Descriptive epidemiology of bronchial reactivity in an adult population: results from a community study

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ABSTRACT The bronchial response to inhaled histamine has been suggested as an epidemiological tool for assessing the prevalence of asthma, though the exact relationship between reactivity and asthma is unknown. Tests of bronchial reactivity to histamine were carried out in 511 subjects aged 18–64 years, randomly selected from the population in two areas of the South of England, who had returned questionnaires on respiratory symptoms. Bronchial reactivity to \( \leq 8 \mu\text{mol} \) histamine was present in 14\% and was associated with positive skin test responses to common allergens and with smoking history. Both of these relationships were in turn dependent on age, skin sensitivity being the more important determinant of reactivity in the young and smoking the more important in older subjects. Bronchial reactivity was least prevalent in the 35–44 year age group. No independent effect on reactivity of sex, social class, or area of residence was detected, and no significant effect from recent respiratory tract infections. Interpretation of the bronchial response to histamine in selected groups of subjects must take account of age, atopic state, and smoking history.

Measurement of the prevalence of asthma is of considerable importance both to those concerned with the aetiology of the condition and to those assessing the effectiveness of the health services in managing it. The Ciba symposium on the identification of asthma concluded that there was no satisfactory method for its identification.\(^1\) Difficulties in standardising and validating questionnaires for the detection of asthma have led to the suggestion that physiological tests, and particularly non-specific bronchial challenge tests, might provide a more objective method of assessing asthma prevalence in epidemiological studies.\(^2\)

Although some support for this may be derived from the American Thoracic Society's definition of asthma as "a disease characterised by an increased responsiveness of the trachea and bronchi to various stimuli..." there is evidence that reactivity is increased in conditions other than asthma—in particular in chronic bronchitis,\(^4\) in cigarette smokers,\(^6\) and after recent upper respiratory tract infections in individuals not considered to be asthmatic.\(^7\) While this suggests a lack of specificity for asthma, these conclusions are based for the most part on studies of small, highly selected groups of patients attending hospitals and clinics, and the results have been inconsistent.\(^8\)\(^9\)

Knowledge of the distribution of bronchial reactivity in the general population is required so that the overall contribution of the different risk factors can be assessed. Three such surveys of adults have been published. Two\(^10\)\(^11\) used subjects with a restricted age range, in whom the confounding effects of age could not be fully assessed, the other\(^12\) was a survey of Boston parents in which a cold air challenge was used, the response to which is likely to be distributed differently from that to histamine and methacholine.\(^13\)\(^14\)

This paper describes the distribution of bronchial reactivity to histamine in a randomly selected sample of adults living in two districts of England. The data were collected during a study of the relationship of symptoms to bronchial reactivity. The need to assess this relationship influenced the design of the study, but results of that part of the study will not be discussed further in this paper.

Methods

A cross sectional survey of respiratory symptoms was
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Conducted in two neighbouring villages in Hampshire and a market town in Dorset. A self administered questionnaire designed to elicit symptoms of asthma and bronchial irritability was given to all residents aged 18–64 years, with supplementary questions on age, sex, occupation, and smoking habits.

**Sample**
The locations selected were within easy reach of Southampton, where part of the study team was based, and in districts where the local health services agreed to the study. Two locations were selected to reduce the chance that any finding would be unduly influenced by specific local factors. These locations were selected from two areas, one of which had a high and one a low to average mortality from asthma.15

The electoral register was used as an initial sampling frame but was updated by fieldworkers during house to house visiting when they delivered the questionnaire. An estimate of the population aged 18–64 years was taken from the 1981 census. Of those who returned the questionnaire a 20% random sample was asked to attend the local general practice or clinic for a histamine challenge test and for skin tests.

**Bronchial Challenge**
Subjects were asked not to smoke in the two hours before their appointment, or take theophyllines or antihistamines within 24 hours or use inhaled bronchodilators within six hours. Subjects whose baseline FEV1 was greater than 60% predicted had a histamine challenge test, the method of Yan et al being used.16 After inhalation of saline increasing doses of histamine were administered, from a starting dose of 0·03 μmol until either a maximum cumulative dose of 4·0 μmol had been delivered or the FEV1 had fallen by more than 20% from the value obtained after saline inhalation. In subjects with no history of asthma or respiratory illness fourfold dose increments were given, starting at 0·06 μmol unless the FEV1 fell by more than 10% from the postsaline value, when doubling increments were given. Subjects with a history of asthma or wheeze were given doubling doses throughout.

A curve fitting technique was used to estimate the dose of histamine that provoked a 20% fall in FEV1 (PD20).17 A maximum dose of 4 μmol was given but extrapolation of the PD20 was allowed up to 8 μmol. Values below 0·03 μmol (or 0·06 if this was the first dose) and above 8 μmol are described as “censored[,]” indicating that there is no exact estimate of the PD20 but knowledge only of whether it is above or below the “censoring” limit.

**Skin Tests**
The weal diameters from skin prick tests for cat fur, mixed grass pollen, and Dermatophagoides pteronyssinus, with saline and histamine controls (Bencard, Brentford, England), were measured after 10 minutes as the mean of two transverse diameters taken at 90° to each other, one of which was the maximum measurable weal diameter. Atopic state was assessed on the basis of the mean response to the three allergens.

**Statistical Methods**
Subjects were categorised as “reactors” if they had a PD20 of 8 μmol histamine or less. The proportion of the population who were reactors was first regressed against several independent variables in a multiple logistic regression, the program used being GLIM.18

Secondly, PD20 was regressed against the same independent variables by the maximum likelihood method of Wolynetz.19 This method estimates the association of mean PD20 with the independent variables by combining data on the proportion of reactors with the values of the PD20 where these are known.

**Conduct of the Survey**
The survey was carried out in February and the reactivity tests were performed from March to early April 1984, before the grass pollen season began. Permission for the study was granted by the ethical committees of Southampton, Basingstoke, and West Dorset, and the project was discussed with and agreed to by the local general practitioners. All subjects had the challenge test and likely side effects explained to them and gave written consent before participating.

**Results**
The overall response to the questionnaire in the population estimated from the electoral roll, with adjustments for those known to have moved or died, for those known not to have been registered, and for the proportion of the population over the age of 64 at the 1981 census, was 61%. It varied from 68% in one village to 51% in the market town. We are unable to comment further on the characteristics of the non-respondents. Of the 873 randomly selected subjects, 522 (60%) came for a histamine challenge test. In a multiple logistic regression, response was significantly \( p < 0·05 \) and independently associated with age, smoking, area of residence, and sex, but not with symptoms, diagnosis, or social class. Response was lower in men (53%), in smokers (53%), in those under 25 (47%) or over 54 years (53%), and in Dorset (55%).

A histamine challenge test was not performed on seven subjects whose FEV1 was less than 60% predicted or in four who were unable to perform a satisfactory forced expiratory manoeuvre. A satisfactory
Distribution of bronchial reactivity to histamine (PD$_{20}$ ≤ 8 μmol) by age, smoking habit, and skin sensitivity to three common allergens

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>18–24</th>
<th>25–34</th>
<th>35–44</th>
<th>45–54</th>
<th>55–64</th>
<th>All ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD$_{20}$ histamine ≤ 8 μmol</td>
<td>No/total (%)</td>
<td>No/total (%)</td>
<td>No/total (%)</td>
<td>No/total (%)</td>
<td>No/total (%)</td>
<td>No/total (%)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smokers</td>
<td>6/46 (13)</td>
<td>10/66 (15)</td>
<td>5/73 (7)</td>
<td>4/52 (8)</td>
<td>2/22 (9)</td>
<td>27/259 (10)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>0/2 (0)</td>
<td>3/29 (10)</td>
<td>3/21 (14)</td>
<td>1/28 (4)</td>
<td>7/36 (19)</td>
<td>14/116 (12)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atopic state</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-atopic</td>
<td>1/27 (4)</td>
<td>1/48 (2)</td>
<td>4/65 (6)</td>
<td>4/55 (7)</td>
<td>10/42 (24)</td>
<td>20/237 (8)</td>
</tr>
<tr>
<td>At least one skin test response &gt; saline control</td>
<td>1/18 (6)</td>
<td>3/44 (7)</td>
<td>3/51 (6)</td>
<td>4/32 (13)</td>
<td>8/30 (27)</td>
<td>19/175 (11)</td>
</tr>
<tr>
<td>At least one skin test response &gt; histamine control</td>
<td>6/13 (46)</td>
<td>14/31 (45)</td>
<td>7/25 (28)</td>
<td>6/19 (32)</td>
<td>1/6 (17)</td>
<td>34/94 (36)</td>
</tr>
<tr>
<td>No skin test performed</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
<td>0</td>
<td>0/1 (0)</td>
<td>0/2 (0)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>Total tested</td>
<td>8/59 (14)</td>
<td>18/124 (15)</td>
<td>14/141 (10)</td>
<td>14/107 (13)</td>
<td>19/80 (24)</td>
<td>73/511 (14)</td>
</tr>
</tbody>
</table>

PD$_{20}$—the dose of histamine that provoked a 20% fall in FEV$_1$, histamine challenge test was carried out on 511 subjects, of whom 73 (14%) had a histamine PD$_{20}$ value of 8 μmol or less. The proportion was higher in men (16%), current smokers (23%), those in manual occupations (15%), subjects living in Dorset (16%), and those with a positive skin prick test response (greater than to the saline control) for at least one allergen (19%).

The proportion of the population who were reactors had a U shaped distribution by age (table 1). It was high in the 18–24 year olds (14%), fell to 10% in those aged 35–44 years, and rose again to 24% in the 55–64 year olds. The initial decline in the proportion of histamine reactors with age was seen in smokers and non-smokers alike (fig 1) and was associated partly with a decrease in the prevalence of positive skin test responses and in mean skin weal diameter (fig 2). It was also, however, associated with an appreciable decline in reactivity among those with the strongest skin reactions (fig 3). The rise in prevalence with age in the older subjects was predominantly among cigarette smokers (fig 1), and occurred despite a continuing fall in the prevalence of positive skin test responses.

Mean skin weal diameter (mm)

% reactive

Fig 1 Proportion of reactive subjects (that is, with a PD$_{20}$—the dose of histamine that provoked a 20% fall in FEV$_1$—of 8 μmol or less) according to age group and smoking history. □ Non-smoker (N); ▮ ex-smoker (E); ■ current smoker (C).

Fig 2 Mean skin weal diameter in response to three allergens according to age group and response to histamine. ■ Reactive (PD$_{20}$—see fig 1—≤ 8 μmol); □ unreactive (PD$_{20}$ > 8 μmol).
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Table 2. Multiple logistic regression of proportion reactive (PD$_{20}$ histamine $\leq 8$ µmol) on skin sensitivity, age, and smoking history

<table>
<thead>
<tr>
<th>Factor</th>
<th>Estimate* (with SEM)</th>
<th>$\chi^2$§ (for full model)</th>
<th>Df</th>
<th>$\chi^2$</th>
<th>Df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean for non-atopic non-smokers</td>
<td>-3.80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean difference between:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smokers and non-smokers</td>
<td>-0.30 (0.91)</td>
<td></td>
<td>4</td>
<td>19.6***</td>
<td>4</td>
</tr>
<tr>
<td>Current smokers and non-smokers</td>
<td>-0.16 (0.73)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase per year of age in:</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smokers</td>
<td>0.027 (0.024)</td>
<td>4.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>0.053 (0.028)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>0.086 (0.023)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin sensitivity (mean weal diameter in mm)</td>
<td>0.822 (0.149)</td>
<td>8.6**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Age 18) x skin sensitivity</td>
<td>-0.018 (0.006)</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*See footnote to table 1.  
§Slope or difference on logistic scale, as indicated by factor, with mean for non-smokers and differences at age 18 and skin sensitivity zero.  
**p < 0.001; ***p < 0.001.

Explanation: $-3.8$ is the logit of the proportion (this is equivalent to 2.2%) of the non-smoking, non-atopic population at age 18 who have a PD$_{20}$ $\leq 8$ µmol. For non-atopic ex-smokers at 18 the logit of the proportion will be $(-3.8) + (-0.3) = 4.1$ (equivalent to 1.6%); for a 48 year old non-atopic smoker it will be $(-3.8) + (-0.16) + (30 \times 0.086) = -1.38$ (equivalent to 20%).

Mean skin weal diameter declined significantly with increasing age, from 1-59 mm in the 18-24 year age group to 0.89 mm in the 55-64 year age group. The difference in mean skin weal response between histamine reactors and non-reactors also declined with age (fig 2). There was no relationship between mean skin weal response and smoking history, even after we had controlled for the effect of age, nor was there a relationship between age and the cutaneous response to histamine.

Multiple logistic regression (table 2) showed independent effects on the proportion reacting to histamine of both smoking and mean skin weal diameter in response to three allergens. There was a significant interaction between the effect of age and the effects of both smoking and skin test responses. These relationships are illustrated in fig 4.

Table 3 shows the maximum likelihood estimates of the regression coefficients when PD$_{20}$ was regressed against the same independent variables after information on the proportion of reactive subjects and values of PD$_{20}$ had been combined. This shows significant relationships between PD$_{20}$ and age

Fig 3. Proportion of reactive subjects (PD$_{20}$—see fig 1—$\leq 8$ µmol) according to age group and mean skin weal diameter.  
- All skin test responses $\leq$ saline control;  
- at least one skin test response $>$ saline control, all responses $\leq$ histamine control;  
- at least one response $>$ histamine control.

Fig 4. Estimated proportion of reactive subjects (PD$_{20}$—see fig 1—$\leq 8$ µmol) according to age among  
(1) non-smoking, non-atopic subjects (———);  
(2) non-smoking subjects with 4 mm mean skin weal diameters (-----);  
(3) non-atopic smokers (-----); and  
(4) current smokers with 4 mm mean skin weal diameter (-----).
Table 3  Regression coefficients (standard errors) of log $PD_{20}$ histamine† on the same independent variables as in Table 2 and using the maximum likelihood method to combine information on censored and uncensored data

<table>
<thead>
<tr>
<th>Factor</th>
<th>Regression coefficient (with standard error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant (mean log$<em>{10}PD</em>{20}$ for non-allergic non-smoker aged 18)</td>
<td>2.911</td>
</tr>
<tr>
<td>Difference between:</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker and non-smoker (age 18)</td>
<td>0.249 (0.449)</td>
</tr>
<tr>
<td>Current smoker and non-smoker (age 18)</td>
<td>0.136 (0.351)</td>
</tr>
<tr>
<td>Increase per year of age in:</td>
<td></td>
</tr>
<tr>
<td>Non-smokers</td>
<td>0.011 (0.011)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>0.028 (0.014)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>0.044*** (0.012)</td>
</tr>
<tr>
<td>Skin sensitivity (mean skin weal diameter (mm) to three common allergens)</td>
<td>0.422*** (0.075)</td>
</tr>
<tr>
<td>(Age 18) × (skin sensitivity)</td>
<td>0.008** (0.005)</td>
</tr>
<tr>
<td>Residual</td>
<td>0.973</td>
</tr>
</tbody>
</table>

* p < 0.05; **p < 0.01; ***p < 0.001.
†See footnote to table 1.

Table 4  Numbers of subjects with $PD_{20}$ histamine† ≤ 8 µmol according to time since last upper respiratory tract infection (URTI)

<table>
<thead>
<tr>
<th>Time of last URTI</th>
<th>$PD_{20}$ ≤8 µmol (&lt; No (%) of Total tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>18 (18)</td>
</tr>
<tr>
<td>&lt; 2 weeks</td>
<td>11 (18)</td>
</tr>
<tr>
<td>&lt; 2 months</td>
<td>12 (11)</td>
</tr>
<tr>
<td>&gt; 2 months</td>
<td>32 (13)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>73 (14)</td>
</tr>
</tbody>
</table>

†See footnote to table 1.

in current smokers (p < 0.001) and mean skin weal diameter (p < 0.001), and a significant interaction between the effects of age and skin sensitivity (p < 0.01). These variables explained 38% of the variation in $PD_{20}$ after the variation due to measurement error had been taken into account.

There was a relationship between initial lung function and bronchial reactivity, but inclusion of initial lung function in the multiple regression did not substantially alter the estimates of the regression coefficients. This relationship was complex and will be described further in a separate article.

When mean skin weal response to the three allergens, smoking history, and the interaction of both these factors with age were taken into account there was no further influence on histamine reactivity from sex, social class, area of residence, or time between the last cigarette and the histamine challenge test.

Ninety nine subjects (19%) had current upper respiratory tract symptoms, another 61 (12%) had had symptoms within two weeks, and a further 107 (21%) in the last two months. A greater proportion of those who had current symptoms or who had had symptoms in the previous two weeks had a $PD_{20}$ of 8 µmol or less (table 4), but this was not significant (p > 0.05), either when symptoms were considered alone or after other variables had been controlled for.

Discussion

NON-RESPONSE

Thirty six per cent of the population did not respond to the initial questionnaire and a further 36% did not come for bronchial challenge tests. This non-response rate makes any estimate of the prevalence of bronchial reactivity unreliable. Comparisons within the sample are, however, likely to be more robust. Bias in the response by one variable is unlikely of itself to alter the relation of that variable to another.20

Two observations confirm that the relationships reported here are comparatively insensitive to differences in the characteristics of the sample. In addition to the 511 randomly selected subjects who had their bronchial reactivity tested, a further 322 subjects were tested because they claimed to have had wheezing or whistling in the chest at any time in the previous 12 months. If the 322 additional subjects are added to the 511 subjects selected at random, the coefficients of the logistic regression remain almost unchanged from those shown in table 2. Secondly, although the distribution of risk factors was different in the two areas, the logistic regression quoted here applies to each area independently and there is no significant difference between the areas in the relationship between reactivity and the independent variables.

RELATIONSHIP BETWEEN BRONCHIAL REACTIVITY AND CIGARETTE SMOKING

There was a strong association between current cigarette smoking and bronchial reactivity in our population above the age of 40 years. This is consistent with other studies,5 21 at least where older age groups have been included. Patients with chronic bronchitis have usually also been shown to have greater reactivity than the normal population.4 5 12 14

Our community study has, however, emphasised the age dependent nature of this relationship.

RELATIONSHIP BETWEEN BRONCHIAL REACTIVITY AND ALLERGY

Our sample showed a strong relationship between the mean skin weal response to three common allergens and bronchial reactivity to histamine. This relationship was negatively associated with age, skin sensitivity being more strongly associated with bronchial reactivity in the young. The relationship between atopy and non-specific bronchial reactivity is again in agreement with the findings of most other
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CONCLUSION
This study has shown bronchial reactivity to a low dose of histamine (8 μmol) in 14% of a randomly selected population aged 18–64 years from two areas of the south of England. Atopy was most commonly associated with increased reactivity but this association declined with age. Smoking was the second most important association and this increased with age, being the more important factor in subjects over 45 years old.

If bronchial reactivity is to be taken as the defining characteristic of asthma, as some authors have come close to suggesting in the past, it should follow that cigarette smoking is commonly associated with this condition, a conclusion that would probably not find general acceptance in Britain and the United States. In Europe, where a clear distinction between asthma and chronic bronchitis has been more widely questioned, an association between hyperreactivity, CARA (Chronische Aspecifische Respiratoire Aandoeningen), and smoking would seem less controversial.

How far the increased reactivity seen in young atopic subjects should be identified with that seen in older smokers will not be clear until more is known of the basic mechanisms of bronchial reactivity. It is important meanwhile that further studies of the distribution of bronchial reactivity in the adult community should take account not only of the atopic state but also of the smoking history and, in particular, the age of the subjects studied.

We would like to thank Miss Karen Snowden, Miss Lesley Neville, Miss Jane McNicol, Mr Edward Thomas, and Mrs Renee Witts for help with the fieldwork; Drs TE Wilson, D David, J Davies, R Lorge, J Coppin, J Norwell, and D Pollard, and the general practitioners of the places surveyed for their assistance; and Drs TE Roberts, P Harker, and D Law for helping to set up the survey. We would like to thank Professor Walter Holland for his encouragement and advice throughout and the Department of Health and Social Security for financial support.

OTHER VARIABLES
Increased bronchial reactivity has been reported in normal subjects with symptomatic upper respiratory tract infections and in selected subjects prone to "infectious asthma," where it has been estimated that up to 55% of upper respiratory tract infections may be associated with clinical attacks of asthma. The increase in the proportion of reactors among those subjects who had had a recent upper respiratory tract infection in our study was not significant, but previous results make it likely that the small difference reported here is real.

Because cigarette smoke causes acute though transient bronchoconstriction subjects were asked not to smoke for two hours before the test. Thirty five (7%) failed to comply and, although they did not show significantly increased reactivity, the number was too small to draw general conclusions about the effect of recent smoking on reactivity. Medication is unlikely to have had an appreciable effect on our overall results since only six of 511 subjects had used a bronchodilator in the 24 hours before histamine challenge, and in five of these the PD_{20} was 8 μmol of histamine or less.

References


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*Thorax* 1987 42: 38-44
doi: 10.1136/thx.42.1.38

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