

A general practice based survey of bronchial hyperresponsiveness and its relation to symptoms, sex, age, atopy, and smoking

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Abstract

The prevalence and associations of bronchial hyperresponsiveness were investigated in a general practice population. The sample was obtained by using every 12th patient on the practice age-sex register, replacing non-responders with corresponding age and sex matched individuals from up to two further 1 in 12 samples. The response rate was 43%; 366 patients were studied. Doubling concentrations of methacholine were given to a maximum of 32 mg/ml or until a 20% fall in forced expiratory volume in one second (FEV₁) occurred (provocation concentration, PC₂₀FEV₁). Bronchial hyperresponsiveness was defined arbitrarily as a PC₂₀FEV₁ of 2 mg/ml or less (or 11 µmol cumulative dose, PD₂₀FEV₁). The prevalence of bronchial hyperresponsiveness was 23%. Bronchial hyperresponsiveness was not associated with age but was more prevalent in women than men (31%: 13%). It was also more common in those who had ever wheezed (39%) and in those who had had an attack of rhinitis in the preceding month (45%, $p < 0.1$), in atopic individuals (30%), and in smokers (32%), but it was not associated with cough or dyspnoea. There was a positive correlation between PC₂₀FEV₁ and resting FEV₁ ($r = 0.288$) and a negative correlation between PC₂₀FEV₁ and mean daily peak flow variability ($r = -0.356$). Stepwise binary logistic regression analysis showed significant independent effects on PC₂₀FEV₁ for mean daily peak flow variability, gender, number of positive skin test responses, resting FEV₁, and mean histamine skin weal area, but no relation with smoking or mean allergen weal area. The prevalence of bronchial hyperresponsiveness was much higher than the prevalence of diagnosed asthma in the practice in 1984 (4.9%). Analysis of case notes of 169 individuals showed that those with bronchial hyperresponsiveness had not attended the practice more frequently for respiratory complaints during the previous five years.

The prevalence of increased bronchial responsiveness to agents such as histamine or methacholine is high in subjects with current

asthma,^{1,2} and bronchial hyperresponsiveness is considered by many to be a cardinal feature of asthma.^{3,4} It is not always found, however, in current symptomatic asthma,⁵ and it is not specific to asthma because it has been shown to occur in chronic airflow limitation,⁶ rhinitis,³ and upper respiratory tract infection,⁷ and also in symptomless individuals with normal lung function.⁸

Most investigators have shown an association between bronchial hyperresponsiveness and atopy⁹⁻¹² but non-atopic asthma is well recognised.¹³ The relation with smoking may vary with age.^{11,14,15} There is a relation between airflow limitation and bronchial hyperresponsiveness,¹⁶ though lung function may be normal in hyperresponsive subjects.

Several mechanisms have been proposed to explain the presence of bronchial hyperresponsiveness, including increased bulk and contractility of bronchial smooth muscle,⁴ mediator release from damaged respiratory epithelium,¹⁷ and imbalance between non-adrenergic inhibitory and non-cholinergic excitatory fibres.¹⁸

Bronchial responsiveness to methacholine or histamine is most commonly expressed in terms of the provocation concentration (PC₂₀) or provocation dose (PD₂₀) of an agent that provokes a 20% fall in forced expiratory volume in one second (FEV₁).³ The intensity of bronchial responsiveness appears to be unimodally distributed in the population.¹⁹⁻²¹

Population studies have shown a prevalence of bronchial hyperresponsiveness that varies from 10.3% to 24.5%,^{10-12,21,22} far in excess of the prevalence of asthma, and especially high in children.²² All studies show strong associations of bronchial hyperresponsiveness with atopy, smoking, and abnormal lung function. Several respiratory symptoms have also been shown to be associated, most commonly wheezing in the preceding 12 months^{10,22-25} but also cough,^{10,21} dyspnoea,^{10,21,24} nocturnal wheeze or dyspnoea,^{23,24} and the "bronchial irritability syndrome."²⁵

The various surveys have used different populations and different methods for bronchial challenge. Studies in children differ from others in that age cohorts are usually studied.^{22,23} Cross sectional studies of adult populations comprise a high proportion of middle aged volunteers, non-smokers, and women.^{11,24} The response rate is generally low for bronchial challenge testing (36-38%)^{1,23,24}; only the Busselton study¹⁰ and the university

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based studies by Cockcroft in younger subjects^{3,12,19} have had a higher response rate. Patients participating in a general health survey¹⁰ and university students are likely to be more motivated to attend. In these studies the proportion who returned a questionnaire was given but no information on non-responders was available.

Our study aimed to determine the associations of bronchial hyperresponsiveness in a representative sample from a local population and by using a general practice population to obtain information on both responders and non-responders to determine the validity of the sample. We used methacholine as the agonist as higher doses can be given without adverse effects and a wider range of bronchial responsiveness identified in the population.²⁶

Methods

All subjects were invited to attend the health centre, where the investigations were conducted from 1984 to 1986. The study was approved by the ethical committee at St Bartholomew's Hospital and informed consent was obtained from each individual.

MEASUREMENTS

A respiratory and smoking history was obtained by means of a computer administered questionnaire similar to that previously described.²²

Skinprick testing was performed with six common inhalant allergens, (Bencard, Brentford—house dust 150% weight to volume (w/v), *Dermatophagoides pteronyssinus* (1.2% w/v), B₂ grass pollen (2.5% w/v), *Aspergillus fumigatus* (5% w/v), cat fur (150% w/v), and dog hair (150% w/v) in addition to histamine (1 mg/ml) and saline control solutions. A skin test response was regarded as positive if the weal was 1 mm greater in diameter than that of the saline control. The number of positive skin test responses and the weal area were recorded.

FEV₁ was measured with a Vitalograph (Vitalograph, Maids Moreton, Buckingham) dry bellows spirometer. Inhalation tests were performed with methacholine chloride (Sigma Chemical Company Ltd, Poole). Subjects had to have an FEV₁ greater than 70% of the predicted value; those who had a history of ischaemic heart disease or were pregnant were excluded.

Methacholine challenge was performed with a De Vilbiss 646 nebuliser driven by compressed air at a flow rate of 6 litres a minute. Solutions were inhaled by tidal breathing for two minutes with the nose clipped. FEV₁ was measured at 30 seconds, 90 seconds, and three minutes after inhalation of each solution. FEV₁ was recorded as the best of two reproducible attempts. Subjects inhaled a control solution of phenol saline (0.4% phenol, 0.275% NaHCO₃, 0.5% NaCl) initially followed by increasing doubling concentrations of methacholine, from 0.06 to 32 mg/ml for those with symptoms and from 0.25 mg/ml to 32 mg/ml for those without symp-

toms. The test was terminated when FEV₁ had fallen by 20% from the lowest of the three values obtained after the control inhalation, or when the highest concentration of methacholine had been administered. FEV₁ was plotted non-cumulatively against the log concentration of methacholine administered to obtain the PC₂₀FEV₁ by interpolation.

Subjects were asked to record their peak flow twice daily (on rising and retiring) for 14 days, using a mini-Wright peak flow meters (Clement Clarke Ltd). Daily peak flow variability was calculated as the difference between the maximum and minimum peak flow values as a percentage of the maximum value.

Retrospective analysis of the general practice notes was carried out by a single observer (C J T) for the five year period June 1982 to June 1987 without knowledge of the subject's PC₂₀ value. Notes were analysed systematically for the number of attendances with the following complaints: upper respiratory tract—tonsillitis, sinusitis, hay fever or rhinitis, "upper respiratory tract infection"; lower respiratory tract—asthma, wheeze, cough, productive cough, or bronchitis.

SUBJECTS

The study was conducted in a four partner general practice in Kingston, Surrey, with a list size of approximately 8000 patients of whom approximately 6000 were aged between 18–75 years. The practice has a particular interest in asthma and atopy and keeps detailed notes. Initially three 1 in 12 systematic samples of all patients aged 18–75 were obtained from the practice age-sex register by taking every fourth card and allocating it systematically to one of three lists. By definition, the three lists were age and sex matched to within a year in age so that non-responders from the first 1 in 12 sample could be replaced by a substitute of the same sex and similar age. We anticipated a low response rate, particularly among young working men, and thus had to approach replacements to obtain a sample that represented the demography of the practice population.

Of the 473 patients selected initially, 47 had moved from the area at the time of the study and six were judged unsuitable to participate because they had carcinoma, severe psychiatric illness, or severe cardiovascular disease. Five with severe asthma requiring regular medication with inhaled or oral corticosteroids were excluded. Thus 415 people were written to and asked if they would be willing to take part in a study of "how the lungs work." It was emphasised in the letter that people who had no evidence of respiratory illness were required as much as people who had. Those who failed to reply to the first letter were sent two further letters.

Of the 240 people (58%) who replied, 179 (43%) agreed to take part in the study, though 21 of these failed to attend. Thus 158 (38%) of the original sample were seen. A further 619 letters were sent to people in the replacement groups, of whom 208 took part, giving an overall sample size of 366 and an overall response rate of 35%.

Table 1 Proportion of subjects studied by age group for the range 18–75 years

Age range	18–24	25–34	35–44	45–54	55–64	65–75	Total
Number studied	34	92	102	54	57	27	366
Total number in practice in this age range	754	1640	1498	767	659	606	5924
% studied	4.5	5.6	6.8	7.0	8.6	4.5	6.2

For the retrospective analysis of attendance with respiratory complaints 169 sets of notes were analysed, stratified for the results of bronchial provocation testing: *group 1*: 50 sets of notes for patients with a PC₂₀FEV₁ of up to 2 mg/ml (bronchial hyperresponsiveness); *group 2*: 51 sets of notes for patients with a PC₂₀FEV₁ above 2 and up to 32 mg/ml (“intermediate” bronchial responsiveness); *group 3*: 68 sets of notes for patients with a PC₂₀FEV₁ above 32 mg/ml (control group).

Notes were selected so far as possible on a 1 in 3 basis from the random list of patients studied, to avoid bias; but because more women had bronchial responsiveness we had to add men to groups 2 and 3 to maintain a constant sex ratio across the groups.

STATISTICAL ANALYSIS

The results were analysed with the χ^2 test for the differences between proportions, Spearman rank correlation, and the BMDPLR statistical package for binary logistic regression analysis (BMDP Statistical Software Inc, Los Angeles). For the purpose of this study we took an arbitrary PC₂₀FEV₁ value of 2 mg/ml or less (PC₂₀FEV₁ \leq 11 μ mol) to identify individuals with bronchial hyperresponsiveness. This is the range we have previously established in patients with asthma²⁷ (similar to that of Cockcroft *et al*¹²). Surgery attendances with respiratory complaints were analysed after

logarithmic transformation by analysis of variance for “upper” and “lower” respiratory tract complaints separately and in combination.

Results

The 366 subjects studied (158 men, 208 women) had an age range of 18–75 (mean 42) years. The age distribution of the sample is shown in table 1. There was a bias towards greater recruitment in the 40–60 year age group as we could not recruit matched replacements for 49 index individuals. The ratio of men to women reflected that in the whole practice (2650:3274 in 1984).

Methacholine challenge was carried out on 318 subjects. It was not performed in 48 subjects because of poor lung function (n = 11), ischaemic heart disease (n = 6), other cardiac disease (n = 2), pregnancy (n = 3), poor cooperation (n = 2), and refusal (n = 24).

Examination of case records showed that the prevalence of diagnosed hay fever or rhinitis and of asthma was slightly higher in the responders (28/366 and 12/366) than in the non-responders (21/647 and 11/647). This was significant for hay fever and rhinitis (7.6%: 3.2%, p < 0.05) but not for asthma (3.3%:1.7%).

RESPONSES TO THE QUESTIONNAIRE

A positive response was obtained from 32 subjects to the question “Have you at any time suffered from asthma?” (12 with symptoms in the last year), from 81 subjects to the question “Have you at any time suffered from attacks of wheezing of the chest?” from 196 people to the question “Have you at any time had attacks of coughing?” (though only 20 of these subjects said that they had regular attacks of coughing) and from 105 people to the question “Have you

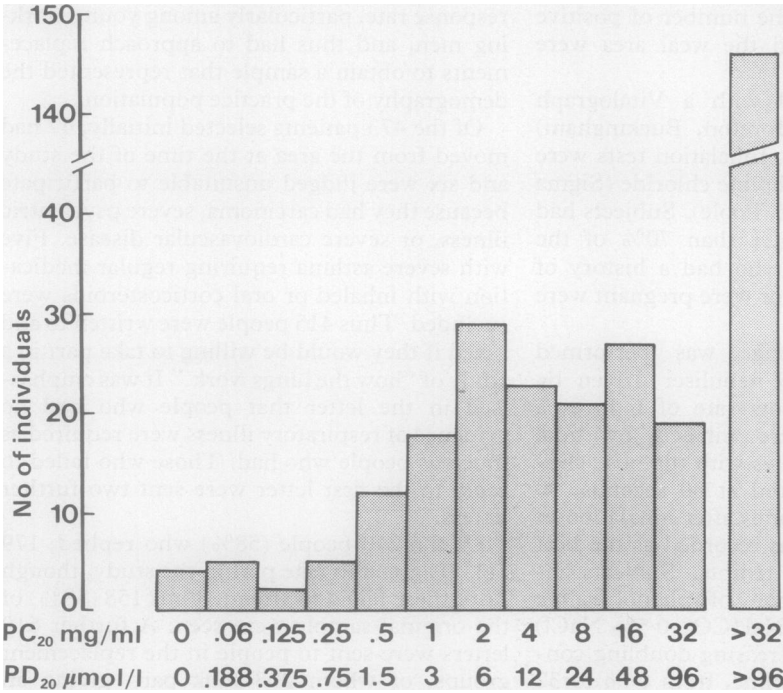


Figure 1 Distribution of bronchial responsiveness. To obtain a PD₂₀ value multiply PC₂₀ values by 3.

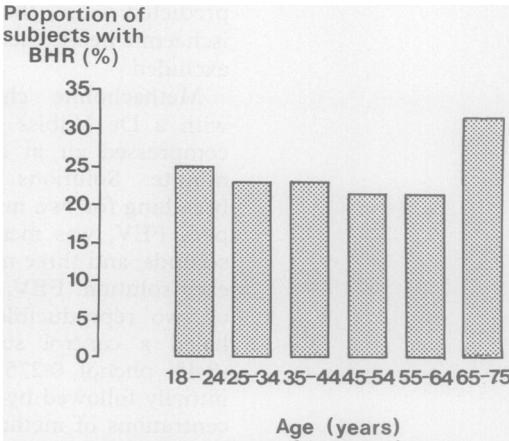


Figure 2 Proportion of subjects showing bronchial hyperresponsiveness (BHR) according to age.

Table 2 Relation between bronchial hyperresponsiveness (BHR) and asthma, rhinitis, smoking, and atopy: number of individuals with each characteristic, percentage with BHR, and significance of relationship*

	<i>Current</i>		<i>Past</i>		<i>Never</i>		<i>Significance (χ^2)</i>
	<i>No</i>	<i>% BHR</i>	<i>No</i>	<i>% BHR</i>	<i>No</i>	<i>% BHR</i>	
Asthma	11	73 (n = 8)	18	33 (n = 6)	280	20 (n = 57)	p < 0.01
Rhinitis	20	45 (n = 9)	64	25 (n = 16)	217	22 (n = 48)	0.1 > p > 0.05
Smoking	96	32 (n = 31)	76	21 (n = 16)	142	18 (n = 25)	p < 0.05
<i>Atopic</i>					<i>Non-atopic</i>		
<i>No</i> <i>% BHR</i>					<i>No</i> <i>% BHR</i>		
125 30 (n = 38)					193 17 (n = 33)		p < 0.01

*Data not available for asthma for nine patients, for rhinitis for 17 patients, and for smoking for 4 patients.

at any time suffered from attacks of shortness of breath?” (only 15 of whom said that their attacks were regular). Ten people said that they woke at night with attacks of dyspnoea and 10 woke at night with attacks of wheeze. Ninety seven subjects answered “yes” to the question “Have you ever suffered from rhinitis or hay fever?” (20 of whom had had such an attack within the past month).

There were 161 (44.5%) lifelong non-smokers, 105 (29%) current smokers, and 96 (26.5%) ex-smokers (that is, they had not smoked any tobacco for at least one month). Fifty one per cent of women and 37% of men had never smoked.

METHACHOLINE PC₂₀FEV₁ VALUES

Bronchial hyperresponsiveness (PC₂₀FEV₁ ≤ 2 mg/ml) was present in 74 subjects (23% of those tested). A 20% fall in FEV₁ was seen in 172 subjects (fig 1).

SKINPRICK TESTING

A response to at least one of the common allergens used was seen in 125 people (39%), who were therefore regarded as atopic.

RELATION BETWEEN SYMPTOMS, PC₂₀FEV₁, SEX, AGE, ATOPY, SMOKING, LUNG FUNCTION, AND CUTANEOUS HISTAMINE RESPONSE

Differences in the prevalence of bronchial hyperresponsiveness with age were not statistically significant (fig 2).

Bronchial hyperresponsiveness was more common in women (31%) than in men (13%; p < 0.001). Positive responses to the question “Have you ever suffered from attacks of wheezing of the chest?” were, however, almost evenly

Table 3 Binary logistic regression of independent variables on bronchial responsiveness (PC₂₀ FEV₁)

Term entered	Degrees of freedom	Log likelihood	Improvement (χ^2)	p
Peak flow variability	1	-82.820	14.832	0.0001
Sex	1	-77.391	10.859	0.001
No of positive skin test responses	1	-71.453	11.875	0.001
Baseline FEV ₁	1	-67.822	7.262	0.007
Histamine weal area	1	-65.875	3.895	0.048

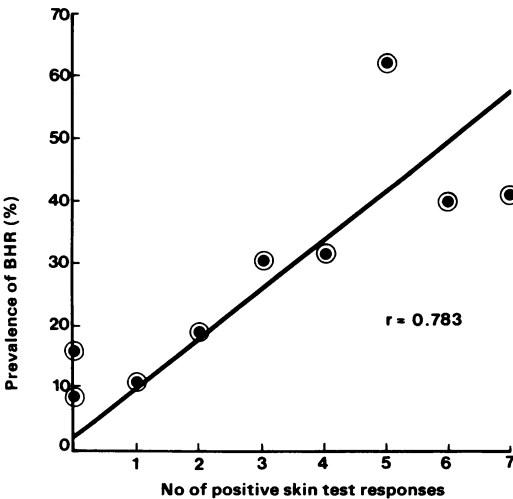


Figure 3 Relation between the number of positive skin test responses and bronchial hyperresponsiveness (BHR).

distributed between the sexes (31% of women and 27% of men). Atopy was slightly more common in men (43%) than in women (35%).

Bronchial hyperresponsiveness was more common in atopic individuals (30.5%) than non-atopic individuals (17%; p < 0.01—see table 2). There was a positive relation between the presence of bronchial hyperresponsiveness and the number of positive skin test responses (r = 0.78, p = < 0.05—see fig 3).

There was a weak but highly significant correlation between PC₂₀FEV₁ and baseline FEV₁ (r = 0.266, p < 0.001) and a negative correlation between PC₂₀FEV₁ and mean daily peak flow variability (r = -0.241, p < 0.001).

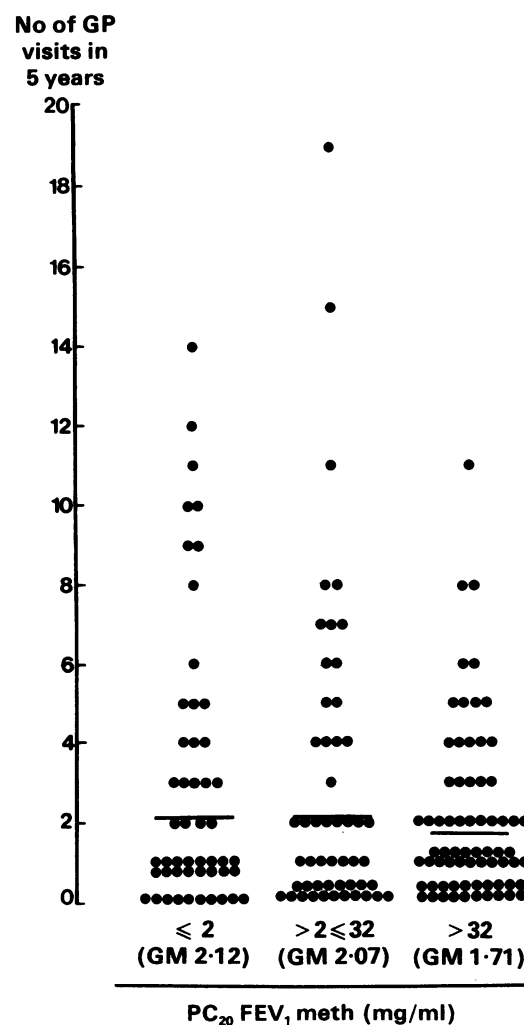
Bronchial hyperresponsiveness was more common in subjects who had experienced at least one attack of wheeze (38%) than in subjects who had never had wheeze (18%; p < 0.001), but was no more common in subjects who had had attacks of cough or dyspnoea than in those who had not (23% v 24%). Bronchial hyperresponsiveness was more common in subjects who had had an attack of rhinitis within the last month (table 2) and was present in 48% of subjects who had ever had an attack of asthma and 73% of subjects who had had an attack of asthma within the last year (table 2). It was present in 18% of non-smokers, 21% of ex-smokers, and 32% of current smokers (p < 0.05; table 2).

Stepwise binary logistic regression analysis of independent predictor variables on bronchial hyperresponsiveness showed significant and independent predictive effects for mean daily peak flow variability, sex, the number of positive skinprick test responses, baseline FEV₁, and histamine weal area (table 3). There was no significant independent effect for mean allergen weal diameter or for smoking.

RETROSPECTIVE ANALYSIS OF ATTENDANCE WITH RESPIRATORY COMPLAINTS

There was no significant difference in numbers of attendances for upper or lower respiratory complaints between the three groups of patients (fig 4). The subjects' characteristics are shown in table 4. The ratio of women to

Figure 4 Number of visits to the general practitioner with respiratory symptoms from June 1982 to June 1987, according to bronchial responsiveness ($PC_{20}FEV_1$, methacholine). GM—geometric mean.



men was 2.4:1, similar to that of the group with bronchial hyperresponsiveness.

Discussion

In this study of a systematic 1:12 sample of a general practice population we aimed to recruit a representative sample of the local population to determine the prevalence and associations of bronchial hyperresponsiveness. Several other community studies have been published since this study started.^{10 11 20-23} Our study differs in the technique of recruitment, the availability of information on non-responders, and the area of study.

The sample shows some bias towards recruitment of individuals from the 40-60 year age group, who tend to volunteer more frequently for studies^{11 24} (table 1). Using replacements for non-responders has minimised but not eliminated this bias because we could not obtain matched replacements for

non-responders from the three lists in all cases—for 49/415 of the initial sample (12%) no replacement was found. The ratio of men to women (about 3:4), however, reflects that in the practice (2650:3274 in 1984).

Study of case records on non-responders confirmed the tendency for symptomatic individuals to attend for tests. The prevalence of current asthma, however, was similar to that in the practice. During 1984, all attenders at the surgery (85% of the practice population attend for some complaint at least once a year) were asked if they had symptoms of asthma in the preceding year as part of a continuous survey²⁷ and the prevalence of current asthma was 4.9% in the age range 18-75, compared with about 4.6% (17/371) in the volunteers (including the five with severe asthma). Although the prevalence among non-responders was lower, the non-responders included multiple replacements for some index individuals and therefore did not represent the practice population. The response rate of 35% was low but similar to that of other studies.^{11 24 25}

The prevalence of bronchial hyperresponsiveness was 23%, on the basis of an arbitrary cut off point of a 2 mg/ml concentration (11 μ mol cumulative dose) of methacholine. The distribution of bronchial responsiveness appeared to be unimodal in the sample. The highest prevalence recorded in other community surveys of adults was 14%, with a cut off point of 8 μ mol histamine and the Yan technique.¹¹ Aerosol characteristics and deposition vary among the different techniques and some techniques are not directly comparable with others.²⁰⁻²² Studies have shown, however that the PD₂₀FEV₁ (dose delivered to the mouth) is comparable between the method of Chai²⁸ and both the tidal breathing method used in this study²⁹ and the Yan technique.³⁰ Higher prevalences of bronchial hyperresponsiveness are recorded in children (23%) and Australian college students³¹ (35%), probably reflecting the age groups studied. The tendency for symptomatic individuals to attend and the practice interest in asthma and atopy may have contributed to the higher prevalence in our sample.

Patients with bronchial hyperresponsiveness might be expected to attend the general practitioner more frequently with respiratory complaints. We were somewhat surprised that this did not appear to be the case, particularly as one fifth of those with bronchial hyperresponsiveness were known to have asthma and the proportions of smokers and of those with rhinitis were also greater in this group. The median attendance of all patients was low, however, with only one to two visits for respiratory complaints in five years, which may reflect a well educated or stoical population who do not attend for minor ailments.

Ten of the 11 subjects with current asthma were women and this may reflect a greater tendency for symptomatic women to attend. Bronchial hyperresponsiveness was more common in women even when those with known asthma were excluded. There was no excess prevalence of wheeze, atopy, or smoking

Table 4 Subjects' characteristics: analysis of attendances with respiratory complaints: number (%) with each characteristic for the three groups of PC₂₀ FEV₁ range

PC ₂₀ FEV ₁ (mg/ml)	Total	Smoking	Rhinitis	Asthma	Positive skin responses	Mean age (y)
≤ 2	50	20 (40)	16 (36)	10 (20)	26 (52)	44.0
> 2, ≤ 32	51	17 (34)	10 (20)	4 (8)	21 (41)	46.0
> 32	68	13 (22)	10 (17)	0	32 (47)	46.8

among the women and female gender was significantly and independently associated with bronchial hyperresponsiveness according to stepwise binary logistic regression analysis. Thus the sex difference is likely to be real. Other community studies have not found a similar sex difference.^{10 11 21} As there is an excess of women with asthma in this practice the finding may be specific to the local population. Some surveys of asthma have shown an increased prevalence of asthma^{32 33} and asthma mortality^{34 35} in women.

Eight of the 11 subjects with current asthma had bronchial hyperresponsiveness whereas three did not. A higher cut off point for PD₂₀FEV₁ would include more true positives but also more false positives³⁶ given that bronchial responsiveness appears to be unimodally distributed in the population.^{19-21 37} Where patients with clearcut asthma are studied the range of values for bronchial hyperresponsiveness clearly differs from that of non-asthmatic subjects.^{3 38} Subjects with less clearly defined symptoms show a wider range of PD₂₀FEV₁.^{37 39} Case histories of the three subjects are not available as they have moved from the practice; they may have had less clearly defined symptoms or seasonal asthma, in which levels of bronchial responsiveness are known to fluctuate.⁴⁰

Of the 74 subjects with bronchial hyperresponsiveness, 63 did not admit to having current asthma. There was a strong association between bronchial hyperresponsiveness and the symptom of wheezing, though 33 subjects had never wheezed. Symptoms of cough and dyspnoea were not associated with bronchial hyperresponsiveness and this was not a function of sample size (fig 3). This may be because cough and dyspnoea are less closely associated with airway narrowing. Dyspnoea, however, has been shown to be a predictor for bronchial hyperresponsiveness when the sample is weighted towards a high proportion of symptomatic individuals.²⁴

Of those with rhinitis in the preceding month, 45% had bronchial hyperresponsiveness but only 20 individuals were affected and the association did not reach significance. Allergen exposure is known to increase bronchial responsiveness in sensitised individuals⁴⁰ and this may explain the greater prevalence of bronchial hyperresponsiveness among those with greater numbers of positive skin test responses.

As in other studies, bronchial hyperresponsiveness was more prevalent in smokers and individuals with a low FEV₁.^{10 11} Smoking was not a significant independent predictor for bronchial hyperresponsiveness when stepwise binary logistic regression was carried out, which suggests that the interrelation with low FEV₁ was a stronger influence. Because of the relatively few individuals in the older age groups we could not look for the interaction of smoking and age with bronchial responsiveness found by Burney and coworkers.¹¹ Peak flow variability was correlated with bronchial responsiveness despite the small numbers with known asthma. The association was indepen-

dent of other factors. Peak flow variability appeared to have a continuous distribution similar to that of bronchial hyperresponsiveness, and the degree of variability seen in asthma⁴¹ is one end of the spectrum.

In summary, the prevalence of bronchial hyperresponsiveness far exceeded that of asthma in this general practice population sample. The phenomenon appeared to be multifactorial in origin with independently significant associations with mean daily peak flow variability, female gender, atopy, resting FEV₁, and histamine wheal area. Despite the associations with asthma and wheezing, some individuals with bronchial hyperresponsiveness were apparently asymptomatic, and overall attendance at the surgery with respiratory complaints was not significantly increased.

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