

Outdoor air pollution and respiratory health in patients with COPD

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Received 10 November 2010
Accepted 24 February 2011
Published Online First
1 April 2011

ABSTRACT

Objectives Time series studies have shown adverse effects of outdoor air pollution on mortality and hospital admissions in patients with chronic obstructive pulmonary disease (COPD) but panel studies have been inconsistent. This study investigates short-term effects of outdoor nitrogen dioxide, ozone, sulfur dioxide, particulate matter (PM₁₀) and black smoke on exacerbations, respiratory symptoms and lung function in 94 patients with COPD in east London.

Methods Patients were recruited from an outpatient clinic and were asked to complete daily diary cards (median follow-up 518 days) recording exacerbations, symptoms and lung function, and the amount of time spent outdoors. Outdoor air pollution exposure (lag 1 day) was obtained from local background monitoring stations.

Results Symptoms but not lung function showed associations with raised pollution levels. Dyspnoea was significantly associated with PM₁₀ (increase in odds for an IQR change in pollutant: 13% (95% CI 4% to 23%)) and this association remained after adjustment for other the pollutants measured. An IQR increase in nitrogen dioxide was associated with a 6% (0–13%) increase in the odds of a symptomatic fall in peak flow rate. The corresponding effect sizes for PM₁₀ and black smoke were 12% (2–25%) and 7% (1–13%), respectively.

Conclusion It is concluded that outdoor air pollution is associated with important adverse effects on symptoms in patients with COPD living in London.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is increasing in incidence worldwide and is currently the sixth leading cause of death.¹ Patients with COPD are prone to acute deterioration in their chronic symptoms. These exacerbations of COPD were first shown to be associated with air pollutants during the London smog episode of 1952.² There is now clear evidence that air pollution at current levels in London affects mortality^{3–4} and that air pollution levels in Europe lead to hospital admissions for COPD.⁵

Panel studies have shown adverse effects at relatively low levels of pollution. One of the earliest panel studies in patients with COPD showed that changes in pollution level were associated with exacerbations of chronic bronchitis.⁶ A study in Merseyside, UK involving 75 patients with COPD reported effects of ozone (O₃) and sulfur dioxide (SO₂) on peak expiratory flow (PEF) and respiratory symptoms recorded daily using diary

Key messages

What is the key question?

► Does outdoor air pollution affect exacerbations, respiratory symptoms and lung function in patients with COPD?

What is the bottom line?

► In patients with COPD living in London, there is evidence for adverse effects of outdoor pollution on symptoms and exacerbations, particularly for PM₁₀, black smoke and NO₂.

Why read on?

► Ecological studies have shown links between outdoor air pollution and increased COPD mortality/morbidity and this study shows similar effects in individual patients, supporting the case for causality.

cards.⁷ A Dutch panel study similarly reported adverse effects of PM₁₀ (particulate matter), black smoke, sulfate and SO₂ on PEF, and effects of black smoke on upper respiratory symptoms in 326 symptomatic adults.⁸ A panel study in Italy reported adverse effects of particles and nitrogen dioxide (NO₂) on forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁) in 29 subjects with COPD,⁹ and similar associations between FEV₁ and particles were reported in a US COPD panel with 24 subjects.¹⁰ A New Zealand COPD panel study in 48 patients found no effect of pollution levels on PEF but observed effects of particles on night-time symptoms and nebuliser use.¹¹ A French study conducted at a similar time to the present study analysed effects of air pollution on COPD exacerbations and reported adverse effects of O₃.¹²

In this paper we examine the effects of a range of air pollutants on COPD exacerbations, respiratory symptoms and respiratory function, including large decrements in PEF, in a panel of 94 patients with moderate to severe COPD selected from a COPD clinic in London and followed over a 2-year period, October 1995–October 1997.

METHODS

Subjects

The East London COPD study was established in 1995 as a prospective study of the role of viral infections and environmental factors in COPD exacerbations.^{13–16} Subjects were patients with

moderate to severe COPD attending an outpatient clinic at the London Chest Hospital, London. Recruitment was from October 1995 to October 1997. Inclusion criteria were: FEV₁ <70% predicted for age and height, β_2 -agonist reversibility <15% or 200 ml^{17 18} and no exacerbations in the previous 4 weeks. Exclusion criteria were asthma, bronchiectasis, carcinoma of the bronchus or inability to complete diary cards. Patients were seen at the clinic monthly during the colder months and 3-monthly during the rest of the year. Patients were also seen acutely at exacerbation and then at a convalescent visit 4–6 weeks post-exacerbation.

Data collected

At recruitment, baseline measurements were made of height, weight, FEV₁, FVC and PEF by rolling seal spirometer (Sensor Medic, Yorba Linda, California, USA), reversibility to 400 μ g of inhaled salbutamol, and arterialised earlobe blood gases.¹⁹ Patients recorded symptoms and lung function daily on diary cards. Patients measured PEF indoors after morning medication using a Mini-Wright peak flow meter (Clement Clarke International, Harlow, UK). They recorded any increase in chronic symptoms during the previous 24 h. Symptoms were categorised as major (dyspnoea, sputum purulence, sputum amount) or minor (nasal discharge/congestion, wheeze, sore throat, cough). Patients recorded bedroom temperature on waking using a 1°C Thermax temperature strip (Thermographic Measurements, Burton, UK). From March 1996 onwards, patients recorded the number of hours spent outdoors. FEV₁ and FVC were also measured in a subsample of 28 patients using a hand-held spirometer (Micro Medical, Rochester, UK). At the outset of the study, patients were taught how to measure and record lung function and symptoms, and were reminded and/or re-educated when they visited the clinic.

Exacerbations

Patients were asked to attend clinic if their symptoms worsened. Exacerbations were identified by symptoms recorded on the diary cards or from the history when patients presented to the physician (TAS), according to the criteria modified from Anthonisen *et al*²⁰ of any two major symptoms or one major and two minor symptoms on two consecutive days.¹³ The first of the 2 days was taken as the onset of the exacerbation. Symptoms present continuously for >5 days prior to the possible onset of an exacerbation were discounted. Patients experiencing an exacerbation were given appropriate medication.

A less severe but more common form of exacerbation was also defined a priori as a fall in PEF of 10 l/min for ≥ 2 days plus a reported increase in dyspnoea. This was termed a 'symptomatic fall in PEF'. The rationale for using this is that patients with COPD, particularly frequent exacerbators, have high psychosocial and depression scores¹³; however, the presence of symptoms together with a change in lung function is more suggestive of an airway effect than psychological effects.

Outdoor air pollution data

Hourly measurements of NO₂, O₃, SO₂ and PM₁₀ were obtained from the national air quality monitoring network station at Bloomsbury Square, central London via the UK National Air Quality Information Archive (<http://www.airquality.co.uk/>). At the time of the study this was the only monitoring station in London for these pollutants. The following pollutant measures were derived: maximum hourly NO₂, maximum 8 h moving average O₃, 24 h mean SO₂ and PM₁₀. The completeness criterion was the availability of at least 75% of the data used to calculate

the summary measure for each day. The PM₁₀ data from this monitor are very closely correlated with the North Kensington site data for the same period ($r=0.95$) and so it was reasonable for the Bloomsbury data to represent background levels. For black smoke there was a network of monitors at that time (unlike for other pollutants) and so we used 24 h average black smoke data from the monitor nearest each patient's home. Missing pollution data were imputed using a standard method.²¹ We chose a priori to analyse 1 day lags (previous day) for all pollutants based on the results of time series studies available at the time.

Statistical methods

Brief details of statistical methods and rationale are given here, but fuller details are given in the online supplement. Symptoms and exacerbations were analysed as binary incidents—that is, the first day of an episode was the 'event'. To distinguish between new episodes of symptom worsening and the continuation of a current episode, a new episode was recorded when that symptom was not recorded in the previous 7 days.

Generalised estimating equations (GEEs) were used for analysis, taking account of variation within and between individuals. Effects of each symptom or exacerbation were modelled separately, with each pollutant level in turn as the main explanatory variable. Control was made for daily temperature (average of minimum and maximum) and season (analysed in four groups—spring, summer, autumn and winter), with estimates of variance robust against misspecification of correlation structure, which was assumed to be independent. Results were obtained as ORs and 95% CIs.

All lung function data (PEF, FEV₁ and FVC) were analysed as deviations from the individual mean to allow for variation between individuals. Lung function data were analysed in three ways. First they were analysed by season and year (4 seasons \times 2 years) to investigate seasonal effects, adjusting for indoor temperature and time spent outdoors using methodology described in previous reports.^{22 23} Secondly, they were analysed using GEEs with Normal errors to summarise effects across the entire time period. Analyses used a first-order autoregressive correlation structure and controlled for temperature and season as described above for symptoms. In addition, a linear time term was included to allow for decline in lung function. Thirdly, lung function was analysed as a binary variable following the method of Hoek.²⁴ For each patient, an adverse event, 'large peak flow decrement', was defined if lung function was >20% below that individual's median value. These binary events were also modelled using GEEs as described above for the symptom data.

Some associations were observed for effects of single pollutants on certain symptoms and so we decided post hoc to fit selected multipollutant models to try to disentangle these effects and aid interpretation.

All effect estimates are presented in two ways: (1) representing a unit change in pollutant level (ppb or μ g/m³ as appropriate) and (2) scaled to an IQR change in that pollutant level to aid interpretation. All analyses used Stata v11.

RESULTS

Summary statistics for subjects and exposure data

A total of 125 patients were recruited, of whom 31 were excluded for the following reasons: not continuously resident in London (13), in the study for <3 weeks (10), patient errors in data recording (1), misplaced diary sheets (1), dementia (1), asthma (1), precancerous illness (1), psychiatric disorder (1) and died (2). Median duration of follow-up was 518 days (range 21–709). Shortened length of follow-up was due to either late

recruitment, moving away or death. Fifteen patients had their series of measurements truncated as it was suspected that use of the measuring instrument was unreliable during the first few weeks. Further patient characteristics are reported in table 1 and show that the series predominantly comprised older males with obstructive lung disease. Mean numbers of symptoms over the period varied considerably among individuals but were on average quite low, suggesting that the condition of some patients was reasonably stable. Mean values for pollutants were: NO₂ 1 h max, 51.4 ppb; O₃ 8 h average, 15.5 ppb; SO₂ 24 h average, 7.5 ppb; PM₁₀ 24 h average, 37.7 µg/m³; black smoke 24 h average, 10.1 µg/m³ (table 2). Data from eight different black smoke monitors were used although the majority of patients (63%) lived nearest to one monitor (Stepney), which was close to the hospital.

Effects on lung function

When lung function was analysed by season, very few statistically significant effects were observed. There was a significant adverse effect of O₃ on PEF in summer 1996 but not in summer 1997. For FEV₁, there was one significant association for SO₂ in spring 1996 but this was not replicated the following year. For FVC, significant negative associations were observed for NO₂, PM₁₀ and black smoke in summer 1996 and SO₂ in spring 1996, but none of these seasonal effects was replicated in 1997 (tables E1–E3 in the online data supplement).

These non-significant findings were confirmed when lung function was analysed over the 2 years combined (table 3). Most regression coefficients were positive not negative, and one (PEF and NO₂) was statistically significant. There was no consistency in findings for PEF, FEV₁ and FVC, again providing no support for any adverse effect of pollution on mean respiratory function (table 3). There was no evidence for effects of any pollutant on

Table 1 Summary statistics for respiratory data October 1995–October 1997

	n	Mean (SD) or %	Median	Minimum	Maximum
Male sex	94	72%			
Age (years)	94	67.5 (8.2)	68.2	40	83
PEF (l/min)	94	224 (79)	220	60	453
FEV ₁ (ml)	28	967 (363)	880	355	1731
FVC (ml)	28	1952 (762)	2010	690	3782
Reversibility	91	6.5 (10.2)	5.3	-31	37
Mean no. of large PEF decrements*	94	14 (26)	2.5	0	122
Mean no. of exacerbations	94	3.1 (3.2)	2	0	16
Mean no. of symptomatic falls in PEF†	94	3.7 (3.7)	2.5	0	16
Mean no. of episodes of dyspnoea‡	94	5.7 (5.4)	3.5	0	20
Mean no. of episodes of change in sputum§	94	2.9 (3.4)	2	0	17
Mean no. of episodes of nasal discharge/congestion	94	2.9 (3.6)	2	0	19
Mean no. of episodes of wheeze¶	94	3.8 (4.5)	2	0	18
Mean no. of episodes of URS**	94	2.7 (3.0)	2	0	14

*Large PEF decrements: PEF <20% × median value.
 †Symptomatic fall in PEFs: defined as fall in PEF 10 l/min for ≥2 days + increase in breathlessness.
 ‡Dyspnoea: defined as an increase in symptom.
 §Sputum changes: defined as a change in sputum purulence or amount.
 ¶Wheeze: defined as an increase in wheeze or increase in tightness of chest.
 **URs: upper respiratory symptoms—increase in sore throat or cough.
 FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.

Table 2 Summary statistics for pollutants and meteorological data October 1995–October 1997

	All months Mean (SD) [median] IQR	Autumn and winter		Spring and summer	
		Mean	Range	Mean	Range
NO ₂ (1 h max, ppb)	51.4 (15.8), [48], 42 to 56	51.3	26 to 163	51.5	24 to 131
O ₃ (8 h ave, ppb)	15.5 (10.7), [14.1], 7.5 to 21.6	9.8	1 to 32	21.6	3 to 74
SO ₂ (24 h ave, ppb)	7.5 (6.3), [5.3], 3.2 to 9.3	9.8	1 to 42	5.5	1 to 74
PM ₁₀ (24 h ave, µg/m ³)	37.7 (17.4), [32.5], 25.9 to 44.9	39.1	10 to 134	35.6	13 to 86
Black smoke* (24 h ave, µg/m ³)	10.1 (9.7), [7], 4 to 13	12.9	1 to 81	7.0	1 to 34
Outdoor temperature (average of min and max, °C)	11.4 (6.0), [11], -1.5 to 27	8.1	-1.5 to 21	15.3	4.5 to 27

*Summary statistics presented for the Stepney black smoke monitor used for 63% of patients.
 PM, particulate matter.

large PEF decrements (table 4), with all ORs close to 1.0 and non-significant.

Effects on exacerbations and symptoms

All ORs for effects of pollutants on exacerbations were >1.0, suggesting adverse effects, but all were non-significant (table 4). Effect sizes were bigger for symptomatic fall in PEF where PM₁₀ and black smoke showed significant adverse effects. The remaining ORs for NO₂, O₃ and SO₂, while not significant, were nonetheless consistently >1.0. ORs for a symptomatic fall in PEF for a change in pollutant level equivalent to the IQR were 1.12 (95% CI 1.02 to 1.25, PM₁₀) and 1.07 (1.01 to 1.13, black smoke). Dyspnoea was significantly associated with PM₁₀ (OR

Table 3 Regression of respiratory function (PEF, FEV₁ and FVC) on pollutant level* (previous day)

	Estimate† (per unit change) (95% CI)	p Value	Estimate‡ (per IQR change)
PEF (l/min) n=94			
NO ₂ (ppb)	0.013 (0.002 to 0.024)	0.026	0.179
O ₃ (ppb)	-0.015 (-0.039 to 0.009)	0.229	-0.211
SO ₂ (ppb)	0.031 (-0.010 to 0.072)	0.133	0.191
PM ₁₀ (µg/m ³)	0.009 (-0.006 to 0.023)	0.253	0.164
Black smoke (µg/m ³)	0.011 (-0.005 to 0.028)	0.180	0.103
FEV ₁ (ml) n=28			
NO ₂ (ppb)	0.005 (-0.106 to 0.116)	0.929	0.071
O ₃ (ppb)	-0.081 (-0.258 to 0.096)	0.369	-1.143
SO ₂ (ppb)	-0.035 (-0.386 to 0.315)	0.843	-0.216
PM ₁₀ (µg/m ³)	0.031 (-0.067 to 0.129)	0.536	0.588
Black smoke (µg/m ³)	0.045 (-0.113 to 0.203)	0.576	0.405
FVC (ml) n=28			
NO ₂ (ppb)	0.071 (-0.189 to 0.332)	0.591	1.000
O ₃ (ppb)	0.162 (-0.238 to 0.562)	0.426	2.288
SO ₂ (ppb)	-0.335 (-1.192 to 0.522)	0.444	-2.043
PM ₁₀ (µg/m ³)	0.187 (-0.017 to 0.392)	0.073	3.561
Black smoke (µg/m ³)	0.166 (-0.218 to 0.551)	0.396	1.498

*In addition to individual pollutants (previous day), each model includes outdoor temperature (average of the minimum and maximum) and season (four categories) plus control for autocorrelation.
 †Estimates represent the change in lung function for a 1 unit change in pollutant level (ppb for NO₂, O₃, SO₂; µg/m³ for PM₁₀, black smoke).
 ‡Estimates represent the change in lung function for an IQR change in pollutant level.
 FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; PM, particulate matter.

Table 4 Large PEF decrements, COPD exacerbations and PEF exacerbations*

Pollutant	OR† (unit change) (95% CI)	p Value	Estimate‡ (per IQR change)
Large PEF decrements			
NO ₂ (ppb)	1.000 (0.995 to 1.004)	0.844	0.994
O ₃ (ppb)	0.996 (0.989 to 1.004)	0.362	0.950
SO ₂ (ppb)	1.001 (0.988 to 1.014)	0.890	1.006
PM ₁₀ (µg/m ³)	0.999 (0.995 to 1.003)	0.712	0.985
Black smoke (µg/m ³)	1.001 (0.991 to 1.011)	0.851	1.009
COPD exacerbations			
NO ₂ (ppb)	1.002 (0.996 to 1.008)	0.469	1.032
O ₃ (ppb)	1.005 (0.987 to 1.023)	0.598	1.070
SO ₂ (ppb)	1.002 (0.982 to 1.022)	0.878	1.010
PM ₁₀ (µg/m ³)	1.004 (0.998 to 1.010)	0.234	1.075
Black smoke (µg/m ³)	1.003 (0.994 to 1.013)	0.497	1.029
Symptomatic fall in PEF			
NO ₂ (ppb)	1.004 (0.999 to 1.009)	0.137	1.058
O ₃ (ppb)	1.002 (0.984 to 1.020)	0.840	1.026
SO ₂ (ppb)	1.004 (0.987 to 1.022)	0.622	1.026
PM ₁₀ (µg/m ³)	1.006 (1.001 to 1.012)	0.029	1.124
Black smoke (µg/m ³)	1.007 (1.000 to 1.014)	0.050	1.066

*In addition to individual pollutants (previous day), each model includes outdoor temperature (average of the minimum and maximum) and season (four categories) plus control for autocorrelation.
 †ORs are for a 1 unit change in pollutant level (ppb for NO₂, O₃, SO₂; µg/m³ for PM₁₀, black smoke).
 ‡ORs are for an IQR change in pollutant level.
 COPD, chronic obstructive pulmonary disease; PEF, peak expiratory flow; PM, particulate matter.

1.13; 95% CI 1.04 to 1.23) for a rise in PM₁₀ across its IQR. No other symptom–pollutant combinations were significant, except O₃ which showed a protective association with nasal discharge/congestion (table 5).

In multipollutant models, the effect size for PM₁₀ on symptomatic fall in PEF remained similar and borderline significant after adjustment for other pollutants (table 6). In contrast, the effects of NO₂ and black smoke were weaker after controlling for PM₁₀. For dyspnoea, the effect of PM₁₀ was slightly stronger and remained significant after adjustment for either NO₂, black smoke or both (table 6). There was no evidence of any adverse effect of NO₂ or black smoke after allowing for PM₁₀.

DISCUSSION

Overall this study provided evidence for adverse effects of outdoor pollution on symptoms and exacerbations in patients with COPD living in London, particularly PM₁₀, black smoke and NO₂. Most symptoms gave ORs >1 but very few associations were statistically significant. Effect sizes were mostly larger for symptomatic fall in PEF compared with COPD exacerbations and gave significant ORs for NO₂, PM₁₀ and black smoke. Symptomatic falls in PEF events were more common than COPD exacerbations and so significance is partly due to increased statistical power. Dyspnoea was associated with higher levels of PM₁₀ but was not significantly associated with any other pollutants. Multiple pollutant models showed that the association between PM₁₀ and dyspnoea was stronger after adjustment for other pollutants, although this analysis was post hoc and conducted to aid interpretation of the findings. In general, symptoms are highly variable in COPD and the appearance of shortness of breath on the diary card may reflect psychological as well as mechanical effects on the airway. The occurrence of shortness of breath with a fall in PEF is suggestive of a mechanical effect on the airway by some stimulus.

Table 5 Worsening symptoms: dyspnoea, sputum purulence or sputum amount, nasal discharge/congestion, wheeze or tight chest and upper respiratory symptoms*

Pollutant	OR† (unit change) (95% CI)	p Value	Estimate‡ (per IQR change)
Dyspnoea n=77			
NO ₂ (ppb)	1.003 (0.997 to 1.008)	0.338	1.036
O ₃ (ppb)	1.005 (0.995 to 1.016)	0.335	1.078
SO ₂ (ppb)	0.996 (0.980 to 1.013)	0.662	0.978
PM ₁₀ (µg/m ³)	1.006 (1.002 to 1.011)	0.008	1.125
Black smoke (µg/m ³)	1.003 (0.994 to 1.012)	0.526	1.027
Sputum changes n=68			
NO ₂ (ppb)	1.006 (0.999 to 1.013)	0.085	1.085
O ₃ (ppb)	1.007 (0.992 to 1.022)	0.370	1.099
SO ₂ (ppb)	1.008 (0.988 to 1.029)	0.446	1.042
PM ₁₀ (µg/m ³)	1.004 (0.997 to 1.011)	0.251	1.082
Black smoke (µg/m ³)	1.004 (0.992 to 1.016)	0.536	1.035
Nasal discharge or congestion n=70			
NO ₂ (ppb)	0.999 (0.991 to 1.006)	0.690	0.979
O ₃ (ppb)	0.984 (0.970 to 0.998)	0.023	0.794
SO ₂ (ppb)	1.011 (0.994 to 1.030)	0.209	1.072
PM ₁₀ (µg/m ³)	1.003 (0.997 to 1.010)	0.296	1.067
Black smoke (µg/m ³)	1.003 (0.992 to 1.013)	0.598	1.026
Wheeze or tight chest n=70			
NO ₂ (ppb)	1.002 (0.996 to 1.009)	0.460	1.033
O ₃ (ppb)	0.992 (0.977 to 1.007)	0.274	0.890
SO ₂ (ppb)	1.002 (0.986 to 1.019)	0.785	1.014
PM ₁₀ (µg/m ³)	1.004 (0.998 to 1.009)	0.187	1.071
Black smoke (µg/m ³)	1.002 (0.993 to 1.010)	0.722	1.014
Upper respiratory symptoms n=73			
NO ₂ (ppb)	0.999 (0.990 to 1.008)	0.849	0.988
O ₃ (ppb)	0.987 (0.969 to 1.005)	0.143	0.829
SO ₂ (ppb)	0.991 (0.971 to 1.012)	0.392	0.947
PM ₁₀ (µg/m ³)	1.000 (0.993 to 1.007)	0.928	0.994
Black smoke (µg/m ³)	1.007 (0.990 to 1.024)	0.435	1.062

*In addition to individual pollutants (previous day), each model includes outdoor temperature (average of the minimum and maximum) and season (four categories) plus control for autocorrelation.
 †ORs are for a 1 unit change in pollutant level (ppb for NO₂, O₃, SO₂; µg/m³ for PM₁₀, black smoke).
 ‡ORs are for an IQR change in pollutant level.
 PM, particulate matter.

When estimated effect sizes were scaled to IQR increases in pollutant level, it was evident that estimated effect sizes were considerable: the odds of a symptomatic fall in PEF increased by 13% when PM₁₀ increased across the IQR, and a similar size effect was observed for dyspnoea. These increases in odds represent a substantial increase in risk, if associations were real and causal, and are stronger than observed effects of raised pollution on COPD hospital admissions.⁵

Effects on neither mean lung function nor the binary large PEF decrements showed consistent trends, despite evidence from other panels that the binary outcome is more discriminating than mean PEF.^{8, 24} This may reflect the high variability of PEF and/or that lung function was measured after taking medication. Importantly, the findings of adverse effects on symptoms but not mean lung function are consistent with results of ecological studies showing associations with acute events such as death, hospital admission and general practitioner consultations. They lend support to the hypothesis that effects of outdoor air pollution are greater among the very vulnerable.

Findings in this London study were consistent with those of Harré in New Zealand¹¹ who reported associations between particles and symptoms with similar effect sizes to ours; however, they also found no associations with lung function.

Table 6 Further investigation of associations with PEF exacerbations and dyspnoea: single and multiple pollutant models*

Model*	Single pollutant models			Multiple pollutant models			
	OR† (unit change)	SE	p Value	OR† (unit change)	SE	p Value	OR‡ (IQR change)
Symptomatic fall in PEF (N=78)							
Model 1							
NO ₂	1.004	0.003	0.137	0.999	0.003	0.709	0.983
PM ₁₀	1.006	0.003	0.029	1.007	0.003	0.042	1.140
Model 2							
NO ₂	1.004	0.003	0.137	1.002	0.004	0.654	1.025
Black smoke	1.007	0.004	0.050	1.005	0.005	0.306	1.049
Model 3							
PM ₁₀	1.006	0.003	0.029	1.006	0.004	0.083	1.126
Black smoke	1.007	0.004	0.050	1.000	0.005	0.953	0.998
Model 4							
NO ₂	1.004	0.003	0.137	0.999	0.004	0.725	0.980
PM ₁₀	1.006	0.003	0.029	1.007	0.004	0.064	1.137
Black smoke	1.007	0.004	0.050	1.001	0.006	0.907	1.006
Dyspnoea n=77							
Model 1							
NO ₂	1.003	0.003	0.338	0.997	0.003	0.380	1.017
PM ₁₀	1.006	0.002	0.008	1.008	0.003	0.007	1.031
Model 2							
NO ₂	1.003	0.003	0.338	1.001	0.004	0.760	0.961
Black smoke	1.003	0.005	0.526	1.003	0.006	0.598	1.159
Model 3							
PM ₁₀	1.006	0.002	0.008	1.008	0.003	0.007	1.156
Black smoke	1.003	0.005	0.526	0.996	0.006	0.455	0.961
Model 4							
NO ₂	1.003	0.003	0.338	0.998	0.004	0.578	0.970
PM ₁₀	1.006	0.002	0.008	1.008	0.003	0.005	1.168
Black smoke	1.003	0.005	0.526	0.998	0.007	0.733	0.979

*In addition to individual pollutants (previous day), each model includes outdoor temperature (average of the min and maximum) and season (four categories) plus control for autocorrelation. Models 1–3 each contain two pollutants analysed together. Model 4 includes all three pollutants.

†ORs are for a 1 unit change in pollution level (ppb for NO₂, O₃, SO₂; µg/m³ for PM₁₀, black smoke).

‡ORs are for an IQR change in pollutant level.

PEF, peak expiratory flow; PM, particulate matter.

Trenga¹⁰ reported effects of PM_{2.5} on FEV₁ in all adults but no effects on PEF. PM_{2.5} data were not available when our study was conducted but since PM₁₀ is dominated by small particles, the comparison with our study is reasonable. The adverse effects of O₃ on exacerbations demonstrated in the Parisian study¹² were stronger than in our study.

The estimated relationships between air pollution and symptoms and lung function in this COPD panel may have been affected by the time patients spent outdoors. Subjects recorded this for part of the study only and so, although we did adjust, full adjustment was not possible.

When this study was designed we chose to limit the use of multiple pollutant metrics to avoid overtesting. In particular we used just one measure for NO₂—1 h maximum—partly because of the belief that the peak drives health effects. However, the correlation between 1 h maximum NO₂ and average daily NO₂ was very high at 0.90, and so the choice would seem unlikely to matter. When our study was conducted, there was a network of black smoke monitors and so we used the monitor nearest to the patient's home to estimate their exposure. The data on the other pollutants all came from a single monitor in central London but the correlation with another monitor for PM₁₀ was high (0.95), suggesting that this was not unreasonable. Even so, the use of multiple monitors may explain the weaker associations observed with black smoke. We modelled exposure to pollution using

previous day pollutant level as others have done, and have not looked at long lags²⁵ which would most probably have produced stronger associations.

Daily diary data provide a powerful tool to investigate effects of air pollution within individuals but are resource intensive and often panels are only able to include a relatively small sample and/or a short follow-up time. The strength of this study was the relatively large sample, 94, and the lengthy 2-year follow-up period. Since compliance was very good, missing data were minimal.

Recent WHO guidelines for PM₁₀ are 20 and 50 µg/m³ for annual and daily averages, respectively. The levels of exposure for this panel were a little higher. The WHO guidelines were largely based on ecological time series studies and cohort data on mortality. This study therefore lends support to the guideline.

In conclusion, in patients with COPD living in London, there is evidence for adverse effects of outdoor pollution on symptoms and exacerbations, particularly for PM₁₀, black smoke and NO₂. The ORs of up to 1.17 for an IQR increase in pollutant level represent substantial effects which would have important public health implications if shown to be real and causal. This deserves further investigation in larger panels.

Funding The East London COPD study was funded by the British Lung Foundation. The statistical analysis for the air pollution analyses was funded by the UK Department of Health.

Competing interests None.

Ethics approval This study was conducted with the approval of the East London and City Health Authority Ethic Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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Journal club

Inactivation of the N-terminal of ACE reduces bleomycin-induced lung fibrosis

This study examined bleomycin-induced lung injury in normotensive mice, termed N-KO and C-KO, which have point mutations inactivating the N- or C-terminal catalytic sites of angiotensin converting enzyme (ACE), respectively. N-KO, but not C-KO mice, exhibited a marked resistance to bleomycin-induced lung injury and fibrosis, as assessed by lung histology and hydroxyproline content (46% increase in hydroxyproline content in C-KO lungs compared with 6.9% in N-KO lungs, $p < 0.001$). Furthermore, the N-KO mice showed enhanced survival when exposed to a dose of bleomycin lethal to wild-type mice. The importance of the tetrapeptide N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), an ACE N-terminal substrate, was demonstrated when N-KO mice were treated with S-17092, a prolyl-oligopeptidase inhibitor that reduces the concentration of AcSDKP. These mice developed lung fibrosis similar to wild-type mice in response to bleomycin injection. Conversely, the administration of AcSDKP to wild-type mice reduced bleomycin-induced lung fibrosis, as assessed by lung hydroxyproline content (7.7 $\mu\text{g}/\text{mg}$ in mice given AcSDKP compared with 12.47 $\mu\text{g}/\text{mg}$ in mice given saline, $p < 10^{-4}$).

These results show that the inactivation of the N-terminal of ACE significantly reduces bleomycin-induced lung fibrosis and implicates AcSDKP as a mediator of this protection. A novel means to increase tolerance to bleomycin and to treat fibrosing lung diseases is thus proposed.

► Li P, Xiao HD, Xu J, et al. Angiotensin-converting enzyme N-terminal inactivation alleviates bleomycin-induced lung injury. *Am J Pathol* 2010;**177**:1113–21.

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Published Online First 26 October 2010

Thorax 2011;**66**:596. doi:10.1136/thx.2010.151894