95% CI) for LRTI at telephone interview</th>
</tr>
</thead>
<tbody>
<tr>
<td>First born child</td>
<td>0.74 (0.56 to 0.98)</td>
<td>0.63 (0.39 to 1.00)</td>
</tr>
<tr>
<td>Number of household residents in 1988 (per resident)</td>
<td>1.17 (1.05 to 1.31)</td>
<td>1.06 (0.89 to 1.26)</td>
</tr>
<tr>
<td>Resident density in 1988 (increasing resident number per room)</td>
<td>1.77 (1.07 to 2.94)</td>
<td>0.86 (0.37 to 2.01)</td>
</tr>
<tr>
<td>Family history of asthma (grandparents, mother, father and siblings)</td>
<td>1.17 (0.87 to 1.56)</td>
<td>1.57 (1.00 to 2.45)</td>
</tr>
<tr>
<td>Infant born during winter (during July/August)</td>
<td>1.91 (1.40 to 2.62)</td>
<td>2.61 (1.62 to 4.21)</td>
</tr>
<tr>
<td>Maternal postnatal smoking</td>
<td>1.47 (1.11 to 1.94)</td>
<td>1.40 (0.89 to 2.18)</td>
</tr>
<tr>
<td>Other resident postnatal smoking</td>
<td>1.45 (1.09 to 1.93)</td>
<td>1.39 (0.89 to 2.18)</td>
</tr>
<tr>
<td>Exclusive breast feeding at home interview</td>
<td>0.60 (0.44 to 0.81)</td>
<td>0.58 (0.35 to 0.95)</td>
</tr>
<tr>
<td>Infant sleeps in a room alone at home interview</td>
<td>0.70 (0.51 to 0.95)</td>
<td>0.79 (0.48 to 1.30)</td>
</tr>
<tr>
<td>Infant sex (male)</td>
<td>1.09 (0.80 to 1.49)</td>
<td>0.87 (0.54 to 1.41)</td>
</tr>
<tr>
<td>Infant birth weight (&lt;2500 g)</td>
<td>0.72 (0.49 to 1.06)</td>
<td>0.77 (0.43 to 1.35)</td>
</tr>
</tbody>
</table>

*Adjusted for postnatal age at interview.
URTI = upper respiratory tract infection; LRTI = lower respiratory tract infection.

Table 2  Relationship between respiratory illness in 1988 and asthma and hay fever in 1995

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Proportion of children with asthma among exposed (%)</th>
<th>Proportion of children with hay fever among exposed (%)</th>
<th>Relative risk (95% CI) for asthma</th>
<th>Adjusted* relative risk (95% CI) for asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early URTI by home interview</td>
<td>38.7% (122/315)</td>
<td>28.8% (156/542)</td>
<td>1.35 (1.11 to 1.63)</td>
<td>1.30 (1.18 to 1.57)</td>
</tr>
<tr>
<td>Antibiotic use by home interview</td>
<td>35.1% (40/114)</td>
<td>31.8% (236/742)</td>
<td>1.10 (0.84 to 1.45)</td>
<td>1.04 (0.80 to 1.36)</td>
</tr>
<tr>
<td>URTI by telephone interview</td>
<td>32.2% (151/469)</td>
<td>31.1% (111/355)</td>
<td>1.03 (0.84 to 1.26)</td>
<td>0.97 (0.79 to 1.19)</td>
</tr>
<tr>
<td>LRTI by telephone interview</td>
<td>41.1% (37/90)</td>
<td>30.7% (226/735)</td>
<td>1.34 (1.02 to 1.75)</td>
<td>1.27 (0.98 to 1.66)</td>
</tr>
<tr>
<td>Early URTI by home interview</td>
<td>20.6% (66/321)</td>
<td>17.8% (97/544)</td>
<td>1.15 (0.87 to 1.53)</td>
<td>1.12 (0.85 to 1.49)</td>
</tr>
<tr>
<td>Antibiotic use by home interview</td>
<td>20.5% (24/117)</td>
<td>18.5% (138/747)</td>
<td>1.11 (0.75 to 1.64)</td>
<td>1.07 (0.73 to 1.57)</td>
</tr>
<tr>
<td>URTI by telephone interview</td>
<td>19.2% (91/474)</td>
<td>18.5% (65/357)</td>
<td>1.04 (0.78 to 1.38)</td>
<td>0.99 (0.75 to 1.33)</td>
</tr>
<tr>
<td>LRTI by telephone interview</td>
<td>26.7% (24/90)</td>
<td>17.9% (133/742)</td>
<td>1.49 (1.02 to 2.17)</td>
<td>1.42 (0.98 to 2.07)</td>
</tr>
</tbody>
</table>

*Adjusted for family history of asthma, exclusive breast feeding at home visit, maternal postnatal smoking, other adult household resident smoking, low birth weight (<2500 g), prematurity (<37 weeks gestation), gas heater in living room, number of household residents in 1995, and age at interview in postnatal weeks. URTI = upper respiratory tract infection; LRTI = lower respiratory tract infection.
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*In a model with older sibling number and young sibling number as separate terms.

The prevalence of asthma data were collected using previously assessed questions.23 27 The prevalence of asthma in this study is slightly higher than that in the full cross sectional survey.10

Discussion

Asthma data were collected using previously assessed questions.23 27 The prevalence of asthma in this study is slightly higher than that in the full cross sectional survey.10 The major reason for non-response to follow up appeared to be migration; loss to follow up did not differ by report of early respiratory illness, minimising selection bias. A history of early respiratory illness, although prospective, was based on parental interview so the possibility of reporting bias must be considered. Other studies which have been used to support the hypothesis that early infection protects against the development of atopic disease have also been based on historical data and there are no prospective data based on documentation of infection by other means. In this study it is possible that an over-enthusiastic positive response to questions on infant respiratory illness and on asthma created a spurious association between the two. Table 1 provides some reassurance that parents were reporting the history of an URTI by home interview. Factors associated with report of an LRTI had estimates of association with wider confidence intervals, partly reflecting the fact that only 10.9% of the sample had experienced an LRTI by this time. The association between a family history of asthma and LRTI in Table 2 suggests that this outcome may reflect the manifestation rather than the existence of an LRTI. We were unable to examine family size and BHR due to the small sample size. The protective effect of large family size and asthma is unlikely to reflect delayed diagnosis among children of larger families as birth order did not relate to asthma and only children were particularly at increased risk of later onset asthma.

There has recently been considerable interest in several studies which have suggested that early infection or immunostimulation in childhood protects against subsequent atopic disease. It is also possible that this apparent protective effect reflects non-causal pathways. For example, among Guinea-Bissau adults measles infection was associated with a reduction in mite sensitisation13 but this might also be explained by an increased mortality from measles in atopic individuals due to the decreased secretion of gamma interferon known to be associated with the atopic state.14 An inverse association was reported between tuberculin responses and atopic disorders in Japanese school children15 but, as the size of the tuberculin response depends on cytokine secretion, a reduced response could reflect decreased gamma interferon secretion in atopic subjects in response to bacterial antigens.16 Tucson children who had more than one non-wheezy LRTI before the age of three had lower IgE levels at six years of age than those with no history of LRTI (OR 0.2), despite having similar IgE cord levels at birth.17 However, infants developing non-wheezy LRTI may be less likely to be atopic because of genetic predisposition or lung structure.

Other studies have reported a positive association between early infection and atopic disease.15 30–32 A cross sectional survey of Aberdeenshire children aged 10–14 in 1964 found that...
family size was inversely related to atopic disease but the parental recall of the number of infections before the age of three was associated with a trend towards increased asthma risk. Thus, studies have provided conflicting results on the relationship between early infection and asthma. It has been pointed out that any relationship between infection and atopy depends on a number of factors including timing, anatomical site, dose, protractiveness, exposure to other infections, and host characteristics, as well as the stage of immunological development and infection type.

The most likely explanations for the association found in our study between early respiratory illness and asthma are that (1) those predisposed to atopy are more susceptible to early respiratory infection, (2) atopy prone infants develop more prominent symptoms with infection (children whose parents reported no illness may still have had a clinically unapparent infection), (3) children who develop a respiratory infection early may also be more likely to develop recurrent respiratory infections, which are known precipitants of asthmatic episodes, or (4) early respiratory infection can prime respiratory tract sensitization and development of atopy at a critical period in early life. The first two alternatives are supported by the findings that children born into a family with a member with asthma have an increased risk of developing an early LRTI and the association between early respiratory illness and asthma is reduced after adjustment for family history. A follow up study with epidemiological data on family history, family size over time, age at onset of asthma as well as serial measurements on immune responses to identified viral, bacterial, and other antigenic stimuli would be required to provide clear information on the role of infection in immune development.

There has been increasing interest in the possible role of antibiotic administration to infants and atopic disease promotion in view of the possible role of commensal and pathogenic micro-organisms to provide Th1 stimulation during early postnatal life, but information has been limited. In our study no association was found between antibiotic use in the first month of life and childhood asthma or hay fever.

The timing of the apparent protective effect of large family size for hay fever appeared to operate at the infant as well as childhood stage. Family size indicators in 1988 and also in 1995 were inversely related to hay fever, with similar effects for a measure of domestic crowding (resident density) at both time periods. The odds ratio for increasing younger or older sibling number were also similar, although the sample size in this study did not allow a complete examination of this issue. The relationship between increasing older sibling number and hay fever (AOR 0.82 (95% CI 0.68 to 1.00)) is of similar strength to that previously reported for the larger study (OR 0.90 (0.84 to 0.96)) but is of borderline significance, partly reflecting the smaller size of this follow up group with an increased likelihood of type 2 error.

This study provides new information on the timing of the protective effect of large family size for asthma. Children with no siblings were particularly more likely to have current asthma if the onset of symptoms was at age four or older. Here, the magnitude and significance of the apparent protective effect of resident number and density for asthma were more evident in 1995 than in 1988 and were independent of these measures in 1988. A dose response trend between increasing sibling number in 1995 and decreasing age at onset of asthma or wheezy breathing was evident in the larger cross sectional study. These findings suggest that the first year of life may not be the most critical time for the protective effect of large household size to be mediated in relation to asthma.

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