Parental and neonatal risk factors for atopy, airway hyper-responsiveness, and asthma

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Abstract

Background—Previous studies have not resolved the importance of several potential risk factors for the development of childhood atopy, airway hyper-responsiveness, and wheezing, which would allow the rational selection of interventions to reduce morbidity from asthma. Risk factors for these disorders were examined in a birth cohort of 1037 New Zealand children.

Methods—Responses to questions on respiratory symptoms and measurements of lung function and airway responsiveness were obtained every two to three years throughout childhood and adolescence, with over 85% cohort retention at age 18 years. Atopy was determined by skin prick tests at age 13 years. Relations between parental and neonatal factors, the development of atopy, and features of asthma were determined by comparison of proportions and logistic regression.

Results—Male sex was a significant independent predictor for atopy, airway hyper-responsiveness, hay fever, and asthma. A positive family history, especially maternal, of asthma strongly predicted childhood atopy, airway hyper-responsiveness, asthma, and hay fever. Maternal smoking in the last trimester was correlated with the onset of childhood asthma by the age of 1 year. Birth in the winter season increased the risk of sensitisation to cats. Among those with a parental history of asthma or hay fever, birth in autumn and winter also increased the risk of sensitisation to house dust mites. The number of siblings, position in the family, socioeconomic status, and birth weight were not consistently predictive of any characteristic of asthma.

Conclusions—Male sex, parental atopy, and maternal smoking during pregnancy are risk factors for asthma in young children. Children born in winter exhibit a greater prevalence of sensitisation to cats and house dust mites. These data suggest possible areas for intervention in children at risk because of parental atopy.

Keywords: asthma, atopy, airway hyper-responsiveness, family history.

Childhood asthma imposes a significant economic and lifestyle burden.1 Certain risk factors for the development of asthma are established, but others are less clearly identified.3–4 Parental atopy and asthma,4,5 family size,6 birth order,7 neonatal exposure to allergens,8–10 environmental tobacco smoke,11–18 and low birth weight and prematurity11,19,20 are suggested determinants, but conflicting results have been reported. The conclusive identification of risk factors may lead to strategies to minimise these risks and so decrease the morbidity due to asthma.

Cigarette smoke is the most common indoor pollutant to which children are exposed.14 Many studies suggest an increased risk of asthma or wheezing in children exposed to cigarette smoke, especially maternal smoking,15–18 with a dose-response relationship.19 Airway responsiveness to methacholine in Italian girls was related to both maternal (odds ratio (OR) 2.92, 95% confidence interval (CI) 1.43 to 5.95) and paternal (OR 2.59, 95% CI 1.36 to 4.95) smoking with a dose-response relationship, but no increased risk was seen in boys.20 This suggests either that girls are more susceptible to exposure to cigarette smoke or that other risk factors in boys (for example, increased atopy) overshadow any effect of passive smoking.

Some studies have suggested that asthma is associated with higher21 or lower22,23 socioeconomic status, whereas others show no consistent association.22,24–26 Low socioeconomic status was not a risk factor for wheeze in Danish infants in the first 18 months27 or for increased airway responsiveness in Australian children.28 There may be considerable confounding of socioeconomic status with parental smoking.29

Atopy is an almost universal characteristic of persistent childhood asthma. The development of atopy has been variably associated with season of birth.4,11,30 Risks for grass sensitisation have been reported to be higher among children born in spring30 or reaching the age of 3 months in the grass pollen season,12 whereas others have found no influence of season of birth.11 Asthma is more common in Swedish children born in the summer months,31 but in New Zealand children with asthma of sufficient severity to be admitted to hospital, no relation was found between month of birth and risk of asthma.32

Family size and birth order may affect atopy and asthma. Von Mutius et al found that, after controlling for confounders, the prevalence of atopy (positive skin tests) decreased with an increasing number of siblings.4 The OR for atopy with one sibling was 0.96, decreasing to 0.67 (p = 0.005) for five or more siblings. Oth-
Risk factors for asthma

ers, however, have reported asthma to be less common in first born children.9

Birth weight has been reported to influence the risk of the development of asthma. In Danish children, after adjusting for socioeconomic status, sex, and maternal smoking, the OR for asthma was 2.3 for those with a birth weight less than 2500 g.12 Increased ORs for asthma (ranging from 2.8 to 3.5) were also found for low birth weight in Austria14 and Germany35. Low birth weight was related to house dust mite sensitisation in the Isle of Wight population (OR 3.4, 95% CI 1.0 to 11.7)13 and is reported to be associated with increased airway responsiveness to histamine16 or exercise.57 Aberdeen children, however, showed no relation between birth weight or prematurity and atopy.58

Hence there remains uncertainty as to the relation between many potential risk factors affecting newborn infants and young children and the development of persistent asthma in childhood and adolescence. To further identify these putative risk factors for asthma we examined relations among parental, neonatal, and perinatal characteristics and the development of atopy, airway hyper-responsiveness, and asthma-like symptoms in a longitudinal epidemiological study of a birth cohort of 1037 New Zealand children followed up to age 18 years.

Methods

SUBJECTS

Between 1 April 1972 and 31 March 1973, 1661 children were born in Dunedin’s one maternity hospital.36 Of these, 1139 children residing in Otago province at age 3 years were invited to participate in a longitudinal multidisciplinary study of health and development. Those 1037 enrolled (91% of those eligible) did not differ from the cohort of 1661 children with respect to recorded perinatal and postnatal factors, except that there were fewer children of lower socioeconomic status in the enrolled sample.

INVESTIGATIONS

Parental and neonatal characteristics were documented in all 1661 children as part of a cross sectional neonatal study.38 Those children enrolled in the longitudinal study were seen every two or three years within one month of their birthday for detailed medical and developmental assessment. Over 85% of the 1037 children were available for review at age 18 years. Parental smoking habits in the perinatal period were recalled when the child was aged 3 years. The family history of asthma and atopic disease and limited information on the child’s respiratory symptoms were obtained from the accompanying adult (usually the mother) when the child was 7 years old.40 A more detailed retrospective history of wheezing, whether diagnosed as asthma or accompanying respiratory infections, recurrent coughing, and manifestations of atopy including ‘hay fever’ and eczema was obtained at the age of 9 years by a questionnaire administered to the parent by a doctor.39

Spirometry was undertaken at each review from 9 to 18 years, recording the best of three acceptable vital capacity (VC) and forced expired volume in one second (FEV1) measurements obtained without recent (within six hours) use of any bronchodilator.41 A Godart water sealed spirometer was used at ages 9 to 15 years and a Morgan rolling seal spirometer with computerised output at age 18 years.

An abbreviated validated four dose five breath methacholine inhalation challenge was first undertaken at the age of 9 years using concentrations increasing in tenfold steps from 0.025 to 25.0 mg/ml.42 Children who showed significant airflow obstruction on initial spirometry (FEV1/VC less than 75%) were not challenged with methacholine, but were re-studied 10 minutes after the inhalation of nebulised salbutamol 5 mg/ml inhaled by tidal breathing for two minutes.

At ages 11, 13, 15, and 18 years the child was questioned about symptoms over the preceding two or three years. Methacholine challenge was repeated at 11, 13, and 15 years, but at 18 years bronchodilator responsiveness was determined in each consenting subject.

Skin prick testing to 11 common allergens was performed in 714 subjects at age 13 years using house dust mite (Dermatophagoides pteronyssinus) (Bencard, UK), grass, cat, dog, horse, kapok, wool, Aspergillus fumigatus, alternaria, penicillium, and cladosporium (all supplied by Hollister-Stier, USA).43 Those tested were representative of all children seen at age 13 years and of the original sample of 1037 children.

DEFINITIONS

‘Symptoms consistent with asthma’ in the children were defined as recurrent wheeze or whistling in the chest, whether or not any provoking allergen, infection, or other cause was identified and whether or not wheezing was labelled as asthma. A parental history of asthma, however, was considered positive only if ‘asthma’ was reported as such. ‘Hay fever’ was defined in the questionnaire as ‘allergy of eyes or nose, causing sneezing or watery eyes or nose’. ‘Atopy’ was defined as one or more positive skin tests with a maximum weal diameter at least 2 mm greater than that produced by the diluent control.44 Airway hyper-responsiveness was recorded if the methacholine PC20 FEV1 was less than or equal to 8 mg/ml. Subjects who did not perform the methacholine challenge because their initial FEV1/VC ratio was <75%, and who showed >10% increase in FEV1 after the inhalation of nebulised salbutamol, were also considered hyper-responsive.45

STATISTICAL ANALYSES

Univariate analysis

Relationships between symptoms of asthma, atopy, and airway responsiveness were related to family history by comparisons of proportions using χ2 tests. Smoking by the mother or father was analysed by trimester of pregnancy.
and the three months after birth and was related to the age of onset of symptoms. Birth weights, grouped by 500 g increments, were related to respiratory symptoms reported to age 9 years and to measurements of lung function (FEV1, VC, and FEV1/VC ratio), airway responsiveness (PC20 FEV1, less than or equal to 8 mg/ml and absolute level of PC20 FEV1), and atopy.

### Multivariate analysis

A series of logistic regressions was performed to determine which parental and perinatal factors were independently related to the development of features of asthma or atopy, or both. The outcome (dependent) variables were symptoms to age 9 years, symptoms at any age from 9 to 18 years, hay fever at any age from 9 to 18 years, airway hyper-responsiveness at any age from 9 to 15 years, atopy (any skin test ≥2 mm weal), and reactivity to house dust mite and cats. The predictor (independent) variables were the parental history of asthma or hay fever, or both, sex of child, season of birth, birth weight (using 3000–3499 g as the reference group), family socioeconomic status at birth, position in family, and exposure to parental cigarette smoking. The models were fitted in a two stage process. All independent variables were included in the first stage. To reduce the number of children excluded because of missing values, only those variables appearing likely to be related (p < 0.1 approximately) in the first stage were included in the second stage.

### Results

#### INFLUENCE OF FAMILY HISTORY

The likelihood of a child being atopic by skin test was strongly correlated with maternal asthma and with hay fever in either parent (table 1). If one parent had either asthma or hay fever, 45.2% of children were atopic compared with 35.2% of those with no such parental history (p = 0.013). There were strong relations between maternal asthma, hay fever, or both and these disorders in the children. This relation also existed for paternal hay fever but not paternal asthma (table 2). If one parent had either asthma or hay fever, 29.0% of children had symptoms of asthma compared with 20.0% of those with no parental history of asthma (p = 0.004), and 55.0% of children had hay fever compared with 37.0% of those with no parental history (p = 0.001). Similarly, there were significant relations between maternal asthma or hay fever, or both, or paternal hay fever, and airway hyper-responsiveness at age 9 years, or at any age between 9 and 15 years (table 3). These relations were stronger if both parents had asthma. The likelihood of showing airway hyper-responsiveness on all occasions tested between 9 and 15 years was increased if both parents had asthma (14.3 v 2.2%, p = 0.03), or hay fever (8.0 v 2.1%, p = 0.05), or one parent had asthma or hay fever (3.9 v 1.6%, p = 0.04).

#### INFLUENCE OF PARENTAL SMOKING

Symptoms of asthma occurring by the age of 1 year significantly correlated with maternal smoking in the last trimester of pregnancy (p = 0.049). There were consistent trends for higher prevalences of symptoms throughout all early childhood years to the age of 9 years if the mother smoked more than 20 cigarettes each day during the first and second trimesters of pregnancy, with an increase in the prevalence of wheezing from between 10 and 15% in children not exposed to smoke to between 20 and 25% in those exposed to smoke (not tabulated). These trends did not achieve statistical significance. Regarding maternal smoking in the first three months after delivery, there was a trend to more wheeze in children of heavy smokers (14.9 v 6.1% in non-smokers, p = 0.075). There was no correlation between

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**Table 1** Percentage of 714 children skin tested with common inhaled allergens at age 13 years showing atopy (any positive test ≥ 2 mm weal) in relation to different parental histories of asthma or hay fever

<table>
<thead>
<tr>
<th>Parent characteristic</th>
<th>Percentage of children with atopy</th>
<th>Parental history positive</th>
<th>Parental history negative</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No at risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>63</td>
<td>42.9</td>
<td>37.7</td>
<td>0.420</td>
</tr>
<tr>
<td>Mother</td>
<td>60</td>
<td>51.7</td>
<td>36.9</td>
<td>0.024</td>
</tr>
<tr>
<td>Either</td>
<td>116</td>
<td>46.6</td>
<td>36.5</td>
<td>0.042</td>
</tr>
<tr>
<td>Both</td>
<td>7</td>
<td>57.1</td>
<td>38.0</td>
<td>0.300</td>
</tr>
<tr>
<td><strong>Hay fever</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>83</td>
<td>48.2</td>
<td>36.8</td>
<td>0.045</td>
</tr>
<tr>
<td>Mother</td>
<td>142</td>
<td>45.1</td>
<td>36.4</td>
<td>0.058</td>
</tr>
<tr>
<td>Either</td>
<td>205</td>
<td>44.9</td>
<td>35.4</td>
<td>0.019</td>
</tr>
<tr>
<td>Both</td>
<td>20</td>
<td>60.0</td>
<td>37.5</td>
<td>0.041</td>
</tr>
<tr>
<td><strong>Asthma or hay fever in either parent</strong></td>
<td>208</td>
<td>45.2</td>
<td>35.2</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Number at risk is number of children whose parent(s) had the listed characteristic.

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**Table 2** Percentage of children reporting diagnosed asthma or hay fever at any time to age 18 years in relation to a positive or negative parental history of asthma and hay fever

| Parent characteristic | Percentage of children with asthma | Percentage of children with hay fever | | Parental history positive | Parental history negative | p Value |
|-----------------------|-----------------------------------|--------------------------------------|---------------------------|---------------------------|---------|
|                       | No at risk |                        |                           |                           |
| **Asthma**            |            |                          |                           |                           |
| Father                | 77         | 27.3                    | 22.2                      | 0.30                      |
| Mother                | 69         | 43.5                    | 20.8                      | 0.000002                 |
| Either                | 139        | 33.1                    | 20.3                      | 0.0019                   |
| Both                  | 7          | 71.4                    | 22.2                      | 0.000009                 |
| **Hay fever**         |            |                          |                           |                           |
| Father                | 101        | 32.7                    | 21.3                      | 0.010                    |
| Mother                | 169        | 28.4                    | 21.2                      | 0.045                    |
| Either                | 247        | 28.3                    | 20.3                      | 0.011                    |
| Both                  | 23         | 47.8                    | 21.9                      | 0.0033                   |
| **Asthma or hay fever in either parent** | 252 | 29.0                     | 20.0                      | 0.0041                   |

Number at risk is number of children whose parent(s) had the listed characteristic.
Table 3 Percentage of children showing hyperresponsiveness (PC20 < 8 mg/ml) at age 9 years and at any test between the ages of 9 and 15 years, in relation to a positive or negative parental history of asthma and hay fever

<table>
<thead>
<tr>
<th></th>
<th>Percentage of children with PC20 &lt; 8 mg/ml at age 9 years</th>
<th>Percentage of children with PC20 &lt; 8 mg/ml at 9-15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No at risk</td>
<td>Parental history positive</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>65</td>
<td>24.6</td>
</tr>
<tr>
<td>Mother</td>
<td>60</td>
<td>26.7</td>
</tr>
<tr>
<td>Either</td>
<td>118</td>
<td>22.9</td>
</tr>
<tr>
<td>Both</td>
<td>7</td>
<td>71.4</td>
</tr>
<tr>
<td>Hay fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>84</td>
<td>23.8</td>
</tr>
<tr>
<td>Mother</td>
<td>152</td>
<td>21.7</td>
</tr>
<tr>
<td>Either</td>
<td>20</td>
<td>21.8</td>
</tr>
<tr>
<td>Both</td>
<td>20</td>
<td>30.0</td>
</tr>
<tr>
<td>Asthma or hay fever in either parent</td>
<td>223</td>
<td>22.0</td>
</tr>
</tbody>
</table>

Number at risk is number of children whose parent(s) had the listed characteristic.

Table 4 Gender differences in asthma and wheezing

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Female</th>
<th>Male</th>
<th>M:F</th>
<th>Female</th>
<th>Male</th>
<th>M:F</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>9.1</td>
<td>5.9</td>
<td>1.54:1</td>
<td>22.4</td>
<td>18.9</td>
<td>1.19:1</td>
</tr>
<tr>
<td>11</td>
<td>12.9</td>
<td>6.3</td>
<td>2.05:1</td>
<td>22.1</td>
<td>14.4</td>
<td>1.53:1</td>
</tr>
<tr>
<td>13</td>
<td>14.7</td>
<td>8.7</td>
<td>1.69:1</td>
<td>39.5</td>
<td>33.8</td>
<td>1.17:1</td>
</tr>
<tr>
<td>15</td>
<td>16.1</td>
<td>12.9</td>
<td>1.25:1</td>
<td>37.9</td>
<td>33.8</td>
<td>1.12:1</td>
</tr>
<tr>
<td>18</td>
<td>14.0</td>
<td>15.6</td>
<td>0.90:1</td>
<td>49.0</td>
<td>61.3</td>
<td>0.80:1</td>
</tr>
</tbody>
</table>

Maternal smoking after the child was aged 3 months and symptoms of asthma at any age, or between paternal smoking and childhood symptoms at any age.

INFLUENCE OF MONTH OF BIRTH

By univariate analysis there was no correlation between the month of birth and diagnosis of asthma (p = 0.39), wheezing (p = 0.27), or airway hyper-responsiveness to methacholine or salbutamol (p = 0.89), nor between season of birth (summer, autumn, winter, spring) and these outcomes, although only 15.0% of children sensitive to mites were born during summer (p = 0.06).

INFLUENCE OF BIRTH ORDER

Of 868 subjects providing this information at age 18 years, 322 (37.1%) were first born children, 276 (31.8%) were second born children, and 270 (31.1%) were third or later in their family. There was no correlation between being first born and atopy (p = 0.21), sensitivity to house dust mite (p = 0.62) or to cats (p = 0.18), or to the development of symptoms of asthma (p = 0.98). Comparing first or second born children with those later born showed no association with atopy (p = 0.13) or sensitivity to house dust mites (p = 0.55), but there was an apparent negative relation with sensitivity to cats, those first or second born being significantly less likely (9.9 v 16.1%) to be sensitive to cats (p = 0.03).

INFLUENCE OF GENDER

There was a male predominance in reported diagnosed asthma and in wheezing symptoms until the age of 18 years, when the gender difference reversed (table 4).

INFLUENCE OF BIRTH WEIGHT

Birth weights were normally distributed between 1420 and 5400 g; 50 subjects were less than 2500 g and 11 less than 2000 g. There was no significant relation between birth weight and diagnosed asthma to age 9 years (p = 0.14), ever having wheezed to age 9 years (p = 0.23), FEV1/VC ratio grouped by 5% decrements from less than or equal to 90% to less than 75% (p = 0.33) at age 9 years, or to asthma reported ever to age 18 years (p = 0.092), for boys and girls together or separately. There was no significant relation between birth weight and the presence or degree of airway hyper-responsiveness (to either methacholine or salbutamol) at age 9 years. Children of low birth weight did not have more airflow obstruction; rather, a slight trend for those with lower birth weight to have higher FEV1/VC ratios at age 9 years was observed. There was no report of diagnosed asthma in those of birth weight less than 2000 g. The reference group with the median birth weight (3000–3499 g) had the highest prevalence of diagnosed asthma. All other birth weight groups had lower, rather than increased, ORs for asthma, but none was significantly different to 1.0 (table 5). There was no significant difference in ORs for boys and girls.

Table 5 Relation between birth weight, atopy, and reported diagnosed asthma and wheezing at age 9 years, and at any age to 18 years, in New Zealand children

<table>
<thead>
<tr>
<th>Birth weight (g)</th>
<th>No of births in full cohort</th>
<th>Atopy (%) of those tested at 13 years</th>
<th>Reported wheezed to 9 years (%) (n=815)</th>
<th>Reported asthma to 9 years (%) (n=815)</th>
<th>Reported asthma to 18 years (%) (n=1002)</th>
<th>Odds ratio for asthma to 18 years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2500</td>
<td>50</td>
<td>37.1</td>
<td>21.4</td>
<td>2.3</td>
<td>8.7</td>
<td>0.26 (0.07 to 0.75)</td>
</tr>
<tr>
<td>2500-2999</td>
<td>171</td>
<td>30.4</td>
<td>22.4</td>
<td>4.8</td>
<td>19.0</td>
<td>0.66 (0.41 to 1.06)</td>
</tr>
<tr>
<td>3000-3499</td>
<td>380</td>
<td>44.2</td>
<td>29.6</td>
<td>10.8</td>
<td>26.2</td>
<td>1.00 (reference group)</td>
</tr>
<tr>
<td>3500-3999</td>
<td>324</td>
<td>36.4</td>
<td>29.3</td>
<td>9.3</td>
<td>20.5</td>
<td>0.73 (0.50 to 1.07)</td>
</tr>
<tr>
<td>4000-4499</td>
<td>99</td>
<td>30.7</td>
<td>34.9</td>
<td>10.8</td>
<td>19.8</td>
<td>0.67 (0.38 to 1.17)</td>
</tr>
<tr>
<td>≥ 4500</td>
<td>13</td>
<td>0</td>
<td>44.4</td>
<td>22.2</td>
<td>15.4</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1037</td>
<td>37.4</td>
<td>28.7</td>
<td>9.1</td>
<td>21.7</td>
<td></td>
</tr>
</tbody>
</table>
There was no increase in atopy in infants of lower birth weight and no correlation between birth weight and specific atopy to house dust mites (p = 0.29) or cats (p = 0.24) in the whole cohort or in either sex.

MULTIVARIATE ANALYSIS

If both parents reported asthma, the OR for symptoms of asthma at any age to 18 years was increased (3.24, 95% CI 1.30 to 8.07, p = 0.01) as was the risk for airway hyper-responsiveness (2.82, 95% CI 1.15 to 6.87, p = 0.02). Airway hyper-responsiveness was also related to paternal hay fever (OR 1.34, 95% CI 1.04 to 1.73, p = 0.03) and to asthma or hay fever in either parent (OR 1.46, 95% CI 1.18 to 1.79, p = 0.0004).

By logistic regression, male sex increased the ORs for the development of atopy (1.43, 95% CI 1.20 to 1.69, p = 0.0001), sensitivity to house dust mites (1.41, 95% CI 1.16 to 1.71, p = 0.0005), sensitivity to cats (1.32, 95% CI 1.00 to 1.75, p = 0.05), and airway responsiveness at any age from 9 to 15 years (1.24, 95% CI 1.03 to 1.49, p = 0.02). There was a nearly significant trend for boys to have an increased OR for symptoms of asthma reported at age 9 years (1.28, 95% CI 0.99 to 1.65, p = 0.06).

Birth in the winter season increased the risk of sensitisation to cats (OR 1.92, 95% CI 1.26 to 2.93, p = 0.003) relative to those born in spring. Birth weight over 4000 g reduced the likelihood of sensitisation to cats (OR 0.17, 95% CI 0.03 to 0.85, p = 0.03 relative to a reference birth weight of 3000–3499 g) and perhaps of atopy in general (OR 0.64, 95% CI 0.40 to 1.03, p = 0.07), but had no effect on the risks for sensitisation to house dust mites. Among children at higher risk of sensitisation (those with parental asthma or hay fever), birth in autumn and winter increased the risk of developing house dust mite allergy (34.2 vs 18.7%, p = 0.040).

There was no consistent independent effect of socioeconomic status on any of the outcome variables.

Discussion

In this cohort of over 1000 children followed up for 18 years the strongest predictor for childhood atopy, airway hyper-responsiveness, and symptoms of asthma was family history, especially of maternal asthma and atopy. Male sex increased the risk of atopy and airway hyper-responsiveness, but was less strongly associated with symptoms, especially during late adolescence. Symptoms were also associated with substantial exposure to passive smoke. Our findings confirm and extend those reported from a longitudinal study of children from birth to age 6 years in Tucson, Arizona.48 Parental asthma increases the OR for asthma to as much as 2.6.5-28 Maternal asthma is generally a stronger predictor of childhood asthma 11-16 than paternal asthma.17-30 Our study differs from some in finding no significant effect of paternal asthma. This may reflect a greater uncertainty regarding a diagnosis of asthma in men because of the higher prevalence of smoking and may also be influenced by the fact that the paternal history was usually obtained from the mother rather than directly from the father. We have confirmed that parental asthma is predictive of airway hyper-responsiveness in children.26 In other studies parental atopy increased the risk of atopy in children two to three times,1,47 but we found on average only a 1.3-fold increase, increasing to 1.6-fold if both parents had hay fever (table 1). A small but significant effect of maternal smoking was evident in this study with an impact seen on the early development of wheezing symptoms, as also reported in the Tucson longitudinal study,46 but less or no effect in older children. In part this may reflect an adverse effect of passive smoking on the smaller airways of young infants, with less adverse effects as lung growth occurs.48 We have shown, however, in earlier publications from our study that, using the random effects model, the impairment of lung function of wheezing children exposed to passive cigarette smoking worsens, whereas initially impaired lung function in wheezing children not exposed to smoke tends to return to normal by the age of 15 years.49

In another study of 8 to 13 year old children in New Zealand there was an increased OR for current wheeze (1.4, 95% CI 1.0 to 2.1) if the primary care giver had smoked since the child's birth, but no increased risk from the mother smoking in pregnancy.50 In the UK National Cohort maternal smoking of more than 15 cigarettes daily and low birth weight were the major correlates of wheezing.50 After adjustment for these factors, all other putative risk factors (socioeconomic status, maternal age, breast feeding) became insignificant. The intensity of exposure to maternal smoke is important in determining the risk of childhood wheezing. Infante-Rivard showed that maternal smoking of over 20 cigarettes daily, when compared with no smoking, had an odds ratio of 2.77 (95% CI 1.36 to 5.66), whereas when all smoking was analysed together, no significant effect was found.4 In our study, although we were unable to show risks as high as these, similar trends are evident, adding further to concerns that parental smoking is a substantive cause of respiratory morbidity in children.

We did not find consistent associations between month or season of birth and atopy or symptoms of asthma, except that birth in the winter months increased the likelihood of sensitisation to cats and (in those at higher risk because of parental asthma or hay fever) to house dust mites. We suspect that these findings relate to a greater exposure to indoor allergens in the winter months when the infant is less likely to be taken outside for any prolonged period. Given the variable findings of many studies we suggest that reported associations between season of birth and development of atopy are likely to be local rather than universal in their applicability.

We were unable to confirm any effect of number of siblings on the development of atopy or asthma in this cohort, differing from...
Risk factors for asthma

both von Mutius et al who reported more atopy in first born children and Businco et al who found less asthma in first born children. Again, local environmental factors may affect exposures in different areas, explaining these apparent contradictions. New Zealand children may all be highly exposed to allergens, particularly house dust mites, overpowering any sibling effects.

We confirmed the sex differences in risk for the development of asthma which had been identified in most previous studies. In an Isle of Wight birth cohort boys had more asthma (OR 1.6) and more positive skin tests (OR 1.8) than girls, while among Danish children boys had increased wheezing in the first 18 months (OR 1.9). Among Australian children, more boys than girls showed airway responsiveness. Our findings do not suggest a relation between atopy or asthma and birth weight. Seidman et al. reviewed over 20 000 17 year old Israeli army recruits and, after adjustment for ethnicity, socioeconomic factors, paternal education, maternal age, and birth order, found that those with birth weights less than 2500 g were at increased risk of developing asthma. In that study, however, only boys were considered and asthma was diagnosed only where there was 'clear medical evidence of present bronchial disease as opposed to episodic attacks'. The higher prevalence of atopy in our median birth weight group is consistent with the higher prevalence of asthma and wheezing in that group. Our findings are similar to those of Kelly et al., who found a trend towards less asthma in Merseyside children of lower birth weight.

In summary, we have shown in a longitudinal study of a birth cohort of over 1000 New Zealand children that the family history of asthma and atopy is the strongest predictor of features of asthma and atopy in the child. Male gender, maternal smoking, and birth in the winter months are also relevant risk factors for symptoms and certain allergy sensitivities, whereas birth weight, birth order, and socioeconomic status were not risk factors for asthma in this cohort. These findings suggest possible areas for intervention in children at risk of developing asthma because of parental atopy. These interventions would logically include the avoidance of maternal smoking during and after pregnancy, the reduction of exposure to relevant allergens, particularly house dust mites in children at risk and cats in all children, but the benefits of such interventions require further study.

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Parental and neonatal risk factors for atopy, airway hyper-responsiveness, and asthma.

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