Eur Respir J, 1994, 7, 881–887
DOI: 10.1183/09031936.94.07050881
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European Respiratory Journal
ISSN 0903 - 1936

# Factors influencing the occurrence of airway hyperreactivity in the general population: the importance of atopy and airway calibre

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*Factors influencing the occurrence of airway hyperreactivity in the general population: the importance of atopy and airway calibre. J. Britton, I. Pavord, K. Richards, A. Knox, A. Wisniewski, I. Wahedna, W. Kinnear, A. Tattersfield, S. Weiss. ©ERS Journals Ltd 1994.*

**ABSTRACT: The factors that determine the occurrence of airway hyperreactivity in the general population are not clearly understood. This study was designed to assess the independent effects of age, atopy, smoking and airway calibre.**

**In a random sample of 2,415 adults aged 18–70 yrs we measured reactivity to methacholine as the dose provoking a 20% fall ($PD_{20}$) in one-second forced expiratory volume ($FEV_1$), atopy as the mean skin wheal response to three common environmental allergens, and airway calibre as the baseline $FEV_1$ in absolute terms, as percent predicted ($FEV_1$ % predicted) and as percent forced vital capacity ($FEV_1$ % FVC).**

**Hyperreactivity, defined as a $PD_{20} \leq 12.25$ µmol, was present in 314 (13%) of the sample, and before adjustment for $FEV_1$ was more common in females (independent odds ratio (OR)=2.05 (95% confidence interval 1.6–2.7)), current smokers (OR=1.89 (1.3–2.6)), atopics (OR=1.39 (1.3–1.5) per mm skin wheal), and in older age groups (OR for age 60–70 yrs relative to 18–29 yrs =2.70 (1.7–4.3)). However, the odds of hyperreactivity were also strongly and independently related to absolute $FEV_1$ (OR=0.46 (0.27–0.77) per litre), $FEV_1$ % predicted (OR=0.96 (0.94–0.98) per percent), and $FEV_1$ % FVC (OR=0.92 (0.90–0.94) per percent; combined chi-square on 3 df =312, $p << 0.0001$). After adjustment for these effects, the independent association with atopy remained unchanged but the effects of sex and smoking were no longer independently significant whilst the effect of age was modified such that increased age was associated with a significantly lower rather than a higher risk of hyperreactivity.**

**These findings demonstrate that at any given age, atopy and airway calibre are the major determinants of hyperreactivity in the general population.**

*Eur Respir J, 1994, 7, 881–887.*

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Keywords: Airway calibre
airway reactivity
atopy

Received: August 3 1993
Accepted after revision December 5 1993

Airway reactivity to nonspecific bronchoconstrictor agents, such as histamine and methacholine, is widely used as a measure of disease in epidemiological studies of asthma and chronic obstructive pulmonary disease (COPD). However, although the associations between airway hyperreactivity, self-reported respiratory morbidity and clinically-defined asthma or COPD are well-established [1–7], these relationships are not close, and the biological relevance of airway hyperreactivity remains uncertain.

Epidemiological and clinical studies of the biological characteristics associated with hyperreactivity have demonstrated, with few exceptions, that airway reactivity is increased in atopic individuals [1, 7–12]. Hyperreactivity also has a complex cross-sectional association with age, being particularly common in infants and young children [13, 14], less frequent in later childhood and adolescence [9, 15], but then more prevalent in older adults [3, 4, 8, 16]. The prevalence of hyperreactivity is also influenced by smoking, although the effect of smoking is also dependent on age, such that most studies have shown hyperreactivity to be increased in older current smokers [4, 5, 7, 8, 11, 12, 17]; whilst in asymptomatic young smokers and in healthy working populations smoking is either unrelated to or associated with a decreased risk of hyperreactivity [3, 18–20]. Most studies have found no relationship between hyperreactivity and sex, but, of those in which a significant sex effect has been reported [6, 11, 17, 20, 21], most have found hyperreactivity to be more prevalent amongst females [6, 11, 20, 21].

However, these biological associations with hyperreactivity are all potentially confounded by airway calibre.

From first principles, it is expected that the effect of a bronchoconstrictor stimulus on airflow will be related to initial airway calibre [22], which is in turn related to age, sex, smoking and atopy. Up to the present time, virtually all cross-sectional studies of hyperreactivity which have included data on lung function have found that airway reactivity tends to be increased in relation to a low initial forced expiratory volume in one second ($FEV_1$), expressed either in absolute terms, in relation to predicted values (% pred), or relative to the forced vital capacity ($FEV_1$%FVC) [1, 3, 5, 6, 16, 17, 23–25]. Recent data from repeated measures of airway reactivity in subjects with asthma have also demonstrated that within subjects, airway reactivity is closely related to $FEV_1$ % pred [26]. Airway calibre is, therefore, a major potential confounder of the biological associations of airway hyperreactivity in the general population, but the extent of the independent effects of initial $FEV_1$ expressed in absolute terms, as % pred and as % FVC on the risk of hyperreactivity have not been determined and indeed few studies have had sufficient statistical power to do so.

In this paper, we present data collected on 2,415 adults, aged 18–70 yrs, sampled at random from a district of Nottingham, who were involved in a broader study of asthma aetiology. We have used these data to explore the independent effects of age, sex, smoking, atopy and initial lung function on the occurrence of airway hyperreactivity.

## Subjects and methods

### *Subjects*

Subjects were identified by systematic sampling from a random starting point in the electoral register of a Local Authority Area in Nottingham. From a total population of approximately 87,000 adults, we identified 7,106 names and wrote to each of these asking them to participate in the study. In the letter, we explained that subjects who were aged under 18 yrs or over 70 yrs on January 1st, 1991, were not eligible for the study. All others were asked to attend their local General Practice surgery or Health Centre for a questionnaire assessment and lung function tests. On attending for the study, subjects were interviewed by a doctor, who explained the protocol, ascertained any medical contraindication to methacholine challenge, and obtained written consent to the study. Subjects then completed a computer questionnaire on respiratory symptoms followed by measurement of spirometry, skin sensitivity to common allergens, and airway reactivity to methacholine. Subjects were asked to abstain from inhaled bronchodilators for 4 h prior to testing, and from oral bronchodilators for 8 h.

Subjects who did not respond to our letter, or who did not attend for assessment were sent a written reminder, and, if possible, were telephoned to establish the reason for not taking part. The names of those we were unable to contact were subsequently checked against local Health Authority records, and updated electoral registers and telephone listings, when these became available, to try to identify those who had moved away from the area. The study was completed between January and May 1991, and was approved by the Nottingham City Hospital and University Ethics committees.

## Methods

$FEV_1$ and FVC were measured after a minimum of 20 min rest after arrival using a dry bellows spirometer (Vitalograph, Buckingham, UK), taking the best of three technically satisfactory measurements. Allergen skin sensitivity was measured by skin prick testing to *Dermatophagoides pteronyssinus*, cat fur and grass pollen solutions, with saline and histamine controls (Bencard, UK); measuring each wheal as the mean of two right-angled diameters, one of which was the largest measurable diameter of the wheal, excluding pseudopods and flares. Airway reactivity to methacholine was measured by the method of YAN *et al.* [27], administering methacholine until $FEV_1$ had fallen by 20% or more from the post-saline value to determine the provocative dose ($PD_{20}$), or until a maximum cumulative dose of 12.25 μmol had been given. Doubling increments of dose from 0.048 μmol were administered to subjects with a past history of asthma or wheezing, and quadrupling increments from 0.096 μmol, changing to doubling increments if $FEV_1$ fell by 10% or more, in persons with no history of asthma or wheeze. $PD_{20}$ values were calculated by linear interpolation on a log dose-response plot. Methacholine was not given to subjects with a baseline $FEV_1$ less than 60% of their predicted value [28], or less than 1.5 *l*.

### *Analysis*

Subjects were categorized as reactive to methacholine if they had a $PD_{20}$ of ≤12.25 μmol. Atopy was expressed as the mean of the three allergen skin prick responses, each corrected for the control response by subtraction of the saline wheal diameter. For descriptive purposes, any individual with a mean skin wheal diameter at least 1 mm greater than the saline control was defined as atopic. Univariate descriptive analyses were carried out on a microcomputer using the SPSS-PC+ statistical package [29], and multiple logistic regression used to estimate the relative odds of reactor status in relation to age, sex, mean skin wheal diameter, smoking status and lung function, using the program EGRET [30].

## Results

Of the original sample of 7,106, we established that 1,586 were outside the specified age-range, or else had died or left the area. We were unable to establish contact with 1,035 individuals, who did not reply to our initial letter or subsequent two reminders, could not be contacted by telephone, but remained listed as living at the given address at the time of the study. Contact was

Table 1. – Number, sex, and atopic, smoking and reactor status of subjects by age

| | Age group | | | | | |
|---|---|---|---|---|---|---|
| | 18–29 yrs | 30–39 yrs | 40–49 yrs | 50–59 yrs | 60–70 yrs | Total |
| Subjects | 402 | 524 | 655 | 486 | 348 | 2415 |
| Females n (%) | 202 (50) | 273 (52) | 320 (49) | 245 (50) | 162 (47) | 1202 (50) |
| Atopics n (%) | 219 (55) | 263 (50) | 261 (40) | 194 (40) | 119 (34) | 1056 (44) |
| Lifetime nonsmokers n (%) | 279 (69) | 290 (55) | 295 (45) | 232 (48) | 129 (37) | 1225 (51) |
| Current smokers n (%) | 91 (23) | 110 (21) | 175 (27) | 103 (21) | 70 (20) | 549 (23) |
| Reactors n (%) | 51 (13) | 68 (13) | 73 (11) | 69 (14) | 53 (15) | 314 (13) |
| % female | 65 | 62 | 66 | 58 | 51 | 61 |

established with 4,485, of whom 1,841 declined to take part, and for whom no further information is available other than gender, where this can be deduced from the listed name. A total of 2,644 subjects, representing between 48–59% of those potentially eligible, attended for the study. There was no difference in the proportions of males and females amongst those who took part and those who did not. Methacholine challenge was contraindicated by a resting $FEV_1$ less than 60% predicted or less than 1.5 *l* in 102 subjects, by pregnancy or breastfeeding in 40, and by significant nonrespiratory illness in 36. Methacholine was refused by 51 subjects. Complete data on lung function, skin wheal responses and methacholine $PD_{20}$ were, therefore, available in 2,415 individuals, of whom 1,202 (50%) were female, 1,225 (51%) lifelong nonsmokers 549 (23%) current smokers, 1,056 (44%) had at least one positive skin test, and 314 (13%) reacted to methacholine. The proportion of females in the sample was unrelated to age, but the proportion of atopics and of lifelong nonsmokers decreased with age (table 1). The proportion of reactive individuals who were female declined with age, though not significantly so.

Multiple logistic regression of reactor status confirmed that without adjustment for initial $FEV_1$, the occurrence of airway hyperreactivity was independently increased in females, in current smokers, in older age groups, and in relation to mean allergen skin wheal diameter (table 2). There was no statistical evidence of multiplicative interaction between any of these variables. The relation with age was nonlinear, showing a significantly lower residual deviance when age was analysed as a categorical variable as in table 1, than as a continuous variable. Atopy was significantly more closely related when included as a continuous variable based on mean allergen skin wheal diameter than as a binary categorical index.

After allowing for the effects of sex, skin wheal diameter, age group and smoking, absolute baseline $FEV_1$, $FEV_1$ % predicted, and $FEV_1$%FVC were each significantly and independently associated with reactor status. Inclusion of these three variables improved the fit of the model substantially, reducing the residual deviance from 1,676 on 2,406 residual degrees of freedom to 1,369 on 2,403 degrees of freedom (Chi-square for reduction on 3 df=312; $p<<0.0001$). With these three variables included, the independent odds ratio for skin wheal diameter was virtually unchanged, the odds ratios for female sex and current smoking were reduced towards unity, and those for increasing age group reversed, such that increasing age was associated with a decreased, rather than increased risk of hyperreactivity (table 3). In this model, the effects of age, sex and smoking were no longer independently significant at the 5% level, though age group had a significant effect if entered without sex and smoking. Removal of sex, smoking and age group produced a model including only skin wheal diameter, $FEV_1$, $FEV_1$

Table 2. – Independent odds ratios, p-values and confidence intervals for the effects of sex, age group, smoking status and mean skin wheal diameter on the odds of reacting to methacholine

| | OR | p-value | 95% CI |
|---|---|---|---|
| Intercept† | 0.03 | | 0.02–0.05 |
| Females | 2.05 | <0.001 | 1.58–2.66 |
| Skin wheal diam. per mm | 1.39 | <0.001 | 1.32–1.47 |
| Age group: 30–39 yrs | 1.38 | <0.001* | 0.90–2.12 |
| 40–49 yrs | 1.36 | | 0.89–2.08 |
| 50–59 yrs | 2.15 | | 1.39–3.34 |
| 60–70 yrs | 2.70 | | 1.68–4.34 |
| Smoking: ex-smokers | 1.05 | <0.001* | 0.76–1.45 |
| current smokers | 1.89 | | 1.34–2.58 |

†: male, nonsmoker, skin test negative, age 18–29 yrs; *: p-value applies to the combined effects of all categories for categorized variables. OR: odds ratio; CI: confidence interval; diam: diameter.

Table 3. – Independent odds ratios, p-values and confidence intervals for the effects of sex, age group, smoking status, mean skin wheal diameter and baseline $FEV_1$, $FEV_1$ % predicted and $FEV_1$%FVC on the odds of reacting to methacholine

| | OR | p-value | 95% CI |
|---|---|---|---|
| Intercept† | 0.14 | | 0.06–0.32 |
| Females | 1.59 | 0.19 | 0.89–2.81 |
| Skin wheal diam. per mm | 1.40 | <0.001 | 1.32–1.48 |
| Age group: 30–39 yrs | 0.85 | 0.06* | 0.51–1.39 |
| 40–49 yrs | 0.49 | | 0.27–0.86 |
| 50–59 yrs | 0.48 | | 0.25–0.94 |
| 60–70 yrs | 0.38 | | 0.17–0.84 |
| Smoking: ex-smokers | 0.98 | 0.19* | 0.68–1.40 |
| current smokers | 1.34 | | 0.95–1.89 |
| $FEV_1$ per litre | 0.46 | 0.003 | 0.27–0.77 |
| $FEV_1$ per % pred | 0.96 | <0.001 | 0.94–0.98 |
| $FEV_1$ per % FVC | 0.92 | <0.001 | 0.90–0.94 |

†: Male, nonsmoker, skin test negative, age 18–29 yrs, $FEV_1$ 3 *l*, 100% pred and 75% FVC; *: p-value applies to combined effects of all categories for categorized variables. $FEV_1$: forced expiratory volume in one second; FVC: forced vital capacity; OR: odds ratio; CI: confidence interval.

Table 4. – Independent odds ratios, p-values and confidence intervals for the effects of mean skin wheal diameter and baseline $FEV_1$, $FEV_1$ % predicted and $FEV_1$%FVC on the odds of reacting to methacholine

| | OR | p-value | 95% CI |
|---|---|---|---|
| Intercept† | 0.10 | | 0.08–0.13 |
| Skin wheal diam. per mm | 1.43 | <0.001 | 1.35–1.52 |
| $FEV_1$ per litre | 0.47 | <0.001 | 0.37–0.59 |
| $FEV_1$ per % pred | 0.96 | <0.001 | 0.95–0.97 |
| $FEV_1$ per % FVC | 0.94 | <0.001 | 0.92–0.95 |

†: skin test negative, $FEV_1$ 3 *l*, 100% pred and 75% FVC. For abbreviations see legend to figure 3.

Table 5. – Independent odds ratios, p-values and confidence intervals for the effects of mean skin wheal diameter, baseline $FEV_1$, $FEV_1$ % predicted and $FEV_1$%FVC, and age on the odds of reacting to methacholine

| | OR | p-value | 95% CI |
|---|---|---|---|
| Intercept† | 0.25 | | 0.16–0.41 |
| Skin wheal diam. per mm | 1.39 | <0.001 | 1.31–1.48 |
| $FEV_1$ per litre | 0.33 | <0.001 | 0.25–0.43 |
| $FEV_1$ per % pred | 0.97 | <0.001 | 0.96–0.98 |
| $FEV_1$ per % FVC | 0.92 | <0.001 | 0.90–0.94 |
| Age group: 30–39 yrs | 0.76 | <0.001* | 0.47–1.22 |
| 40–49 yrs | 0.40 | | 0.24–0.67 |
| 50–59 yrs | 0.35 | | 0.20–0.61 |
| 60–70 yrs | 0.25 | | 0.13–0.46 |

†: skin test negative, $FEV_1$ 3 *l*, 100% pred and 75% FVC, age 18–29 yrs; *: p-value applies to effect of all categories of age group. For abbreviations see legend to table 3.

% predicted and $FEV_1$%FVC, in which the independent effect of each of these variables was strong and highly significant (total Chi-square on 4 df=470; $p<<0.001$, table 4), and virtually unaffected by reintroduction of age group into the model (table 5). Substitution of $FEV_1$ as a standardized residual adjusted for age, sex and height rather than as % predicted or % FVC did not improve the fit of the model.

A diagnosis of asthma confirmed by a doctor was reported by 191 (8%) of the sample. Exclusion of these individuals from the analysis had virtually no influence on the magnitude or significance of the independent effects listed in table 5. The results of the analysis presented in Table 5 were also not appreciably affected if restricted to either males or females.

## Discussion

This analysis was conducted to establish the relative importance and independent effects of age, sex, atopy, smoking and airway calibre on the occurrence of airway hyperreactivity in the general population. The sample size of 2,415 adults challenged with methacholine represents one of the largest samples reported in the literature to date. Although the precise participation rate is difficult to measure, because of inaccuracies in electoral and Health Authority records, our sample probably represents about 54% of the unselected target population, a participation rate which is low in absolute terms but which compares favourably with most previous studies of airway reactivity in general population samples. We are unable to assess our participation rate in relation to age, but there was no indication that either sex attended preferentially. There was some evidence that smokers tended not to take part, since the proportion of current smokers in our sample was 23%, which is 9% lower than the average for the East Midlands Region [31]. However, the overall prevalence of hyperreactivity in the sample of 13%, defined in terms of a $PD_{20}FEV_1$ of ≤12.25 µmol, is very similar to our previous estimates using a comparable level of stimulus with inhaled histamine or methacholine in random population samples [8, 32]. We chose to categorize individuals as reactive or not, rather than use a continuously distributed measure of airway reactivity, such as the dose-response slope, principally for ease of comparison with previous studies.

Before adjustment for airway calibre, our results for the effects of atopy, age and smoking on the prevalence of hyperreactivity were also broadly consistent with the findings of previous studies, showing, as expected, that the risk of hyperreactivity was increased in atopic subjects [1, 7–12], in current smokers [4, 5, 7, 8, 11, 12, 17], and to a lesser though significant extent, in the older age groups [3, 4, 8, 16]. The magnitude of the effect of atopy was lower than in many previous studies, though this is due in part to our analysis of atopy as a continuous rather than a binary variable. The adjusted odds ratio of 1.39, therefore, applies to the effect of atopy per millimeter skin wheal diameter, and since the average skin wheal diameter in atopic individuals was 2.75 ml, the mean increase in odds for atopy was, therefore, of the order of 3.8. Our finding of an approximately twofold increase in risk of hyperreactivity in women is slightly unusual, since the majority of previous studies have found no significant sex effect. However, of at least five studies in which a significant sex effect has been reported [6, 11, 17, 20, 21], four have reported similar results to ours [6, 11, 20, 21]. In contrast to our previous experience [8, 12], we found no statistical evidence of an interaction between the effects of atopy and age, or between smoking and age. In view of previous reports that the risk of hyperreactivity may be increased in a dose-dependent fashion in relation to the extent of current smoking [33, 34], we looked for, but found no evidence of, this relationship in our data.

The principal findings of our study were that atopy and baseline airway calibre were strongly and highly significantly associated with hyperreactivity, and that the independent effects of age, sex and smoking were confounded by, and were substantially less powerful predictors than, airway calibre. After adjustment for age, sex, atopy and smoking, baseline $FEV_1$ in absolute terms, as % predicted and as % FVC were all significantly and independently related to hyperreactivity. Inclusion of these variables in the model influenced the significance of the effects of sex, smoking and age, such that exclusion of any one of these variables no longer affected the fit of the model to a significant degree. If age, sex or smoking were added individually to a model comprising

atopy and the three $FEV_1$ indices, only age exerted a significant independent effect, but this was substantially different from that observed before adjustment for airway calibre, such that higher age became associated with a substantially lower, rather than higher risk of hyperreactivity. Whilst the effect of age in this model is not entirely independent because of the component of age in the $FEV_1$ % predicted variable, the implication is that normal sized airways in older individuals are relatively unlikely to be hyperreactive.

The odds ratios for female sex and current smoking were diminished by the adjustment for $FEV_1$ but remained greater than unity, suggesting that, although not significant in this study, these variables may have some biological influence independent from airway calibre, as has previously been suggested for current smoking [33, 34]. In contrast, however, the odds ratio for atopy was virtually constant in all models analysed, implying that the effect of atopy was fully independent of the other variables considered. Thus, the simplest model in which all independent variables were significantly related to hyperreactivity was that presented in table 5, and included atopy, $FEV_1$, $FEV_1$ % predicted, $FEV_1$%FVC, and age. The principal determinants of hyperreactivity in the general population at any age are, therefore, atopy and airway calibre.

The effect of airway calibre in our study is complex, as it includes independent components of increased risk from an $FEV_1$ which is low in absolute terms, or in relation to the predicted value for age, sex and height, or in relation to the FVC. This is the first time that independent effects from each of these three indices on the risk of hyperreactivity have been described. This finding may appear, at first sight, to be anomalous, since $FEV_1$, $FEV_1$ % predicted, and $FEV_1$%FVC would be expected to be closely correlated. However, the finding of independent effects on the risk of hyperreactivity by each of these indices of airway calibre is biologically plausible, since each index would be expected to identify, independently, a separate subgroup of individuals with increased risk of hyperreactivity. Subjects with normal but small airways are expected to be hyperreactive from first principles, since flow through the airway is dependent on the fourth power of the radius [22]. A given degree of circumferential shortening of airway smooth muscle will, therefore, cause greater obstruction to flow in relatively small airways, even if the airway is normal. Individuals with normal but small airways will be identified most directly from the absolute value of the $FEV_1$, since the $FEV_1$/FVC ratio in these circumstances should be normal, whilst the $FEV_1$ % predicted could be either low or high. However, subjects with diseased airways do not necessarily have an $FEV_1$ which is low in absolute terms, since large individuals may still have a high absolute $FEV_1$ despite their airway disease. Relative narrowing of airways in these circumstances, for example by mucosal oedema or smooth muscle hypertrophy, would be expected to amplify the response to an inhaled bronchoconstrictor and, thus, cause hyperreactivity. These subjects would be expected to have a low $FEV_1$ as % predicted or as % FVC, rather than a low absolute $FEV_1$. Finally, it is feasible for an individual with airway disease to have an $FEV_1$ which is low in relation to either the predicted value or the FVC, though not necessarily both, depending on the premorbid $FEV_1$ % predicted level and the extent to which the FVC is preserved. Collectively, therefore, the three indices of airflow may identify, with varying degrees of overlap, separate groups of individuals at increased risk of hyperreactivity. That these independent effects have not been described previously may be because investigators have not looked for them, or because previous studies may not have had sufficient statistical power to identify them.

That the effect of atopy was virtually independent of airway calibre in our study is, to an extent, inconsistent, since atopic individuals are more likely to have asthma and, therefore, airway narrowing. However, our finding is supported by similar evidence from at least one previous cross-sectional population study [1], and suggests that increasing atopy invokes an increasing risk of airway hyperreactivity, which is relatively unrelated to the effect of airway calibre. This would be biologically consistent with a sensitizing effect on the airway, the mechanism of which is unknown but might involve epithelial shedding or damage, permitting more rapid and direct access of inhaled bronchoconstrictors to the airway muscle, or release of endogenous bronchoconstrictor mediators in the airway, which prime airway smooth muscle to threshold levels of contractility, so that the effect of an inhaled bronchoconstrictor on airflow is then amplified. Whilst these effects would be expected to have at least some degree of influence on resting airway calibre, our data suggest that the contribution of airway calibre is, in fact, small compared with that of sensitization in the normal population. Independent effects of atopy and airway calibre are also consistent with evidence that patients with asthma are significantly more reactive for a given baseline $FEV_1$ than patients with COPD [35], since patients with asthma are more likely to be atopic. Our finding is also consistent with pharmacological evidence that beta-agonists, which combine mast cell stabilizing and other anti-allergic effects with airway smooth muscle relaxant activity, induce a greater degree of improvement in airway reactivity for a given degree of bronchodilatation than anticholinergic agents, which act more specifically as smooth muscle relaxants [36].

The practical relevance of our findings relate principally to the meaning and interpretation of measurements of airway reactivity in epidemiological studies. Enthusiasm for the use of these measurements arose principally from the need for an objective marker of the occurrence of asthma, encouraged by the apparently close association between hyperreactivity and asthma in selected clinical populations. Subsequent experience suggests that although hyperreactivity is undoubtedly a marker of respiratory morbidity, it is far from exclusive to asthma [37]. The findings of the present study suggest that in cross-sectional analysis, the occurrence of hyperreactivity reflects primarily the presence of either atopy, or airflow which is low in relative or absolute terms, or both.

Hyperreactivity is, therefore, expected to be associated with respiratory disease, but is unlikely to distinguish between clinical diagnoses and will inevitably be found in an appreciable proportion of normal individuals. This interpretation is consistent with the documented epidemiological associations of hyperreactivity with morbidity in the general population, and raises the question of whether reactivity measurement provides biological information of value over and above that contained in knowledge of atopy and maximal airflow.

***Acknowledgements:*** The authors thank the many general practitioners and Health Centre staff in Gedling for allowing access to their premises and facilities and for their good humour throughout the study, and the British Lung Foundation and the National Asthma Campaign for financial support.

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