

# Factors affecting peak expiratory flow variability and bronchial reactivity in a random population sample

Bernard G Higgins, John R Britton, Susan Chinn, Kam Kwong Lai, Peter G J Burney, Anne E Tattersfield

## Abstract

**Background**—Bronchial reactivity measurements are widely used in epidemiological studies to provide an objective marker of asthma. There are, however, several potential advantages of measuring peak expiratory flow (PEF) variability instead, particularly in large studies. PEF variability and bronchial reactivity were compared in a population sample to assess the relationships of the two measurements to factors known to be associated with airways disease, and to compare their response rates.

**Methods**—Subjects aged 18–65 were randomly selected from the electoral register of an administrative area in eastern England and randomised to attend either for a bronchial challenge test measuring the provocative dose of methacholine producing a 20% fall in FEV<sub>1</sub> (PD<sub>20</sub>), or to measure PEF at two hourly intervals during waking hours for one week. Skin tests with common allergens were performed and a smoking history obtained. PEF variability was expressed as the amplitude % mean (highest – lowest × 100/mean).

**Results**—A total of 273 subjects (69%) collected a PEF meter but a completed record sheet was returned by only 247 (62%); this was still significantly more than the 202 subjects (54%) who attended for and successfully completed a challenge test. Amplitude % mean was higher in women than in men (9.7% v 8.5%). In multiple regression analysis amplitude % mean increased significantly with age, mean skin weal diameter, and with current smoking. The odds of having a PD<sub>20</sub> below 24.5 μmol increased with mean skin weal diameter and were greater in current smokers. Neither age nor sex had a significant effect on bronchial reactivity but there were significant interactions between age and the effects of both smoking and atopy.

**Conclusions**—The higher response rate associated with the use of PEF variability measurement, and the association with factors implicated in the pathogenesis of airways disease, suggest that PEF variability would be a useful measurement to employ in epidemiological studies.

The inclusion of an objective measurement of bronchial reactivity in epidemiological investigations of asthma overcomes some of the problems of identifying asthma in the community and enables comparisons to be made between studies performed in different countries. It has become clear, however, that bronchial reactivity does not have as precise a relationship to the clinical diagnosis of asthma as was originally thought.<sup>1–5</sup> There are, in addition, several practical problems associated with the measurement of bronchial reactivity in the community, including the invasive nature of challenge tests, the necessity of having a doctor present during the test, and the difficulties of obtaining a conventional measurement of reactivity such as the provocative dose of methacholine producing a 20% fall in FEV<sub>1</sub> (PD<sub>20</sub>) in most subjects in a random population sample when dosage of bronchoconstrictor agents is limited by side effects.

We have explored the use of serial peak expiratory flow (PEF) recordings to try to circumvent some of these problems. In addition to the practical benefits, this method has the advantage of measuring directly the diurnal variability of airway calibre which is a cardinal feature of asthma. We have shown that collection of PEF recordings from previously untrained subjects is feasible, and that the data can be analysed to provide a numerical index of PEF variability which shows the expected relationship to the diagnosis of asthma.<sup>6</sup> Although these findings suggest that the use of PEF variability might be an alternative to measurement of bronchial reactivity for community surveys of asthma prevalence, there are several unanswered questions. Our earlier study was performed in a small random sample together with a group of subjects selected because of respiratory symptoms, and did not permit an adequate consideration of the association of PEF variability with such factors as atopy and smoking. These associations are important since the value of PEF variability as an epidemiological tool would be questionable if it showed no relationship to factors implicated in the development and clinical diagnosis of airways disease. Furthermore, the possibility that measurement of PEF variability would be more acceptable to subjects in a community setting, and thereby achieve higher response rates, has not been explored.

We have therefore measured PEF

Respiratory Medicine Unit, City Hospital, Nottingham  
B G Higgins  
J R Britton  
A E Tattersfield

Department of Public Health Medicine, UMDS, St Thomas' Campus, London  
S Chinn  
K K Lai  
P G J Burney

Reprint requests to:  
Dr B G Higgins,  
Freeman Hospital,  
Newcastle upon Tyne  
NE7 7DN, UK

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variability and bronchial reactivity in a random sample of the population aged 18–65 from a semirural area in eastern England. Our aims were to compare the response rates of the two methods in conditions which imposed the kind of logistic difficulties that would be encountered in a major epidemiological study, to define the relationship between PEF variability and atopy and smoking in a random population sample, and to compare this with the relationship between bronchial reactivity and the same factors.

## Methods

### SUBJECTS

The study was conducted in South Kesteven, an electoral district in Lincolnshire covering an area of 364 square miles. The population of 99 653 (established 1984) is divided between three towns and numerous villages. A random start systematic sample of 1100 names was drawn from the electoral register of the area and randomised into two groups, one to undergo bronchial challenge testing with methacholine and the other to keep a record of serial PEF measurements.

Subjects were sent a letter explaining the purpose of the study and asking them to keep an appointment for a challenge test or to collect a peak flow meter. A prepaid envelope and a reply slip were enclosed with the initial letter and the subjects were asked to inform us whether or not they would participate. The letter explained that we only wished to test those aged 65 or under, and older subjects were asked to indicate on the reply slip if they would not attend for reasons of age. A second letter containing the same information was sent to all non-responders three weeks after the first approach. Tests were conducted at several health centres throughout the area to reduce the travel required and, if necessary, subjects were visited at home. Attempts were made to contact all subjects who did not reply to either letter by visiting their address and, if possible, the test was rearranged at this time.

Approval for the study was obtained from the ethics committees of Nottingham City Hospital, South Lincolnshire Health Authority, and the South Lincolnshire General Practitioner Committee.

### QUESTIONNAIRE

Information on respiratory symptoms, smoking history, age, and sex was obtained from all subjects using the bronchial symptoms

Table 1 Response in the sample drawn from electoral register

	Challenge test group	PEF group
Ineligible	170	158
Refused	145	103
Moved within area: not traced	9	6
Not accounted for	11	12
Attended for test	212	273
Total	547	552

Table 2 Distribution of sex, age, atopy, and smoking history among the subjects with complete data for all parameters

	Challenge test group	PEF group
Sex		
Men	85 (50%)	104 (48%)
Women	86 (50%)	114 (52%)
Age median (range)	39 (18–64)	41 (18–64)
Atopy		
Atopic*	60 (35%)	80 (37%)
Non-atopic*	111 (65%)	138 (63%)
Smoking		
Non-smoker	75 (44%)	107 (49%)
Ex-smoker	33 (19%)	42 (19%)
Current smoker	63 (37%)	69 (32%)

\*Atopic—any skin weal  $\geq 2$  mm greater than saline weal; non-atopic—no skin weal  $\geq 2$  mm greater than saline weal.

questionnaire of the International Union Against Tuberculosis (IUAT). This was completed before performing bronchial challenge tests or starting peak flow recordings.

### BRONCHIAL CHALLENGE TESTS

The initial letter to the subjects included a request to abstain from cigarettes and bronchodilators for six hours before attending the test centre. On arrival the subjects rested while informed consent was obtained, the questionnaire completed, and skin tests performed. Recordings of forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) were then made with a dry bellows spirometer (Vitalograph, Buckingham, UK) until two successive FEV<sub>1</sub> measurements were within 5% of each other, the highest of these being taken as the baseline reading. Subjects were excluded from challenge testing if their baseline FEV<sub>1</sub> was less than 60% predicted, if the FEV<sub>1</sub>/FVC ratio was less than 50%, if they had recently experienced a serious illness, or if they were pregnant.

Bronchial challenge tests were performed by the method of Yan *et al* using methacholine inhaled from De Vilbiss No 40 nebulisers which had all been shown by prior testing to have an output in the range 0.0025–0.0035 ml per activation. After completing baseline spirometry subjects inhaled normal saline followed by increasing concentrations of methacholine with measurement of FEV<sub>1</sub> one minute after each dose, always recording the highest of two readings within 5% of each other. Quadrupling increments of methacholine from a starting dose of 0.096  $\mu$ mol were then given until the FEV<sub>1</sub> fell by 10–19% when the test continued with doubling increments. For subjects with a history suggestive of asthma the starting dose was 0.048  $\mu$ mol and doubling increments were used throughout. The test ended when the FEV<sub>1</sub> had fallen by 20% or more, or a cumulative dose of 12.25  $\mu$ mol methacholine had been given.

### PEAK FLOW RECORDINGS

On arrival subjects completed the questionnaire and skin tests were performed. Subjects were then shown how to use a mini Wright

Table 3 Relationship between PEF variability and skin weal diameter, age, sex, and smoking history. Regression coefficients for amplitude % mean and absolute amplitude are for log<sub>10</sub> transformed values; coefficients for mean PEF values are untransformed

	Mean (SE) multiple regression coefficients		
	Amplitude % mean	Absolute amplitude	Mean PEF
Non-atopic non-smoking male aged 18	0.781 (0.058)	1.616 (0.050)	657.0 (19.7)
Addition per mm increase in mean skin weal diameter	0.026 (0.011)**	0.019 (0.009)*	-8.5 (3.7)*
Addition per year of age	0.002 (0.001)*	†	-2.2 (0.4)***
Difference if:			
Female	0.084 (0.033)**	-0.039 (0.027)	-137.4 (10.8)***
Ex-smoker	-0.052 (0.041) }*	-0.035 (0.035)	18.6 (13.9)
Current smoker	0.059 (0.036) }	0.054 (0.031)	-10.3 (12.3)

\*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001; †coefficient negligible.

peak flow meter and how to fill in a purpose designed record sheet with spaces for recordings at two hourly intervals throughout the day, commencing at 02:00 hours. They were asked to record their PEF within 15 minutes of the times shown every day for a week during waking hours. It was emphasised that spaces should be left blank rather than insert inaccurate data if a measurement was missed.

Subjects were asked to return the meter and completed record sheet by post and were given a strong stamped addressed envelope for this purpose. If the meter was not returned by post subjects were visited at home.

SKIN TESTS

Skin prick tests were performed on the ventral aspect of the forearm using *Dermatophagoides pteronysinus*, grass pollen, and cat dander as test reagents with histamine and saline as controls. Skin weal size was measured after 10 minutes as the mean of the largest diameter and that at right angles to it, excluding any pseudopodial outgrowths.

ANALYSIS OF RESULTS

The results of the challenge tests were analysed by a curve fitting method<sup>8</sup> to determine the methacholine PD<sub>20</sub>. Extrapolation of the curve to one doubling dose above the maximum dose administered—that is, to 24.5 μmol—was carried out if the FEV<sub>1</sub> had not

fallen by 20% after the maximum dose of methacholine.

Peak flow records were first scrutinised to detect possible falsification of results. The variability of PEF in each subject was then determined as amplitude % mean<sup>6</sup>:

$$\frac{\text{highest PEF reading} - \text{lowest}}{\text{mean}} \times 100$$

To calculate the response rates, subjects aged over 65, those who had left the electoral district, and those who had died since the electoral register was compiled were excluded from analysis. Subjects who were ill or could not be traced were counted as non-responders. Numbers responding for each survey method were compared by the χ<sup>2</sup> test.

Smoking history was determined from two questions, one asking if subjects had ever smoked on a daily basis for at least a year, and the second if they had smoked at all in the last month. Subjects answering both questions affirmatively were classified as current smokers, those answering both negatively as non-smokers, and those who had had no cigarettes in the last month but had smoked for a year or more in the past were classified as ex-smokers.

The mean skin weal diameter of each subject was calculated by subtracting the saline control value from each of the house dust, grass, and cat weal diameters, and taking the mean of these three values.

The relationship between amplitude % mean and age, sex, mean skin weal diameter, and smoking history was determined by multiple linear regression with amplitude % mean as the dependent variable. Sex and smoking were entered as categorical factors using three levels of smoking representing current, ex-smokers, and non-smokers. Identical analyses were performed with the two components of amplitude % mean, amplitude and mean PEF as dependent variables. A similar analysis was performed for the results of bronchial challenge tests but in this case multiple logistic regression was used with reactor status as the categorical dependent variable, a reactor being defined as a subject with a PD<sub>20</sub> value below 24.5 μmol. The interactions between age and both atopy and smoking were tested for significance. The effect of controlling for baseline FEV<sub>1</sub> on the relationship between bronchial reactivity and

Table 4 Effects of skin weal size, age, sex, and smoking history on the odds of having a PD<sub>20</sub> methacholine <24.5 μmol. Coefficients are for log<sub>e</sub> (odds). Significance levels based on difference in deviance compared with χ<sup>2</sup> distribution. Age coefficients for current and ex-smokers are for difference compared with non-smokers

Factor	Estimate (SE)	
Non-atopic non-smoking male aged 18	-3.46 (1.68)	
Addition per mm increase in mean skin weal diameter	1.48 (0.52)**	
Difference if:		
Female	-0.13 (0.43)	
Ex-smoker	5.67 (3.00) }***	
Current smoker	4.53 (1.70) }	
Addition with age (per year):	0.06 (0.03)	
in ex-smokers	-0.15 (0.08) }	Smoking/age interaction
in current smokers	-0.08 (0.04) }	
Interaction between age and skin weal diameter	-0.03 (0.01)*	

\*p < 0.05; \*\*p < 0.01.

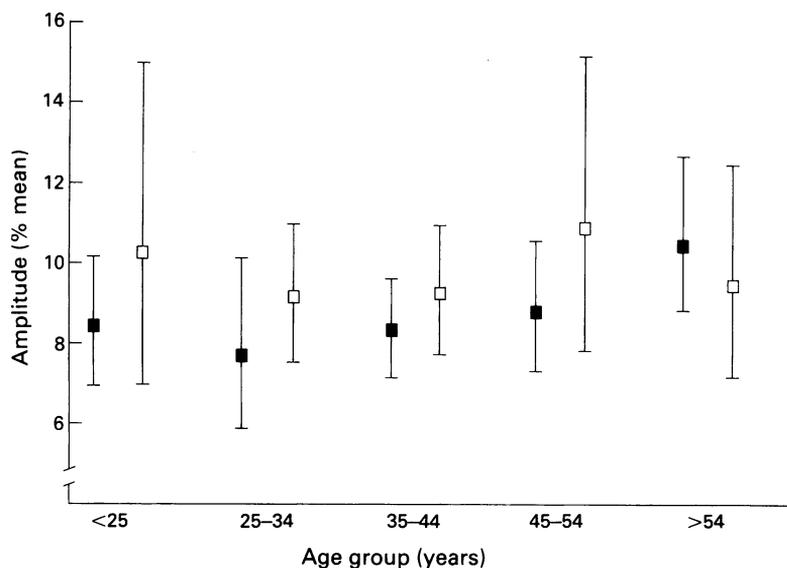


Figure 1 Mean (95% confidence intervals) amplitude % mean by mean skin weal size and age group. Atopic subjects (□) are those with one or more skin weals  $\geq 2$  mm; non-atopic subjects (■) are those with all skin weals  $< 2$  mm.

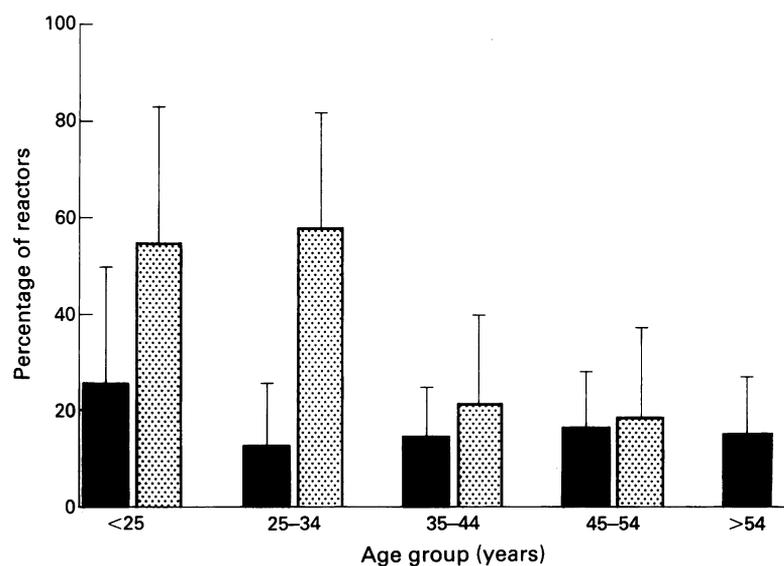


Figure 2 Percentage of reactors ( $PD_{20} < 24.5 \mu\text{mol}$ ) with 95% confidence limits by age and atopy status. Atopic subjects (▨) are those with one or more skin weals  $\geq 2$  mm; non-atopic subjects (■) are those with all skin weals  $< 2$  mm. The atopic subject group  $> 54$  years is not shown since it contains only three subjects.

smoking was determined.  $\log_{10}$  transformed values of amplitude % mean and  $PD_{20}$  were used throughout. The regression analyses were performed using the statistical program GLIM.

## Results

### RESPONSE RATES

After exclusion of subjects aged over 65 and those who had moved outside the area or died since the electoral register was constructed, 377 subjects were eligible for a bronchial challenge test and 394 for measurement of PEF variability. A total of 212 subjects (56.2%) attended for challenge tests, and 273 subjects (69.3%) accepted a PEF meter (table 1). However, 26 subjects failed to return an adequate PEF record so that

only 247 (62.3%) could be analysed. Challenge tests could not be performed in 10 cases because of low  $FEV_1$  ( $n = 8$ ) or poor spirometric technique ( $n = 2$ ) leaving 202 (53.6%) completed tests. The difference between response rates (62.3% *v* 53.6%) is significant (difference = 8.7%; 95% confidence interval = 8.1%;  $p < 0.05$ ).

Incomplete questionnaires, skin test-refusal, or unsatisfactory skin tests excluded data from a further 29 subjects from the full regression analysis for PEF variability and 31 subjects from the full analysis of bronchial reactivity. The age, sex, and smoking characteristics of the subjects included in the analysis are given with their atopic status in table 2.

### COMPLETENESS OF PEF DATA

For each available two hourly time point a total of 1729 PEF readings was possible—that is, seven days in each of 247 subjects. At all times from 08:00 to 22:00 hours inclusive the number of measurements recorded was between 72% and 80% of the possible total. The percentage fell to 21% at 06:00 and 15% at midnight. Few measurements were made at 02:00 or 04:00 hours.

### RELATIONSHIP OF PEF VARIABILITY TO AGE, SEX, ATOPY, AND SMOKING HISTORY

Amplitude % mean was higher in women than in men (9.7% *v* 8.5%,  $p < 0.05$ ) and this was the only factor which had a significant effect on PEF variability when considered alone. In multiple regression analysis, after controlling for sex, amplitude % mean showed a significant increase with increasing age, was lower in ex-smokers and higher in current smokers than in non-smokers, and increased with increasing mean skin weal diameter (table 3). There was no interaction between age and smoking nor between age and atopy (fig 1).

The differences in amplitude % mean seen with smoking and atopy were produced by changes in both absolute amplitude and mean PEF. Absolute amplitude increased with skin weal diameter and was higher in current smokers: mean PEF showed the converse changes (table 3). In contrast, both absolute amplitude and mean PEF were lower in women and mean PEF decreased with age; the changes in mean PEF with age and sex were greater than those in absolute amplitude, accounting for the increase in amplitude % mean with age and female sex.

### RELATIONSHIP OF BRONCHIAL REACTIVITY TO AGE, SEX, ATOPY, AND SMOKING HISTORY

A total of 45 subjects (22.3%) had a  $PD_{20}$  methacholine  $< 24.5 \mu\text{mol}$ . The odds were significantly greater in current smokers and with increasing skin weal diameter (table 4). Allowance for baseline  $FEV_1$  made little difference to the effect of smoking. Age and sex did not significantly alter the odds of having a  $PD_{20}$  below  $24.5 \mu\text{mol}$ . There was, however, a significant interaction between age and atopy (as defined by their product) with a

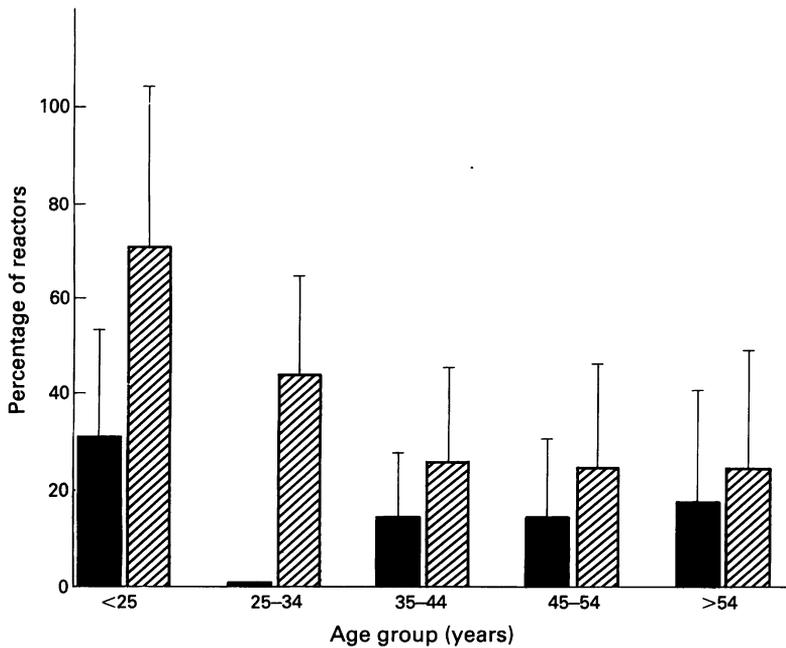


Figure 3 Percentage of reactors ( $PD_{20} < 24.5 \mu\text{mol}$ ), with 95% confidence limits, by age and smoking history. Current smokers (▨) and non-smokers (■) are shown; there were few ex-smokers in the younger age groups and they are omitted.

decline in the effects of atopy with increasing age (table 4, fig 2), and between smoking and age, the increased reactivity in current smokers being less pronounced with age (table 4, fig 3).

### Discussion

The associations of bronchial reactivity with smoking and atopy have been reported previously, but this is the first time that the relations of these factors to PEF variability have been studied in randomly selected subjects. Although bronchial reactivity and PEF variability are both measures of airway lability, they are obtained in different ways and are likely to reflect different aspects of airway behaviour. The results from this study in randomly selected subjects, however, show that both measurements vary with factors known to be associated with airways disease. The strength of the associations of the two measurements with these factors cannot be compared since the measurements were not made in identical subject groups.

Amplitude % mean was positively associated with mean skin weal diameter, the increase with increasing weal diameter being produced by complementary changes in absolute amplitude (increase) and mean PEF (decrease). The difference is present in all age groups except those aged > 54 years (fig 2). Atopic status is one of the major risk factors for the development of asthma and any proposed measure of airway lability would be expected to show a relationship to atopy. Such an association might also be expected on the basis of the changes which occur when allergen challenge is carried out under controlled laboratory conditions<sup>9-11</sup>: airway calibre falls as an immediate response to allergen

challenge followed several hours later by an increase in bronchial reactivity. Natural exposure of atopic asthmatic subjects to allergen would thus be expected to lower PEF readings directly and to increase the susceptibility to bronchoconstrict when exposed to other stimuli, leading to increased PEF variability.

The odds of having a methacholine  $PD_{20}$  below  $24.5 \mu\text{mol}$  also increased as skin weal diameter increased. Several previous surveys have shown a relationship between atopic status and bronchial hyperreactivity.<sup>12-17</sup> Seasonal variation in bronchial reactivity has been found in wheat workers<sup>18</sup> and in a community population selected because of occasional wheeze,<sup>19</sup> and these changes are assumed to be related to seasonal changes in allergen levels. In the laboratory allergen challenge can produce an increase in bronchial reactivity<sup>9-11</sup> and the airway response to allergen can be predicted from a prior knowledge of the histamine  $PD_{20}$ .<sup>20-23</sup> We also found, as in a previous study,<sup>13</sup> an interaction between age and atopy with a significant reduction in the proportion of atopic subjects with measurable  $PD_{20}$  values with increasing age.

Current smokers had higher levels of amplitude % mean than non-smokers or ex-smokers. The difference between smoking categories was slightly more pronounced in the younger age groups but this trend was not statistically significant. The increased values in young current smokers suggest that the effect of cigarettes on the airways can occur after relatively short exposure. As with atopy the changes in amplitude % mean with smoking history were contributed to by an increase in the absolute amplitude and a decrease in mean PEF.

Most studies which have considered the effects of cigarette smoking on bronchial reactivity in community samples have shown, as in the present study, an increased proportion of smokers among subjects with a measurable  $PD_{20}$  value.<sup>13 24-28</sup> In some such studies the effects of smoking have been seen mainly in subjects with low baseline airway calibre,<sup>27 28</sup> a finding consistent with the theory that long term smoking alters bronchial reactivity through an effect on airway calibre. There is also evidence of short term effects of smoking on airway calibre and bronchial reactivity,<sup>29 30</sup> and in our study the increased proportion of current smokers with a measurable  $PD_{20}$  was present, as with amplitude % mean, in all age groups and was, in fact, more obvious in the younger age groups as shown in fig 3. The figure may exaggerate the extent of the increase in the youngest age group which contained only seven smokers, but the results suggest that smoking can alter bronchial reactivity after relatively short exposure when changes in airway calibre would be expected to be minimal. The effect of smoking on bronchial reactivity remained after controlling for baseline  $FEV_{1}$ , again favouring the suggestion that smoking may have a more direct influence on reactivity.

Previous reports which have considered the

effects of age on bronchial reactivity have generally, like the present study, been based on cross sectional surveys. Studies which have included both children and adults have shown a fall in the proportion of reactors to methacholine and cold air with increasing age,<sup>31,32</sup> the lowest levels being seen in subjects in their forties. In adults there appears to be an increase in the number of reactors as age increases above 40–50 years,<sup>33–36</sup> although one recent study has shown the opposite.<sup>37</sup> In combination these results tend to suggest a U-shaped distribution with reactivity greatest in early and late adult life. In contrast to PD<sub>20</sub>, amplitude % mean showed a small steady increase with age (fig 2). This appears to be due principally to the well recognised decline in mean PEF with age, since absolute amplitude was relatively constant across the age range studied. Although the age related variation in amplitude % mean was significant it was not large, the expected value for amplitude % mean in a non-smoking non-atopic man changing from 6.6% at age 20 to 8.5% at age 60.

There was no difference in PD<sub>20</sub> values between men and women, and no consistent association with sex has been reported in adults.<sup>15,37</sup> Both mean PEF and absolute amplitude were lower in women than in men, but the difference was proportionately larger for mean PEF so that amplitude % mean was significantly greater in women. In our sample more women than men had a history of asthma (9.7% *v* 6.1%) which may account for some of the difference in PEF variability between the sexes, but amplitude % mean was also higher in women in the subjects who reported no asthma. In practice the sex difference could be allowed for in studies using amplitude % mean measurements as is currently done for other indices of lung function such as FEV<sub>1</sub>.

One of the main reasons for performing this study was to compare response rates for the two survey methods. In terms of the number of people attending for a challenge test or to collect a PEF meter there was a distinctly better response with PEF recordings. Some subjects failed to return their PEF record, however, and some were unable to complete challenge tests, so that the final difference was 8.7%. Of the 26 subjects who accepted a PEF meter but failed to return a completed record 23 claimed to have posted it, and it is difficult to disbelieve them all. Some packages were returned in a damaged state and it is possible that some were lost in the postal system. Even allowing for these losses PEF recordings were associated with a higher response rate than challenge tests and this is likely to be the case in future studies, at least when conducted in adults in countries with high literacy rates.

In addition to the difference in response rates the use of PEF recordings was much simpler logistically than challenge tests, although this is difficult to quantify formally. PEF meters can be distributed more quickly than challenge tests can be performed, even

by experienced personnel. Appointment systems for PEF recordings are easier to organise and several subjects can be instructed together. If subjects need to be visited at home it is much easier to deliver a PEF meter and give instructions than to perform a challenge test, and the PEF method can be used by non-medically trained personnel.

There are limitations to PEF measurements. Some researchers may not feel comfortable with the lack of supervision the method entails. The need to correct for age and sex adds a minor complication. Perhaps most important is the finding from a previous study, in subjects selected because of a history of wheeze, that subjects who had been given a diagnosis of asthma were separated more clearly from non-asthmatic subjects by use of bronchial reactivity than by PEF variability measurements.<sup>38</sup> However, there was little difference between the measurements when the relationships to respiratory symptoms were compared.

In summary, we have confirmed in a random population sample that bronchial reactivity measurements are associated with atopy and smoking, and have shown that these factors are also related to increased PEF variability. The effects of atopy and smoking on bronchial reactivity show interactions with age which we did not find for PEF variability but, despite this difference, our findings suggest that measurement of PEF variability is a suitable alternative to bronchial challenge tests for epidemiological studies. In particular, it may be more suitable for studies involving repeated measurements in which its greater acceptability and absence of censored data would be important. A measure of PEF variability can be obtained in all subjects in a population sample who accept a peak flow meter; it appears to produce a higher response rate than bronchial challenge tests and is associated with factors known to be related to airways disease.

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