

Effects of air pollution on symptoms and peak expiratory flow measurements in subjects with obstructive airways disease

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Abstract

Background – Evidence from laboratory studies suggests that air pollution can produce bronchoconstriction and respiratory symptoms in selected subjects, but the relevance of these findings to exposure to natural pollution is unclear. This study was performed to determine whether air pollution at typical levels found in the UK has demonstrable effects on respiratory function and symptoms in subjects with airways disease.

Methods – Seventy five adult patients with diagnoses of asthma or chronic obstructive pulmonary disease (COPD) were studied for a period of four weeks during which they kept records of their peak expiratory flow (PEF) rates, symptoms (wheeze, dyspnoea, cough, throat and eye irritation), and bronchodilator use. Thirty six patients in whom the provocative dose of methacholine causing a 20% fall in FEV₁ was below 12.25 µmol were classified as reactors. Ambient air pollution was measured with absorption spectroscopy.

Results – There were modest but significant increases in PEF variability, bronchodilator use, and wheeze with increasing sulphur dioxide levels; bronchodilator use, dyspnoea, eye irritation, and minimum PEF readings were related to ozone levels. In the subgroup of reactors falls in mean and minimum peak flow and increases in wheeze, dyspnoea, and bronchodilator use were associated with increases in levels of both sulphur dioxide and ozone. Some associations were seen with pollution levels on the same day, but for others the pollution effects appeared to be delayed by 24 or 48 hours. Pollution levels did not breach the WHO guide levels during the course of the study.

Conclusions – Increases in environmental levels of ozone and sulphur dioxide are associated with adverse changes in peak flow measurements and both ocular and respiratory symptoms in subjects with obstructive airways disease. Although the peak flow and symptom changes were modest, they occurred at pollution levels below current WHO guide levels.

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In the past 40 years the nature of air pollution in the UK has changed markedly. Whilst the Clean Air Act of 1956 led to a reduction in the pollution associated with the burning of coal, the emission of other pollutants such as those from vehicle exhausts has steadily increased. Despite recognition of, and concern about, these changes, our knowledge of the health consequences of modern pollution remains limited.

The air pollutants which have been studied in greatest detail are ozone, sulphur dioxide, and nitrogen dioxide; the latter two are derived particularly from combustion engines and power stations while ozone is of a more complex derivation. It is clear that all these gases can produce adverse effects on lung function under laboratory conditions in both asthmatic and normal subjects,¹⁻⁶ but changes cannot be demonstrated in all studies.⁷⁻⁹ Furthermore, whilst studies in the laboratory are useful for exploring potential effects of pollution and for elucidating mechanisms of action, the artificial circumstances of the experiments, involving complex exercise protocols, make it difficult to extrapolate the findings to the natural exposure of the general population during everyday living.

The effects of pollution in the general population have been examined previously and some studies have identified associations between pollution and the rates of admission, or emergency visits to hospital, in patients with respiratory disease.¹⁰⁻¹² Admission rates are, however, a relatively crude measure of response and reflect events only in a few subjects. Furthermore, most of these epidemiological studies have been conducted in North America where pollution levels tend to be higher than in the UK and where cofactors that mediate the response to pollution – such as temperature and humidity¹³ – also differ. Much less information is available from the UK, particularly with regard to ozone.

To determine whether air pollution at levels found in the UK has demonstrable adverse effects on respiratory function and symptoms we have studied a group of patients with clinically established diagnoses of asthma or chronic obstructive pulmonary disease (COPD) using daily measurements of symptoms and peak expiratory flow (PEF) to monitor changes with varying levels of pollution.

Methods

The study was performed using the pollution monitoring system in Halton health district.

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This includes the towns of Widnes and Runcorn which face each other across the River Mersey.

SUBJECTS

Subjects were selected from two general practices, one in Widnes and one in Runcorn, with catchment areas close to the pollution monitoring system. To obtain a representative sample of subjects with asthma and COPD a one-in-four random start systematic sample was taken of patients with these diagnoses from the disease registers of the general practices. The 153 patients selected were each sent a letter, countersigned by their general practitioner, explaining the nature and purpose of the study and asking them to attend their practice surgery if willing to take part. A reply slip and stamped addressed envelope were included so that appointments could be rearranged if necessary.

PROTOCOL

On arrival subjects received a detailed explanation of the study and written consent was obtained. Subjects then filled in a respiratory symptom questionnaire based on that of the International Union against Tuberculosis and Lung Disease (IUAT) and a bronchial challenge test using methacholine was performed. The subjects were shown how to complete both a PEF record sheet and a symptom record sheet and were asked to keep a record of PEF values and symptoms for 28 days.

The completed sheets were returned to the practice surgery from where they were collected for analysis. All subjects failing to return record sheets were contacted by telephone or home visit to attempt to retrieve the data.

BRONCHIAL CHALLENGE TESTS

Bronchial challenge tests were performed using the method described by Yan *et al*¹⁴ but using equivalent doses of methacholine. Spirometric measurements were made until two forced expiratory volume in one second (FEV₁) readings within 0.05 litres of each other were recorded; the higher of these two measurements was taken as the baseline FEV₁. Three inhalations of N saline from a De Vilbiss No 40 nebuliser were then administered and the FEV₁ measurement repeated one minute later as for the baseline measurement. Methacholine was then given in increasing doses, with an FEV₁ measurement one minute after each, starting at a dose of 0.06 µmol and increasing by doubling increments. The challenge test was stopped when FEV₁ fell to 80% or less of the post-saline value, or when a maximum dose of 12.25 µmol methacholine had been given.

Subjects were excluded from challenge testing if they had a baseline FEV₁ of less than 50% of their predicted value.

PEF MEASUREMENTS

Subjects were taught the standard method of measuring PEF and were asked to record the

highest of three values on each occasion. The PEF record sheets contained spaces for recording PEF values at two hourly intervals commencing at 02.00 hours each day. The subjects were asked to make these measurements within 15 minutes either side of the time shown on the record sheet and to omit measurements at times when they were away from Widnes or Runcorn. They were asked to make measurements for a total of 28 days if possible.

PEF records were accepted for analysis if they included at least five days with two or more PEF readings. Most subjects either completed all 28 days or only returned 1–2 days and were thus excluded.

SYMPTOM RECORDS

The symptom record sheet consisted of visual analogue scales (10 cm lines) for five symptoms comprising wheeze; shortness of breath; cough; throat irritation; and eye irritation. The subjects were asked to rate the severity of each symptom at the end of each day on a scale from "none" to "worst ever". Subjects were also asked to record their daily bronchodilator inhaler usage. Records were accepted for analysis if they included a minimum of five days on which visual analogue scores had been clearly marked.

POLLUTION MEASUREMENTS

Pollution levels were measured using the Opsis system (Opsis AB, Lund, Sweden) which uses differential absorption spectroscopy. A beam of light at visible and ultraviolet frequencies is transmitted to a receiver approximately 500 metres away. The receiver contains an optical fibre system connected to a spectrometer which scans the light beam and determines which frequencies have been absorbed by gases traversing the beam. Since pollutant gases each absorb light at a characteristic frequency, the atmospheric concentration of the selected gases can be determined. The spectrometer is linked to a computerised recording system which stores pollutant levels continuously. The system can therefore be used to determine pollution levels at a particular time point or levels can be averaged over a time period. In this study 24 hour mean levels were used.

Two receivers were sited in Halton district, one at the municipal building in Widnes, and the other at Runcorn town hall.

DATA TRANSFORMATION

The provocative dose of methacholine causing a 20% fall in FEV₁ (PD₂₀FEV₁) was calculated from the challenge test results using linear interpolation between points on the dose-response curve. Subjects were considered to be reactors if they had a PD₂₀ methacholine of <12.25 µmol.

From the PEF records the daily mean and minimum PEF values were obtained and the daily PEF variability was calculated as the amplitude % mean:

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

The visual analogue scales were measured to give a daily score for each symptom. It was originally intended to analyse these scores as continuous variables but, because there were a significant number of days (the precise number varying between symptoms) for which the score was zero, the distribution of the visual analogue data was not Normal for any symptom. Such a distribution cannot be adequately Normalised by any transformation and the data were therefore analysed using a logistic model to estimate the effect of pollution levels on the odds of experiencing each symptom. For this purpose days were simply classified as positive or negative for the presence of symptoms irrespective of the symptom severity.

The problem of zero values also affected the bronchodilator results and therefore a logistic model was again used for analysis.

REGRESSION ANALYSIS

The relation between PEF variables and pollution levels was determined using multiple regression analysis. Amplitude % mean, mean and minimum PEF were taken in turn as the dependent variable. After allowing for between subject differences in the dependent variable the 24-hour mean levels of ozone, sulphur dioxide, and nitrogen dioxide were entered into the model to determine the effects of pollution levels measured on the same day.¹⁵ The same day pollutant levels were then removed and replaced in turn by the 24 hour lag and 48 hour levels to look for delayed effects. The possibility that PEF measurements might be subject to a learning effect was tested by entering the day of measurement into the models.

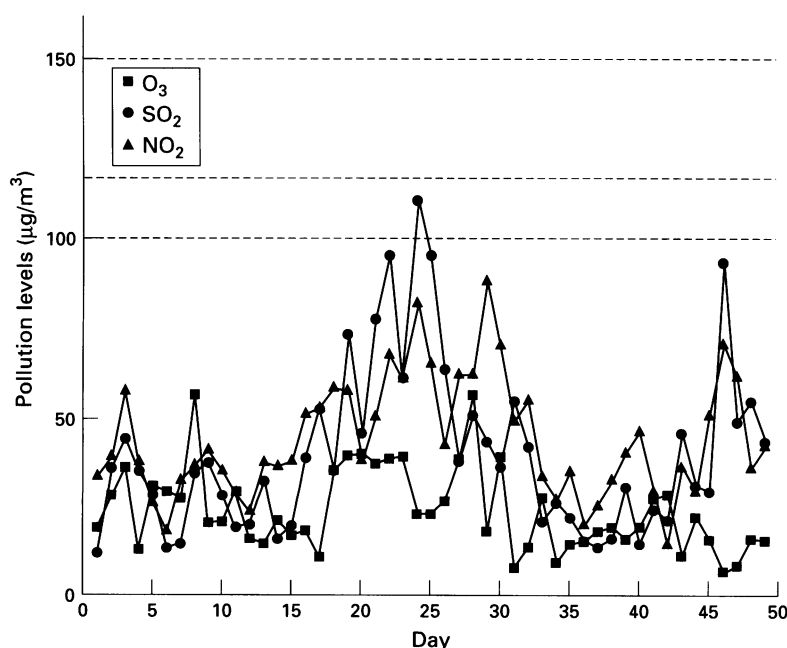


Figure 1 Mean daily values of ozone, sulphur dioxide, and nitrogen dioxide (in $\mu\text{g}/\text{m}^3$) during the study period. Day 0 is 15 August. The dotted lines show the WHO guide levels for (from top downwards) nitrogen dioxide, sulphur dioxide, and ozone.

Table 1 Mean (range) data of subjects completing PEF measurements

Sex	37 M:38 F
Age (years)	50 (18–82)
Atopic:non-atopic*	50:21
Smokers	
Current	19 (26%)
Ex-smokers	23 (31%)
Non-smokers	32 (43%)
FEV ₁ (l)	2.30 (0.35–4.15)
FEV ₁ (% pred)	80 (16–135)
PEF variability (%)	21.6 (1.83–60.3)

Four subjects refused skin tests and 1 failed to answer smoking questions on the questionnaire.

*Atopic = any skin weal ≥ 2 mm larger than control weal.

The same analyses were then repeated on the subgroup who reacted to methacholine.

The analysis of symptom and bronchodilator scores was similar but performed using logistic regression. All analyses were performed using the statistical program GLIM.

Results

SUBJECTS

Of the 153 subjects selected from the general practice registers 95 attended the surgery, filled in a symptom questionnaire, and took away a peak flow meter. Seventy five of these subjects returned an acceptable PEF record chart. Satisfactory symptom sheets were available in 62 subjects.

Of the 75 subjects with adequate PEF records 47 had a diagnosis of asthma, 10 had been told they had COPD, and 10 believed they had both asthma and COPD. Eight claimed to have neither diagnosis but all had a history of wheeze. Thirty six subjects (28 with a diagnosis of asthma only) had a PD₂₀ methacholine of $<12.25 \mu\text{mol}$ and were classified as reactors, 18 were non-reactors, and 21 were not able to perform a challenge test because their FEV₁ was too low. Further subject details are given in table 1.

POLLUTION LEVELS

During the study period the maximum 24 hour levels of ozone, sulphur dioxide, and nitrogen dioxide were, respectively, $55 \mu\text{g}/\text{m}^3$, $117 \mu\text{g}/\text{m}^3$, and $84 \mu\text{g}/\text{m}^3$. The corresponding WHO guide levels are $125 \mu\text{g}/\text{m}^3$ for sulphur dioxide and $150 \mu\text{g}/\text{m}^3$ for nitrogen dioxide. The ozone guideline is given for eight hourly averages and is $100\text{--}120 \mu\text{g}/\text{m}^3$: the maximum eight hourly level in Halton was $71 \mu\text{g}/\text{m}^3$. Levels throughout the study period are shown in fig 1.

RELATION OF PEF MEASUREMENTS TO POLLUTION LEVELS

Amplitude % mean increased significantly with increasing levels of sulphur dioxide, but not with ozone or nitrogen dioxide. The effect of sulphur dioxide was observed with levels from the same day or levels 24 hours previously (table 2). In the methacholine reactors the effect of sulphur dioxide was less marked but there was a significant relation between amplitude % mean and the 24 hour lag ozone level.

There was only one association of borderline significance (with ozone) when pollutant levels

were compared with mean and minimum PEF levels in the subject group as a whole. However, in the methacholine reactors the combined effects of the pollutants and the independent effects of both sulphur dioxide and ozone, but not nitrogen dioxide, showed a significant relationship to falls in mean and minimum PEF (table 2).

None of the associations between PEF measures and pollution were significantly affected by inclusion of daily temperature in the regression model, nor by allowing for a learning effect by controlling for the day of measurement.

RELATION BETWEEN SYMPTOMS AND POLLUTION LEVELS

In the 62 subjects who completed symptom record sheets significant associations were ob-

served between wheeze and sulphur dioxide levels, and between both dyspnoea and eye irritation and ozone levels. In addition, sulphur dioxide levels were related to dyspnoea, and ozone levels to wheeze, in the hyperreactive subjects (table 3). Cough and throat irritation showed no consistent relation with any pollutant and nitrogen dioxide levels were not consistently related to any symptom.

RELATION BETWEEN BRONCHODILATOR USE AND POLLUTION LEVELS

There was a significant association between bronchodilator use and levels of both ozone and sulphur dioxide. These associations were present in both the hyperreactive subjects and the whole subject group (table 4).

Table 2 Mean (SE) regression coefficients from multiple regression analyses of PEF measurements on pollution levels in all subjects ($n=75$) and reactors ($n=36$)

	All subjects			Reactors		
	Same day	24-hour lag	48-hour lag	Same day	24-hour lag	48-hour lag
Mean PEF (l/min)						
O ₃	-0.084 (0.056)	-0.080 (0.054)	-0.092 (0.052)	-0.186 (0.086)*	-0.217 (0.090)*	-0.256 (0.086)**
SO ₂	-0.021 (0.031)	0.003 (0.033)	0.021 (0.032)	-0.087 (0.054)	-0.044 (0.058)	0.012 (0.057)
Minimum PEF (l/min)						
O ₃	-0.140 (0.067)*	-0.121 (0.068)	-0.121 (0.065)	-0.280 (0.116)*	-0.314 (0.118)**	-0.267 (0.115)*
SO ₂	-0.062 (0.039)	-0.048 (0.041)	-0.001 (0.040)	-0.168 (0.071)*	-0.078 (0.076)	-0.026 (0.075)
Amplitude (% mean)						
O ₃	0.193 (0.125)	0.219 (0.126)	0.193 (0.122)	0.213 (0.194)	0.410 (0.197)*	0.210 (0.191)
SO ₂	0.167 (0.072)*	0.191 (0.076)*	0.022 (0.075)	0.157 (0.120)	0.083 (0.127)	0.005 (0.126)

* $p<0.05$; ** $p<0.01$.

Coefficients are adjusted for the effects of the other pollutants measured and show the change in each PEF measurement with a $10 \mu\text{g}/\text{m}^3$ increase in pollutant level. Coefficients for nitrogen dioxide were not significant and are omitted for brevity. Values for amplitude % mean are for \log_e (amplitude % mean) $\times 100$.

Table 3 Odds ratios (95% confidence interval) from multiple logistic regression analyses of symptoms on pollution levels in all subjects ($n=62$) and reactors ($n=33$)

	All subjects			Reactors		
	Same day	24-hour lag	48-hour lag	Same day	24-hour lag	48-hour lag
Wheeze						
O ₃	1.18 (0.99 to 1.41)	1.19 (0.99 to 1.43)	1.18 (0.99 to 1.40)	1.10 (0.84 to 1.43)	1.12 (0.85 to 1.46)	1.50 (1.14 to 1.97)**
SO ₂	1.14 (1.03 to 1.26)*	1.22 (1.09 to 1.37)***	1.14 (1.02 to 1.27)*	1.26 (1.08 to 1.47)**	1.57 (1.30 to 1.89)***	1.24 (1.06 to 1.45)**
Dyspnoea						
O ₃	0.97 (0.82 to 1.14)	1.07 (0.91 to 1.27)	1.20 (1.02 to 1.41)*	1.01 (0.80 to 1.27)	1.19 (0.94 to 1.50)	1.36 (1.08 to 1.72)**
SO ₂	1.03 (0.94 to 1.14)	1.07 (0.96 to 1.18)	0.94 (0.85 to 1.05)	1.04 (0.90 to 1.20)	1.17 (1.00 to 1.37)*	1.03 (0.89 to 1.20)
Cough						
O ₃	1.05 (0.91 to 1.22)	1.10 (0.95 to 1.28)	0.97 (0.85 to 1.12)	1.01 (0.82 to 1.24)	1.23 (1.00 to 1.53)	1.02 (0.83 to 1.24)
SO ₂	1.03 (0.95 to 1.12)	1.04 (0.95 to 1.13)	1.02 (0.94 to 1.12)	1.09 (0.96 to 1.24)	1.05 (0.91 to 1.20)	1.00 (0.87 to 1.15)
Throat symptoms						
O ₃	1.04 (0.89 to 1.22)	1.19 (1.01 to 1.40)*	1.00 (0.86 to 1.17)	1.17 (0.93 to 1.47)	1.25 (0.99 to 1.58)	1.00 (0.80 to 1.24)
SO ₂	1.01 (0.92 to 1.11)	1.00 (0.91 to 1.10)	0.96 (0.87 to 1.06)	1.06 (0.92 to 1.21)	1.06 (0.91 to 1.23)	1.01 (0.87 to 1.17)
Eye symptoms						
O ₃	1.14 (0.95 to 1.36)	1.22 (1.03 to 1.46)*	1.05 (0.89 to 1.24)	1.00 (0.78 to 1.28)	1.12 (0.88 to 1.43)	1.11 (0.87 to 1.41)
SO ₂	1.08 (0.97 to 1.20)	1.11 (0.99 to 1.24)	1.10 (0.99 to 1.21)	1.19 (1.01 to 1.40)*	1.21 (1.01 to 1.45)*	1.08 (0.91 to 1.28)

* $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Coefficients are adjusted for the effects of the other pollutants measured. Coefficients for nitrogen dioxide were not significant and are omitted for brevity. The coefficients show the change in the odds of experiencing symptoms with every $10 \mu\text{g}/\text{m}^3$ increase in pollutant levels.

Table 4 Odds ratios (95% confidence interval) from multiple logistic regression analysis of any bronchodilator use on pollution levels in all subjects ($n=71$) and reactors ($n=33$)

	All subjects			Reactors		
	Same day	24-hour lag	48-hour lag	Same day	24-hour lag	48-hour lag
Bronchodilator						
O ₃	1.29 (1.02 to 1.62)*	1.44 (1.14 to 1.82)**	1.12 (0.91 to 1.39)	1.26 (0.92 to 1.73)	1.44 (1.05 to 1.97)*	1.13 (0.84 to 1.52)
SO ₂	1.11 (0.97 to 1.26)	1.16 (1.01 to 1.34)*	1.12 (0.98 to 1.27)	1.18 (0.99 to 1.42)	1.23 (1.02 to 1.50)*	1.31 (1.09 to 1.58)**

* $p<0.05$; ** $p<0.01$.

Coefficients are adjusted for the effects of the other pollutants measured. Coefficients for nitrogen dioxide were not significant and are omitted for brevity. The coefficients show the change in the odds of using bronchodilators during the day for every $10 \mu\text{g}/\text{m}^3$ increase in pollutant levels.

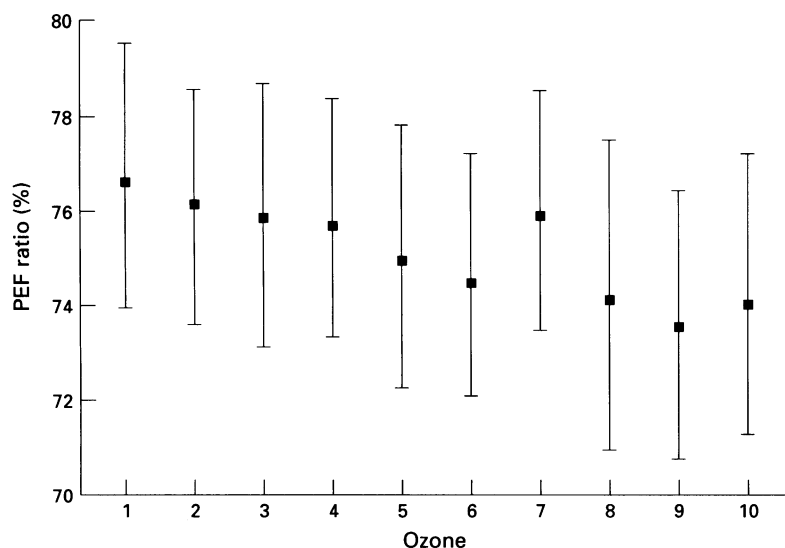


Figure 2 Relation between PEF ratio (minimum daily PEF/subject's best PEF $\times 100\%$) in reactors and ozone measured on the same day. Ozone data are grouped into deciles with lowest levels in group 1.

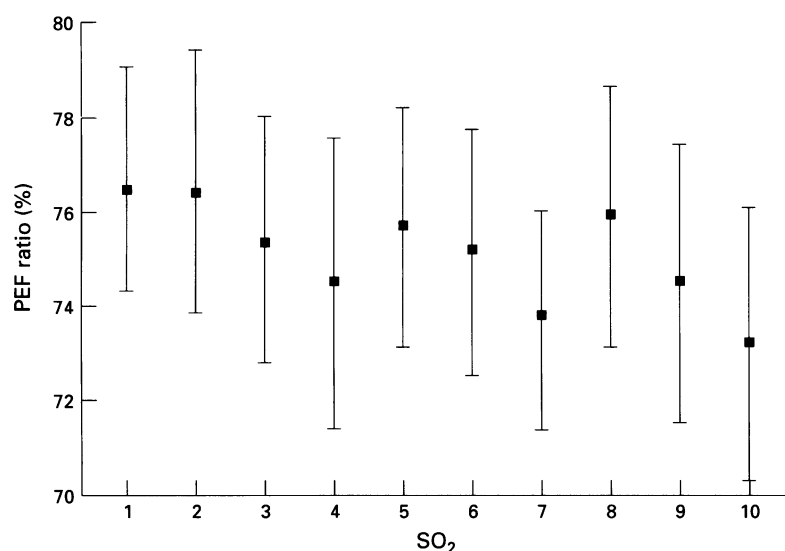


Figure 3 Relation between PEF ratio (minimum daily PEF/subject's best PEF $\times 100\%$) in reactors and sulphur dioxide measured on the same day. Sulphur dioxide data are grouped into deciles with lowest levels in group 1.

MAGNITUDE OF POLLUTION RELATED CHANGES

Changes in PEF with pollution are best illustrated by correcting for the large between subject differences in absolute PEF. In figs 2 and 3 a PEF ratio (minimum daily PEF/best PEF recorded during the study) is plotted against pollution with pollution values divided into deciles. The 3% fall in PEF from lowest to highest pollution decile represents a change in absolute terms of approximately 13 l/min for each pollutant (based on the group's average PEF of 450 l/min).

Discussion

We have studied a group of 75 subjects with diagnoses made by their general practitioners of either asthma or chronic bronchitis and shown that ambient air pollution had significant effects on respiratory symptoms and bronchodilator usage, eye symptoms, and PEF readings. We

are not aware of any previous study in the UK showing respiratory effects from natural exposure to ozone.

We looked at mean PEF values as a simple measurement of airway function throughout the day and amplitude % mean as a measure of PEF variability.¹⁵ We also analysed the daily minimum PEF values in an attempt to avoid masking changes in mean PEF by subjects, who had open access to their bronchodilator inhalers, using extra doses of bronchodilator in response to any increase in symptoms caused by pollution. The symptoms we measured were chosen because they have been reported by subjects exposed to these pollutants in the laboratory. We also looked at the late effects of pollution (using measurements of pollution from 24 and 48 hours before the PEF/symptom measurements) because earlier studies from other countries have suggested that effects may be delayed. Because we considered so many symptom/PEF outcomes and therefore performed a large number of statistical tests, and because pollution levels on any day tend not to differ greatly from those of the previous day, it would be inappropriate to overemphasise the importance of any individual regression coefficient, but rather to consider the general pattern of the results. The study should be regarded as of an exploratory nature, examining whether pollution has any demonstrable effect on respiratory health measurements in UK conditions rather than determining the precise effects of specific pollutants on specific symptoms.

Of the gases studied ozone and sulphur dioxide showed consistent effects on both symptoms and respiratory function whereas nitrogen dioxide appeared to have no demonstrable effects when levels of the other pollutants were allowed for. Although there is little previous information available concerning the effects of air pollution in the community at the levels, and in the climatic conditions, found in the UK, the three pollutants considered here have all been studied in considerable detail in the laboratory. The laboratory studies have generally used the gases in isolation and in higher concentrations than those commonly found in UK cities, but based on the results of these studies there was reason to believe that effects might be seen with all three agents.

Although occasional studies have failed to show any change in lung function with exposure to sulphur dioxide,⁸ most have shown clear decreases.^{3,4,16-18} A dose-response relation can be demonstrated.^{16,17} In one group of mild asthmatic subjects the mean sulphur dioxide concentration necessary to increase specific airway resistance by 100% was estimated at 2000 $\mu\text{g}/\text{m}^3$.¹⁶ Changes have been shown at lower concentrations, however,^{3,17,18} and it seems likely that more severe asthmatics would react at lower levels. Nonetheless, it is perhaps surprising that changes were seen in our study when the highest 24 hour level reached was 117 $\mu\text{g}/\text{m}^3$; although two hourly values reached 273 $\mu\text{g}/\text{m}^3$ this is still well below the levels usually employed in the laboratory.

We are not aware of any other report of the

effect of sulphur dioxide on serial lung function and symptoms in a UK community, but our findings are consistent with studies in which hospital admissions for respiratory problems have been shown to increase in association with raised sulphur dioxide levels.^{11 12} Although studies are still few in number, and although some epidemiological studies have failed to show effects of sulphur dioxide,^{19 20} it appears that this pollutant may continue to have adverse respiratory effects in the community despite the falls in ambient levels which have occurred since clean air measures were introduced.

Acute ozone-induced falls in lung function parameters have been seen in several laboratory studies of asthmatic and non-asthmatic subjects.^{12 21 22} Furthermore, studies of children in rural American settings (where ozone levels tend to be high) have shown that daily spirometric measurements vary with changes in ambient ozone levels.²³ American epidemiological studies in adults have also shown evidence of adverse effects related to ozone levels.^{11 24}

Our study has shown an association between ozone levels and both respiratory function and symptoms. The changes were again seen at levels lower than those used in laboratory studies and were best seen, as with sulphur dioxide, in the subjects with measurable methacholine reactivity. Although this seems intuitively appropriate, previous studies have not always shown increased sensitivity to ozone in those with reactive airways.²⁵

Nitrogen dioxide has been widely studied and there is some evidence of a weak effect of this agent on respiratory function both in laboratory studies^{5 6} and in the community.^{20 26} However, several other studies have failed to show noteworthy changes in respiratory function in subjects with airflow obstruction^{7 9 27 28} and in our study we found no significant independent association with either PEF or symptom measurements. Nitrogen dioxide did appear to have some effect if entered in regression models as the only pollutant, but any such effect disappeared when sulphur dioxide was included. Levels of nitrogen dioxide and sulphur dioxide were closely correlated and, in these circumstances, it may be difficult to demonstrate separate effects of both agents.

Two additional problems with our study merit discussion. Firstly, it is difficult to be certain how well measurements of ambient pollution corresponded to the individual exposures of our subjects. In particular, we do not know to what levels subjects were exposed when indoors. This possible inaccuracy should not nullify our conclusion that environmental sulphur dioxide and ozone affect lung function and symptoms, since any error of this type is more likely to weaken a statistical association than strengthen it. However, the possibility that we have failed to identify an effect of nitrogen dioxide because of unavoidably incomplete measurements must be acknowledged.

A second problem is that we measured a limited number of pollutants and it is possible that the changes demonstrated were produced by other covarying agents. In particular, in the time since the study was conceived there have

been several papers pointing to a role for particulate matter, especially for those particles with an aerodynamic diameter of 10 μm or less (PM_{10}). One such study in students in the Utah Valley measured PEF, symptoms and bronchodilator use, as in our study, and found a relation between all these measurements and PM_{10} .²⁹ Other American studies have shown associations between PM_{10} and school absence,³⁰ emergency room visits,³¹ and mortality from respiratory conditions.³² In Europe diary studies in children have also suggested that respiratory symptoms vary with PM_{10} levels.^{20 33} Thus, particulates may account for some of the changes shown in our study, particularly those associated with sulphur dioxide rather than ozone since some studies which have measured both particulates and ozone have shown independent effects of ozone.^{34 35}

The changes in lung function that we have found are modest even where statistically significant. For example, the changes in mean PEF over the range of pollutant levels encountered in our study would be of the order of 10–15 l/min. However, even a relatively small shift in grouped measures of lung function could, if extrapolated to a large population of subjects with airflow obstruction, produce a considerable increase in morbidity. Furthermore, the grouped data will conceal variation between the responses of individuals, with some likely to show more significant deterioration in association with increases in pollution.

In conclusion we have shown that sulphur dioxide and ozone at levels found in a typical British summer are associated with a fall in PEF values, an increase in PEF variability, increases in subjective measures of wheeze, dyspnoea and eye irritation, and increased use of bronchodilators. Since the levels of both sulphur dioxide and ozone were low in comparison to WHO guidelines, our findings suggest the need to reconsider these thresholds.

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