The relation of adult bronchial responsiveness to serious childhood respiratory illness in the ECRHS

Susan Chinn\textsuperscript{a,*,} Christer Janson\textsuperscript{b}, Cecilie Svanes\textsuperscript{c}, Shyamali Dharmage\textsuperscript{d}, Deborah Jarvis\textsuperscript{e}

\textsuperscript{a}Department Public Health Sciences, King’s College London, 5th floor Capital House, 42 Weston Street, London SE1 3QD, UK
\textsuperscript{b}Respiratory Medicine and Allergology, University of Uppsala, 751 85 Uppsala, Sweden
\textsuperscript{c}Department Thoracic Medicine, 5021 Haukeland Hospital, Bergen, Norway
\textsuperscript{d}Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, School of Population Health, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Level 2, 723 Swanston Street, Carlton, Vic 3053, Australia
\textsuperscript{e}Respiratory Epidemiology and Public Health Group, NHLI at Imperial College London, Emmanuel Kaye Building, London SW3 6LR, UK

Received 22 May 2006; accepted 5 September 2006
Available online 16 October 2006

KEYWORDS
Bronchial responsiveness; Respiratory infection; Atopy; Spirometry; Smoking; Body mass index

Summary
Background: Respiratory symptoms in adulthood have been found to be associated with childhood respiratory infection, but few studies have analyzed adult bronchial responsiveness (BHR) with adequate adjustment for known risk factors.
Objective: To estimate the relation of BHR with serious childhood respiratory infections in a large population study.
Methods: The European Community Respiratory Health Survey (ECRHS) was a cross-sectional population-based survey in 34 centers. Data on serious respiratory infections before the age of 5 years and possible confounders were obtained from a questionnaire administered in the clinic. Blood samples were taken for measurement of total immunoglobulin E (IgE) and specific IgE to four common allergens, and spirometry and bronchial challenge with methacholine were performed. A continuous measure of BHR was analyzed by multiple regression, in 11,282 participants, in relation to serious respiratory infection and other potential risk factors, adjusted for center and major determinants of adult BHR.
Results: Those reporting a serious childhood respiratory infection had greater BHR, by an amount corresponding to approximately 0.23 doubling doses (95% confidence interval 0.02–0.44) of the amount of methacholine causing a 20% fall (PD\textsubscript{20}) in forced expiratory volume in 1 s (FEV\textsubscript{1}). All childhood factors explained less than 0.3% of variation in BHR in addition to over 20% by factors measured in adulthood. The relation of BHR to BMI was confined to smokers.

*Corresponding author. Tel.: +44 20 7352 8121 x3522; fax: +44 20 7351 8322.
E-mail address: s.chinn@imperial.ac.uk (S. Chinn).

0954-6111/5 - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2006.09.004
Introduction

Despite that bronchial responsiveness (BHR) is the objective measure of choice in epidemiological studies on asthma few studies have analyzed BHR in relation to childhood respiratory infections. One report suggested that a severe respiratory tract infection in the 1st year of life was a risk factor for increased BHR 20 years later, while another found raised BHR in 7-year-old children who had four or more lower respiratory tract infections in the first 3 years of life, but lower BHR in those who had repeated viral infections. Arshad et al. found relations between asthma at age 10 and repeated chest infections at 1 and 2 years of age, but not with BHR. Gómez et al. reported greater BHR in 71 young adults who had had viral bronchiolitis in infancy than in 32 controls.

The major risk factors for increased BHR in adulthood are atopy, smoking and reduced lung function. In the small study of Gómez et al. results were unadjusted, while Vonk et al. adjusted for several factors in their analysis of 597 adults, but did not include airway caliber. This report assesses the relation of severe respiratory tract infection before the age of 5 years, and other childhood risk factors, to adult BHR in ECRHS I, taking into account the major potential confounding factors.

Methods

Subjects

The protocol for ECRHS I has been described in detail. In 1991–1993 participating centers studied an area defined by pre-existing administrative boundaries, with a population of at least 150,000 people. A sampling frame was used to select randomly at least 1500 men and 1500 women aged 20–44 years, who were sent a self-completed postal questionnaire. A random sample of responders was invited to stage 2, which included an administered questionnaire, measurement of lung function, and both blood sampling and bronchial challenge in 34 centers. Ethical approval was obtained for each center from the appropriate ethics committee, and written consent was obtained from each participant.

Questionnaire data

The question ‘Did you have a serious respiratory infection before the age of five years?’ was of primary interest. Due to reported associations with asthma or lung function, number of siblings and exposure to day care before the age of 5 years, pet keeping (cat, dog or bird) in childhood, paternal and maternal smoking in childhood, were considered as variables of secondary interest, as was current pet keeping due to possible confounding with childhood exposure. ‘Don’t know’ was an accepted answer to childhood questions other than those about pet-keeping. Participants were divided into never smokers, ex-smokers and current smokers based on answers to the questions ‘Have you ever smoked for as long as one year?’ and ‘Do you now smoke, as of one month ago?’

Conclusions: We found an effect of serious childhood respiratory infection on adult BHR, but this was small in comparison to relations of BHR to IgE-sensitization and airway caliber. © 2006 Elsevier Ltd. All rights reserved.
20. For presentation some results were converted to approximate change in \( \text{PD}_{20} \) in doubling dose units using the conversion factor of two units of slope equal to one of \( \log \text{PD}_{20} \) to base 10.\textsuperscript{14}

**Statistical analysis**

The association between BHR slope and all childhood and pet exposure variables was examined as described above, with adjustment for center, sex, age, smoking, an age-smoking interaction, height, baseline FEV\(_{1}\), expressed as a standardized difference from an internally derived predicted value and as a percentage of FVC, season of testing, log total IgE and sensitization to four allergens, including titers as measures of degree of sensitization.\textsuperscript{12} Interactions of sensitization with center were included as heterogeneity was detected in the relations with BHR.\textsuperscript{12} Number of siblings was included, as categories 0, 1, 2, 3, 4 or more, and its interaction with day care before the age of 5 years.\textsuperscript{8} Pet keeping in adulthood was categorized into pets allowed in the house or not, and in the case of cats and dogs further subdivided into whether allowed in the bedroom or not. The interaction of serious respiratory infection with family history of allergic disease was assessed. A smoking-BMI interaction was investigated in a previous analysis of the ECRHS I data, as it has been suggested that smoking and obesity\textsuperscript{16} may each cause asthma, and the interrelations are complex as smokers tend to gain weight on quitting.\textsuperscript{17} That analysis supported inclusion of the interaction in the current analysis,\textsuperscript{18} in contrast to the earlier findings.\textsuperscript{13} In the multivariable analysis of BHR slope no non-linearity with BMI was detected, so BMI was therefore treated as continuous in subsequent analyses, as in the previous report,\textsuperscript{13} except for graphical presentation. The sex-BMI interaction was also assessed. Terms included in a previous analysis,\textsuperscript{13,18} the variable of primary interest, i.e. childhood respiratory infection, or other variables with a \( P \)-value of less than 0.1 were retained after backwards selection. The coefficients of interest in the final model were examined for between center heterogeneity.\textsuperscript{19}

**Results**

In total 12,975 participants had a BHR slope. The majority of these had data for the early life variables (Table 1).

**Elimination of potential risk factors**

There was no evidence for an interaction of BMI and sex \( (P = 0.57) \) or of number of siblings and day care \( (P = 0.46) \), or of serious respiratory infection in childhood with family history of allergic disease \( (P = 0.70) \). Variables were eliminated in order as follows: current cat in house \( (P = 0.89) \); current dog in house \( (P = 0.74) \); father smoked \( (P = 0.66) \); day care before the age of five years \( (P = 0.46) \); exposure to bird in childhood \( (P = 0.47) \); number of siblings \( (P = 0.33) \); mother smoked \( (P = 0.32) \); bird in house \( (P = 0.14) \); exposure to dog in childhood \( (P = 0.13) \); and exposure to cat in childhood \( (P = 0.18) \). Hence of the variables not included in previous analyses only serious respiratory infection and family history of allergic disease were retained in the model.

**Relation of BHR to serious childhood infection**

Effect estimates for the childhood risk factors remaining in the model are shown in Table 2, for 11,282 participants. A reported serious respiratory infection before the age of 5 years \( (P = 0.033) \) was associated with reduced slope, i.e. increased BHR, compared to no exposure. The inclusion

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No n (%)</th>
<th>Yes n (%)</th>
<th>Don’t know n (%)</th>
<th>Total n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious respiratory infection before 5 years</td>
<td>11,053 (85.6)</td>
<td>1197 (9.3)</td>
<td>661 (5.1)</td>
<td>12,911</td>
</tr>
<tr>
<td>Did you go to play-school or nursery with older children before the age of 5 years?</td>
<td>6230 (48.2)</td>
<td>6462 (50.0)</td>
<td>237 (1.8)</td>
<td>12,929</td>
</tr>
<tr>
<td>Did your father ever smoke regularly during your childhood?</td>
<td>4206 (32.5)</td>
<td>8318 (63.2)</td>
<td>427 (3.3)</td>
<td>12,951</td>
</tr>
<tr>
<td>Did your mother ever smoke regularly during your childhood, or before you were born?</td>
<td>9297 (71.8)</td>
<td>3491 (26.9)</td>
<td>168 (1.3)</td>
<td>12,956</td>
</tr>
<tr>
<td>Household cat in childhood</td>
<td>6851 (53.0)</td>
<td>6071 (47.0)</td>
<td>—</td>
<td>12,922</td>
</tr>
<tr>
<td>Household dog in childhood</td>
<td>6730 (52.1)</td>
<td>6197 (47.9)</td>
<td>—</td>
<td>12,927</td>
</tr>
<tr>
<td>Household birds in childhood</td>
<td>7111 (55.0)</td>
<td>5815 (45.0)</td>
<td>—</td>
<td>12,926</td>
</tr>
<tr>
<td>Family history of allergic disease</td>
<td>4544 (35.0)</td>
<td>6938 (53.5)</td>
<td>1493 (11.5)</td>
<td>12,975</td>
</tr>
<tr>
<td>Current pet keeping</td>
<td>None or outside only</td>
<td>Allowed indoors, not in bedroom</td>
<td>Allowed in bedroom</td>
<td>12,975</td>
</tr>
<tr>
<td>Cat</td>
<td>10,333 (79.9)</td>
<td>505 (3.9)</td>
<td>2087 (16.1)</td>
<td>12,925</td>
</tr>
<tr>
<td>Dog</td>
<td>11,033 (85.3)</td>
<td>619 (4.8)</td>
<td>1277 (9.9)</td>
<td>12,929</td>
</tr>
<tr>
<td>Birds</td>
<td>11,652 (90.1)</td>
<td>1275 (9.9)</td>
<td>—</td>
<td>12,927</td>
</tr>
</tbody>
</table>

*Included not ascertainable due to no siblings or ‘Don’t know’ in parents.
of the ‘don’t know’ category for serious respiratory infection reduced the overall significance (P = 0.070).

### Major adult determinants of BHR

The previously considered risk factors, IgE sensitization and degree of sensitization with interactions with center, FEV₁, FEV₁/FVC, height, sex, season of testing smoking and its interactions with age and BMI, together explained 24.2% of the variation in BHR slope. Adding all the other factors considered, reported serious respiratory infection or attended daycare before the age of 5, family history of allergic disease, parental smoking, exposure to pets in childhood or currently, explained an additional 0.2%. The adjusted R² values were 0.220 and 0.221, respectively. With adjustment for childhood respiratory infection and family history of allergy, between center heterogeneity in the relations of IgE sensitization to each allergen was still present, and log total IgE, FEV₁, as difference from predicted and as percentage of FVC, and height each remained strongly associated with BHR. Women had lower mean slope, i.e. greater BHR, than men (P < 0.001). There was no association of BHR with season of testing. The differences in trend of BHR with BMI between the three smoking groups were marginally statistically significant (P = 0.086), with virtually no trend in non-smokers (P = 0.45) and negative trends of slope with BMI in ex-smokers and current smokers. The difference in trend with BMI from non-smokers was similar in ex-smokers and smokers, so these groups were combined. The estimates in approximate doubling doses of PD20 in Table 3 show a statistically significant difference (P = 0.039) in trend with BMI between ever smokers and never smokers. It also shows that mean BHR between those reporting a serious respiratory infection in childhood was greater by approximately only –0.29 doubling doses of PD20 than those reporting no such infection (95% confidence interval –0.44 to –0.02). The interaction of age and smoking status was not statistically significant (P = 0.50), and was omitted in the Table 3 model. These differences in the models in Tables 2 and 3 had little effect on the P-values associated with serious respiratory infection before the age of 5 years or family history of allergic disease, as shown.

No heterogeneity between centers was detected for any of the estimates in Table 3. The interaction between BMI and smoking was re-estimated treating BMI as categorical, and shown in Fig. 1, overweight and obese smokers having lower mean approximate PD20, i.e. increased BHR, compared to other groups.

### Discussion

This analysis has shown a weak, but positive, relation between reported serious childhood respiratory infection and increased BHR. The difference in mean BHR between those reporting serious childhood respiratory infection and those who did not was small, corresponding to 0.2 doubling doses PD20, approximately. The observed effect may be an underestimate, for two reasons. Some misclassification of childhood infections is likely, due to error in recalling an early childhood event as a young adult. Second, in common with most studies relying on recall, we were unable to differentiate between lower and upper respiratory tract infections, or between bacterial and viral infections. Using data from a longitudinal birth cohort Illi et al.² found opposite effects of lower respiratory tract infections and repeated viral infections in the first 3 years of life, on BHR at age 7 years, so effects of the former may be diluted by the latter in the ECRHS. Arshad et al. analyzed recurrent chest infections, i.e. more than one in a year, in the first 4 years of life, finding no relation to BHR at age 7 years.³

Only three studies have previously analyzed childhood infections in relation to adult BHR.¹¹ Vonk et al.¹ found a very strong relation of BHR to serious doctor-treated respiratory tract infection in the 1st year of life, in atopic and non-atopic young adults in Groningen. Atopy was defined as a positive skin prick test to any one of several allergens. From our previous analyses of ECRHS data this is not sufficient to represent the relation of BHR to atopy, the relation varying between different allergens and with degree of IgE sensitization,¹² and they did not adjust for

### Table 2

Mean difference in BHR slope by exposure to serious respiratory infection before the age of 5 years and family history of allergy.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Difference in mean slope from no exposure*</th>
<th>95% confidence interval for difference*</th>
<th>P-value for difference from reference group</th>
<th>P-value for any difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious respiratory infection</td>
<td>–0.14</td>
<td>–0.26 to –0.01</td>
<td>0.033</td>
<td>0.070</td>
</tr>
<tr>
<td>Serious respiratory infection—‘don’t know’</td>
<td>–0.09</td>
<td>–0.26 to 0.08</td>
<td>0.288</td>
<td></td>
</tr>
<tr>
<td>Family history of allergic disease</td>
<td>–0.12</td>
<td>–0.20 to –0.04</td>
<td>0.004</td>
<td>0.015</td>
</tr>
<tr>
<td>Family history—unascertainable or ‘don’t know’</td>
<td>–0.06</td>
<td>–0.18 to 0.07</td>
<td>0.373</td>
<td></td>
</tr>
</tbody>
</table>

*Estimates are mutually adjusted, and also adjusted for center, sex, log total IgE, height, baseline FEV₁ as difference from predicted, FEV₁/FVC, height, season of testing, age, smoking status, BMI, and age/smoking and smoking/BMI interactions, after backwards stepwise multiple regression.
In three centers of the ECRHS no statistically significant relation between current asthma or BHR was found with serious respiratory infection in childhood, but in this smaller sample, and with BHR dichotomized, less adjustment for confounding was possible, and less power available. The results of Gómez et al. were unadjusted for other risk factors, and hence hard to interpret.

Although the ECRHS has the weakness that we cannot be sure of the exact nature of ‘a serious respiratory infection in the first 5 years’, it has a number of strengths. BHR as a continuous outcome was analyzed for over 11,000 people, while other studies included less than 1000 in multivariable analyses of dichotomized BHR, and therefore with less power on two counts. The ECRHS analysis enabled inclusion of major risk factors for BHR, possible interactions, and testing of heterogeneity between the 34 centers. Although small, and weakly statistically significant, the relation of BHR to early respiratory infection was consistent across the centers, and robust to inclusion or exclusion of other potential childhood risk factors.

Table 3

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Estimate (DD PD20)*</th>
<th>95% confidence interval for difference*&lt;br&gt; (DD PD20)</th>
<th>P-value for difference from reference group</th>
<th>P-value for any difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious respiratory infection: difference from ‘no’</td>
<td>-0.23</td>
<td>-0.44 to -0.02</td>
<td>0.031</td>
<td>0.064</td>
</tr>
<tr>
<td>Serious respiratory infection—‘don’t know’: difference from ‘no’</td>
<td>-0.15</td>
<td>-0.43 to 0.12</td>
<td>0.276</td>
<td></td>
</tr>
<tr>
<td>Family history of allergic disease: difference from ‘no’</td>
<td>-0.20</td>
<td>-0.33 to -0.06</td>
<td>0.004</td>
<td>0.016</td>
</tr>
<tr>
<td>Family history—unascertainable or ‘don’t know’: difference from ‘no’</td>
<td>-0.10</td>
<td>-0.30 to 0.11</td>
<td>0.360</td>
<td></td>
</tr>
<tr>
<td>Trend with BMI—difference between ever-smokers and non-smokers</td>
<td>-0.03</td>
<td>-0.07 to -0.00</td>
<td>0.039</td>
<td></td>
</tr>
</tbody>
</table>

*Estimates are mutually adjusted, and also adjusted for center, sex, IgE sensitization with center interactions, log total IgE, height, baseline FEV₁, as difference from predicted, FEV₁/FVC, height, season of testing, age, smoking status and trend with BMI in non-smokers.

![Figure 1](image-url) Mean difference in BHR from normal weight participants in non-smokers — and ever-smokers —— in approximate doubling dose units of PD2₀, adjusted for sex, age, IgE sensitization with center interactions, log total IgE, height, baseline FEV₁, as difference from predicted, FEV₁/FVC, height, season of testing, reported serious respiratory illness in first 5 years and family history of allergic disease.

Airway caliber or BMI. In three centers of the ECRHS no statistically significant relation between current asthma or BHR was found with serious respiratory infection in childhood, but in this smaller sample, and with BHR dichotomized, less adjustment for confounding was possible, and less power available. The results of Gómez et al. were unadjusted for other risk factors, and hence hard to interpret.
weeks of uterine life, each continue to grow in this period.21 Lower airway infections during this critical period of lung development appear to increase bronchial responsiveness, which may be carried over to adult life. Two cohort studies have found adult lung function to be lower in those who experienced pneumonia in early childhood.22,23 In the larger of these studies lung function was also reduced, to a lesser extent, in those who had had whooping cough.22 Hence early childhood infections may increase BHR through reducing lung function in addition to a direct effect. Although we adjusted for FEV1 and FEV1/FVC, and showed in a previous analysis that results were independent of how adjustment for lung function was made,13 we cannot totally rule out residual confounding of lung function accounting for the relation of BHR to reported serious respiratory infection in the first 5 years.

A previous analysis of the ECRHS data suggested that BHR was positively associated with BMI.13 However in that paper we did not investigate a smoking-BMI interaction, in common with previous authors on the subject of asthma and obesity, and later found that the relation of BHR to BMI was confined to smokers and ex-smokers.18 Although the statistical significance of the interaction term was not strong it is nevertheless true that had we included it in the original analysis we would have drawn a different conclusion. In adults the evidence for a positive relation between BHR and BMI is weak.

Childhood respiratory illness has been shown to be associated with increased BHR in adulthood but effects are small in comparison to those of IgE-sensitization, airway caliber and smoking, and will only be detected in large epidemiological studies.

References