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# Environmental factors and hospitalisation for COPD in a rural county of England

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### What this paper adds

#### **What is already known on this subject?**

Studies undertaken in urban areas have shown that increases in air pollution are associated with increased hospital admissions for chronic obstructive pulmonary disease (COPD). However, it is not known if such associations exist at the lower pollutant concentrations found in more rural areas.

#### **What does this study add?**

In a much more rural population than previously studied, we found that increases in ambient carbon monoxide, nitric oxide, nitrogen dioxide, and oxide of nitrogen concentrations were associated with increases in hospital admissions for COPD. Further studies in more rural areas are required to confirm these findings and investigate the possible presence of threshold values below which the effects of the pollutants on COPD cannot be observed.

## ABSTRACT

**Background:** Chronic Obstructive Pulmonary Disease (COPD) is a major global cause of morbidity and mortality. Studies in urban areas have shown associations between air pollutants and hospital admissions for COPD. We investigated if temporal variations in air quality are associated with hospital admissions for COPD in a rural region with lower concentrations of air pollutants than previously studied.

**Methods:** Daily COPD admissions were recorded for patients attending 3 hospitals in the county of Norfolk, England, between January 2006 and February 2007. Records were combined with daily information on concentrations of 6 air pollutants (carbon monoxide, nitric oxide, nitrogen dioxide, oxides of nitrogen, ozone and fine particulates), airborne pollens, temperature, and influenza incidence. A case-crossover analysis was used to examine the association between air pollution and daily admissions.

**Results:** There were 1,050 admissions for COPD over the study period. After adjustment for temperature, pollen and respiratory infections, each 10  $\mu\text{g}/\text{m}^3$  increase in CO was associated with a 2% percent increase in the odds of admission. Values of 17%, 22%, and 9% were observed for NO, NO<sub>2</sub> and NO<sub>x</sub> respectively. No associations were observed with O<sub>3</sub> or PM<sub>10</sub>.

**Conclusion:** Amongst a population of a less urbanised area than previously investigated, this study found evidence that ambient pollutant concentrations were still associated with the risks of hospital admission for COPD.

## INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major global cause of morbidity and mortality. It is currently the fifth leading cause of mortality in England and Wales [1]. It is a disease of chronic inflammation of the lower airways [2] characterised by airflow obstruction which is usually progressive and not fully reversible. Exacerbations (sudden onset worsening of respiratory symptoms) may require hospitalisation, with around ten percent of patients dying during admission and up to 40% dying within one year [3].

In economically developed countries, COPD is almost always associated with a history of smoking. However, under 20% of smokers develop COPD and those who do may have a genetic susceptibility to the allergens in cigarette smoke and possibly to other aero-allergens or contaminants [4]. Once lung pathology is initiated by cigarette smoke other factors may precipitate further damage or exacerbate symptoms. While the majority of exacerbations are caused by infectious agents, there is evidence that some requiring hospitalisation are due to atmospheric pollution [5]. Determining factors that may trigger exacerbation may allow modification of patient medication or lifestyle at times of particular risk. This may include warning susceptible patients to stay indoors when outdoor environmental conditions are poor [6, 7].

COPD hospital admissions in the UK display seasonality, with a fourfold week to week variation, and peak admissions tending to occur in mid winter [6]. The lung function of patients can be reduced in cold weather [8] and they can display reduced lung function with increased air pollution [9]. Symptom exacerbations may also be triggered by bacterial or viral infections [5, 8]. However, it is thought that airborne pollutants interact with infections to produce inflammation of the lower respiratory tract [10], and the resultant inflammatory response worsens the patient's symptoms. Particulates (PM<sub>10</sub>), sulphur dioxide (SO<sub>2</sub>), oxides of nitrogen (NO<sub>x</sub>) and ozone (O<sub>3</sub>) have been shown to induce airway inflammation both in healthy individuals and in those with pre-existing allergic lung disease [10, 11, 12, 13].

Epidemiological studies have demonstrated an increase in COPD hospitalisations and mortality during periods of high air pollution [9, 12, 14, 15, 16, 17, 18, 19, 20]. However, previous work has been undertaken in major conurbations, for example Barcelona [9, 12, 16, 21], London [9, 19, 22, 23], Birmingham, UK [19, 24], Milan [9, 19, 24]), Paris [9, 19, 24], Rome [17, 24], Stockholm [24], and

Cleveland, Denver and Los Angeles [18]. The mean or range in values reported by some of these studies are given in Table 1. A problem is that exposure to pollutants will often be much higher in urban study populations compared to the wider population of COPD patients. This is because, with the exception of ozone, pollution levels are generally higher in large cities. A meta-analysis by Brunekreef *et al* [13] and work by Næss *et al* [20] in Oslo, amongst others, raise questions around the existence of thresholds for health effects of some air pollutants. It is not clear if COPD patients living in less urbanised areas will be impacted by changes in air quality in the same way as patients in large conurbations.

**Table 1: Pollution concentrations reported in previous work**

<i>Study</i>	<i>Location</i>	<i>Pollutant</i>	<i>Mean values or range of observed concentrations</i>
<i>Anderson et al, 1997 [9]</i>	Amsterdam, Barcelona, London, Milan, Paris, Rotterdam	NO <sub>2</sub>	42 – 67 µg/m <sup>3</sup>
		O <sub>3</sub>	20 – 69 µg/m <sup>3</sup>
<i>Hajat et al, 1999 [22]</i>	London	NO <sub>2</sub>	33.6 µg/m <sup>3</sup>
		O <sub>3</sub>	17.5 µg/m <sup>3</sup>
		CO	0.8 mg/m <sup>3</sup>
		PM <sub>10</sub>	28.5 µg/m <sup>3</sup>
<i>Fusco et al, 2001 [17]</i>	Rome	NO <sub>2</sub>	86.7 µg/m <sup>3</sup>
		O <sub>3</sub>	27.0 µg/m <sup>3</sup>
		CO	3.6 mg/m <sup>3</sup>
<i>Atkinson et al, 2001 [19]</i>	Birmingham, London, Milan, Rome, Paris, Stockholm, The Netherlands, Barcelona	O <sub>3</sub>	26.0 – 66.6 µg/m <sup>3</sup>
		NO <sub>2</sub>	35.6 – 147.0 µg/m <sup>3</sup>
		CO	0.7 – 7.9 mg/m <sup>3</sup>
<i>Næss et al, 2006 [20]</i>	Oslo	NO <sub>2</sub>	2 – 73 µg/m <sup>3</sup>
		PM <sub>10</sub>	7 – 30 µg/m <sup>3</sup>
<i>Medina-Ramón et al, 2006 [18]</i>	36 US cities including Chicago, Detroit, Los Angeles, St Louis.	O <sub>3</sub>	15.0 – 63.0 µg/m <sup>3</sup>
		PM <sub>10</sub>	15.9 – 44.0 µg/m <sup>3</sup>

Based in the rural county of Norfolk, England, with a population of just over 830,000 residents, this study investigates if associations are present between temporal variations in air quality and hospital admissions from COPD in a predominantly rural area. Norfolk has an economy based on agriculture and service industries, with very little heavy industry, and road transport is the main pollution source

[25]. Hence air pollution is greatest during the working week. The city of Norwich is located centrally within Norfolk. Norwich is the largest city in the county and is the focus for employment and leisure. It has a population of approximately 160,000, which is below the threshold at which very high levels of air pollution are likely to occur [25]. The rest of the county is predominantly agricultural in nature, with most of the population living in market towns or smaller settlements. We examine whether variations in concentrations of air pollutants are a risk for hospital admissions amongst a group of well characterised COPD patients in Norfolk.

## **MATERIALS AND METHODS**

### **Study subjects**

Information on hospital admissions from COPD exacerbations between 3 January 2006 and 3 February 2007 was collected as part of the MATREX study being undertaken at the University of East Anglia. MATREX is a single blind randomised controlled trial to determine the effectiveness and cost utility of manual chest physiotherapy techniques in the management of exacerbations of COPD. Researchers identified and screened patients  $\geq 18$  years of age admitted for respiratory symptoms at the three hospitals serving the county. The criteria for eligibility were a clinical diagnosis of COPD and an acute exacerbation. The diagnostic criteria used were those defined by the British Thoracic Society & NICE [26]. These were; progressive, predominantly irreversible airflow obstruction, forced Expiratory Volume in the first second (FEV1) that was  $<80\%$  of the predicted value, and a ratio of FEV1 to Forced Vital Capacity (FVC) of less 0.7. While a minimum age of 18 years was specified, 90.2% of patients for which age at admission was available were aged over 60 years.

Information was available from one hospital for the full 13 months of study, whilst data for the other two were available for the final 11 and 2 months of the study respectively. The hospital with the full 13 months of data is located in the main city of Norwich, whilst that with 11 months of data was located in the coastal town of Gorleston in the east of the county, and that with 2 months of data was located in the town of Kings Lynn in the west.

### **Study design**

A case-crossover analysis was used to examine the association between ambient air pollution and COPD admissions. Environmental factors and influenza incidence at the time of admission to hospital were compared with values of the same variables preceding the admission.

## Analysis

Air pollution measures for the Norwich Centre air quality monitoring site were obtained from the UK Air Quality Archive monitoring data [27]. The Norwich site offered the most complete record of a range of pollutants over the period of the study. Variables assessed were CO, NO, NO<sub>2</sub>, NO<sub>x</sub>, and O<sub>3</sub>. SO<sub>2</sub> was not assessed since there are no significant sources of this pollutant in the study area and levels were below the threshold of detection (3 µg/m<sup>3</sup>) for the Norwich Centre unit for 274 (69.0%) of days during the period examined.

Daily average and maximum 24 hour recorded values of each pollutant were determined for the period 3 January 2006 to 3 February 2007 inclusive. Technical problems led to PM<sub>10</sub> data not being recorded at the Norwich location between 19 June 2006 and 8 October 2006. Hence data from a site in the nearby town of Gorleston, within the study area and covering the full thirteen months, were used instead. Values at the two sites were similar; for the period 1 January 2006 to 3 February 2007 for which data was available for both Norwich and Gorleston, average daily PM<sub>10</sub> values were strongly correlated ( $r = 0.856$ ,  $p < 0.001$ ). The Norwich database also had 3 days with no NO<sub>x</sub> data and 2 days with no O<sub>3</sub> data. Average values for the days immediately preceding and after the missing data were used to complete the dataset.

Pollen data was supplied by the National Pollen Aerobiology Research Unit (NPARU). The data were recorded in the city of Cambridge, the closest location for which measurements were available, being approximately 30 miles to the southeast of Norfolk. The number of birch, oak and grass pollen grains per m<sup>3</sup> of air was determined for the period 13 March 2006 – 18 September 2006 inclusive, the pollen season. No data was available on pollen concentrations outside these dates as concentrations are close to zero. Total daily counts for all three species combined were used.

Maximum and minimum air temperatures were determined from average values supplied by the British Atmospheric Data Centre for 10 land surface observation stations in the UK Meteorological Office MIDAS network in Norfolk [28]. The locations were chosen to be widely dispersed across the county. A technical fault meant temperature information was not available for the period 9 January 2007 to 31 January 2007. Temperatures recorded at the Gorleston air quality monitoring site were used for this period.

No local data was available on the incidence of influenza. Hence weekly incidence of flu-like illness data for England and Wales was obtained from the Health Protection Agency as an indicator of the background respiratory infection burden. As the information was only available for 7 day periods, compared to the daily nature of the other variables, a seven day prior-moving-average value of incidence was used in order to provide temporal smoothing.

The case-crossover models [18, 29, 30] were fitted in the SPSS 14 package. For each patient, environmental factors on the day of admission to hospital (lag zero) or one, two or three days preceding admission (the case period) were compared with values of the same variables seven days preceding the case day (control period). The framework was modelled using binary logistic regression, where the outcome was coded 1 for admission days and 0 for control days, and the explanatory variables were the environmental variables and influenza incidence recorded for each corresponding day. Control days relatively close in time to the event day reduce confounding due to seasonal effects and slowly changing patient characteristics, such as deterioration of lung function over time [13, 18]. Seven days between the case and control observations ensured that the control observations were sufficiently distant from admission to have been unlikely to have affected lung function. It also meant that case and control observations occurred on the same day of the week. Nevertheless, to test the sensitivity of the results to the selection of case-control timeframe, case-control periods of zero compared with seven, one and eight, two and nine and three and ten days preceding admission were assessed.

Studies have suggested that the association between mean air temperature and morbidity may follow a U-shaped function [31, 32]. Therefore, maximum air temperature was modelled as a categorical variable with temperatures  $\pm 2.5^{\circ}\text{C}$  from the overall average ( $13.9^{\circ}\text{C}$ ) being the baseline comparator. Minimum temperatures were also modelled as a categorical variable with each category having a  $5^{\circ}\text{C}$  range. The baseline was the highest minimum temperature recorded.

Since the pollutants assessed showed a high degree of collinearity, each was modelled separately in the statistical analyses. All pollutants were measured in  $\mu\text{g}/\text{m}^3$  with the exception of CO ( $\text{mg}/\text{m}^3$ ). To allow direct comparison, CO concentration was expressed as  $\mu\text{g}/\text{m}^3$  in the conditional logistic regression analyses.

## RESULTS

During the time period of the study, there were 1,050 admissions for COPD that met the inclusion criteria. For the one hospital providing data for the full thirteen months of the study, minimum admissions were in April 2006 (6.0%) and maximum in January 2006 (10.4%). The majority of admissions took place on a Monday (34.3%). Minimum admissions were zero, maximum 10 per day with a mean of 1.55 (standard deviation 1.94) and median 1.00.

Univariate analysis showed that the levels of airborne pollutants were almost always higher on case days than on control days (Table 2). The results in Table 2 are for lag 0 (admission day) to 7 days prior to admission (control day). Similar values were reported for a 1 (case day) to 8 (control day) lag and are not repeated here. A comparison with Table 1 shows that, with the exception of O<sub>3</sub>, concentrations of which are generally higher in rural areas, recorded values are lower than those observed elsewhere, with many concentrations being less than half those encountered in previous research.

**Table 2: Average concentration of airborne pollutants. Case and control days compared**

<i>Pollutant</i> ( $\mu\text{g}/\text{m}^3$ )	<i>Control days (seven days prior to admission)</i>				<i>Case days (day of admission)</i>			
	<i>minimum</i>	<i>maximum</i>	<i>mean</i>	<i>Standard deviation</i>	<i>minimum</i>	<i>maximum</i>	<i>mean</i>	<i>Standard deviation</i>
<i>CO</i>	105.20	408.10	194.46	80.93	108.70	432.20	204.73	119.97
<i>NO</i>	0.45	25.64	6.90	10.90	0.58	28.56	8.07	18.46
<i>NO<sub>2</sub></i>	7.93	40.71	22.02	8.45	8.35	42.97	22.93	8.79
<i>NO<sub>x</sub></i>	9.11	76.30	32.48	22.05	9.84	83.39	35.18	33.97
<i>Ozone</i>	19.45	66.34	43.91	21.23	19.54	68.53	45.06	21.00
<i>PM<sub>10</sub></i>	9.77	34.27	19.87	8.51	10.04	35.03	20.47	9.27

Conditional logistic regression analysis showed that there was no significant association between the odds of admission and background respiratory infection, pollen or minimum environmental temperature at any of the case-control periods considered. Analysis with maximum temperature as predictor showed that likelihood of hospital admission was significantly reduced at maximum ambient temperatures of 6.4 – 11.3<sup>0</sup>C when lags of one to eight days were compared (Odds ratio (OR) 0.767,

95% confidence interval (CI) 0.604 – 0.975,  $p = 0.030$ ). The baseline comparator was maximum temperature 11.4 – 16.4°C.

The effects of the mean daily concentration of each pollutant on the odds of admission are shown in Table 3. Table 3 compares findings when case-control periods of lag 0-7 and 1-8 were used. Odds ratios and 95% confidence intervals are given for each pollutant alone (unadjusted) and controlling for maximum temperature, pollen and influenza infections (adjusted). In general adjustment tended to strengthen associations with air pollutants, and in the case of NO at lag zero days, made the association with odds of admission statistically significant. Analyses using maximum daily levels of each pollutant gave similar results in terms of significance and magnitude of effect, and are hence not replicated here.

<i>Pollutant</i>	<i>Odds Ratio (95% CI)</i>			
	<i>Lag 0-7, unadjusted</i>	<i>Lag 0-7, adjusted<sup>1</sup></i>	<i>Lag 1-8, unadjusted</i>	<i>Lag 1-8, adjusted<sup>1</sup></i>
<i>CO</i>	1.010* (1.001-1.019)	1.015** (1.005-1.025)	1.013* (1.001-1.025)	1.018** (1.005-1.031)
<i>NO</i>	1.055 (0.993-1.120)	1.076* (1.009-1.148)	1.131* (1.015-1.260)	1.170** (1.040-1.316)
<i>NO<sub>2</sub></i>	1.130* (1.023-1.248)	1.196** (1.071-1.334)	1.148** (1.037-1.272)	1.220** (1.092-1.362)
<i>NO<sub>x</sub></i>	1.035* (1.002-1.068)	1.050** (1.014-1.087)	1.067** (1.018-1.119)	1.093** (1.038-1.151)
<i>O<sub>3</sub></i>	1.026 (0.985-1.069)	1.015 (0.964-1.069)	0.987 (0.947-1.029)	0.952 (0.906-1.002)
<i>PM<sub>10</sub></i>	1.079 (0.980-1.188)	1.101 (0.988-1.226)	1.056 (0.961-1.161)	1.054 (0.949-1.170)

<sup>1</sup> adjusted for maximum temperature, pollen, and influenza infection

\*  $p < 0.05$ , \*\*  $p < 0.01$

**Table 3: Odds of hospital admission at case-control periods of lag 0-7 and 1-8 days associated with a 10 µg/m<sup>3</sup> increase in concentration.**

With the exception of unadjusted NO lag 0-7 days, higher concentrations of CO, NO, NO<sub>2</sub>, and NO<sub>x</sub> were positively and statistically significantly associated with odds of admission at a lag of zero and one day preceding hospitalisation. Associations were strengthened by adjustment and were generally strongest when a lag of 1-8 days was chosen. There was no significant association between likelihood of hospitalisation and concentration of ozone or PM<sub>10</sub> for any of the case-control comparisons. When lags of 2 - 9 and 3 - 10 days were examined, no statistically significant associations were observed with any of the pollution variables.

## DISCUSSION

Measures of respiratory infection incidence, pollen load and minimum air temperature were not found to be associated with the likelihood of hospitalisation for COPD. However, when lags of up to 8 days from the date of admission were studied, there was a positive association between the odds of admission and measured concentrations of CO, NO, NO<sub>x</sub>, and NO<sub>2</sub>. This was so both before and after adjustment for maximum temperature, respiratory infection and pollen. After this period, no associations were observed.

**Our choice of a case-crossover design mirrors a number of other studies that have used the same methodology to assess the effect of short-term change in air pollution on hospital admission for COPD [18, 29, 35, 36].** Nevertheless, it is difficult to directly compare the results reported here with previous studies since earlier work has either examined rate of admission [9, 17,18,19] or odds of death [16, 20] or numbers dying [15]. Other workers have examined all respiratory admissions [14, 23], or have grouped COPD with other conditions including asthma or chronic bronchitis [17, 19, 24, 32, 37]. Hajat *et al.* [22] studied primary care consultations for all lower respiratory tract disease. Nevertheless, previous work has generally suggested a small but statistically significant association between acute exposure to NO<sub>2</sub>, CO, O<sub>3</sub> and PM<sub>10</sub> and COPD hospitalisation [9, 12, 17, 18, 19, 35, 36, 38]. **In particular, our work supports the findings of Yang *et al* [38] in Vancouver. Studying hospital admissions in those aged at least 65 years, they also found that NO<sub>2</sub> and CO were associated with admissions.** In studies where a significant association occurred, the lag between exposure and admission varied from same day to two days preceding admission.

**In contrast to some previous work**, we did not find statistically significant associations with PM<sub>10</sub> or O<sub>3</sub>. **However, Yang *et al.* [35] also found no association with PM<sub>10</sub> in the Taiwanese city of Taipei on cool days (<20°C), conditions which mirror those of the UK.** The lack of a significant association with PM<sub>10</sub> in **our work may also in part** be because we had to use particulate data from a different monitoring station to that which provided other concentrations, although the effect size for PM<sub>10</sub> was similar to that observed for the other pollutants. Given that O<sub>3</sub> concentrations were generally higher than those observed elsewhere, it is surprising that we did not find a strong relationship with this pollutant. **However, again, no relationship with O<sub>3</sub> was reported by Yang *et al.* [35].**

**Strengths of the study include the fact that it** benefits from a clearly defined population of rigorously diagnosed COPD patients, something that was not been available to many other studies, although a consequence is that we have a relatively small sample size compared to some other works. **In addition, hospital admissions may be expected to be a more sensitive indicator of any effect of air pollution on health than mortality [36].** The use of a case-crossover analytical design means that our ability to detect changes in admission risk associated with relatively small variations in pollutant concentrations was robust. **While some previous workers have used a time series generalised linear models, Lee *et al* [36] have shown that case-crossover studies produced similar results when analysing the effect of short-term change in air pollution. Case-crossover analyses have the advantage that subject-specific variables such as age and gender do not act as confounders [35].** Furthermore, whilst the selection of interval between the case and control day is somewhat subjective, we undertook a sensitivity analysis **(for example, six, eight and ten days) and found seven days to be optimal due to the cyclic nature of pollution tends associated with different traffic levels on different days of the week (lowest on Sunday; peak midweek). A seven day case-control interval is in line with previous work undertaken in study areas where air pollution is highly correlated with traffic flow [36].**

**Limitations include the fact that we did not assess the cumulative effect elevated exposure to high levels of pollution for a long period of time. Use of a seven day lagged average, for example, as in the study of Yang *et al* [38] might give greater insight into the effect of individual pollutants.** In common with other studies, we were not able to measure personal exposure to pollutants, but rather relied upon ambient concentrations. We acknowledge that concentrations may

vary markedly over a small geographic range and indoor and outdoor exposure can be very different [13, 33]. Furthermore, exposures will be influenced by individual activity patterns [13]. Similarly, this study did not assess the effect of one or more pollutants in combination. It may be that some pollutants act synergistically in inducing airway inflammation although, as illustrated by Fusco *et al* [17] and Yang and Chen [35], multi-pollutant models can be unstable due to collinearity and there is some controversy regarding their use. It is possible that some of the pollutants act as a surrogate for an unmeasured contaminant, and it is this that initiates lung disease; Norris *et al* [34], for example, showed that CO was strongly correlated with ultrafine particles in a study of asthma admissions. Furthermore we did not have information on local influenza incidence, as it is not collated at this scale, and hence used data for England and Wales. While displaying the same seasonal trends, local incidence may vary somewhat in both number of cases reported, duration of any outbreaks, and timing of peak incidence.

In conclusion, based on the analysis of a population of a much less urbanised area than has previously been investigated, this study found evidence that ambient pollutant concentrations were associated with the risks of hospital admission for COPD. Further studies in more rural areas are required to confirm these findings and investigate the possible presence of threshold values below which the effects of the pollutants on COPD cannot be observed.

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## **COMPETING INTERESTS**

None

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